Study Book

EMFACE®






EMFACE
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Simultaneous Emission of Synchronized Radiofrequency and HIFES™ for Non-invasive Facial Rejuvenation

A unique combination of RF and HIFES

Facial aging is a complex process resulting not only from skin aging but also from changes in the volume and density of the underlying structures, including the fascial system, facial ligaments, and facial muscles.[1] EMFACE is the first device in the non-invasive facial aesthetic segment that utilizes the simultaneous application of Synchronized RF and HIFES technology to treat multiple facial layers simultaneously.

EMFACE effect on facial skin

The loss of the amount of elastin and collagen and quality impairment of the remaining fibers contribute to the worsening of skin quality and skin aging.[2] EMFACE uses unique Synchronized RF along with the real-time impedance-based system to quickly heat the skin tissue to 40-42°C[3], the temperature needed to stimulate an increase in fibroblast activity, leading to an increased synthesis of new collagen and elastin fibers.[4] In addition, the old collagen and elastin fibers decompose and denature and are rebuilt again.[4]

Clinical studies on EMFACE focusing on structural changes demonstrated a prominent skin remodeling effect. These studies found that collagen increase ranged between 26 - 27% and elastin increase ranged between 110-129% two to three months following the procedure.[3,5] Additional study[6] investigating changes in skin texture and facial appearance reported a 36.8% wrinkle reduction and 25.3% skin evenness improvement three months post procedure.

Although Synchronized RF heating ensures skin texture improvement, treating only textural concerns is not enough. As we age, facial tissue becomes saggy due to changes in the facial musculature and laxity in the connective tissue. Therefore, it is necessary to target the underlying structures to achieve a more youthful appearance.

EMFACE effect on facial muscles

To achieve a complete and more targeted approach to treating all facial layers, the EMFACE utilizes HIFES technology, specifically designed to target the small delicate facial muscles. Facial muscles undergo atrophy and loss of muscular tone due to aging, similarly to the skeletal muscle, and also due to the long-term use of neurotoxins.[7,8]

HIFES technology selectively induces supramaximal contractions in the facial elevator muscles. The intense contractions are strong stimuli that trigger a tissue response leading to promotion of muscle protein synthesis[9,10] and to myofiber renewal[11]. Such processes lead to structural remodeling of the targeted muscles, which has been seen in EMFACE study[12] showing 19.2% increase in muscle density and 21.2% increase in number of myonuclei, which provide the muscle with nutrition. These results were coupled with reduced fibrotic and fat infiltration within the muscle tissue at two months post-procedure.

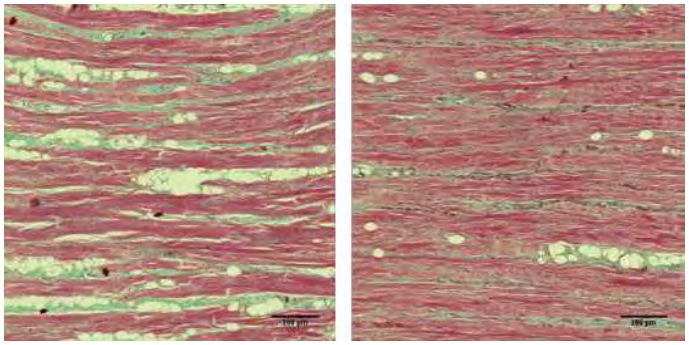


Figure 1: Histologic images of muscle tissues before (left panel) and 2 months after (right panel) the treatment with the EMFACE device.

The structural changes do manifest as increased resting muscular tone, which is necessary for maintaining the lifted facial appearance. The weaker the facial muscles are, the higher muscle effort is needed to avoid sagging and to hold the overlying tissues in place.[13] When being too weak, they become unable to hold the tissue, resulting in e.g. eyebrow drop or cheek sagging. When the resting muscle tone is increased, the muscles have the strength large enough to hold the overlying tissue in place without dropping and without the need to stay contracted.[13] EMFACE was found to increase the muscle tone by 30%[14] which was then shown to lead to an overall lifting effect by 23.1%.[6]

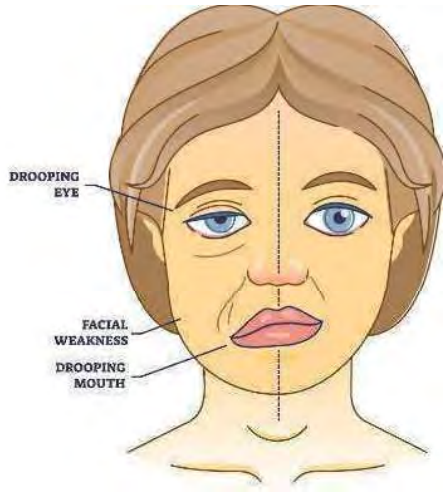


Figure 2: Visualization of the effect caused by weakened facial muscles on the left in comparison to healthy muscles on the right.

The synergy of RF and HIFES

The expression of HSP or SC is higher when the muscle is exposed to the simultaneous delivery of heating of around 40°C and supramaximal contractions compared to individual or consecutive energy applications.[15,16] This simultaneous delivery induces a strong signal, which is followed by a stronger response in the skin, muscle and fascial tissue, leading to more pronounced structural remodeling. [9,10,17–19]

Aside from the muscle and skin tissues, the EMFACE also affects the subdermal connective tissue. The facial fascial framework is largely composed of elastin, collagen, and connective tissue, and their degradation is part of the aging process. Synchronized RF heating with EMFACE may support the fascial framework via collagen and elastin remodeling, similar to what has been documented in previous skin tissue studies. In addition, the fascial support structures have also been found responsive to mechanical stimuli, which in case of EMFACE is delivered with HIFES stimulation.[20] The combination of both the heating and mechanical stress on the fascial support structures may lead to fascial remodeling, leading to increased fascial tightness and elasticity.[20]

Clinical effects

Due to the unique design and energy delivery, EMFACE applicators do not induce the stimulation of the depressors since the stimulation of the depressors could potentially lead to a worsening of rhytides. The forehead application targets the frontalis muscle (brow elevator) and corresponding fascias while avoiding the depressors in the glabella. Restoring the tonus of the frontalis muscle and tightening the fascias in combination with the skin remodeling leads to reduced horizontal forehead lines, brow elevation, and skin texture improvement.

The cheek application primarily targets the more superficial muscles of the cheeks (zygomaticus major/minor & risorius), which are all interconnected elevating units. In contrast, other deeper muscles, such as masseter m. are unaffected. Stimulation of these superficial muscles leads to an elevation of the entire cheek, increasing the midfacial volume and improving the nasolabial fold. Increasing the pull of these elevators further leads to a repositioning not only of the midface but of the lower facial soft tissues. The resulting clinical effect is a reduction in jowls and an increase in jawline contouring. The combined effect of HIFES with Synchronized RF manifests as an overall textural improvement of the skin.

Concluding comments

EMFACE uses Synchronized RF and HIFES energies simultaneously to target all facial layers; skin, fascia, connective tissue framework, and facial muscles to achieve full-face aesthetic remodeling. Affecting all these layers in a noninvasive manner leads to a textural improvement of the skin, wrinkle reduction, and an overall lifting effect visible in the cheeks and the forehead. Aside from multiple clinical studies using various evaluation methods, the results of the procedure are supported by a high patient satisfaction rate of 91.2%[21].

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The mechanism of EMFACE stimulation of muscle after the application of botulinum based neurotoxin

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***Abstract* — EMFACE is a new device that induces supramaximal muscle contractions of delicate facial muscles while heating the skin and underlying tissues. However, many EMFACE patients are users of botulinum based neurotoxins that are used to immobilize facial muscles in order to prevent repetitive skin folding. As such, facial muscles of these patients should not be contrated during EMFACE treatments. However, clinical studies have shown that it is possible to induce contractions of these muscles by external stimulation such as during EMAFCE. However, the mechanism of how it is possible is not entirely known.**

Keywords—Botulinum toxin, BOTOX, HIFES, EMFACE, Stimulation, Facial, Muscle

I. Introduction

Neuromodulators in aesthetic medicine, such as Botox, Dysport, Xeomin or Jeuveau have become the most frequently sought nonsurgical aesthetic procedure[1]. Type A botulinum-based neurotoxins have a myriad of clinical indications[2]. They are most frequently utilized to treat dynamic facial rhytides[3] involving the glabella, frontalis and periocular regions. Botulinum neurotoxins block neurotransmitter release in the synaptic neuromuscular junction to block voluntary muscle contraction. With blocked contractions, wrinkle formation is prevented as the overlying skin is not being repetitively folded during daily activities and thus aids in maintaining a more youthful skin appearance.[4,5] By decreasing the contraction strength of some facial depressor muscles, there is temporary increased tone of elevating facial muscles. There are also secondary effects such as reduction in erythema which may allow greater light reflection.

Recently, a novel device EMFACE was introduced to stimulate botulinum neurotoxin-blocked muscles to prevent muscle atrophy. EMFACE is able to stimulate the blocked facial muscle even though it is not possible voluntarily. In fact, the use of external stimulation on neurotoxin-blocked muscles has already been documented in multiple studies [6,7], however, the mechanism of how it is possible is not exactly known.

Although it is not entirely clear, all these suggest that external stimulation has the ability to bypass the effect of botulinum neurotoxins. The goal of this paper is to summarize existing knowledge on the topic and provide a viable hypothesis that could explain why such an effect is demonstrated during an EMFACE treatment.

II. The physiology of muscle contraction

To better understand the effect of botulinum neurotoxin, it is necessary to first explain the standard function of the neuromuscular junction and muscle contraction. The neuromuscular junction is responsible for the chemical transmission of an electrical impulse from the nerve to the muscle, to produce a muscle contraction. When a nerve impulse in the form of action potential reaches a nerve ending, voltage-gated calcium (Ca2+) channels are activated, which causes an influx of Ca2+ ions into the presynaptic neuron from the extracellular space. In the presynaptic neuron, the calcium cations interact with synaptic vesicles and enable their association with the presynaptic membrane. After the fusion of synaptic vesicles with presynaptic membrane, the content of the vesicles – neurotransmitter acetylcholine (Ach) is released into the synaptic cleft - quantal release.[8]

Under normal conditions, the released Ach transmits the electrical signal to the muscle fiber by depolarizing the muscle fiber membrane. Depolarized muscle membrane activates sarcoplasmic reticulum where Ca+ ions are stored and releases them.[8] The presence of the Ca+ ions in the muscle fiber results in a sliding process between actin and myosin filaments which slide alongside each other resulting in muscle contraction. The muscle contraction lasts as long as the Ca+ ions are present in the muscle fiber, however, Ca+ ions are quickly (fraction of second) returned into the sarcoplasmic reticulum unless there is another action potential that again increases the level of Ca+ ions or keeps it at the same level.[8] The collective shortening of the sarcomeres is the molecular mechanism behind a muscular contraction.[9]

III. The effect of botulinum neurotoxin

Botulinum based neurotoxin is affecting the process of muscular contraction at the level of neuromuscular junction. When applied, it works as a protease and prevents the fusion of the vesicles with the presynaptic membrane[10]. Without this fusion, the Ach cannot be released into the neuromuscular junction and trigger the muscle contraction as described above. It is a chemical denervation that causes partial paralysis of the innervated muscle. However, such

paralysis is not causing any damage to the nerve or the neuromuscular junction and is not permanent[11].

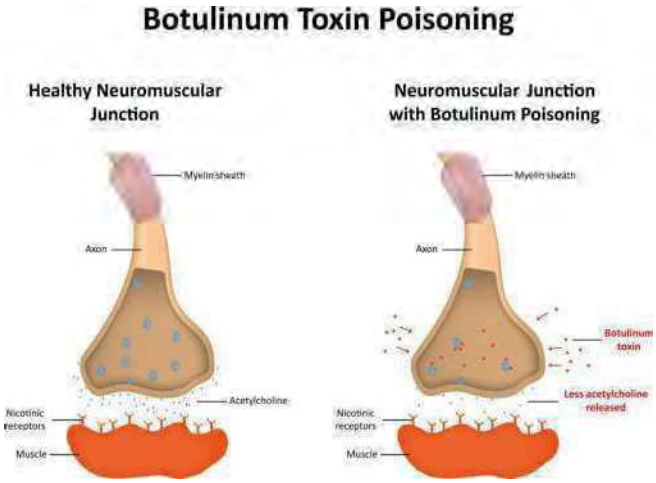


Figure 1: Botulinum toxin blocks the release of acetylcholine to neuromuscular junction, which does not allow the signal transmission into the muscle and thus blocks the muscle contraction.

IV. External stimulation of botulinum-paralysed muscle

There are two approaches to induce muscle contraction externally. First, muscles can be stimulated by applying an external electrical field to the muscle innervating neuron, where it induces an action potential, which is then carried to the neuromuscular junction.[12] Muscle can also be stimulated directly, as the muscle itself is an electrically excitable tissue.[13] If the muscle is stimulated through the neuron and, the whole muscle or all muscles innervated by this neuron are stimulated and contracted. With direct stimulation of the muscle tissue, only those muscle fibers in the electrical field are affected and a high stimulation intensity is needed to induce such contraction.[14] To contract the entire muscle by direct stimulation of the muscular tissue, a critical number of muscle fibers must be recruited.[13]

Multiple studies have shown it is possible to stimulate even the botulinum-paralysed muscles [7,15]. However, it is not entirely clear how such stimulation overcomes the barrier made by the botulinum neurotoxin. Upon the application of botulinum toxin, the membrane of the presynaptic neuron should be practically impermeable to Ach molecule due to its size as the the fusion of vesicles and presynaptic membrane ("quantal release") is blocked. Yet, the clinical trials are showing that externally it is possible to overcome this barrier and although the mechanism of how this happens is not entirely clear, several hypotheses were proposed to explain such mechanism:

Non-quantal Ach release

One of the possible explanations could be the non-quantal Ach release. It has been shown that aside from the above-described quantal release of Ach, also a non-quantal release occurs at the neuromuscular junction[16].

Non-quantal Ach release was proposed to be caused by the high-affinity choline transporter, which under normal physiological conditions returns the inactivated Ach (choline) from the synaptic cleft back to the nerve ending. Experimental findings indicate that this transporter may also transport the Ach to the neuromuscular junction. Its activity appears to be dependent on the concentration of calcium in the cytoplasm, which correlates with the firing rate of the neuron (number of induced action potentials)[16–18]. Considering that maximum firing rate of a neuron during voluntary muscle contractions reaches up to 25 Hz[19], while with external stimulation it is possible to induce firing rates in the order of hundreds of Hz, it could be assumed, that with an increased firing rate frequency, also the cytoplasmic calcium concentration increases, thus also increasing the level non-quantal Ach release.

Based on such findings, it could be hypothesized that such a non-quantal release of small amounts of Ach into the synapse still occurs, even in botulinum toxin denervated muscle. However, during voluntary contractions, the amount of the Ach is not sufficient to cause depolarization and the muscles thus remain relaxed. By applying an external high-frequency electrical field that surpasses the frequency of brain signals, the activity of the high-affinity choline transporter could be elevated, leading to exaggerated non-quantal release of Ach in amounts sufficient enough to cause muscle depolarization and contraction.

Additionally, a long-term insufficient concentration of Ach in the synapse, due to the application of botulinum toxin can lead to an increased expression of n-acetylcholine receptor (nAChR) on the postsynaptic membrane and therefore also to increase in the sensitivity of the muscle to Ach [20,21]. A lower amount of Ach would thus be needed to induce such depolarization.

Direct stimulation of the muscle fiber membrane

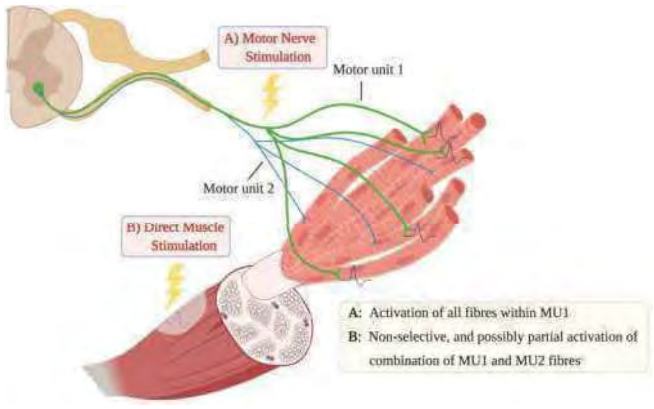


Figure 2: The principle of direct muscle stimulation vs. motor nerve stimulation. With nerve stimulation, the nerve is stimulated and signal propagates towards the muscle, while with direct stimulation the muscle fiber is stimulated directly. Image adopted from Guo et al.[22]

Another possible explanation for the externally induced contraction of botulinum-denervated muscles could be via the direct stimulation of the postsynaptic membrane. The

external electrical field could possibly induce action potential directly on the muscle fiber membrane and thus trigger the influx of Ca+ ions into the muscle fiber to contract the muscle.

Nevertheless, multiple studies contradict such hypothesis. Studies investigating the use of external stimulation of muscles fully denervated by physical transection showed that very high intensity (pulses in ms) is needed to depolarize the muscle fiber membrane and induce contractions of these muscles directly, while EMFACE uses lower energy pulses in μs.[23,24] Furthermore, with direct muscle fiber membrane stimulation it is difficult to stimulate the entire muscle, rather it has been shown to stimulate only a portion of the muscle, while with EMFACE the entire muscles are contracted.

However, all these conclusions regarding the direct muscle stimulation are based on studies performed on skeletal muscles only. Facial muscles are of significantly different proportion and are much more superficial located in low depths of 3-8 mm[25]. All this may influence the response. As the facial muscles are more delicate, lower intensity may suffice to irritate the muscle membrane. Since the thickness of some facial muscles may be as small as 0.5mm[26], it may be possible that such stimulation is able to recruit enough muscle fibers to induce contraction of the entire muscle. In addition, this could actually explain the non-stimulation of the masseter muscle during the EMFACE treatment. In the vast majority of patients the masseter is not stimulated and it could be explained by the fact that the neuronal branch innervating the muscle is not in the application field, but also by the fact that masseter muscle is one of the largest facial muscles with thickness of up to 3.5mm[27] and during the treatment not enough muscle fibers are recruited to induce full masseter activation.

V. Summary & Conclusion

It is clear that it's possible to externally stimulate botulinum-denervated muscles, yet, the underlying mechanism is not. Current paper proposes a possible explanation of this phenomenon based on the existing knowledge of the processes on the neuromuscular junction and muscle contraction. However, multiple different factors may play a role in the mechanism. More experimental studies are needed to fully understand why it is possible to externally stimulate the botulinum-paralysed muscles.

In regard to EMFACE specifically, a study by Chilukuri et al.[28] showed that during the EMFACE treatment the botulinum-denervated muscles are being contracted and what is most important, the EMFACE treatment does not interfere with the effect of botulinum toxin itself. No negative effects of the EMFACE stimulation on the efficacy of the botulinum toxin were found.

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Simultaneous Emission of Synchronized Radiofrequency and HIFES for Non-invasive Facial Rejuvenation: The Mechanism of Action

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Abstract

EMFACE is a unique device specifically developed for non-invasive face lifting and wrinkle reduction by targeting all facial layers; skin, connective tissue framework, and facial muscles. It utilizes both Synchronized RF and HIFES technologies simultaneously. Heating the facial tissue to effective temperatures and HIFES stimulation of only specific facial muscles results in a combined effect that causes textural changes to the skin, smoothing, wrinkle reduction, facial repositioning, and an overall lifting effect. The simultaneous and targeted manner of both technologies yields unique benefits by inducing a synergistic effect in the facial soft tissues that cannot be achieved by using these technologies consecutively or as a standalone procedure.

Keywords: HIFES, Radiofrequency, Simultaneous, Application, Supramaximal, Contraction, Muscle, Fat, Reduction, Hypertrophy, Face, Lift

Introduction

Facial aging is a continuous and unstoppable process resulting from age-related changes in all structures present in the face: skin, fat, muscle, fascia, and bone.[1,2] Age-related changes of all facial soft tissues start at different decades and progress at different speeds, which vary between individuals of different gender and ethnicity. All changes together result in reduced support for the bone-overlying soft tissues, which then follow the effect of gravity. Repositioning and restructuring the affected tissues and layers is the aim of aesthetic procedures via surgical and non-surgical procedures.[1,2]

Amongst non-invasive aesthetic procedures, radiofrequency (RF) is considered the gold standard for facial skin treatment.[3] The effect of RF on the skin tissue is based on dermal heating, which leads to structural changes within the skin and the overall improvement in skin quality.[4] However, these skin heating procedures focus solely on improving skin quality and textural improvement, but not the overall facial appearance.

The overall facial appearance is not only influenced by skin quality but also by the facial volume and density of the underlying structures, including the fascial system, facial ligaments, and facial muscles. Therefore, the extent of facial laxity is a composite effect of all implicated structures of which the facial muscles and their interconnection with the skin play a fundamental role.[5]

The most frequently performed non-surgical treatment to date is the administration of soft tissue fillers, which help to restore facial volume.[6] However, soft tissue fillers only attempt to cover the aging symptoms and do not affect facial muscles, which play a crucial role in natural skin mobility.[7] Currently, the only way to alter facial muscles is through a surgical lift procedure, where the skin and fat tissues are separated from the muscle, and the muscles are then repositioned.[8]

Recently, HIFES technology has been introduced to the market to target the facial muscles and their connective tissue frameworks for lifting and tightening of the facial contours. This novel technology induces electrical fields to contract facial muscles selectively. These delicate facial muscles are crucial for supporting the facial soft tissues and play a structural role in a more youthful appearance.

EMFACE is the first device on the market utilizing the simultaneous application of both the synchronized RF and HIFES technologies for non-invasive facial lifting and wrinkle reduction. While the HIFES technology targets the muscle and overlying fascial tissue, the synchronized RF heating induces structural changes to the dermal and subdermal architecture. This approach ultimately results in an improved appearance through changes in all facial tissue layers.

The Role of Facial Muscles and Fascial Framework in Aesthetic Appearance

It is widely accepted that facial skin changes over time, with facial wrinkles being only the tip of the iceberg. Loss of structural support due to volume depletion and changes to the facial muscles and their connective tissue framework results in an increased soft tissue laxity which is additionally influenced by the effects of gravity. Facial muscles have been found to age through the process of sarcopenia, which manifests as a loss of muscle mass and volume, similar to skeletal muscles.[9,10] Since the facial muscles are interconnected via the fascial system and the overlying skin, weakening of these muscles may result in a visible descent of the tissue sagging as we age. The weaker the facial muscles are and the lower is the resting muscle tone, the higher muscle effort is needed to avoid sagging and to hold the overlying tissues in place. When being too weak, they become unable to hold the tissue, resulting in e.g. eyebrow drop or cheek sagging. When the resting muscle tone is increased, the muscles have the strength large enough to hold the overlying tissue in place without dropping and without the need to stay contracted.

Specifically, the muscles in the cheeks are interconnected by the midfacial superficial musculoaponeurotic system (SMAS).[11] Weakening of the cheek muscles, especially the zygomaticus muscles, allows for the hypothesis that as we age, the resulting facial muscle weakness can promote midfacial soft tissue descent, resulting in the increased severity of the nasolabial fold, formation of jowls, and loss of jawline contour.[12] Targeting these muscles and its surrounding connective tissue architecture might allow for midfacial soft tissue repositioning.

Also, the same muscle weakening could be expected for the frontalis muscles due to aging or long-term use of neurotoxins. The frontalis muscles are largely responsible for eyebrow movements[13]. Their connection with the skin is ensured via the supra-frontalis fascia (located superficial to the frontalis muscle) and the sub-frontalis fascia (located deep below the frontalis muscle). Aging of the forehead structures may result in eyebrow ptosis[14] and heaviness, which along with skin aging, may lead to laxity and wrinkle formation in the region.

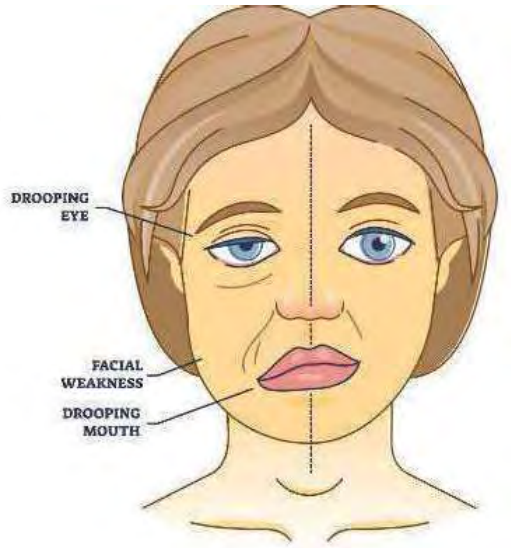


Figure 1: Visualization of the effect caused by weakened facial muscles on the left in comparison to healthy muscles on the right.

In contrast to skeletal muscles, the facial muscles are embedded in a connective tissue framework that interconnects all tissues from bone to skin. Interestingly, in addition, they are connected directly to the brain via the cranial nerves and are responsive to emotional input and the limbic system. Emotional states affect facial contours via resting tone of the muscles and the SMAS. Therefore, the facial muscles need to be seen within their connective tissue environment and addressed accordingly. Assuming that facial muscles affect skin movement alone without the support of a connective tissue environment creates an incomplete picture of facial muscle anatomy.

The combination of age-related facial changes results in an alteration of the facial shape which cannot be

improved by targeting the skin alone. Therefore, more **profound treatment algorithms need to be applied to address age-related facial changes.**[15,16] This may include addressing **deeper fascial and muscle layers together**, as they have the ability to promote facial repositioning; treating the skin alone will not have such comparable effects.

How EMFACE Targets Facial Muscle and Fascial Tissues?

The Mechanism of HIFES Stimulation

Increased laxity of the overlying skin and the connective tissue framework increases the disconnect between muscular contraction and skin movement; this is more prevalent as we age. Therefore, inducing positive changes to the connective tissue and facial muscle unit will restore the connection between the layers, rejuvenating all layers, including the skin.

The EMFACE utilizes HIFES technology, specifically designed to selectively induce supramaximal contractions of small delicate muscles in the face. The technology generates strong electrical fields that affect the underlying neuronal and muscle tissue. These electrical fields depolarize the membrane of the motor neurons that innervate the muscle. When the motor neurons are depolarized, a signal is created that travels along the neuron, all the way to the neuromuscular junction - the place where the motor neuron is connected to the muscle. These signals overcome the barrier of the neuromuscular junction and progress to the muscle, which is thus forced to contract. This process bypasses the voluntary intention of the brain, inducing a forced contraction through electrical stimulation.

During each treatment, energy is applied to the facial soft tissues, and muscular contractions are induced. The HIFES technology induces up to 250 energy impulses per second (= 250 Hz), which does not allow any time for the facial muscles to relax in between the individual signals. As the muscle is unable to relax, with additional stimuli it is forced to contract even further which continuously builds up the contraction power with every additional signal. The appropriate selection of these two factors (electrical field strength and frequency) results in the so-called “supramaximal contraction”.

Although it is poorly understood how and to what extent the facial muscles adapt to external stimuli, research studies conducted in skeletal muscles have revealed that heat shock proteins (HSP) and satellite cells (SC) may be activated by intense muscle exercise as a response to the applied stimuli.[17,18] HSP are the signaling molecules playing a crucial role in muscle remodeling through the promotion of muscle protein synthesis.[19,20] SCs are muscle-derived stem cells responsible for myofiber development and renewal.[21] In a resting state, the SCs remain quiescent, ready to be activated, and provide differentiation to create new myonuclei to existing muscle fibers or generate new muscle fibers. Together, HSP and SC activation can support muscle micro-protein structure alterations. In a healthy muscle this may lead to densification of the muscle tissue and to overall improvement of the muscle quality. In atrophied muscle, the muscle structure alteration may lead to hypertrophic response reversing the atrophy. However, it is not only the muscle reacting to the signaling molecules. It has also been documented that the fascial layer remodels itself in response to heat and mechanical stimuli.[22]

Future studies will need to identify similarities between skeletal and facial muscles or provide conclusive evidence that facial muscles behave similarly or differently when targeted by external stimuli.

The Role of Synchronized RF Heating on Facial Muscles and Fascial Framework

Simultaneously with the HIFES stimulation, the EMFACE delivers Synchronized Radiofrequency that heats the facial tissue. Such stimuli affect the connective tissue framework and the facial muscle unit with consecutive adaptive changes to the overlying facial soft tissues.

According to previous studies on skeletal muscles[19,20,23–25], HSPs can also be activated by heat within the range of 40℃. Together with the muscular contractions, the heat thus may further increase the levels of released HSP[26,27], this effect has been shown in abdominal muscle [28,29], gluteal muscle [30,31], or in the muscles of the upper extremity.[29,30] A recent study by Kinney et al.[32] measured the facial muscle temperature during the treatment with the EMFACE device and showed that the temperatures in the targeted muscle tissues reached up to 40℃, indicating that a similar

effect could also be seen in the facial muscles during the EMFACE treatment.

The primary effect of Synchronized RF heating on the subdermal tissues can be seen in the fascial framework. The fascial framework primarily consists of collagen and elastin, which are known to be heat responsive. Therefore, heating to adequate temperatures may induce remodeling of collagen and elastin within the fascial framework, leading to increased elasticity and tightness of the fascial web.[22]

Clinical Effect of EMFACE on Facial Muscles and Fascial Tissues

Forehead application

The EMFACE applicators are designed to target specific muscles of the face. The forehead applicator has been designed to specifically target the frontalis muscle and its surrounding connective tissue environment, composed of the supra-frontalis fascia (located superficial to frontalis muscle) and of the sub-frontalis fascia (deep to frontalis muscle), enveloping the only eyebrow elevator like a sleeping bag. The applied stimulus during the treatment with the EMFACE device affects the connective tissue framework and the facial muscle unit simultaneously, which have a soft tissue thickness in the range of 3 – 7 mm[33] for the forehead. The applied energy induces changes to the entire unit, which results in its structural alteration. A tighter fascia (sleeping bag) allows for the relaxation of the enveloped muscle, which in turn most likely reduces its baseline contractile tonus. The latter effect is clinically visible in the form of reduced horizontal forehead lines. Since the frontalis muscle is an eyebrow elevator, strengthening formerly atrophied frontalis muscle may aid with eyebrow ptosis and lead to brow elevation.

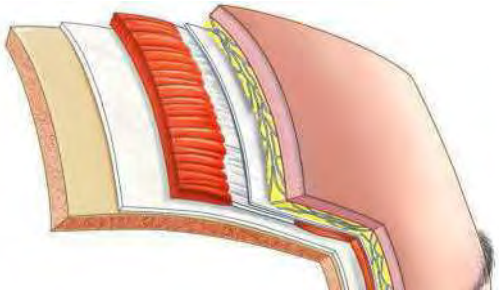


Figure 2: The frontalis muscles is enveloped by the supra-frontalis and sub-frontalis fascias. The condition of both the muscle and the fascias affects the overall appearance of forehead.

Affecting the connective tissue framework and the facial muscle unit of the forehead indirectly influences the glabellar muscles. All upper facial muscles (consisting of frontalis, procerus, corrugator supercilii, and orbicularis oculi) connect with the skin at the level of the upper margin of the eyebrow both in the midline and laterally. Affecting the frontalis m. will indirectly influence the eyebrow depressors and cause, most likely, a **change in their position** (relative to the underlying bone) by being pulled upward. Muscular contractions of the glabellar muscles are not observed during the treatment. The effect is thus indirect, only due to the supporting fascial framework, which stabilizes and guides muscular actions.

Cheek application

The cheek applicators are designed to stimulate the zygomaticus major and minor muscles and the risorius muscle.



Figure 3: The cheek muscles stimulated by EMFACE cheek applicators: Zygomaticus major & minor muscles and risorius muscle.

The zygomaticus minor muscle is attached to the skin at the nasolabial fold. The zygomaticus major muscle is connected to the underlying maxilla by a connective tissue sheet termed the transverse facial septum.[34] This septum forms the inferior boundary of the midfacial fat compartment and forms a biomechanical unit with the overlying muscle. Stimulating this unit allows for conformational change of the septum, elevating the entire cheek, increasing the midfacial volume[2], and improving the nasolabial fold.[35]

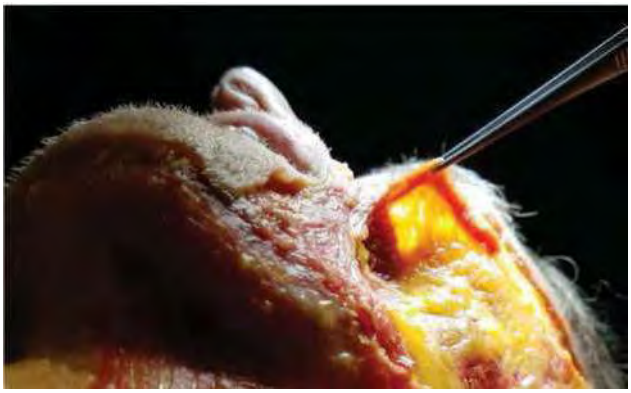


Figure 4: Cadaveric dissection of the left side of the face showing the transverse facial septum connecting the zygomaticus major muscle to the maxilla. Image taken from Cotofana et al.[34]

Repositioning the midfacial soft tissues, especially the superficial fat compartments, influences the balance between total facial elevators and depressors. The platysma is the strongest facial depressor, due to its extent and fascial connection to the SMAS, the superficial temporal fascia, and the orbicularis oculi muscle. Decreasing the caudally oriented vector of the midface will shift the balance toward the zygomatic facial elevators, allowing for repositioning not only midfacial but lower facial soft tissues. The resulting clinical effect is a reduction in jowls and an increase in jawline contouring. In addition, the masseter muscle, deeper muscles of facial expression like the buccinator or levator anguli oris do not display muscular contractions during the treatment.

It is important to note, facial muscles are not expected to increase in their thickness as compared to the structural changes observed in skeletal muscle following strength training. However, these delicate muscles do keep their genetically predisposed thickness: frontalis muscle approx. 3 mm[36], zygomaticus major approx. 3.6 mm[37], and approx. 0.5 mm for the zygomaticus minor[38] and risorius muscles.[39] Future studies will need to identify similarities or differences between these muscle groups.

The effect of EMFACE on muscle structure has been investigated in a study by Kinney et al.[32], who found a 19.2% increase in muscle density and a 21.2% increase in the number of myonuclei after four EMFACE treatments. Structural changes post-EMFACE treatments were also suggested in a study by Halaas et al.[40], who used ultrasound echogenicity to evaluate muscle quality, also called muscle tone. In this study, the muscle quality increased by 30%.

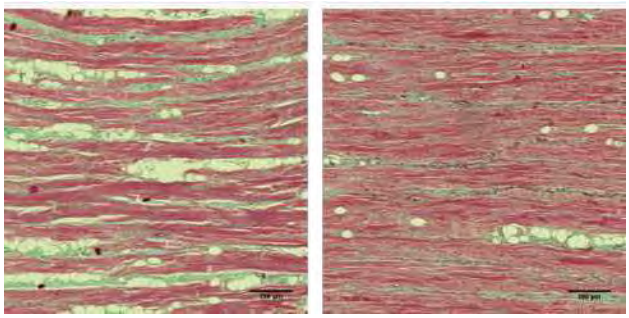


Figure 5: Histologic images of muscle tissues before (left panel) and 2 months after (right panel) the treatment with the EMFACE device[32].

Additionally, clinical studies on the EMFACE device further support the proposed mechanism of action. A clinical study by Kinney and Boyd et al.[41] investigating EMFACE found a brow lifting effect of 23.1% coupled with 91.2% patient satisfaction. In addition, a study by Halaas and Gentile et al.[42] reported a 36.8% wrinkle reduction. These studies additionally revealed that clinical changes peak at approximately 2 to 3 months post-treatment, which is in line with the time frame needed for structural changes to be implemented into the connective tissue framework and the facial muscle unit.

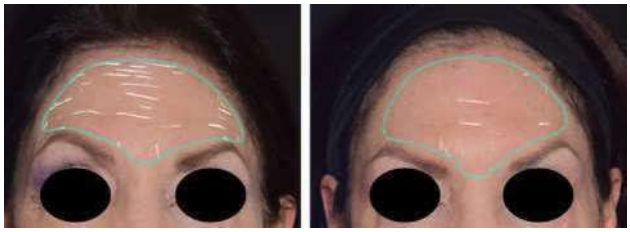


Figure 6: Example of patient results in wrinkle reduction as evaluated by automated software. Baseline on the left and 1 month after on the right. Taken from Halaas et al.[42]

The effect of EMFACE on facial skin tissue

Regarding skin, fine lines and wrinkles accompanied by loss of skin volume are usually the first indicators of skin aging, a normal physiological process influenced by genetic and hormonal changes. However, external factors also influence aging, e.g., exposure to UV radiation, skin[43,44], smoking[45], diet, air pollution[46], or chemicals and toxins.[47,48] During the skin aging process, the dermal blood vessel structure is disrupted, and in turn, the dermis is not supplied with

nutrition and oxygen, thus slowing cellular regeneration.

The major building blocks of the skin are collagen and elastin fibers, responsible for skin elasticity and firmness. These components are also affected by aging. During the aging process, collagen and elastin synthesis decreases, collagen bundles lose their extensible configuration and become fragmented[48], and the elastin fiber network is degraded, leading to the loss of structural integrity of microfibrils.[49] As the extracellular matrix is degraded, skin thickness is also reduced.[50,51]

As a result of aging, collagen and elastin deficiencies are the main cause of wrinkle formation. Amount of skin collagen and elastin is deacreasing every year due to aging process. It is estimated that adult skin loses 1%[52] of overal collagen content annualy.

Effect of RF heating

RF heating is known to address aging factors within the skin effectively. EMFACE utilizes a novel Synchronized RF electrode that allows the simultaneous application of an RF field together with HIFES, which is impossible with any other RF technology. During the 20-minute treatment, the skin tissue is heated to 40-42°C. This therapeutic temperature range is reached within the first 2 minutes of the treatment, as documented by the thermal probe measurements and by thermal camera by Kent et al.[53]

Radiofrequency current flow achieves the heating through the dermal and subcutaneous tissues. As the RF current flows through the tissue, a portion of the RF energy is absorbed by the tissue, transforming the energy into heat and the desired thermal effect. The level of RF energy absorption in the tissue depends on the RF frequency[54] and tissue impedance[55], among other factors. Since the skin, muscle, and fat tissues have different impedances[56], it is possible to selectively target the energy and achieve the thermal effect only in the desired tissue(s).

When the therapeutic temperature is reached in the skin tissue for the desired time period, the hydrogen bonds tying the collagen fibers together begin to unwind, and collagen denaturation occurs. However, these temperatures do not lead to permanent damage.[57] As the tissue dissipates the mentioned thermal effect, the bonds begin to renature, and the skin's architecture is changed to a more youthful level.[57] After repeating this process during multiple treatments, the structure of older collagen and elastin fibers is changed. It begins to take on the structure similar to newly formed collagen and elastin fibers.

This thermal effect is also accompanied by a heat-induced wound healing response and increased fibroblast activity. Fibroblasts are the dermal cells responsible for producing new collagen and elastin fibers. As we age, their activity decreases to a level equivalent to an overall "net loss" of fibers. This means that the amount of newly formed fibers does not exceed the number of fibers being degraded, which accelerates the appearance of skin aging. Nevertheless, studies have shown that heat stress increases fibroblast activity, leading to an increased synthesis of collagen and elastin - neocollagenesis & neoelastogenesis.[58]

RF heating supports the skin to regain its volume, elasticity, and a more youthful appearance by restoring the collagen and elastin fiber structure and enhancing the synthesis of new collagen fibers.

Clinical studies on EMFACE, which focused on structural changes, demonstrated a prominent skin remodeling effect. The outcomes of a study performed on a porcine model by Kent et al.[53] correlated with the human histology study by Goldberg et al[59]., as both found that collagen increased by 27% and 26%, respectively. In addition, elastin was found to have doubled in the study by Kent et al.[53], while in the Goldberg study[59], the elastin levels increased by 129%.

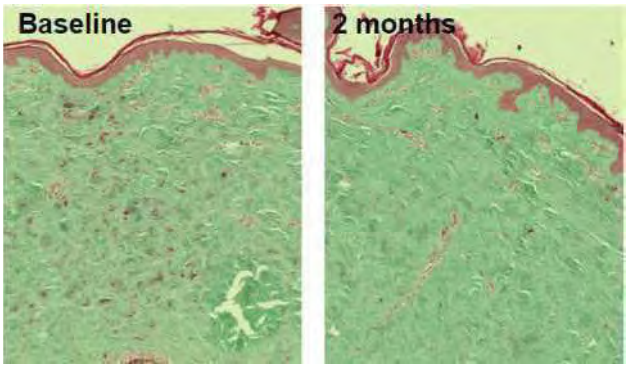


Figure 7: Densification of the collagen fiber network at 2 months post EMFACE treatment (right) in comparison to baseline (left) documented in Kent et al.

The effect on skin has also been documented in additional studies. For example, a study by Halaas and Gentile et al.[42] reported 36.8% wrinkle reduction and

25.3% skin evenness improvement. Wrinkle improvement was also reported in a study by Cohen et al.[60] Similar to the muscle studies, the skin results also peaked at 2 to 3 months post-treatment.

The Effect of EMFACE on Fat Tissue

During the treatment with EMFACE, the temperature in the fat tissue does not exceed the 43°C[61] needed for induction of an apoptotic process. Any direct effects in the fat tissue thus have not been observed.

Summary

EMFACE is a unique device specifically developed for non-invasive face lifting and wrinkle reduction by targeting all facial layers; skin, connective tissue framework, and facial muscles. It utilizes both Synchronized RF and HIFES technologies simultaneously. Heating the facial tissue to effective temperatures and HIFES stimulation of only specific facial muscles results in a combined effect that causes textural changes to the skin, smoothing, wrinkle reduction, facial repositioning, and an overall lifting effect. The simultaneous and targeted manner of both technologies yields unique benefits by inducing a synergistic effect in the facial soft tissues that cannot be achieved by using these technologies consecutively or as a standalone procedure.

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Novel Technology for Facial Muscle Stimulation Combined With Synchronized Radiofrequency Induces Structural Changes in Muscles Tissue: Porcine Histology Study

Aesthetic Surgery Journal
2023, Vol 00(0) 1–8
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https://doi.org/10.1093/asj/sjad053
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Abstract

Background: With age, facial muscles lose the ability to complete contractions properly, resulting in limitation of facial expressions and fat shifting, and leading to skin creases and wrinkling.

Objectives: The aim of this study was to determine the effects of the novel high intensity facial electromagnetic stimulation (HIFES) technology combined with synchronized radiofrequency on delicate facial muscles, using an animal porcine model.

Methods: Eight ($n = 8$, 60-80 kg) sows were divided into the active group ($n = 6$) and the control group ($n = 2$). The active group underwent four 20-minute treatments with radiofrequency (RF) and HIFES energies. The control group was not treated. Histology samples of muscle tissue were collected by a punch biopsy (6 mm in diameter) from the treatment area of each animal at baseline, 1-month, and 2-month follow-up. The evaluation included staining of the obtained tissue slices with hematoxylin and eosin and Masson's trichrome to determine the changes in muscle mass density, number of myonuclei, and muscle fibers.

Results: The active group showed muscle mass density increase (by 19.2%, $P < .001$), together with elevated numbers of myonuclei (by 21.2%, $P < .05$) and individual muscle fibers, which increased from 56.8 ± 7.1 to 68.0 ± 8.6 ($P < .001$). In the control group, no significant changes were seen in any of the studied parameters throughout the study ($P > .05$). Finally, no adverse events or side effects were observed in the treated animals.

Conclusions: The results document favorable changes after the HIFES + RF procedure at the level of the muscle tissue, which may be of great importance in terms of maintenance of facial appearance in human patients.

Editorial Decision date: February 28, 2023; online publish-ahead-of-print March 8, 2023.

Aging is a multifactorial process that affects all body structures, causing emotional distress through altering of the visual appearance and thus self-perception.[1–3] In the face, the skeleton, ligaments, muscles, adipose tissue, and skin undergo age-related changes at a different pace, however all structures interact with each other. Therefore, changes in one structure affect others.[4] Facial muscles are one of the most affected structures. Muscle changes can be promoted by age and gradually lose their mass and function after the third decade of life.[5] The imbalance between the degradation and synthesis of new muscle fibers leads to functional setbacks, recognized as sarcopenia.[6] Atrophic changes in the muscle tissue can also result from neuromodulators such as botulinum toxin type A injections.[7,8] The deconditioned muscles manifest themselves with loss of strength, disorganized sarcomere spacing, and decrease in plasma

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membrane excitability, all of which lead to decreased muscle twitch time and twitch force.[5,6] Because the facial structures are intertwined, changes in one structure can manifest themselves in other structures, and as a result of this deterioration in muscle function certain facial expressions may be limited, and changes in adjacent structures can be seen as well, such as fat shifting and skin wrinkling.[4]

Facial muscles are a type of striated muscles that (in contrast to skeletal counterparts, which facilitate movement of entire body parts) are embedded in a connective tissue framework that interconnects all tissues from bone to skin to perform facial emotional expressions and mastication.[9] Recently high-intensity focused electromagnetic (HIFEM) technology synchronized with radiofrequency (RF) has been proven to be safe and effective in muscle strengthening of the large skeletal muscle groups; however, due to the physiological differences between skeletal and facial muscles, novel high intensity facial electromagnetic stimulation (HIFES) technology with synchronized radiofrequency was developed to strengthen delicate facial muscles to combat the signs of aging.[1,10–12] Regarding muscle action, there is a substantial difference between voluntary and induced muscle contractions. The general mechanism of voluntary muscle contraction starts with a signal from the brain—an action potential. It is essentially an electrical impulse that travels through the motor neuron to the synapses (neuromuscular junction), releasing the neurotransmitter and influencing the membrane's electrical potential, causing depolarization and activation of muscle contraction, followed by the relaxation phase.[13,14] The novel HIFES technology, however, induces so-called supramaximal contractions independent of brain activity. Moreover, due to the tailored stimulation frequency, the muscle contractions are considerably intensified because the relaxation phase does not follow every single stimulus. The synchronized RF aids the effect of the HIFES field by heating the muscle tissue within a safe range of temperatures (below 42°C), activating protein synthesis and increasing the expression of heat-shock proteins, which help with muscle regeneration and growth.[15,16] Additionally, RF heating leads to neocollagenesis and neoelastinogenesis, creating firm, tightened, lifted, and smooth skin.[17]

The HIFES technology synchronized with radiofrequency has the potential to treat the vast majority of facial imperfections because it is able to target both muscle and connective tissues. However, the aim of this animal histology study is to investigate its effects and safe use on muscle remodeling, focusing on the structural organization of this tissue.

METHODS

This prospective, single-center animal study was approved by the Institutional Animal Care and Use Committee and the Ethics Committee for Animal Protection of the Ministry of Agriculture of the Czech Republic. The study was initiated in June 2021 and was completed in September 2021. It was performed in association with and supervised by a veterinary institute certified for good laboratory practice. All animals were stabled at the veterinary institute, so the veterinarian and veterinary staff handled the animal care to ensure animal welfare during the study. After performing all the planned procedures and collection of all samples, the animals were euthanized by an analgesic overdose (T61 a.u.v. inj, Intervet International B.V./MSD AH, Boxmeer, the Netherlands) administered by a veterinarian.

Animal Model and Treatment Settings

Eight large white pigs ($n = 8$ females, 60-80 kg of live weight) were utilized for this trial. Six sows ($n = 6$, active group) underwent four 20-minute treatments on the forehead once a week with simultaneous application of HIFES and RF. Two sows ($n = 2$, control group) were not treated. The control group was established to reduce the number of punch biopsies taken from the treated animals and to allow them to heal properly. In addition, all treated animals had blood tests and were examined to ensure their health and to rule out any possibility of unexpected interference with results. The treatments were delivered by noninvasive self-adhesive, hands-free EMFACE applicators (BTL Industries, Boston, MA) emitting both RF and HIFES energies and covering approximately 53 cm^2 (Figure 1). Both energies were set at 100% intensity. In addition, optical fiber sensors were inserted into the treated muscles under the applicator (LumaSense Flurotropic Thermometer; Lumasense Technologies, Santa Clara, CA) to monitor the temperature during the treatment. An infrared camera measured the skin temperature immediately after the treatments (Fluke Ti300; Fluke Corporation, Everett, WA).

During the treatment and collection of punch biopsies, the animals were kept under general anesthesia for easier manipulation and comfort. At first, the premedication for anesthesia consisting of Tiletamine + Zolazepam (Zoletil 100 Virbac; Carros, France) + Ketamine (Narketan, Vetoquinol; Lure Cedex, France) + Xylazine (Sedazine, Fort Dodge; Overland Park, KS), each medicine dosed at 2 mg/kg, was administered intramuscularly. Then, an intravascular cannula was placed into the ear's vein to infuse propofol 2% MCT/LCT (Fresenius; Bad Homburg, Germany), dosed at 1-2 mg/kg to maintain anesthesia. The animal's heart activity was monitored by electrocardiogram. A certificated veterinarian oversaw the animals during the entire treatment sessions and follow-ups, including assessment of adverse events and side effects related to the study device.

Three samples of muscle tissue per animal were collected by a punch biopsy (6 mm in diameter) taken from the treatment area on the forehead (active group) and a corresponding place on the forehead of those in the control

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Figure 1. Visualization of the self-adhesive, hands-free EMFACE applicator intended to treat the forehead area in human patients.

group. All samples were collected in the anesthetized animals before the first treatment, and at 1-month and 2-month follow-ups, to minimize the suffering of the sows. After the sampling procedure, the wound was disinfected, closed with 2 clamps, and covered with an adhesive bandage to protect the wound from infection.

Evaluation of Muscle Changes

Each muscle sample was stored in a container with 10% neutral buffered formalin (in a sample-to-fixative ratio of approximately 1:30) to preserve the tissue condition at the time of collection. The samples were then embedded in paraffin wax, sliced on the microtome, and stained with hematoxylin and eosin (H&E) and with Masson's trichrome for visualization in longitudinal and transverse cross-sections.

The hematoxylin has to be oxidized into hematein to gain staining abilities, and because it is positively charged it dyes the nucleus in a dark-blue color.[18,19] The eosin is negatively charged and stains the proteins and cytoplasm pink.[20] The staining process starts with immersing the slides in H_2O to clean the formalin and rehydrate the samples. Then, the slides are dyed with hematoxylin, rinsed, and stained with eosin. Next, the dyed sample is dehydrated with alcohol because some substances can be better dissolved. Then the alcohol is rinsed again, and the sample is mixed with a mounting medium and covered with a coverslip.[20] The muscle cells consist of myofilaments and intermediate filaments in the cytoplasm, which after H&E staining appear deep pink, with multiple nuclei dyed in dark blue color, allowing analysis of the morphology of each structure.[19,21]

Masson's trichrome staining consists of 3 dyes, a Weigert hematoxylin that stains the nucleus (dark brown), an acid stain (Ponceau–Fuschin) which stains muscle fibers (red), and a phosphotungstic acid (orange G), a decolorizing agent, which diffuses out of the collagen fiber while leaving the muscle cells stained red.[22–24] Additionally, Goldner's stain III (light green SF yellowish) dye was utilized to stain collagen fibers green and erythrocytes orange.[22,25] The staining process starts with refixing the samples in Bouin solution, which improves the quality of the stain. The slide is rinsed with tap water and stained with Weigert hematoxylin and again rinsed with tap and distilled water. Then it is dyed with an acid stain, rinsed with distilled water, immersed in phosphotungstic acid, and stained with Goldner's stain III. At this point, the sample is rinsed in distilled water and differentiated with 1% acetic acid, washed again in distilled water, dehydrated with alcohol, and cleaned with xylene. The last step is to mount the sample with a mounting medium and cover it with the coverslip.[22]

All stained slices were then visualized under a light microscope and photographed with Hitachi Axio Scan.Z1 (Carl Zeiss AG; Oberkochen, Germany) with a 20×/0.8NA Plan-Apochromat objective. The primary outcome measures included calculating muscle mass, the number of myonuclei located on the periphery of the sectioned muscle fibers, the number of muscle fibers, and the diameter of individual muscle fibers. The evaluation was performed with semiautomatic processing and analytic software ImageJ (National Institutes of Health; Bethesda, MD) in the predefined regions of interest (ROI) of 122,500 μm^2.

The descriptive statistic was calculated (mean, standard deviation) when analyzing the obtained quantitative data. To determine the statistical significance of the changes the Friedman test, followed by the Nemenyi test, for pairwise comparisons was performed. In addition, a Wilcoxon rank sum test was done to compare independent data. For all statistical analyses, the significance level of α=.05 was set.

RESULTS

All animals recovered from the anesthesia without any complications. No treatment-related side effects were observed in any of the animals or on the histological evaluation. In total, 24 muscle samples were collected during the study period, with each sample sliced, stained (3 slices per each staining, 144 slices in total), and evaluated to determine the primary outcomes. In general, there was no difference between the groups (P value > .05) in any of the measured outcomes at baseline. However, as the study progressed, the active group showed significant changes at the follow-ups and when compared with the control group. The temperature measurements revealed elevated

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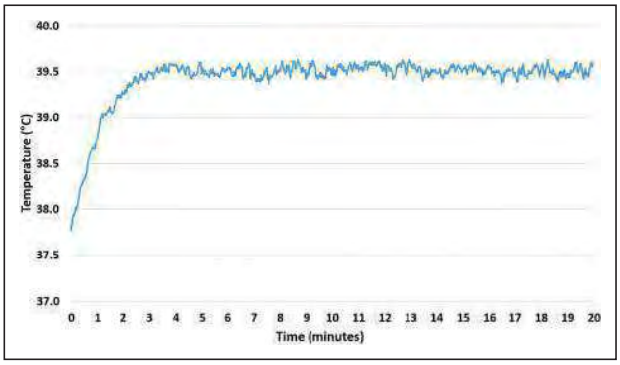


Figure 2. The temperature development in the muscle tissue during the therapy. The temperature rises to 39.5°C within 2 minutes and stays essentially unchanged for the rest of the therapy time.

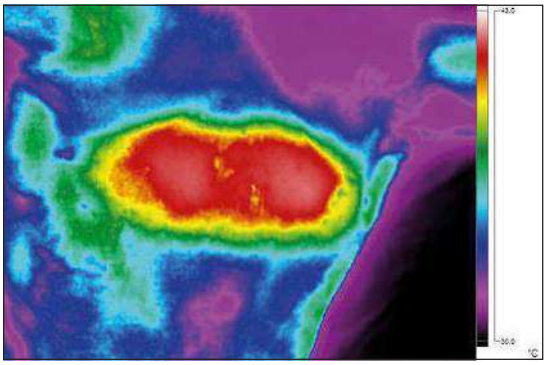


Figure 3. The skin temperature measurements were taken immediately after the treatment. The maximum surface temperature in the treatment area was just above 42°C, not exceeding 42.5°C. A thermal image taken by an infrared camera Fluke Ti300 (Fluke Corporation; Everett, WA).

muscle temperature from the onset of therapy, exceeding the 39°C within 2 minutes and stabilizing at the level of approximately 39.5°C in the third minute of therapy (Figure 2). The skin temperature measurements showed safe values at the level of 42°C (Figure 3).

The Evaluation of Muscle Mass

In the active group, the average muscle area in the ROI was 60810.1 μm^2 at baseline. At a 1-month follow-up visit, the average muscle area had significantly increased to 69223.2 μm^2 (*P* value = .003). Finally, the increase peaked at a 2-month follow-up visit with the average muscle area being 72474.4 μm^2 (*P* value < .001). Compared to baseline, the average muscle density was increased by 13.8% at 1 month and 19.2% at the 2-month follow-up visit in the active group. The observed changes in the examined histology slices are visualized in Figures 4, 5. In the control group, the baseline muscle area was 61711.4 μm^2 and did not show any substantial changes during the 1-month (61455.6 μm^2, *P* value > .05) or 2-month (62076.1 μm^2, *P* value > .05) follow-up.

The Number of Myonuclei

The average number of nuclei in the active group increased from 146.6 ± 24.9 (baseline) to 161.7 ± 26.7 (10.3% increase) at the 1-month follow-up visit, and up to 177.7 ± 30.7 (21.2% increase) at 2-month follow-up. The changes were significant at both follow-up visits (*P* value < .05). In the control group, however, the change in the nuclei count was insignificant (*P* value = .75 at 1 month; *P* value = .57 at 2 months), because it rose slightly from 136.7 ± 21.7 (baseline) to 140.3 ± 20.4 at 1 month and stayed at 140.3 ± 18.8 at 2 months.

The Number and Size of Muscle Fibers

In the active group, the average number of fibers in the ROI was 56.8 ± 7.1 at baseline, gradually increasing to 62.5 ± 9.2 fibers (10.1% increase, *P* value = .03) at 1-month follow-up. Analogous to the muscle density and myonuclei, the fiber count peaked at a 2-month follow-up visit with 68.0 ± 8.6 fibers (19.8% increase, *P* value < .001) per ROI. In the control group, the number of fibers was 56.3 ± 6.5 at baseline, with little to no increase throughout the study (57.3 ± 9.6 at 1 month, *P* value = .48; 58.2 ± 6.7 at 2 months, *P* value = .32). The changes in the number of muscle fibers compared with the control group were significant at the 2-month follow-up (*P* value = .004).

The increase in the diameter of the muscle fibers was visible in the active group throughout the study period. At baseline, the average muscle fiber size was 32.6 ± 2.5 µm, with a size of 33.6 ± 2.3 µm at 1-month follow-up and 37.8 ± 5.3 µm at 2 months (*P* value < .05). In the control group, no significant changes were observed (*P* value > .05), because the average muscle fiber size was 32.5 ± 0.31 µm throughout the study. The change in the relative frequency distribution of measured fibers can be seen on the histogram in Figure 6. Results indicate that the number of small-sized fibers considerably decreased over the course of the study. At the same time, there were increased numbers of thicker muscle fibers in follow-up samples from the active group. The histogram shows that the most common fiber size per ROI was between 30-40 µm in diameter at baseline. At the follow-ups, the number of fibers with a diameter greater than 40 µm was most abundant in the ROI.

DISCUSSION

In this study we evaluated the effects of novel HIFES technology combined with synchronized RF on deconditioned

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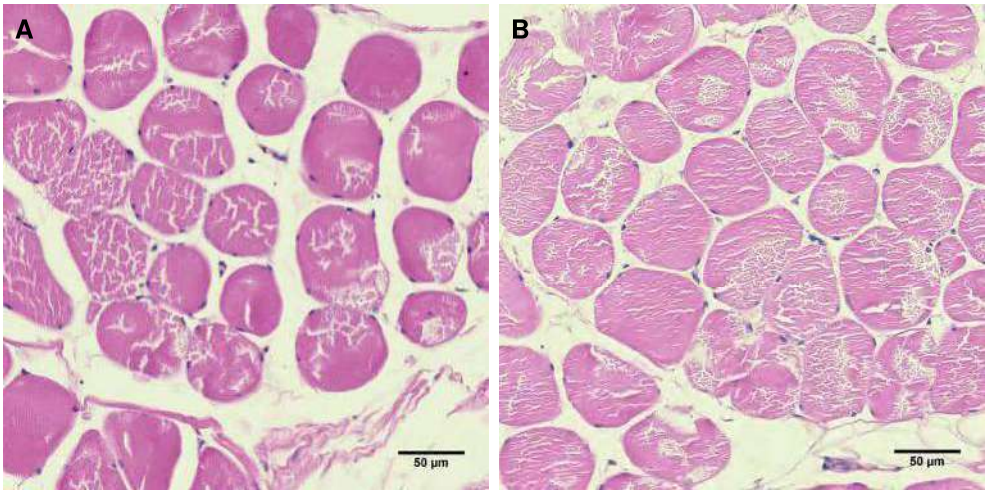


Figure 4. A cross-sectional view of the muscle tissue in the active group stained by hematoxylin and eosin, taken at (A) baseline and (B) 2-month follow-up. The pink represents the muscle tissue with dark purple nuclei at the periphery. The muscle tissue is noticeably denser after treatments in the assessed regions of interest.

muscle tissue. Based on the data obtained, we observed a consistent and significant increase in all studied parameters related to the quality and function of the muscle tissue. During the study, no treatment-related issues or side effects were observed in any of the animals or histological samples. The measured temperatures in the muscle tissue as well as on the surface showed that the heat was within the safe but effective limits. The results indicated that the simultaneous application of HIFES + RF safely and effectively targets the muscle tissue while promoting muscle remodeling and structural improvement.

Facial muscles are subject to the ravages of time together with the rest of the body tissues. Age-related muscle deconditioning and weakening are associated with loss of muscle quality and quantity manifested as a decrease in muscle mass and the number of fibers, and altered myofibrillar protein expression.[26] Therefore, this animal histology study aimed to observe these indices as the main markers for successful treatment of the deconditioned muscle tissue.

Throughout the study, the active group showed significant improvement in all measurements. The overall muscle mass increased by 19.2% at a 2-month follow-up, which may be attributed to the densification of muscle fibers while they increased in diameter at the same time (Figure 4). There is evidence that an increase in muscle mass is correlated with higher muscle strength and function.[27] Such changes can have beneficial implications when it comes to the treatment of human patients and restoration of facial appearance, which relies on the functional muscle tissue that interconnects with the skin. Also, the increased muscle mass indicates the substitution of adipose and connective tissue with muscle tissue (Figure 5), accompanied by muscle fiber growth both in size (+15.9%) and quantity (+19.8%). In human patients, studies have shown that the increase in muscle thickness in the crosswise direction induced by facial exercise has a positive effect on facial rejuvenation because it contributes to firmer and more elastic facial skin with a decrease in mimetic muscles linked to sagging of the face.[28,29] Therefore HIFES facial therapy might provide a first attempt standardized facial protocol to mitigate the loss of bulk and lift in facial aging, as a postoperative treatment or a stand-alone regimen.

The last marker of the changes occurring in the muscle tissue during the study period was the number of myonuclei, which correlates with the size of muscle fibers.[30] The significant increase in the number of myonuclei (+21.2%) may be attributed to satellite cells, which are activated during exercise.[31,32] Because supramaximal muscle stimulation is an effective alternative to exercise, these satellite cells fuse with the muscle fibers and donate their nucleus to the fiber to increase the regenerative and remodeling responses of the muscle fibers.[32–34]

The mild difference in the number of muscle fibers observed at 1-month follow-up when compared to control is most likely due the short observation period. As Kadi et al showed in their review, the effects of satellite cell activation take approximately 50-90 days to propagate fully, which corresponds to our 2-month follow-up observation, when the increase of muscle fibers was found to be highly significant when compared to the control group (P value = .004).[35] Nonetheless, all markers increased gradually in the active group and no significant changes were observed in the control group, and we can attribute the results seen in the active group to the HIFES + RF sessions.

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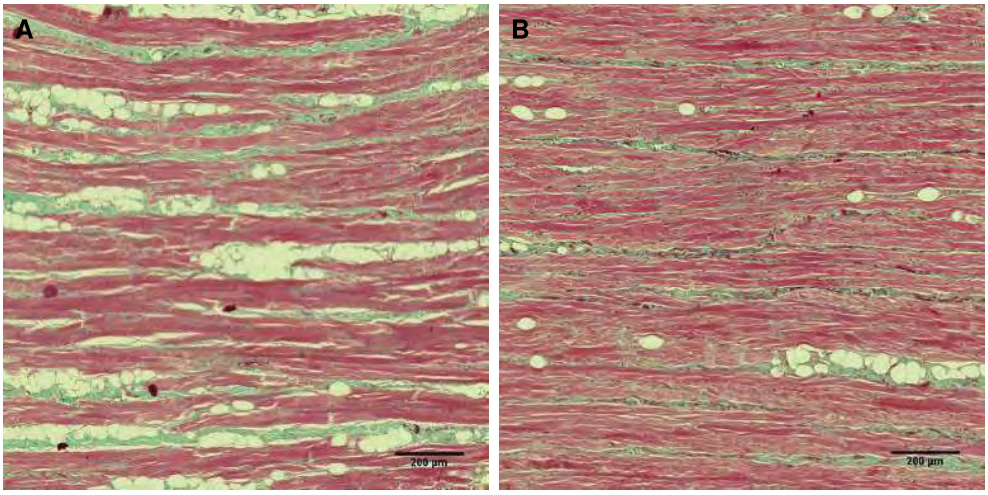


Figure 5. A longitudinal view of the muscle tissue stained by Masson's trichrome, taken at (A) baseline and (B) 2-month follow-up. The red color represents the muscle tissue, whereas the green color documents the presence of the intersected collagen fibers with lipid droplets without color. At baseline, the muscle fibers were relatively sparsely distributed, which changed at the 2-month follow-up. There was a noticeable increase in muscle fiber density together with a decrease in the fat tissue infiltration.

One of the limitations of this study was the use of a porcine animal model instead of human patients. Nonetheless, given the invasive nature of the study procedures, this animal model was found most suitable for the purpose of this study. Pigs have been successfully employed in biomedical research because of their remarkable similarity to humans in anatomy, physiology, immune system, and genome. These similarities provide sufficient insight to consider the biological processes transferable to humans.[36] Another limitation was the treatment area. Although the novel HIFES technology was designed to target all facial muscles, the trial was conducted on the pigs' foreheads only. The sow's cheek area was found to be problematic in terms of applicator placement and biopsy acquisition. However, the forehead area was eligible for treatments, because sow's forehead muscles are not intensively used by the animals, and therefore may correspond with deconditioned human muscles in the face. Also, all procedures were undertaken in a way to minimize animals' suffering. Taking samples from muscles of mastication in pigs may lead to pain during feeding and loss of appetite, resulting in weight loss and compromising the long-term results of the experiment. Nonetheless, we believe that the obtained results can be applied generally to the facial muscle groups because they all are subject to the same processes of deterioration.[37] Regarding the length of the follow-up, the animals were not kept with the general population, to lower the chances of infection or injury and overall bias from keeping them in uncontrolled conditions. Due to a long isolation with only study animals stress was considered a potential risk factor, and so there are no data available later than 2-month follow-up. This study was designed to investigate the immediate to short-term response of the tissue, and the 2-month period was deemed sufficient. The study's focus was to provide a basic understanding of the induced changes, which might provide insight into the effects of the simultaneous use of the investigated technologies with implications for use in human patients. In total, there were 144 evaluated tissue slices in this study, ensuring a reliable data count for conducted statistics. Also, 4 different aspects characterizing changes at the muscle tissue composition level were assessed, providing a comprehensive description of the effects of the investigated technology. In sum, this study offers a new method of noninvasive facial rejuvenation with the potential to contribute to the understanding of facial muscle aging in further detail. Future studies will benefit from using human patients to verify the findings described, and utilizing more objective methods (such as ultrasound) for a comprehensive analysis of the events occurring in the facial muscle tissue related to facial rejuvenation. Future human studies of a noninvasive nature should also consider including muscle testing of facial muscles to measure the improvement of facial expressions after the treatments, while establishing a longer follow-up period to document the long-term effects of the procedure.

CONCLUSIONS

This animal histology study aimed to evaluate the effectiveness and safety of the simultaneous application of novel HIFES technology and synchronized radiofrequency. The results documented by the histological analysis indicate

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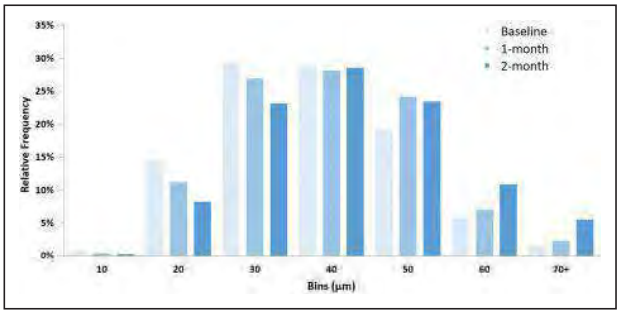


Figure 6. The histogram represents the relative frequency distribution of the muscle fiber sizes in the active group samples. The interval width was chosen to be 10 µm. The muscle fibers of greater diameters were more frequently present at 2-month follow-up.

treatment effectiveness for improving overall muscle quality; the active group significantly improved in all studied parameters. The safe use of this technology was also documented. No adverse effects occurred, and there were no unusual findings when assessing histology samples.

Disclosures

Drs Kinney and Bernardy are clinical investigators for BTL Industries (Boston, MA). Dr Jarošová is an associate of the Veterinary Research Institute (Brno, Czech Republic).

Funding

BTL Industries (Boston, MA) was the sponsor of this study and provided the study device. However, no funding for authorship and publication of this article was provided.

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Facial Plastic Surgery & Aesthetic Medicine
Volume 0, Number 0, 2023
© American Academy of Facial Plastic and Reconstructive Surgery, Inc.
DOI: 10.1089/fpsam.2023.0015

Facial Plastic Surgery & Aesthetic Medicine

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Novel Approach to Facial Rejuvenation by Treating Cutaneous and Soft Tissue for Wrinkles Reduction: First Experience from Multicenter Clinical Trial

Richard Gentile, MD,[1,*] and Yael Halaas, MD, FACS[2]

Abstract

Background: Facial aging is determined by skin quality and the condition of underlying muscles, which contribute to the overall appearance by lifting heavy facial structures.

Objective: This study aims to assess the safety and effectiveness of the novel radiofrequency (RF) and high-intensity facial muscle stimulation (HIFES) technology for treating wrinkles by facial tissue remodeling.

Methods: This trial assessed the 3-month data of 24 subjects seeking facial wrinkles treatment. All subjects received four treatments, with a device utilizing RF and HIFES. The evaluation included a two-dimensional photographs assessment according to the Fitzpatrick Wrinkle and Elastosis Scale (FWES) and a three-dimensional (3D) photograph analysis for facial appearance. Therapy comfort and subject satisfaction were assessed.

Results: Based on the data of 24 subjects (56.5 ± 2.0 years, skin types I–IV), the significant improvement increased up to 3 months (-2.3 points, $p < 0.001$) post-treatment. 3D photographs analysis documented notable cutaneous and structural rejuvenation and coincided with FWES evaluation, underlining the positive subjective appreciation of the results with 20.4% average wrinkle reduction at 1 month, further increasing to 36.6% wrinkle reduction at 3 months.

Conclusion: Documented by both subjective and objective evaluation tools, the RF and HIFES procedure for facial rejuvenation was found to be effective for treatment of wrinkles and skin texture.

ClinicalTrials.gov Identifier: NCT05519124.

Introduction

In recent years, various noninvasive and minimally invasive procedures have been developed, mainly for skin tightening,[1–4] primarily utilizing ultrasound, radiofrequency (RF), or laser energy. The RF modality has become widely adopted due to its ability to induce production of new collagen and elastin fibrils while enhancing the existing connective tissue structures, and cellular metabolism.[5] Nonetheless, when it comes to facial appearance, counteracting only the signs of skin aging is part of the solution.[6–9] The loss of density of underlying muscles plays an important role in overall facial appearance.[10]

The direct relationship between facial muscles and skin appearance is based on the muscle toning effect that improves the density and quality of facial muscles, hence

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KEY POINTS

Question: Is the radiofrequency (RF) and high-intensity facial muscle stimulation (HIFES) technology effective in the treatment of facial wrinkles?

Findings: The significant wrinkle reduction was documented by evaluation of digital photographs using Fitzpatrick Wrinkle and Elastosis Scale and three-dimensional analysis.

Meaning: The findings suggest that the RF and HIFES technology are an effective approach for wrinkle treatment.

making the attached skin firmer and more elastic.[11] Weakening of the cheek muscles (especially zygomaticus muscles) can promote midfacial soft tissue descent, resulting in the increased severity of the nasolabial fold, formation of jowls, and loss of jawline contour.[12] Muscle remodeling can help to change the face contour by lifting effect that highly contributes to the overall facial appearance.[13]

To target both skin and facial muscle, monopolar RF and high-intensity facial muscle stimulation (HIFES) technology are combined in the novel device, which uniquely synchronizes both technologies to address the overall facial appearance. The mechanism of RF treatment is based on the oscillating electrical currents that flow through the skin tissue, where they are transformed into heat.[2,14] The novel HIFES technology generates a strong electrical field that depolarizes the motor neurons innervating the facial elevators: frontalis muscle, zygomaticus major and minor, and risorius muscle.

Depolarization of these motor neurons results in supramaximal contractions of these muscles.[15,16] The selectivity of the technology enabling the stimulation of only the elevator muscles is ensured by the design of the applicators, which contain multiple segments, whereas the HIFES energy is generated only in certain segments overlying the elevator innervating muscles. The repeated application of HIFES results in the initiation of muscle protein synthesis and may lead to the densification of the muscle tissue and its overall improvement.[17–21]

As documented in previous research, neocollagenesis and neoelastinogenesis are initiated after the RF therapy, and the improvements in skin appearance and properties are usually noticeable a few weeks after the treatment.[14,22,23] In addition, the heat delivered by RF supports the effect of HIFES through improved blood circulation, which increases nutrient supply,[24,25] promoting the muscle remodeling and regeneration of existing muscle fibers.[26,27]

This study aims to evaluate the safety and effectiveness of the novel device for facial wrinkles and rhytides treatment. We hypothesize that this novel treatment may facilitate the natural healing process following the thermal effects of RF and workload from HIFES, conceivably resulting in wrinkle reduction and skin tone improvement.[24]

Methods

Study population

Twenty-four subjects (1 male and 23 females, for more details see Table 1) were enrolled at two study sites. At the time of enrollment, the inclusion and exclusion criteria and the subject medical history were reviewed. Inclusion criteria were subjects aged 21 years and older, understanding of the investigative nature of the treatment concerning potential benefits and side effects, presence of clearly visible wrinkles in the treatment area, willingness and ability to abstain from partaking in any facial treatments other than the study procedure during study participation, and willingness to comply with the study instruction to return to the clinic for the required visits and to have photographs of their face taken.

Subjects who met any exclusion criteria, such as metal implants, local infection, or unhealed wounds in the treated area, were excluded from participation in the study.

Ethical consideration

This multicenter single-arm open-label interventional study was approved by the Advarra Institutional Review Board, and its conduct adhered to the ethical principles of the 1975 Declaration of Helsinki. All patients voluntarily provided informed consent before any study-related procedure was performed. Each patient was assigned a unique subject identification number for anonymization.

Treatment protocol

All patients received treatments with the novel EMFACE (BTL Industries, Inc., Boston, MA) device using RF and HIFES technology for the noninvasive reduction of wrinkles, rhytides, and overall improvement in facial contours. The treatment was performed on the forehead and both cheeks at the same time using adhesive single-use applicators. Before each therapy, the treatment area was cleared of any cosmetics, lotions, jewelry, and prominent hairs. The treatment administration phase consisted of four 20-min treatment visits, delivered 5–10 days apart. At each therapy, the intensities of RF and HIFES

Table 1. Baseline patient characteristics ($N = 24$)

	All cases
Patients	24
Gender	
Male	1 (4.2%)
Female	23 (95.8%)
Age (years)	
Mean	56.5 ± 2.0
Range	34–75
Median	59.5
Skin types	
I	1
II	13
III	6
IV	4

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stimulation (on a scale of 0%–100%, where RF was set to 100% by default) were adjusted according to the patient's feedback concerning any possible discomfort.

All patients were required to complete all four treatments and three follow-up visits: immediately after the last treatment, at 1-month, and at 3-month follow-up (±10 days). Patients were monitored and examined for the occurrence of any adverse events throughout the study duration.

Data collection and evaluation

At baseline and all follow-up visits, two-dimensional (2D) photographs of the face were taken and evaluated according to the Fitzpatrick Wrinkle and Elastosis Scale (FWES). Three independent evaluators assigned the FWES score to the subjects' pre- and post-treatment photographs to assess wrinkle severity as per Table 2.

The three-dimensional (3D) automated analysis was performed using two standardized systems to evaluate the severity of wrinkles, skin evenness, and texture. A 3D photographic imaging system LifeViz® Mini (QuantifiCare S.A., France) was used to capture facial images of 13 patients that were to be evaluated.[28] At baseline and both 1- and 3-month follow-up visits, the 2D photographs were taken from the left, right, and front views of the face at multiple angles, and compiled into a 3D model by using Quantificare software suite. 3D models were evaluated for the wrinkle severity and skin evenness by analyzing the combination of depth, length, and width of the wrinkles in the treated areas according to the subject's age, gender, and skin type.

Every analysis was assigned with a score ranging from −10 to +10. A negative score means the wrinkle severity and skin evenness are worse than in the average individual, and positive scores >0 (i.e., average) indicate how much better the patient's result is than in the case of an average individual of similar age, gender, and skin type as a concerned subject.

Similarly, photographs of 11 subjects were taken using the Vectra® H2 camera (Canfield Scientific, Inc.), and were analyzed for wrinkle severity and skin texture using the included Sculptor® software.[29] The results were determined as a score based on the intensity of the measured instance on a scale of 0–100, where 100 means the highest possible score reflecting excellent skin condition.

The 5-point Likert scale Subject Satisfaction Questionnaire (SSQ) was administered after the final treatment and at all follow-up visits to assess patients' satisfaction with the therapy results. The Therapy Comfort Questionnaire including the visual analog scale (0—no pain, 10—maximum bearable pain) and 5-point Likert scale was administered after the final treatment session.

Statistical methods

The descriptive statistic was calculated (mean, standard error mean, and median value). All data were analyzed for statistical significance. Paired variables measured at multiple time points were tested by repeated measures analysis of variance followed by a post hoc Tukey honestly significant difference test used to analyze the significance of observed changes. The significance level was set to $\alpha = 0.05$ (5%).

Results

Out of the recruited 24 subjects (56.5 ± 2.0 years, skin type I–IV), 17 completed the 3-month follow-up visit. All patients received wrinkle treatment with parameters set according to the patient's feedback. During the treatment, the intensities ranged from 50–100% for HIFES and 80–100% for RF.

FWES evaluation

The FWES evaluation resulted in a baseline value of 5.2 ± 0.4 points (class II, median value = 5.0 points). At a 1-month follow-up visit, the FWES score decreased to 3.8 ± 0.5 points (median value = 3.5, −1.4 points, $p < 0.001$; class II). The results peaked 3 months after the last treatment ($p < 0.001$), averaging a score of 2.9 ± 0.4 points (median value = 3.0 points, −2.3 points, class I).

3D analysis

Evaluating 3D photographs with QuantifiCare® software, the patient's baseline average wrinkle score was subaverage with −1.3 ± 0.6 points. Gradually, it improved showing an average difference of +3.1 ± 0.5 points ($p < 0.001$) at 1-month follow-up, as shown in Figure 1. The improvement was maintained up to 3 months with an average score increase of +4.4 ± 0.6 points ($p < 0.001$). The skin evenness (3.5 ± 0.4 points at baseline) of the whole face was enhanced on average by +3.7 ± 0.5 points at a

Table 2. Wrinkle severity according to the Fitzpatrick Wrinkle and Elastosis scale

Class	*Wrinkling*	*Score*	*Description*
I	Fine wrinkles	1–3	Mild: fine texture changes with subtly accentuated skin lines
II	Fine-to-moderate depth wrinkles with a moderate number of lines	4–6	Moderate: distinct popular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia
III	Fine-to-deep wrinkles, numerous lines with or without redundant skin folds	7–9	Severe: multipapular and confluent elastosis (thickened, yellow, and pallid) approaching or consistent with cutis rhomboidalis

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Fig. 1. Seventy-five-year-old patients before (left) and at 1 month after (right) the final treatment with the EMFACE device. Photographs were taken using the 3D photograph imaging system LifeViz® Mini (QuantifiCare S.A., France). 3D, three-dimensional.

1-month follow-up visit ($p<0.001$). At the 3-month follow-up, a significant improvement ($p<0.001$) by $+5.1\pm0.6$ points was achieved.

The photographs evaluated in Vectra Sculptor software analogically showed a wrinkle improvement noticeable from the 1-month follow-up when the score increased by $+11.3\pm2.2$ points ($p<0.001$) against the baseline (53.0 ± 3.7 points). The improvement peaked at 3 months with an average score increase by $+17.6\pm2.8$ points ($p<0.001$). The skin texture (75.0 ± 3.8 points at baseline) was enhanced by $+11.6\pm4.1$ points at a 1-month follow-up visit, and by $+17.7\pm2.5$ points at 3 months (both $p<0.001$).

Despite the use of different 3D analysis software tools, desired changes were observed in all subjects with fine or pronounced wrinkles resulting in fuller and lifted cheeks 1 and 3 months after the final treatment as shown in Figures 2 and 3. Average subject's improvement rate was quite similar for both software, achieving 36.8% (QuantifiCare) and 36.5% (Vectra) improvement at 3 months for wrinkles and 24.2% (QuantifiCare) and 26.2% (Vectra) for skin evenness and texture, respectively.

Subject satisfaction and therapy comfort

The majority of patients (87.5%, $N=21$) agreed that the therapy was comfortable and 91.7% ($N=22$) patients reported no or minimal discomfort during the treatment. There were no negative responses from the SSQ evaluation immediately after the treatment. At 1- and 3-month follow-ups, satisfaction with results was high, achieving 95.5% and 95.0%, respectively. In addition, 87.5% of patients reported more lifted and tighter skin after the treatment during the whole study. The lifting effect is demonstrated in Figure 4. No adverse events or treatment-related side effects were observed.



Fig. 2. Forty-six-year-old patients before (left) and at 3 months after (right) the final treatment with the EMFACE device. Photographs were taken using the 3D photograph imaging system LifeViz® Mini (QuantifiCare S.A., France).

Discussion

The appearance of facial wrinkles and rhytides was significantly ($p<0.05$) improved after the treatment using a novel device combining RF and HIFES technologies. The FWES results showed a shift from class II (5.2 ± 0.4 points) to class I (2.9 ± 0.4 points) indicating only fine wrinkles. The 3D analysis demonstrated a significant wrinkle (36.6%) and skin texture (25.2%) improvement maintained up to 3 months. The majority of patients (90.9%) agreed the therapy was comfortable and there were no negative responses from the SSQ. In addition, patients were satisfied especially with the lifting effect visible after the final treatment and with treatment results (83.3%) in general—outcomes leading to minimization of signs of aging.



Fig. 3. Sixty-two-year-old patients before (left) and 3 months after (right) the final treatment with the EMFACE device showing wrinkle severity improvement with visible jawline definition.

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Fig. 4. Sixty-year-old patient at the 1-month follow-up visit after the final treatment with the EMFACE device with pronounced lifting effect on the cheeks. Photographs were taken using the 3D photograph imaging system LifeViz® Mini (QuantifiCare S.A., France).

In this study, the skin quality, determined by wrinkle, evenness, and texture analysis, improved most at 3 months. These outcomes corresponded with findings of Kent et al.[30] and Goldberg and Lal,[31] confirming the fact that collagen and elastin structural remodeling within 3 months after the RF treatment resulted in skin rejuvenation. In addition, the outcomes demonstrated by Kinney and Jarosova[32] and Halaas[33] presented positive muscle changes, especially densification and overall function improvement shown at the 3 months post-RF+HIFES treatments.

This benefit of synchronized use of RF and HIFES technologies to the overall facial appearance was supported by our findings accompanied by high patients' satisfaction with a lifting effect, reported by 87.5% of the treated subjects. Although our study was not primarily focused on the lifting effect, these findings suggest that remodeling of facial muscles considerably contributes to the lifting of the facial structures. In addition, as heat responsive, the collagen and elastin remodeling was initiated after RF heating and supported the lifting effect by increasing the skin elasticity and tightness.

Current therapies for facial rejuvenation often include invasive surgical facelift procedures, botulinum neurotoxin-based injections, and skin fillers. Despite them being effective, they are still considered (minimally) invasive and could be associated with a number of side effects and drawbacks, such as long recovery, or scarring, and also limited effectiveness on the underlying muscles.[34–36]

The use of a novel device offers a way to overcome most of these disadvantages. The device combines the synchronized effect of RF on the skin tissue with selective stimulation of the underlying fibromuscular tissue and fascia using HIFES technology. This combination poses as an interesting opportunity for targeting facial wrinkles. Moreover, as documented herein, the combined treatment is fully noninvasive and highly comfortable with minimal or mild discomfort.

To achieve reliable wrinkle improvement evaluation, two methods were used—FWES based on blinded evaluators and 3D automated analysis due to the potential limitations of the former. Overall, the considerable consistency of the FWES and 3D analysis results was documented, evidencing the positive effect of the treatment on wrinkles and skin texture. Also, to include a wide range of patients with well-visible facial wrinkles, subjects of varying ages were enrolled (34–75 years). Nonetheless, desired changes were observed in all subjects with fine or pronounced wrinkles resulting in fuller and lifted cheeks after the treatment, regardless of the demography.

Future research on larger and specific patients' groups, for example, those manifesting a certain degree or severity of wrinkles and rhytids, would be of great value to expound on the effectiveness of the treatment by EMFACE device for wrinkle reduction and to improve facial appearance.

Based on our findings, the EMFACE device may be recommended for the noninvasive treatment of wrinkles and overall facial skin appearance. EMFACE offers a noninvasive, pleasant, and fast alternative to current facial therapies or surgeries.

Conclusion

The treatment by a novel EMFACE device simultaneously delivering RF and HIFES resulted in a significant improvement in overall facial appearance. Based on the outcomes from 3D analysis and FWES evaluation, the procedure leads to decreased facial wrinkle severity (36.6%) and improved skin quality (25.2%). The treatment proved its safety since no adverse events were documented.

Authors' Contributions

Conceptualization of the study was carried out by R.G., methodology was by R.G. and Y.H., formal analysis was by R.G. and Y.H., investigation was done by R.G. and Y.H., resources were taken care by R.G. and Y.H., writing—original draft, was done by R.G., writing—review and editing, was by R.G. and Y.H., and supervision was carried out by R.G. and Y.H.

Author Disclosure Statement

The study was sponsored by BTL Industries. The investigators may be contracted to speak or present this study on behalf of BTL Industries.

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Funding Information

This Institutional Review Board-approved study was sponsored by BTL Industries.

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Novel Approach to Facial Rejuvenation by Treating Skin and Muscle Tissue for Facial Lifting: Preliminary Data from Multicenter Clinical Trial

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2. Boyd Beauty, Birmingham, MI, USA

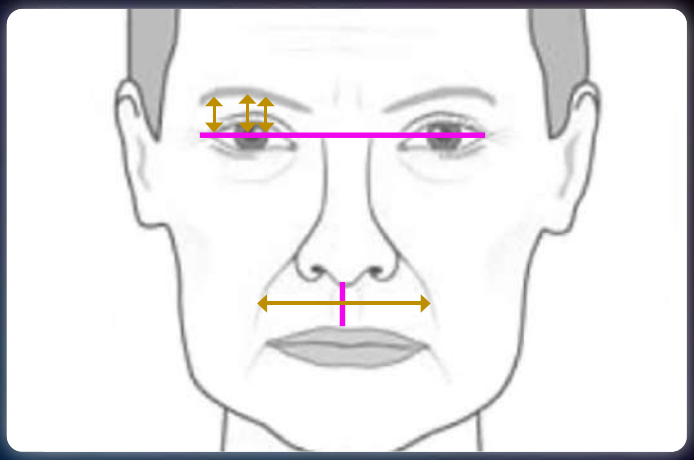
Accepted at American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

+23.1%
Lifting Effect

95.2%
Patient Satisfaction

Methodology

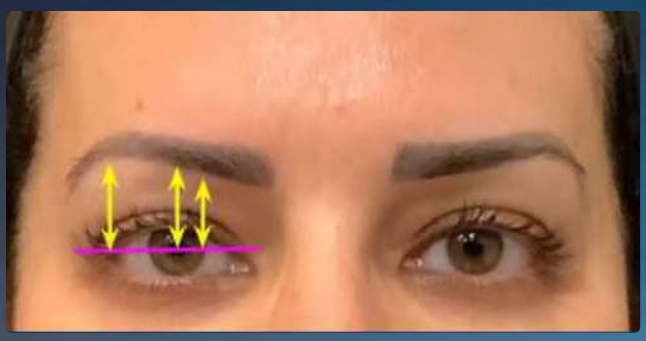
- 24 patients recruited at two sites
- Four 20-minute full face treatments
- Lifting effect assessed as:
  - Brow lift: Distance of eyebrow from the pupils' line at several points
  - Cheek lift: Distance between left and right nasolabial fold
- Patient satisfaction & Treatment comfort



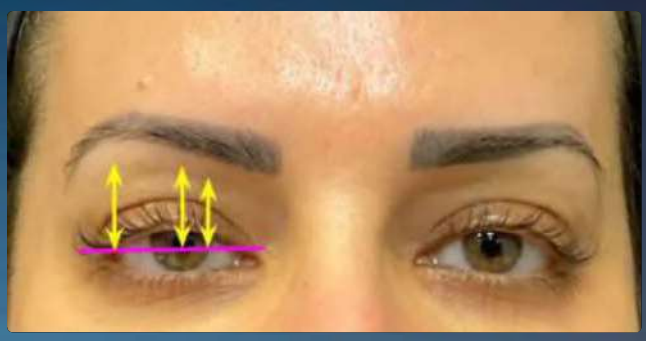
Measurement locations of the lifting effect

Example of eyebrow lift results

44 year old patient
Eyebrow lift +2 mm on average



Baseline



Follow up

Histological Analysis of Human Skin Indicates Quantitative Increase of Collagen and Elastin Fibers after Synchronized Radiofrequency with Facial Muscle Stimulation

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Presented at American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022, Denver, CO.

+27%
Increase in Collagen

+129%
Increase in Elastin

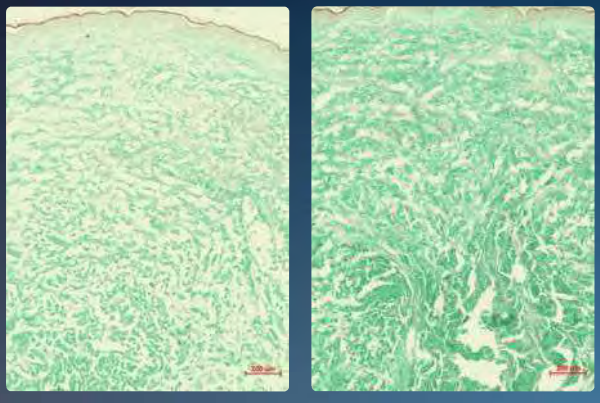
Methodology

- 7 patients allocated to Active (N=6) and Control (N=1) groups
- Active group: Four 20-minute RF+HIFES full face treatments (Control group - no treatments)
- Punch biopsies of skin tissue collected at baseline, 1-month and 3-month follow-ups
- Evaluation of digital photographs, satisfaction, comfort and safety

Preliminary Results

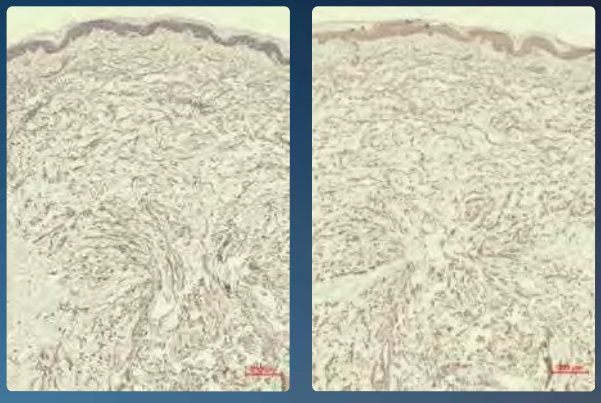
- Increased levels of elastin and collagen at 1-month and 3-month follow-ups
- Visible improved facial appearance
- Patients report high rates of satisfaction with the treatment
- No adverse events

Collagen - Trichrome Stain



Baseline | 3 months

Elastin - Orcein Stain



Baseline | 3 months

Novel technology for Facial Muscle Stimulation Combined with Synchronized Radiofrequency Induces structural changes in Muscles tissue: Porcine Histology Study

Brian Kinney, MD[1]; Jan Bernardy, DVM[2]; Rea Jarosova MSc[2]

1. Division of Plastic Surgery, The University of Southern California Keck School of Medicine, Beverly Hills, CA, USA
2. Veterinary Research Institute, Brno, Czech Republic

Presented at 41st Annual Conference of the American Society for Laser Medicine and Surgery. 2022; San Diego, CA

+19.2%
Increase in Muscle Density

+21.2%
Increased nr. of Myonuclei

+19.8%
Increased nr. of Muscle Fibers

Methodology

- 8 Large white pigs (60-80 kg) divided into 2 groups
- Active group (6 sows): Four 20-minute treatments of forehead
- Control group (2 sows): No treatment
- Punch biopsies of muscle tissue collected at baseline, 1 and 2 months after last treatment

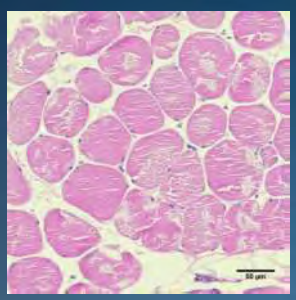
Results

- All results in active group were significant
- Control group showed insignificant changes
- Muscle temperature during treatment up to 39.5°C

Example of muscle tissue samples



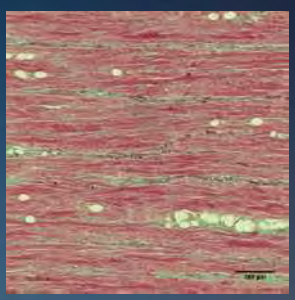
Baseline



2 Months After



Baseline



2 Months After

A Combined Effect of Novel HIFES Technology with Synchronized Radiofrequency for Qualitative Improvement of Facial Muscles

Yael Halaas, M.D., FACS[1]

1. Yael Halaas, MD, New York, NY, USA

Accepted at American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

+30%

Increase in Muscle Tone

Methodology

- 10 enrolled patients
- Four 20-minute simultaneous treatments on the forehead and the cheeks
- Ultrasound scans of m. frontalis and m. zygomaticus major taken at baseline, immediately after last treatment, 1 month after last treatment, and 3 months after last treatment
  - Echogenicity measurements
- Subject satisfaction
- Therapy comfort assessment

Results

- Interim findings suggest:
  - Enhanced muscle structure and quality
  - Enhancement of facial visual appearance
  - High patient satisfaction

Ultrasound scans of the frontalis muscle

Darker representation of the muscle at the after scan indicates densification of the muscle and increased muscle tone.



Baseline



After the last treatment

Effects of noninvasive synchronized radiofrequency and novel HIFES: Histological analysis of Porcine dermal Collagen and Elastin

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2. Veterinary Research Institute, Brno, Czech Republic

Accepted for American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022, Denver, CO.

+26%
Increase in Collagen

+110%
Increase in Elastin

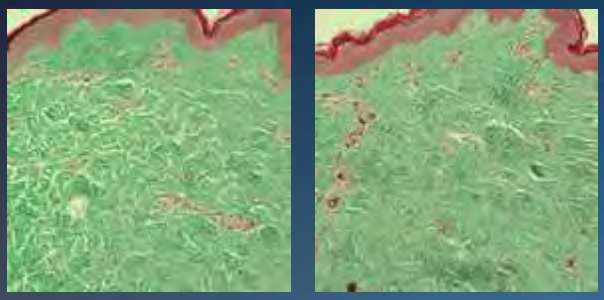
Methodology

- 8 Large White female pigs, 60-80 kg
- Active (N=6): Four 20-minute treatments on belly
- Control (N=2): Untreated
- Three biopsy explants obtained at baseline, 1 and 2 months post-reatment

Results

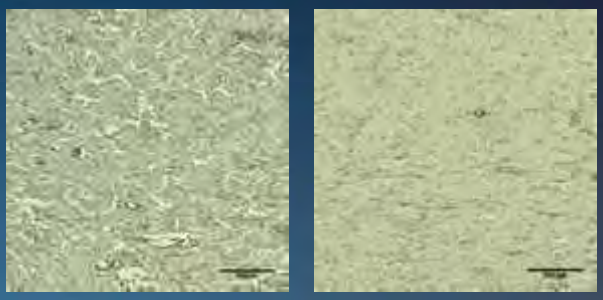
- Active group showed highly significant changes
- Elastin and collagen did not change in control group
- Skin temperature was maintained at 40 – 42°C throughout the treatment.
- No adverse events observed

Collagen - Trichrome Stain



Baseline | 2 Months After

Elastin - Orcein Stain



Baseline | 2 Months After

Novel Approach to Facial Rejuvenation by Treating Skin and Muscle Tissue for Wrinkles Reduction: Preliminary Data from Multicenter Clinical Trial

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2. Gentile Facial Plastic and Aesthetic Laser Center, Youngstown, OH, United States

Accepted for American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

95.0%
Patient Satisfaction

+25.3%
Skin Evenness Improvement

-36.8%
Wrinkle Reduction

Methodology

- 24 subjects (23 females, 1 male)
- Four 20-minute full face treatments
- Evaluation of
  - Wrinkle severity via automated 3D photo assessment
  - Patient satisfaction
  - Treatment comfort



Sixty-two year old patient



Baseline



3M FU

Novel HIFES and RF Technology for Comprehensive Facial Enhancement and Volume Improvement in Patients

Yael Halaas, M.D.[1], Charles M. Boyd, M.D.[2], Richard Gentile M.D.[3], Suneel Chilukuri M.D.[4], Lesley Clark-Loeser, M.D.[5]

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+1.65 ml

Average Volume Improvement in Upper Cheeks

-1.08 ml

Average volume change of the lower face (jowls)

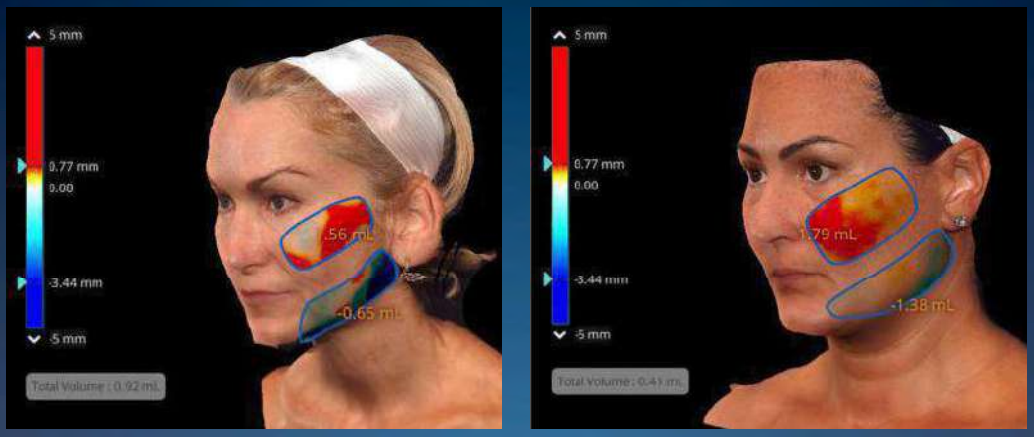
Methodology

- A total of 47 patients from four studies underwent four full-face EMFACE treatments.
- Evaluation of 3D photographs using Quantificare and Vectra systems:
  - Volume change in the upper cheek
  - Volume change in the lower face

Preliminary Results

- Study outcomes have demonstrated a noticeable improvement in facial shape, which can be attributed to the volume shift.

Examples of volume changes observed three months after EMFACE treatments.



Holistic Approach for Noninvasive Facial Rejuvenation by Simultaneous Use of High Intensity Focused Electrical Stimulation and Synchronized Radiofrequency

A Review of Treatment Effects Underlined by Understanding of Facial Anatomy

Suneel Chilukuri, MD

KEYWORDS

• Face • Fillers • High intensity focused electrical stimulation • Radiofrequency • Neuromodulators • Noninvasive

KEY POINTS

- Facial aging is a continuous process resulting from age-related changes in all structures present in the face. Such complex anatomy needs to be considered when it comes to noninvasive treatments for improving facial appearance. The facial muscles especially should be seen within their connective tissue environment and addressed accordingly.
- Novel HIFES and Synchronized RF technology was developed to target facial layers in synergy. Its effects show that it is a viable option for noninvasive face lifting and wrinkle reduction.
- It has been documented that HIFES and Synchronized RF does not interfere with the effects of neuromodulators or dermal fillers and can be safely and effectively used in patients injected with either of them, to deliver satisfactory improvement of overall facial appearance.

INTRODUCTION

Facial aging is a continuous process resulting from age-related changes in all structures present in the face: skin, fat, muscle, fascia, and bone.[1,2] Age-related changes of all facial soft tissues start at different decades and progress at various paces, which vary between individuals of different gender and ethnicity. All changes together result in reduced support for the bone-overlying soft tissues, which then follow the effect of gravity. Thus, a loss of structural support owing to volume depletion and changes to the facial muscles and their connective tissue framework results in increased soft tissue laxity.

The Role of Facial Muscles and Fascia Framework in Aesthetic Appearance

Facial muscles have been found to age through the process of sarcopenia, which manifests as a loss of muscle mass and volume, similar to skeletal muscles.[3] Because the facial muscles are interconnected via the fascial system and the

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Facial Plast Surg Clin N Am ■ (2023) ■–■
https://doi.org/10.1016/j.fsc.2023.06.006
1064-7406/23/© 2023 Elsevier Inc. All rights reserved.

overlying skin, weakening of these muscles may result in a visible descent of the tissue as we age (**Fig. 1**). The weaker the facial muscles are, and the lower the resting muscle tone is, the higher that muscle effort is needed to avoid sagging and to hold the overlying tissues in place. When too weak, they become unable to hold the tissue, resulting in eyebrow drop or cheek sagging. When the resting muscle tone is increased, the muscles are then able to hold the overlying tissue in place without dropping and without the need to stay contracted.

Specifically, the muscles in the cheek are interconnected by the midfacial superficial musculoaponeurotic system (SMAS).[4] Weakening of the cheek muscles, especially the zygomaticus muscles, allows for the hypothesis that as we age, the resulting facial muscle weakness can promote midfacial soft tissue descent, resulting in the increased severity of the nasolabial fold, formation of jowls, and loss of jawline contour.[5] Targeting these muscles and their surrounding connective tissue architecture might allow for midfacial soft tissue repositioning. Also, the same muscle weakening could be expected for the frontalis muscle owing to aging or long-term use of neurotoxins. The frontalis muscle is mainly responsible for eyebrow movements. Its connection with the skin is ensured via the suprafrontalis fascia (located superficial to the frontalis muscle) and the subfrontalis fascia (located deep below the frontalis muscle). Aging of the forehead structures may result in eyebrow ptosis[6] and heaviness, which along with skin aging, may lead to laxity and wrinkle formation in the region.

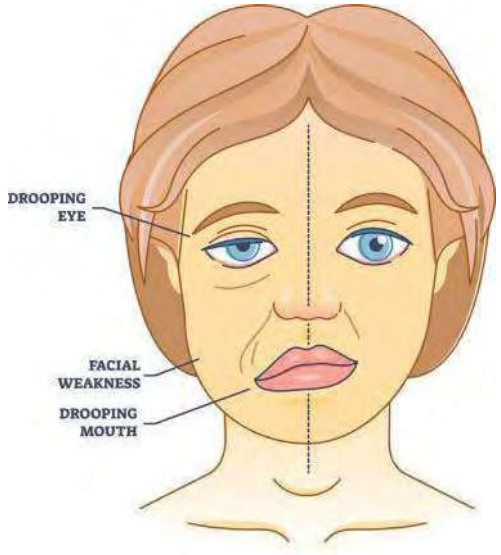


Fig. 1. Visualization of the effect caused by weakened facial muscles on the left in comparison to healthy muscles on the right.

In contrast to skeletal muscles, the facial muscles are embedded in a connective tissue framework that interconnects all tissues from bone to skin. Interestingly, they are connected directly to the brain via the cranial nerves and are responsive to emotional input and the limbic system. Emotional states affect facial contours via resting tone of the muscles and the SMAS. Therefore, the facial muscles need to be seen within their connective tissue environment and addressed accordingly. Assuming that facial muscles affect skin movement alone without the support of a connective tissue environment creates an incomplete picture of facial muscle anatomy.

Treatment Alternatives

Repositioning and restructuring the facial tissues and layers is the aim of aesthetic procedures via surgical and nonsurgical means.[1,2] Among noninvasive aesthetic procedures, radiofrequency (RF) is considered the gold standard for facial skin treatment. The effect of RF on the skin tissue is based on dermal heating, which leads to structural changes within the skin and the overall improvement in skin quality.[7] However, these skin heating procedures focus solely on improving skin quality and textural improvement, but not the overall facial appearance, which is also influenced by the facial volume and density of the underlying structures, including the fascial system, facial ligaments, and facial muscles. Therefore, the extent of facial laxity is a composite effect of all implicated structures of which the facial muscles and their interconnection with the skin play a fundamental role.[8]

The most frequently performed nonsurgical treatment to date is the administration of soft tissue fillers, which helps to restore facial volume. However, soft tissue fillers only cover the aging symptoms and do not affect facial muscles, which play a crucial role in natural skin mobility.[9] When it comes to muscles, the application of neurotoxins is yet another popular solution, although its primary effects are also limited to one tissue only. Currently, the only way to reliably alter facial muscles is through a surgical lift procedure, where the skin and fat tissues are separated from the muscle, and the muscles are then repositioned.[10]

Overall, the combination of age-related facial changes results in an alteration of the facial shape, which cannot be improved by targeting one type of tissue alone. Therefore, more profound treatment algorithms need to be applied to address age-related facial changes.[11] This may include addressing deeper fascial and muscle layers

together, as they have the ability to promote facial repositioning.

Recently, HIFES technology synchronized with RF heating has been introduced with the EMFACE (BTL Industries Ltd, Boston, MA, USA) device, to target the facial muscles and their connective tissue frameworks for lifting and tightening of the facial contours. HIFES technology induces electrical fields to contract facial muscles selectively. These delicate facial muscles are crucial for supporting the facial soft tissues and play a structural role in a more youthful appearance. While the HIFES targets the muscle and overlying fascia tissue, the Synchronized RF heating induces structural changes to the dermal and subdermal architecture. This approach can ultimately result in an improved appearance through changes in all facial tissue layers.

TARGETING FACIAL TISSUES BY NONINVASIVE HIFES AND SYNCHRONIZED RADIOFREQUENCY TECHNOLOGIES

Mechanics of HIFES for Facial Muscle Stimulation

HIFES technology was specifically designed to selectively induce supramaximal contractions of small delicate muscles in the face, namely the frontalis muscle on the forehead and zygomaticus major muscles, zygomaticus minor muscles and risorius muscles on the cheeks (**Fig. 2**). The technology generates strong electrical fields, delivered by its specifically designed applicators, that affect the underlying neuronal and muscle tissue. These electrical fields depolarize the membrane of the motor neurons that innervate the muscle. When the motor neurons are depolarized, a signal is created that travels along the neuron, all the way to the neuromuscular junction—the place where the motor neuron is connected to the muscle. These signals overcome the barrier of the neuromuscular junction and progress to the muscle, which is thus forced to contract. This process bypasses the voluntary intention of the brain, inducing a forced contraction through electrical stimulation.



Fig. 2. The cheek muscles stimulated by HIFES technology: zygomaticus major and minor muscles and risorius muscle.

The HIFES stimuli repeat with such frequency that the facial muscles are not allowed to relax in between the individual signals. As the muscle cannot relax, with additional stimuli, it is forced to contract even further, which continuously builds up the contraction power with every additional signal. The appropriate selection of these 2 factors (electrical field strength and frequency) results in the so-called supramaximal contraction. Although it is poorly understood how and to what extent the facial muscles adapt to external stimuli, research studies conducted in skeletal muscles have revealed that heat shock proteins (HSP) and satellite cells (SCs) may be activated by intense muscle exercise as a response to the applied stimuli.[12] HSPs are the signaling molecules playing a crucial role in muscle remodeling through the promotion of muscle protein synthesis.[13] SCs are muscle-derived stem cells responsible for myofiber development and renewal.[14] In a resting state, the SCs remain quiescent, ready to be activated, and provide differentiation to create new myonuclei to existing muscle fibers or generate new muscle fibers. Together, HSP and SC activation can support muscle microprotein structure alterations. In a healthy muscle this may lead to densification of the muscle tissue and to overall improvement of the muscle quality. In atrophied muscle, the muscle structure alteration may lead to hypertrophic response reversing the atrophy. However, it is not only the muscle reacting to the signaling molecules. It has also been documented that the fascial layer remodels itself in response to heat and mechanical stimuli.[15] Nonetheless, the future studies will need to identify similarities between skeletal and facial muscles or provide conclusive evidence that facial muscles behave similarly or differently when targeted by external stimuli.

The Role of Synchronized Radiofrequency Heating on Facial Muscles and Framework

Simultaneously with the HIFES stimulation, the Synchronized RF that heats the facial tissue is delivered. Such stimuli affect the connective tissue framework and the facial muscle unit with consecutive adaptive changes to the overlying facial soft

tissues. According to previous studies on skeletal muscles,[13,16] HSPs can also be activated by heat within the range of 40°C. Together with the muscular contractions, the heat thus may further increase the levels of released HSP,[17] although this effect has been shown in abdominal muscle[18] or gluteal muscle.[19] A recent study by Kinney and colleagues[20] measured the facial muscle temperature during the treatment with HIFES and RF and showed that the temperatures in the targeted muscle tissues reached up to 40°C, indicating that a similar effect could also be seen in the facial muscles during the simultaneous treatment.

Furthermore, the primary effect of Synchronized RF heating on the subdermal tissues can be seen in the fascial framework. The fascial framework primarily consists of collagen and elastin, which are known to be heat responsive. Therefore, heating to adequate temperatures may induce remodeling of collagen and elastin within the fascial framework, leading to increased elasticity and tightness of the fascial web.[15]

The Role of Synchronized Radiofrequency Heating on Skin Tissue Rejuvenation

The same effect for the fascia can also be seen in the skin tissue. Regarding skin, fine lines and wrinkles accompanied by loss of skin volume are usually the first indicators of skin aging, a normal physiologic process influenced by genetic and hormonal changes with contribution of external factors.[21] During the skin aging process, the dermal blood vessel structure is disrupted, and in turn, the dermis is not supplied with nutrition and oxygen, thus slowing cellular regeneration.

The major building blocks of the skin are collagen and elastin fibers, which are responsible for skin elasticity and firmness. During the aging process, collagen and elastin synthesis decreases, and collagen bundles lose their extensible configuration and become fragmented. The elastin fiber network is degraded, leading to the loss of structural integrity of microfibrils. As the extracellular matrix is degraded, skin thickness is also reduced. It is estimated that adult skin loses 1% of overall collagen content annually.[22]

The EMFACE device uses a novel Synchronized RF electrode that allows the simultaneous application of an RF field together with HIFES. As the RF current flows through the tissue, a portion of the RF energy is absorbed, transforming the energy into heat and the desired thermal effect. During the 20-minute treatment, the skin tissue is heated to 40°C to 42°C. This therapeutic temperature range is reached within the first 2 minutes of the treatment, as documented by the thermal probe measurements.[23] The level of RF energy absorption in the tissue depends on the RF frequency and tissue impedance, among other factors. Because the skin, muscle, and fat tissues have different impedances,[24] it is possible to selectively target the energy and achieve the thermal effect in the desired tissues.

When the therapeutic temperature is reached in the skin tissue for the desired time period, the hydrogen bonds tying the collagen fibers together begin to unwind, and collagen denaturation occurs. However, the above-mentioned temperatures do not lead to permanent damage. As the thermal effect dissipates, the bonds begin to renew, and the skin's architecture is changed to a more youthful level. After repeating this process during multiple treatments, the structure of older collagen and elastin fibers is changed, similar to newly formed collagen and elastin fibers.[25] This thermal effect is also accompanied by a heat-induced wound-healing response and increased fibroblast activity. Fibroblasts are the dermal cells responsible for producing new collagen and elastin fibers. As we age, their activity decreases to a level equivalent to an overall "net loss" of fibers. This means that the amount of newly formed fibers does not exceed the number of fibers being degraded, which accelerates the appearance of skin aging. Nevertheless, studies have shown that heat stress increases fibroblast activity, leading to an increased synthesis of collagen and elastin–neocollagenesis and neoelastinogenesis.[25] Overall, synchronized RF heating supports the skin to regain its volume, elasticity, and a more youthful appearance by restoring the collagen and elastin fiber structure and enhancing the synthesis of new collagen fibers.

CLINICAL EFFECTS OF HIFES AND SYNCHRONIZED RADIOFREQUENCY ON FACIAL TISSUES

Because of the unique design and energy delivery, HIFES does not induce the stimulation of the depressors because it could potentially lead to a worsening of rhytides. The forehead application targets the frontalis muscle (brow elevator) and corresponding fascias while avoiding the depressors in the glabella. Restoring the tonus of the frontalis muscle and tightening the fascias in combination with the skin remodeling thus lead to reduced horizontal forehead lines, brow elevation, and skin texture improvement. The cheek application primarily targets the more superficial muscles of the cheeks (zygomaticus major/minor and risorius), which are all interconnected elevating units. In contrast, other deeper muscles,

such as the masseter muscle, are unaffected. Stimulation of these superficial muscles leads to an elevation of the entire cheek, increasing the midfacial volume and improving the nasolabial fold. Increasing the pull of these elevators further leads to a repositioning not only of the midface but also of the lower facial soft tissues. The resulting clinical effect is a reduction in jowls and an increase in jawline contouring. Furthermore, the combined effect of HIFES with Synchronized RF manifests as an overall textural improvement of the skin.

Clinical studies focusing on structural changes after HIFES and RF demonstrated a prominent skin remodeling effect. These studies found that collagen increase ranged between 26% and 27%, and elastin increase ranged between 110% and 129% 2 to 3 months following the procedure.[23,26] Research[27] investigating changes in skin texture and facial appearance reported a 37% wrinkle reduction and a 25% skin evenness improvement 3 months after the procedure. The processes induced in muscle tissue led to structural remodeling of the targeted muscles, which has been documented by Kinney and colleagues,[20] showing a 19% increase in muscle density and a 21% increase in the number of myonuclei. These results were coupled with reduced fibrotic and fat infiltration within the muscle tissue at 2 months after the procedure (**Fig. 3**).

The structural changes do manifest as increased resting muscular tone, which is necessary for maintaining the lifted facial appearance. The weaker the facial muscles are, the higher the muscle effort that is needed to avoid sagging and to hold the overlying tissues in place. When too weak, they become unable to hold the tissue, resulting in, for example, eyebrow drop or cheek sagging.[2] Recently, HIFES and RF was found to increase the muscle tone by 30%,[28] which was then shown to lead to an overall lifting effect by 23%.[29] Aside from multiple clinical studies using various evaluation methods, the results of the procedure are supported by a high patient satisfaction rate of 91%.[29]

APPLICATION OF HIFES AND SYNCHRONIZED RADIOFREQUENCY THERAPY WITH CURRENTLY USED PROCEDURES FOR IMPROVEMENT OF FACIAL APPEARANCE

HIFES Effects on Neurotoxin-Blocked Muscles

Neuromodulators in aesthetic medicine, such as Botox, Dysport, Xeomin, or Jeuveau, have become some of the most frequently sought nonsurgical aesthetic procedures with type A botulinum–based neurotoxins having a myriad of clinical indications. They are most frequently used to treat dynamic facial rhytides[30] involving the glabella, frontalis, and periocular regions. Botulinum neurotoxins block neurotransmitter release (Acetylcholine; Ach) in the synaptic neuromuscular junction and block voluntary muscle contraction. With blocked contractions, wrinkle formation is prevented, as the overlying skin is not being repetitively folded during daily activities and thus aids in maintaining a more youthful skin appearance.

Botulinum-based neurotoxin affects the process of muscular contraction at the level of neuromuscular junction. When applied, it works as a protease and prevents the fusion of the vesicles with the presynaptic membrane.[31] Without this fusion, the Ach

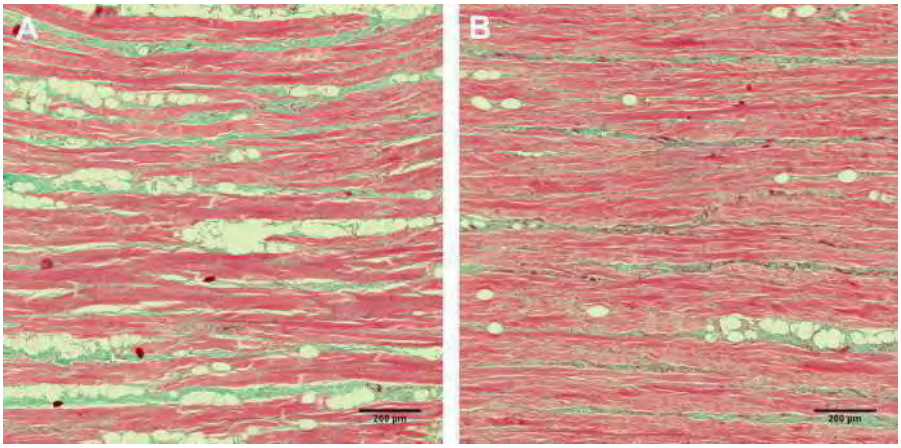


Fig. 3. Histologic images of muscle tissues before (*A*) and 2 months after (*B*) the treatment with the HIFES and RF. Red represents muscle tissue; green represents intersected collagen fibers, and white rounded cells are adipocytes.

cannot be released into the neuromuscular junction and trigger the muscle contraction. It is a chemical denervation that causes partial paralysis of the innervated muscle. However, such paralysis is not causing any damage to the nerve or the neuromuscular junction and is not permanent.[32]

Studies have shown it is possible to stimulate even the botulinum-paralyzed muscles.[33,34] However, it is not entirely clear how such stimulation overcomes the barrier made by the botulinum neurotoxin. Upon the application of botulinum toxin, the membrane of the presynaptic neuron should be practically impermeable to Ach molecules owing to its size as the fusion of vesicles and presynaptic membrane ("quantal release") is blocked. Nevertheless, clinical trials are showing that externally it is possible to overcome this barrier, and although the mechanism of how this happens is not entirely clear, several hypotheses were proposed to explain such mechanism, particularly the nonquantal Ach release[35] and direct stimulation of postsynaptic membrane.[36]

Research has shown that a nonquantal release of small amounts of Ach into the synapse still occurs, even in botulinum toxin denervated muscle. However, during voluntary contractions, the amount of the Ach is not sufficient to cause depolarization, and the muscles thus remain relaxed. By applying an external high-frequency electrical field that surpasses the frequency of brain signals, the activity of the high-affinity choline transporter could be elevated, leading to exaggerated nonquantal release of Ach in amounts sufficient enough to cause muscle depolarization and contraction. In addition, an insufficient long-term concentration of Ach in the synapse, owing to the application of botulinum toxin, can lead to an increased expression of n-acetylcholine receptor on the postsynaptic membrane and, therefore, also to an increase in the sensitivity of the muscle to Ach.[37] A lower amount of Ach would thus be needed to induce such depolarization.

On the other hand, the conclusions regarding the direct muscle stimulation are based on studies performed on skeletal muscles only. Facial muscles are of significantly different proportions and are much more superficially located in low depths. All this may influence the response. As the facial muscles are more delicate, lower intensity of stimulus may suffice to irritate the muscle membrane. Because the thickness of some facial muscles may be as small as 0.5 mm,[38] it may be possible that such stimulation is able to recruit enough muscle fibers to induce contraction of the entire muscle.

Regardless of the mechanism, HIFES technology is seemingly able to stimulate botulinum neurotoxin–blocked muscles in order to prevent risk of muscle atrophy. HIFES stimulates blocked facial muscle even though it is not possible voluntarily. Recent findings[39] showed that during the EMFACE treatment the botulinum-denervated muscles are being contracted, and what is most important, it does not interfere with the effect of botulinum toxin itself. No negative effects of the HIFES and RF procedure on the efficacy of the botulinum toxin were found.

Synchronized Radiofrequency and Dermal Fillers Treatment

Injection of dermatologic fillers is one of the most common procedures that is used in aesthetic medicine for rejuvenation of the face. These gellike substances are used for the treatment of wrinkles by injecting filler beneath the skin so it restores lost volume and more contour to the face. Fillers can be divided into 2 categories. First, the biodegradable fillers that are not permanent and can last up to 12 months, losing their effectiveness with time and eventually being metabolized. Fillers that are currently available stimulate neocollagenesis, so the effect persists longer to some extent.[40] Such dermal fillers that are currently used and approved by the Food and Drug Administration (FDA) are hyaluronic acid, calcium hydroxylapatite, and poly-L-lactic acid. The second group of nonbiodegradable fillers are long-term solutions for wrinkles, but there is a much bigger risk of complications. There are only 2 nonbiodegradable fillers approved by the FDA: polymethylmethacrylate microspheres and liquid injectable silicone (LIS), but LIS was approved only for intraocular use.[41]

Concerns have been voiced among patients and practitioners regarding RF treatments in that dermal filler would break down if they underwent RF treatment, or even worse, that the patient's skin would get damaged under RF applicators. Nevertheless, there exists plenty of evidence in the literature about safety of RF treatment over the area injected with dermal fillers.[42–44] In addition, there even exist devices that are using RF energy during dermal filler injection. In study by Kim and colleagues,[45] it was found that using RF during filler injection is a safe and effective method to treat especially mobile areas like the nasolabial fold. Overall, the findings prove that increasing the temperature of the tissue above normal levels is safe for the filler's stability. Depending on the system used, RF devices for noninvasive skin treatments elevate the tissue temperature no more than 65°C. On the other hand, the current dermal fillers are usually autoclaved, and therefore, bear considerable thermal stability. For instance, hyaluronic acid fillers are usually sterilized at a temperature of 120°C before one can observe

negative effects of heightened temperatures.[46] Furthermore, the literature shows that use of RF with dermal fillers is safe for treated tissue itself if using RF treatments at normal clinical temperatures up to 65°C, which is far beyond the temperature range achieved during EMFACE therapy. Nevertheless, more studies are needed to rule out any possible doubt, especially studies using human participants treated with different ranges of RF intensity and time exposure as well as using multiple different commercially available dermal fillers.

SUMMARY

The novel EMFACE device was developed for noninvasive face lifting and wrinkle reduction by targeting all facial layers, framework, and facial muscles by simultaneously using Synchronized RF and HIFES technologies. Heating the facial tissue to effective temperatures and HIFES stimulation of only specific facial muscles result in a combined effect that causes textural changes to the skin, smoothing, wrinkle reduction, facial repositioning, and an overall lifting effect. The simultaneous and targeted manner of both technologies yields unique benefits by inducing a synergistic effect in the facial soft tissues that cannot be achieved by using these technologies consecutively or as a stand-alone procedure. It poses no risk to patients who underwent neuromodulator or dermal filler procedures and can be safely and effectively used in patients injected with either of them to deliver satisfactory improvement of overall facial appearance.

CLINICS CARE POINTS

- In a long-time botox using patients, the visible contractions start at a higher intensity and after a longer period of time, however in all the patients, the visible contractions were always achieved
- It is normal to observe asymmetrical contractions, when in doubt please palpate the subject. You can adjust the HIFES intensity for each applicator separately
- This therapy uses the radiofrequency, therefore be aware of patients' hydration

DISCLOSURE

Dr S. Chilukuri is a clinical advisor to BTL Industries Ltd. Nonetheless, no funding for authorship and publication of this article was provided, and the author declares no other conflict of interest related to this article.

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Original Article

OPEN

First Evidence of Cutaneous Remodelling Induced by Synchronized Radiofrequency Aided by High-Intensity Facial Muscle Stimulation: Porcine Animal Model

David E. Kent, MD,* Klaus Fritz, MD,†‡ Carmen Salavastru, MD,‡§ Rea Jarosova, MSc, PhD,‖ and Jan Bernardy, MVD, PhD‖

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BACKGROUND The quality of one's facial appearance diminishes with aging as skin and underlying soft tissues deteriorate. Connective tissue and musculofascial degeneration leads to skin laxity and wrinkles developing.

OBJECTIVE To evaluate the effects of synchronized radiofrequency with high intensity facial stimulation technology on dermal collagen and elastin fibers in a porcine model.

MATERIALS AND METHODS Eight sows were divided into Active (N = 6) and Control (N = 2) groups. Synchronized radiofrequency and high intensity facial stimulation were delivered to the ventrolateral abdomen. The Active group received four 20-minute treatments, once a week. Control group was untreated. Skin biopsy sample were histologically analyzed for connective tissue changes pre- and post-treatment. Data were analyzed statistically ($\alpha = 0.05$).

RESULTS In the Active group: the collagen-occupied area at baseline was $1.12 \pm 0.09 \times 106\ \mu m^2$ and increased by +19.6% ($p < .001$) at 1-month and by +26.3% ($p < .001$) 2 months post-treatment; elastin-occupied area at baseline was $0.11 \pm 0.03 \times 106\ \mu m^2$ and increased by +75.9% ($p < .001$) at 1-month and +110.8% ($p < .001$) at 2-months follow-up. No significant changes ($p > .05$) found in the Control samples.

CONCLUSION Collagen and elastin fiber content increased significantly after treatments. Connective tissue in the treatment area was denser up to 2-months post-treatment.

Facial aging is a complex process involving changes in facial anatomy.[1] Various skin components, underlying muscle, and fibromuscular fascia are involved.[2–4] The fascial framework and the dermis consist of fibroelastic connective tissue primarily composed of collagen and elastin.[5,6] The muscles, fascia, and skin quality degenerate because of intrinsic and extrinsic factors, causing the skin to become slack and fragile.[7–9] Elastin and collagen content decline when there is an imbalance in protein turnover as the degradation of collagen is accelerated, whereas its synthesis is diminished. This lack of balance (dysregulation) causes further deterioration of connective tissue. There is a loss of tissue structural integrity and elasticity because of increased degradation of functional collagen and decreased collagen production. Fine lines (rhytids), wrinkles, and saggy skin are some signs of aging.[10–14]

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The authors have indicated no significant interest with commercial supporters.

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Dermatol Surg 2024;00:1–4
http://dx.doi.org/10.1097/DSS.0000000000004028

Radiofrequency (RF) causes neocollagenesis in the skin at temperatures of 40 to 45°C.[15] Thermal energy destabilizes the collagen fiber.[16] This collagen structure disruption results in the stimulation of fibroblasts needed for increased neocollagenesis and neoelastogenesis.[17]

The HIFES modality aims to remodel and tone delicate facial muscles, counter the sagging appearance of skin, and improve the facial contour with increased volume.[18] To maximize the benefits of facial treatments, a novel device using synchronized RF with HIFES was developed. Combining these 2 different technologies targets superficial (dermal) and deep (muscle and fascia) tissue components. The simultaneous application of RF and HIFES technologies may be useful in improving facial appearance characterized by sagging, wrinkles, and rhytids.

This veterinary study aimed to evaluate the effects of synchronized radiofrequency and HIFES technology on porcine skin, particularly effects of the therapy on collagen and elastin fibers in the dermis, through a noninvasive hands-free applicator.

Materials and Methods

This veterinary study protocol was approved by the Ethics Committee for Animal Protection of the Ministry of Agriculture of the Czech Republic. Before the study, the animals underwent blood tests to assess their condition and health status. Animals were kept at ambient room temperature and fed a cereal diet. The study was conducted on 8 female large white pigs (*Sus scrofa* domesticus),

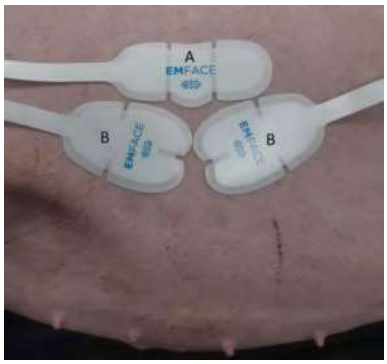


Figure 1. Illustrative set-up of the hands-free, self-adhesive device applicators on the ventrolateral abdomen of a sow that received active simultaneous RF and HIFES treatment. In human subjects, applicator A is intended for the forehead and B for the cheeks.

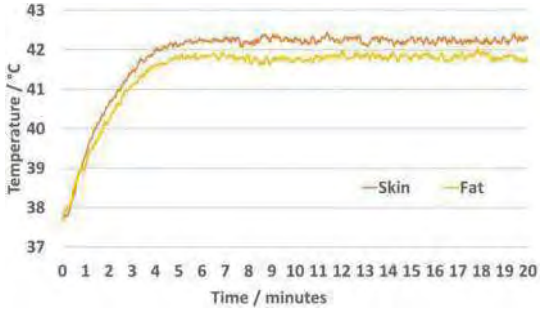


Figure 2. Thermoprobe measurement results during the treatment. The threshold temperature of approximately 40 to 42.5°C was reached in the dermis within the first 2 minutes and maintained in the range for the rest of the treatment time. The temperature in the fat was also monitored, showing about half a degree lower temperatures than the dermis.

weighing between 60 and 80 kg. There were 2 study groups, namely, the active group with 6 sows receiving simultaneous RF and HIFES therapy under general settings, and the control group with 2 untreated sows.

The synchronized RF and HIFES treatments were delivered with a study device (EMFACE, BTL Industries Inc, Boston, MA) through noninvasive self-adhesive electrode applicators placed on the ventrolateral part of the abdomen of the sows (Figure 1). The area covered by the electrode applicator had a diameter of 15 cm, and the treatment lasted 20 minutes at 100% power setting. The temperature in the dermis and subcutaneous fat layer was measured using a fiber optic temperature probe (LumaSense Flurotropic Thermometer) inserted into the tissue using an 18-G 1.5-inch injection needle. Treatment was done once per week for a total of 4 weeks. Treated sows were kept under full general anesthesia during the introduction to the surgical hall and the entire treatment phase, which lasted up to approximately 1 hour before awakening again.

Skin samples were collected by punch biopsy (6 mm diameter, Kruse Buster) from the treatment area (in the active group) and in the analogous anatomical area of the untreated control animals. Biopsies were obtained pretreatment (baseline) and post-treatment (1-month and 2-months follow-ups) in all animals including the control. After biopsy sampling, the wounds were dressed.

Histologic Analysis

The tissue samples from the punch biopsy were processed and sectioned in preparation for Orcein and Trichrome staining protocol. After staining, slides were mounted and observed. In total, 6 slices were prepared out of every biopsy sample.

Collagen

Masson's trichrome procedure was followed for collagen-specific staining. Collagen fibers were selectively stained and developed a green color. The stained samples were mounted to a microscopy slide.

Elastin

Visualization of elastin fibers was done with Orcein staining protocol. The elastin fibers were selectively stained and developed a brown-dark color.

The slides were observed and photographed using an automated slide scanning microscope (Hitachi Axio Scan.Z1, Carl Zeiss AG, Germany; 20×/0.8NA Plan-Apochromat objective) in a bright field. Quantitative analysis of collagen and elastin was performed with the Image J software based on semi-automatic segmentation in the Hue-Saturation-Brightness color system. The appropriate threshold differentiating the collagen and elastin fibers from the background was identified in the selected regions of interest (ROI = 1800 × 1,200 μm). After the collagen and elastin fibers were selected, their densities were expressed as the occupied area (square micrometers), which the fibers encompassed in the studied images' ROI.

Statistical analysis Student *t*-test and repeated measures analysis of variance test were performed with significance level set at $\alpha = 0.05$. Post-hoc Tukey honest significant test was conducted for multiple comparisons.

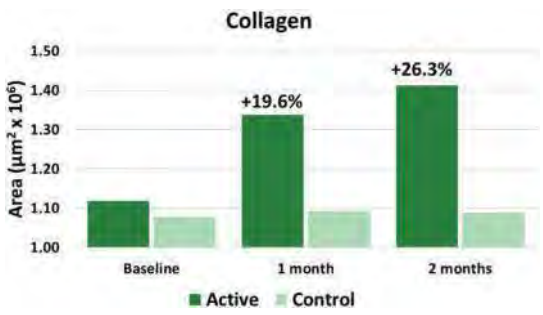


Figure 3. In the active group, the collagen fibers ($p < 0.001$) increased, occupying a greater area after 2 months follow-up compared to baseline. No significant change occurred in the control group.

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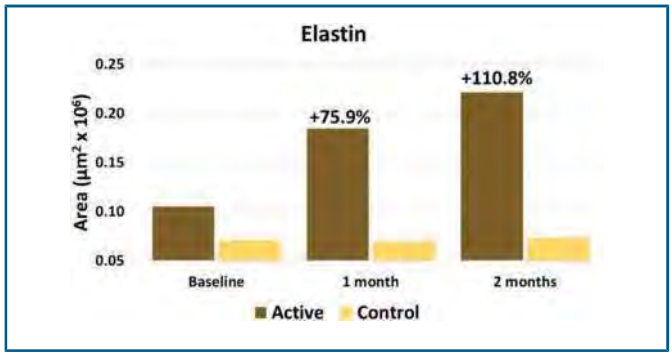


Figure 4. In the active group, the elastin fibers ($p < 0.001$) increased, occupying a greater area after 2 months follow-up compared to baseline. There was no significant change in the control group.

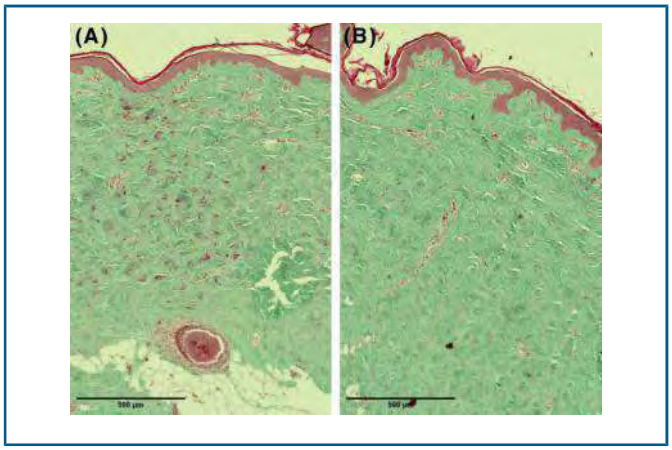


Figure 5. Bright-field visualization of collagen fibers stained by trichrome stain, active group sample. The collagen fibers appear in green color. In the slide on the right (2-months follow-up, B), the collagen fibers are noticeably denser, occupying a greater area when compared to the left (baseline, A).

Results

All the sows were in good health and condition before and during the study duration. The animals recovered from anesthesia without any complications. The dermal temperature was maintained slightly above 42°C, although not exceeding 42.5°C. The measurements in the fat layer showed a temperature elevation to approximately 41.9°C, elucidating the nature of the temperature gradient observed during the treatment (Figure 2). There were no side effects or adverse events related to the treatment.

Collagen

In the active group, the average area occupied by collagen was $1.12 \pm 0.09 \times 106\ \mu m^2$ at baseline. The average collagen-occupied area increased to $1.34 \pm 0.08 \times 106\ \mu m^2$ and $1.41 \pm 0.07 \times 106\ \mu m^2$ at the 2-month follow-up. Compared with baseline, in the active group, the average collagen amount increased ($p < .001$) at both post-treatment follow-ups. In the control group, there was no significant difference ($p > .05$) in collagen fibers, because the collagen content fluctuated in the range of 1.08 ± 0.04 to $1.09 \pm 0.05 \times 106\ \mu m^2$ throughout the whole study. There was a significant difference ($p < .001$) in the collagen-occupied sample area at both the 1-month (+19.6%) and 2-month (+26.3%) follow-ups (Figure 3) when comparing treated and control samples.

Elastin

In the active group, the mean elastin-occupied area at baseline was $0.11 \pm 0.03 \times 106\ \mu m^2$. At the 1-month follow-up, the average elastin amount was $0.19 \pm 0.02 \times 106\ \mu m^2$. At the 2-month follow-up, the area encompassed by elastin increased further to $0.22 \pm 0.03 \times 106\ \mu m^2$. Compared with baseline, the average elastin-occupied area increased at both follow-ups ($p < .001$). At both, the 1-month (+75.9%) and 2-month (+110.8%) follow-ups, the amount of elastin was significantly different ($p < .001$) comparing the active and control group (Figure 4). In the control group, there were no significant changes ($p > .05$) in elastin density at the follow-up points, elastin content ranged between $0.71 \pm 0.04 \times 106$ to $0.73 \pm 0.06 \times 106\ \mu m^2$.

Exemplary samples of the collagen (Figure 5A,B) and elastin (Figure 6A,B) microscopic evaluation results of the active group are shown below.

Discussion

This study evaluated the effects of synchronized RF and HIFES on porcine skin. Histologic analysis of connective tissue structural proteins in the dermis showed a statistically significant increase in collagen and elastin content at 1 month and 2 months post-treatment. All the treated animals in the study recovered well after each treatment and did not experience any complications or adverse events.

Collagen production and remodeling are vital in tissue regeneration and may be beneficial to promote connective

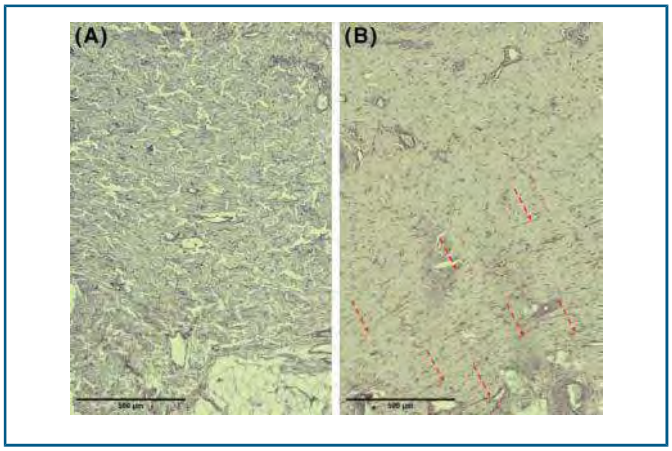


Figure 6. Bright-field visualization of elastin fibers stained by Orcein stain (active group sample). The baseline sample (left, A) has noticeably fewer elastin fibers, observed as dark/brown filaments (indicated by red arrows), than the 2-month follow-up (right, B). The surrounding collagen tissue (pale grey) also appears denser and better organized at 2 months post-treatment.

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tissue fascia repair in the skin of the face. In this study, collagen content increased by +19.6% at 1 month and +26.3% at 2 months post-treatment follow-up. Elastin content increased by +75.9% at 1 month and +110.8% at 2 months after treatment, indicating that combined RF and HIFES enhanced expression of both structural proteins. The HIFES modality, in combination with RF, is intended for noninvasive improvement of skin tissue quality. Therefore, if confirmed in human subjects, this treatment method may be an alternative to current, invasive procedures aimed at improving facial appearance.[19–23]

To achieve a therapeutic effect on the skin, reaching the desired tissue temperature is key. Sustaining a lower, moderate therapeutic temperature between 40 and 45°C is essential for treatment effectiveness to circumvent cutaneous tissue necrosis and side effects because of overheating.[24] As shown in Figure 2, the dermal temperature measured via a thermal probe reached 40°C within the first 2 minutes from the start of the treatment and was maintained in the range 40 to 42.5°C for the duration of the treatment. This temperature is the target therapeutic range, which ensures treatment efficacy without affecting the underlying fat tissue, as intended during facial treatments. However, the effect on the fat should be a subject of further studies to fully rule out any alterations in response to the treatment.

The control group and temperature tracking were objective evaluation methods. Alternatively, immunofluorescence and scanning electron microscopy may be used for comprehensive connective and adipose tissue analysis. Gross examination of subcutaneous adipose tissue would expound the knowledge about the effects of sublipolytic temperatures on the underlying fat tissue structure in the treated area.[25,26]

Conclusion

The novel RF + HIFES technology for targeting facial skin, fascia, and muscles was investigated with a focus on the changes in the skin tissue using a porcine animal model. The study results showed that the procedure induces a denser network of collagen and elastin fibers in porcine skin after treatment with synchronized radiofrequency and HIFES observed through histologic analysis and skin temperature measurement. The enhanced collagen and elastin expression observed in this study may be beneficial for skin remodeling and revitalization if replicated in human subjects.

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Check for updates

Received: 6 September 2023 | Revised: 4 December 2023 | Accepted: 20 December 2023

DOI: 10.1111/jocd.16165

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Remodeling of facial soft tissue induced by simultaneous application of HIFES and synchronized radiofrequency provides nonsurgical lift of facial soft tissues

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Abstract

Background: The application of radiofrequency (RF) and HIFES on the body provides improvement in skeletal muscle tissue, reduction in fatty tissue, reorganization of connective tissue, and skin texture improvement. However, overall facial appearance relies on both skin and underlying structures, specifically muscles and connective tissue which have to be treated as one unit to achieve proper care while preserving fatty layers that define youth facial appearance.

Aims: The aim of this study is to find whether the effect of novel RF + HIFES is safe and can induce the lifting of soft tissue and overall improvement in facial appearance.

Methods: In this study, 21 subjects were enrolled. The therapy was administered in four 20-min treatments on the forehead and cheeks. Photographs were evaluated by a Global Aesthetic Improvement Score (GAIS) and linear measurements of facial tissue lifting at 1- and 3-month follow-ups. Volumetric changes in the cheek area were investigated as well. The patients' satisfaction, safety, and comfort were documented throughout the study.

Results: The data indicated improvement in overall facial appearance, and 23% of average lifting was found in brows ($p = 3.14 \times 10^{-12}$) and cheeks ($p = 6.00 \times 10^{-15}$). The assessment of digital photographs showed an improvement in 100% of patients at 3-month follow-up. The treatments were safe, accompanied by high therapy comfort and subject satisfaction of 98%.

Conclusions: The treatment by simultaneous RF and HIFES technology produces significant changes to the overall facial appearance, characterized by the lifting of facial tissues.

KEYWORDS
facelift, facial muscles, HIFES, noninvasive, RF

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1 | INTRODUCTION

Perception of human beauty changes over time and differs by culture. Nevertheless, there is a particular trait that we rely on despite the history or socio-geographical factors—the youthful facial appearance. Facial tissue changes, marked as aging of the face, are continuous and complex biological processes that never stop progressing. There is a constant demand for innovative approaches to influencing facial aging and slow down the biological clock.

Various extrinsic factors, as well as intrinsic ones, are involved in facial aging. Typical environmental outside factors are pollution,[1] sun exposure—specifically ultraviolet radiation, and gravity. Overall, these factors lead to pigmentation spots and wrinkles.[2] Diet, smoking, and lifestyle are, to a certain extent, involved.[3] Oppositely, intrinsic factors are linked with different facial compartments that undergo anatomical and physiological changes over time.

Various structures of the face undergo different aging processes; these compartments are skin, muscle, ligaments, and bone. Among the most noticeable manifested aging signs are the appearance of wrinkles, sagging skin, and loss of facial contours and volume. These changes occur due to decreased collagen and elastin content and the dissimilar aging progress in different face compartments. Alteration in facial structure and appearance is also notably exacerbated by elevator muscle deconditioning. The loss of support for facial tissues results in a shift in position and modified structure of soft tissues with their abovementioned compartments.[4] The focus should be placed on each facial compartment, but with an emphasis on the muscle tissue. The midface is linked by a superficial musculoaponeurotic system (SMAS), with zygomaticus muscles playing a dynamic role.[5] Weakening of these muscles can lead to gradual atrophy and sagging, resulting in nasolabial folds, marionette lines, and jowls.[6] By activating these muscles and associated connective tissue, their original form can be improved or preserved, and the midfacial soft tissue can be repositioned.

To achieve specific effects, numerous surgical and nonsurgical aesthetic procedures have been developed to combat facial aging.[7] Among noninvasive procedures, radiofrequency (RF) is considered the gold standard for skin treatment. The principle of technology is based on dermal heating providing structural changes, thus resulting in an overall improvement in skin texture and quality.[8] However, this modality does not target the underlying structures that lift and tighten the overlying tissues. To overcome this limitation, minimally invasive treatments used for volume restoration are utilized; however, they do not provide an effect on underlying muscles crucial for natural skin mobility as well.[9] The most efficient but radical approach is rhytidectomy, the surgical facelift that brings the postoperational drawbacks, counting a lengthy recovery period, scarring, and other related risks.[10]

The latest advancement in noninvasive facial aesthetic treatments is HIFES technology which can target the delicate muscle tissue and connective tissue framework of the tissues of facial expression (SMAS and perhaps to some extent the muscles of mastication and their fascia).[11,12] The HIFES technology generates strong electrical fields, that affect the underlying neuronal and muscle tissue. These electrical fields depolarize the membrane of the motor neurons that innervate the muscle. When motor neurons are activated, a signal travels to the neuromuscular junction, where the neuron connects to the muscle. This signal makes the muscle contract involuntarily, bypassing the brain's control. High-intensity facial stimulation prevents the facial muscles from relaxing between signals, causing continuous contractions. Adjusting the electrical field strength and frequency leads to a "supramaximal contraction."

A holistic solution emerged in applying RF and HIFES to treat skin and muscles in one procedure, aiming for noninvasive skin rejuvenation and lifting of facial structures. The HIFES technology induces electrical fields to contract facial muscles selectively,[13] since the tonus of facial muscles is crucial to ensure the support to surrounding soft tissues. Repeated application of HIFES initiates muscle protein synthesis and can induce the densification of the muscle tissue.[14] By contrast, changes induced by RF heating involve dermal structure and subdermal architecture.[15] As was found with previous research specifically neocollegenesis and neoelastogenesis occur a few weeks after the RF therapies which are recorded as overall improvement in skin appearance and its properties.[16] The application of these two modalities in one treatment has a positive effect on improved blood circulation, leading to a boost in nutrient supply caused by the supportive effect of RF andHIFES.[17] Combining these technologies targets all-important facial tissue compartments, aiming to maintain a youthful appearance.

The study objective was to evaluate the safety and efficiency of the novel technology combining Sync RF and HIFES. During the therapy, synchronized radiofrequency (skin and underlying connective tissue heating) and HIFES (muscle toning) are simultaneously administered. The aim is to document the changes to facial tissues, namely the lifting of facial structures resulting in a naturally youthful appearance.

2 | MATERIALS AND METHODS

2.1 | Study population

This single-arm, open-label study enrolled 21 (three males and 18 females) patients in the age range of 24–60 years (45.17 ± 11.20 on average) with Fitzpatrick type ranging from I to V, at two sites. Selection criteria included healthy adult subjects (over 21 years old) of any gender with clearly visible sagging skin in the treated area. The main exclusion criteria were metallic implants, local infection, or unhealed wounds in the treated area. Limits were not applied to ethnic backgrounds or skin types, all adults seeking treatment who fall within inclusion criteria, and do not meet any of the exclusion criteria, were eligible for enrollment. Detailed instructions about the study were given to all enrolled subjects after providing written consent. The study design and treatment protocol were approved by the Advarra Institutional Review Board and followed the ethical guidelines of the 1975 Declaration of Helsinki.

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2.2 | Study design

Therapy consisted of four 20-min treatments given once a week. The HIFES and RF energies were administered simultaneously on all treated areas (i.e., both cheeks and forehead) by self-adhesive, single-use applicators connected to the EMFACE device (BTL Industries Ltd., Boston, MA). The parameters of the therapy were adjusted according to patient feedback and tolerability on a scale 0%–100% separately for both RF and HIFES. Patients were treated in the supine position without the use of anesthesia. Before the treatment, the face was cleared of cosmetic products, jewelry, or prominent hair.

2.3 | Data collection and evaluation

The 2D digital photographs were evaluated at baseline, and at 1- and 3-month follow-up visits. The photographs were graded for the magnitude of change in facial appearance by three independent evaluators, using the GAIS score based on a 5-grade scale (−1—worse, 0—no change, 1—improved, 2—much improved, 3—very much improved).

The lifting effect was assessed by the measurements of eyebrow lift in 2D digital photographs (front view), based on the methodology described by other authors,[18] (Figure 1). Additionally, the cheek lift was assessed by measuring the width of the line between both nasolabial creases at the middle level between the upper line of the lip and the crease root of the nose in front and side view (Figure 2). Safety and adverse events were monitored throughout the study.

Secondary outcomes included the measurement of volumetric changes in the cheek and mandibular region based on the 3D models reconstructed from photographs taken by VECTRA® H2 camera (Canfield Scientific Inc., US). Particularly, the measured areas (bilaterally) were the malar part of the face, specifically around the occurrence of the malar eminence,[19] and the inferior part between the cheekbone and mandibular area in the buccal region.[20]

The subject's satisfaction with the results was documented throughout the study by the 5-point Likert scale Subjects' Satisfaction Questionnaire consisting of four questions related to facial appearance improvement, lifting of facial tissues, perception of appearance improvement, and overall satisfaction with treatment results. Additionally, a Therapy Comfort Questionnaire (combining a 5-point Likert scale and 10-point Visual Analog Pain scale) was given to the subjects after the last treatment.

For the evaluation of obtained data, the descriptive statistics (mean and standard deviation), together with repeated measures ANOVA were used followed by Tukey HSD tests. The statistical tests were run at the level of significance $\alpha = 0.05$ (5%).

Written consent was provided, by which the patients agreed to the use and analysis of their data.

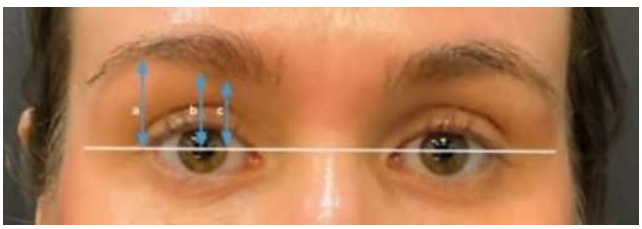


FIGURE 1 Visual guidance to the eyebrow lift effect measurements: different distances from reference line intersecting left and right lateral canthus from (a) lateral canthus, (b) medial limbus, (c) center of the pupil to lower line of the eyebrow.

3 | RESULTS

Of 21 subjects, 18 completed all the scheduled treatment sessions and follow-up visits. The treatment settings were well tolerated achieving 35%–75% for HIFES and 100% of RF (with one subject tolerating 75% of the RF output).

3.1 | Subjective outcome scoring

The evaluation of 2D digital photographs according to GAIS showed significant ($p < 0.05$) gradual improvement with the peak at 3-month follow-up when 100% of patients were graded at least as improved. An average improvement of 0.9 ± 0.3 points was achieved when rating 1-month photographs, which further increased to 1.1 ± 0.3 points at the 3-month follow-up visit (Figure 3).

3.2 | Evaluation of the lifting measurement

Assessment of the lifting effect showed significant ($p < 0.05$) improvement for every measurement compared in each of the follow-up visits to the baseline. Both the midpart (cheek lift) and upper part of the face (brow lift) showed the peak of the treatment effect at the 3-month follow-up visit. The average eyebrow lift was 16.5% at 1-month follow-up ($+2.58 \pm 0.66$ mm; $p = 1.07 \times 10^{-8}$)

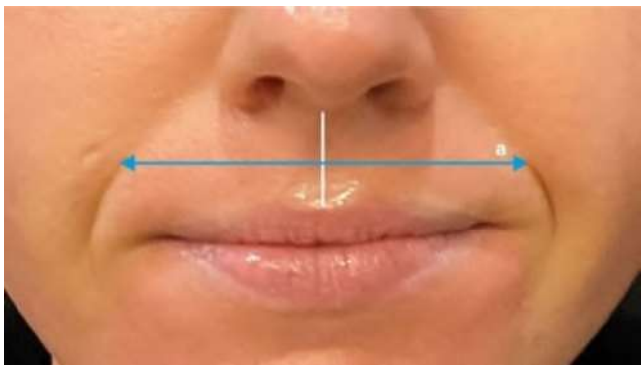


FIGURE 2 Visual guidance to cheek lift effect measurements: (a) distance between nasolabial creases in half line root of nose and lip crease, intersecting a white reference line in the middle.

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FIGURE 3 Comparison of the baseline (left) and after-the-treatment visit photographs. Improved suppleness of skin and reduction in wrinkles in the periorbital area and forehead can be seen.

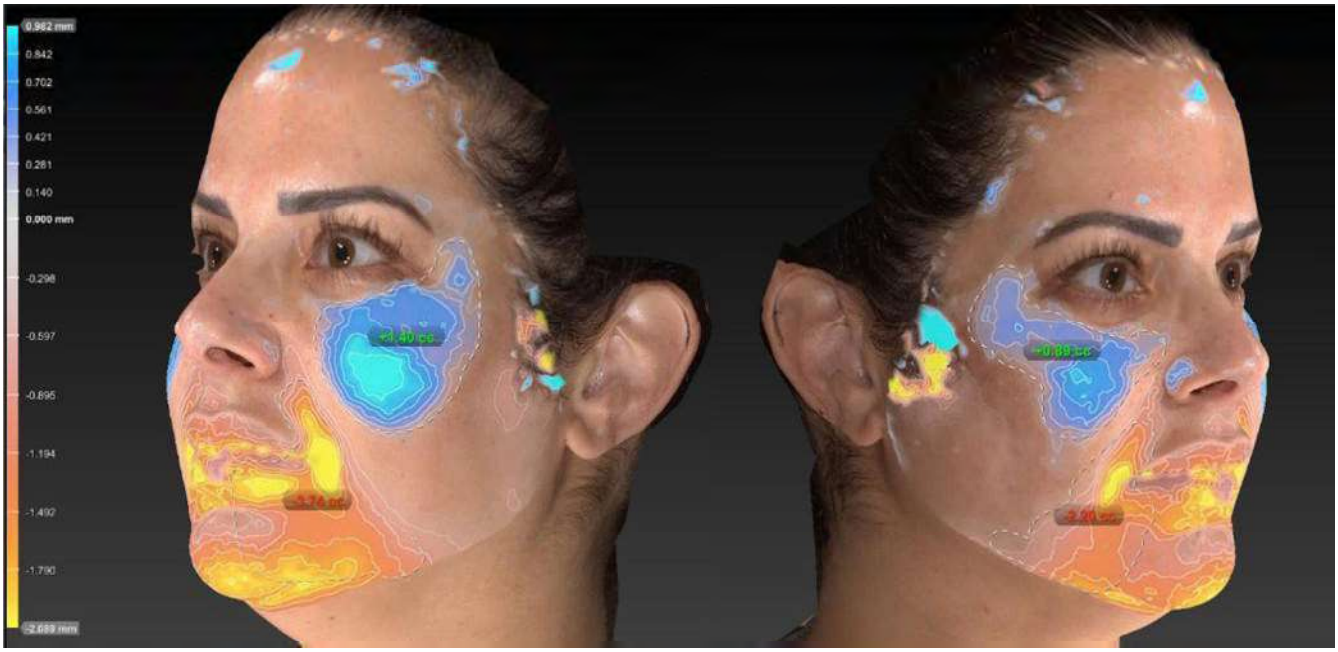


FIGURE 4 Vectra 3D photograph volumetric analyses: the change of volume in face at baseline and 3 months follow-up visit measured on left and right side.

and 22.2% (+3.25 ± 0.74 mm; $p = 3.14 \times 10^{-12}$) at 3 months. The maximum average increase in eyebrow lift at 3 months was measured from the medial limbus distance with a value of 3.79 mm. Conversely, the changes of the least magnitude were detected from the point of the center of the pupil, which was 2.41 mm at 3 months. The average cheek lift effect measured from the frontal view progressed from 1 to 3 months, reaching +3.09 ± 1.96 mm ($p = 2.08 \times 10^{-11}$) to +3.83 ± 1.80 mm ($p = 6.00 \times 10^{-15}$), respectively (Figure 4).

3.3 | Computed 3D photograph volumetric analysis

An increase of volume in the upper part of the midface in the region of malar eminence reached, on average, +0.95 ± 0.38 mL in 1 month and + 1.27 ± 1.08 mL in the 3-month follow-up visit. Conversely, the decrease was detected in the lower part of the midface in the buccal region where it reached −1.35 ± 0.86 and − 1.06 ± 0.5 mL on average at 1 months and 3 months. Both volume changes were counted for each side of the face and averaged. Total volume gain for both sides was 2.53 ± 2.1 mL at 3 months on average.

3.4 | Subject comfort and satisfaction

The presented data are consistent with the results obtained from 18 patients at the 3-month follow-up visit. Satisfaction of the patients was reported as very high, remaining constant during the study, resulting in average satisfaction of 98.2%. All subjects agreed that their appearance in the treatment area improved after the treatments. A more lifted feeling of skin in the treatment area was reported from 94.4% of subjects. Most patients (85.7%, $n = 18$) agreed the therapy was comfortable, with an average pain score of 1.4 ($n = 18$) on the visual analog scale, classifying the treatment as not painful. None of the patients perceived the therapy as uncomfortable. No adverse events or side effects occurred during the treatment.

4 | DISCUSSION

According to the findings of this study, based on both objective and subjective means of evaluation, the noticeable enhancement to sagging facial soft tissues and gradual restoration of facial contours was documented after the simultaneous application of HIFES+RF.

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It is crucial to target all facial layers with a preferred focus on muscle tissue when it comes to noninvasive facial treatments. These muscles are weakened with age, causing specific manifestations in each part of the face. In the midface, the cheeks are interconnected by the midfacial superficial musculoaponeurotic system,[7] where the zygomaticus muscles are involved. Deconditioned and atrophied muscles can progressively cause the descent of soft tissues, which externally appear as nasolabial folds (marionette lines) and jowls.[8] Stimulating muscles and related connective tissue matrix can help secure its original position and shape or allow for midfacial soft tissue repositioning.

Similarly, in the upper third part of the face, the frontalis muscle is the primary determiner of eyebrow movements.[21] Frontalis is interconnected to other supra-frontalis layers, including the skin, and sub-frontalis fascia to deeper layers.[22] Aging-related changes of this complex may lead to eyebrow ptosis[23] and connective tissue degeneration resulting in laxity and wrinkle formation.

The anatomical structures in the mid and upper face crucial for the overall facial appearance are specifically targeted by the EMFACE device due to the unique synergy of HIFES and synchronized RF. This procedure allows for comfortable facial treatments, delivered noninvasively while addressing the key tissue layers. The magnitude of achieved results accompanied by very high patient satisfaction suggests that HIFES+RF constitutes in some circumstances a feasible alternative to current solutions such as rhytidectomy or microinvasive neurotoxin-based injections and fillers, which attract increasing attention nowadays.[3] Although the concurrent approaches possess high efficiency, the long recovery period, non-negligible risk of adverse effects, and lesser comfort level may not be acceptable for all patients. In addition, invasive procedures may cause scarring, and neurotoxin overuse may build up a resistance to active substances.[24] On the contrary, noninvasive treatment by RF and HIFES avoids any downtime or unpleasant risks, as documented in this study.

The different evaluation methods used in this study pointed to consistent results regarding favorable changes in facial appearance. These changes, captured by digital photographs, were expressed in objective linear measurements of lifting effect amounting to +23% at 3 months. Correspondingly, an overall improvement in facial appearance was seen in 100% of patients, as documented by subjective visual scoring with GAIS.

The outcomes from 2D photograph analyses indicated a considerable shift in soft tissues that resulted in volume changes in the face. 3D photographs evaluation showed volume shifts and reduction in the jowl region and, conversely, a volume increase in the zygomatic part of the face. This positive volume shift in the malar regions accounted for an absolute average difference of 2.5 ± 2.1 mL in total. Such results approximate the effect of fillers and limited autologous fat grafting, which have mainly a local effect fixed on application placement not involving different parts and tissues of the face. Additionally, the effect is unstable over time and must be revived to gain desired results. Generally, the best outcome can be achieved by a combination of different approaches; with invasive procedures, the positive volume gain can reach up to 5.7 ± 2.9 mL on average in the midface region[20]; however, the risks connected to invasive procedures are present.

The combination of invasive and noninvasive methods is also efficient. RF and HIFES can be successfully combined with neurotoxin therapy in which induced paralysis of muscles in one area, to avoid formation of wrinkles, is supplemented by HIFES energy stimulation in another.[15] The prevention from dropping and loss of tonus in the face, especially in the forehead area where the frontalis muscle is conditioned, may be ensured.

Simultaneous application of HIFES and RF induces changes in the soft tissues and stimulates directly or indirectly the different compartments of the face bringing a holistic approach to the rejuvenation of the face. Concretely, the densification and muscle function improvement by HIFES produce a more contoured and compact visual appearance of the face.[6] Coupling with the heating effect of RF inducing structural changes originating from collagen and elastin remodeling,[25] overall skin revitalization due to synergistic effect, occurs. In addition, the therapy was perceived as comfortable and not painful, accompanied by high patient satisfaction of 98.2% in this study.

Although positive and consistent results from various measurements suggest the efficacy of the investigated technology for facial soft tissue lifting and rejuvenation, the sample size of 17 patients at 3 months may lead to underpowered statistics. Also, the utilization of 2D and 3D photographs does not provide further insight into changes in delicate facial anatomy induced by the simultaneous application of HIFES+RF. Therefore, further investigation is needed to correlate data from 2D and 3D analyses related to volumetric changes in the midface and lifting effect with the functional changes in facial tissues. This can be achieved by assessment of the entire cheek volume change to insight comprehensive changes. Future research would benefit from studies comparing RF+ HIFES with standalone HIFES or standalone RF to find whatever is the specific effect of combined or standalone modalities to provide thorough guidance to practical application. The longevity of the effects at 6 and 12 months post procedure is currently unknown. In addition, augmentation of the volume effects would be a possibility with more treatment sessions.

5 | CONCLUSION

Simultaneous noninvasive treatment by Synchronized RF and HIFES facilitates changes to the overall facial appearance by targeting both skin and delicate facial muscles. Specifically, the therapy induces favorable volumetric changes to the cheek and mandibular area while delivering a considerable lifting effect to the sagging facial contours. Since being safe and accompanied by high satisfaction, it poses a valuable alternative or complementary solution to current mini-invasive and invasive procedures.

AUTHOR CONTRIBUTION

All authors contributed equally.

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FUNDING INFORMATION

The study was sponsored by BTL Industries, which provided the study device. However, no funding for the authorship and publication of this article was provided.

CONFLICT OF INTEREST STATEMENT

The authors have declared they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The Investigation Review Board (IRB) approved the study and registered at ClinicalTrials.gov (NCT05525026). All subjects voluntarily signed a written consent form to have their faces photographed and published.

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How to cite this article: Kinney BM, Boyd CM. Remodeling of facial soft tissue induced by simultaneous application of HIFES and synchronized radiofrequency provides nonsurgical lift of facial soft tissues. *J Cosmet Dermatol*. 2024;00:1-6. doi:10.1111/jocd.16165

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Treating Facial Palsy

Aesthetic nurse prescriber Michelle McLean provides insight into facial palsy and treatment options within aesthetic medicine

Facial paralysis, or facial palsy, is a common neuropathy with an annual incidence of 70 cases per 100,000 members of the population in the UK.[1] It may be more following COVID-19 infection and its reported possible side effects, although more research is needed into this area to confirm any hypothesis.[2,3]

Patients with concerns about facial paralysis frequently present to aesthetic clinics hoping to achieve better facial balancing through aesthetic treatments. Increased patient knowledge and awareness of non-surgical procedures and the advancement of injection techniques have led to a significant shift from surgical to non-surgical and combined approaches.

As a clinician, a sound understanding of facial paralysis is essential when treating patients presenting with facial palsy, and considerations should be made to ensure that treatment positively impacts both the physical and psychosocial care of patients.

Causes of facial palsy

Facial paralysis, or facial palsy, generally refers to weakness or total loss of movement of the facial muscles resulting from temporary or permanent damage to the facial nerve.[4] Facial palsy can be a congenital disorder, meaning it presents at the time of birth due to delivery traumas and genetic or malformative diseases.[5] It can alternatively be acquired, possibly appearing at any time during life due to infective, inflammatory, neoplastic, traumatic or iatrogenic causes, and affecting people of any age.[5]

Site	Aetiology
Intracranial	• Acoustic neuroma • Stroke (forehead spared) • Brain stem tumour
Intratemporal	• Bell's palsy (diagnosis of exclusion Herpes zoster oticus, Ramsay-Hunt syndrome) • Middle ear infection • Trauma: ◦ Surgical ◦ Temporal bone fracture ◦ Lacerations anterior/inferior to the tragus
Extratemporal	• Parotid tumours
Miscellaneous	• Sarcoidosis, polyneuritis

Table 1: Causes of facial nerve palsy[10]

The most common known cause of facial paralysis is generally idiopathic with no apparent reason: Bell's palsy.[6] Other facial nerve palsies can be related to several conditions: Ramsay-Hunt syndrome (caused by herpes zoster outbreak), cholesteatoma, parotid gland tumours, Lyme disease, otitis media, HIV, leprosy, amyloidosis, Guillain-Barré syndrome and sarcoidosis (autoimmune diseases), diabetes and strokes (**Table 1**).[6-8] Infection reports account for 7% of presenting cases, trauma 10-23% and tumours 2-2.5%.[9]

When facial paralysis presents, there is damage or injury to a particular branch of the facial nerve and the correlated muscles.[1] Facial nerve damage can result from various causes frequency of these is as yet unknown.[1]

Facial paralysis can be identified as unilateral (affects one side of the face), which is most commonly seen, or bilateral (affects both sides) – a rarer presentation.[1] The symptoms of facial palsy can vary between patients depending on the underlying cause and severity of the condition.[1]

In some cases, the weakness or paralysis may be mild and only affect certain areas of the face, such as the mouth or eyelid. In more severe cases, the entire face may be affected, including the ability to close the eye on the affected side.[11]

Medical treatment for facial palsy depends on the underlying cause of the condition. In some cases, the condition may improve on its own over time. In the UK, patients experience a considerable variation in care pathways, including medication, physical therapy and surgery.[12] A face-to-face consultation should establish if the patient has a confirmed diagnosis of facial palsy, and the severity of their condition. In the absence of a confirmed diagnosis, the clinician must refrain from treatment and refer the patient back to their GP for further investigation.

In an upper motor neurone palsy, the frontalis is spared, and the patient can still wrinkle the forehead on the affected side. There is no effect on the eyelid or closure of the eye itself. Various causes of upper motor neurone facial palsy include multiple sclerosis, stroke, intracranial tumours, HIV and infections such as syphilis.[13]

Lower motor neurone lesions are associated mostly with Bell's palsy, and around 10 to 40 people per 100,000 are

affected annually.[14] A lower motor neuron palsy presents with a total unilateral palsy presentation.[14] Other lower motor neuron lesions are associated with Ramsay-Hunt Syndrome.[14]

It is important for clinicians to refrain from attempting to diagnose patients with facial palsy. Diagnosis should be established through the patient's GP/NHS secondary care pathway to determine the condition's underlying cause. These individuals possess extensive training and experience in this field, so patients should be referred on to them.

Successful treatment of patients relies on assessing the individual's presentation in-clinic, rather than focusing solely on the cause of paralysis. An all-encompassing understanding of the patient is essential for effective treatment since symptoms are unique to each patient and a generalised approach will not suffice. Analysing the patient's psychosocial wellbeing and the impact of paralysis on their daily life is crucial in identifying their specific concerns and objectives.

Damage to the facial nerve CN VII, whether inflammation or compression, can trigger substantial variable symptoms depending on the lesion site and the branch affected, which can be permanent or reversible.[15,16] Symptoms can include a visible mouth droop, flattening of the nasolabial fold, inability to close the eye and smoothing of the brow on the damaged side.[15,16]

The main causation of Bell's palsy suggests it relates to the herpes simplex virus.[15] Therefore, understanding the facial nerve complexity and its variability is pivotal for clinicians in the non-surgical medical aesthetics arena to treat nerve-related injuries/conditions, and prevent damage whilst providing satisfactory results to patients.

Aesthetics as a potential cause of facial paralysis

From an aesthetic perspective, nerve injury secondary to dermal fillers, although rare, can occur, whether it be through blunt or sharp force. The facial nerve can undergo trauma through direct injection into a nerve by needle or cannula, or through compressing and excessive massaging of dermal fillers, which can result in sensory or motor deficit.[17] Threads and dental block procedures can also result in nerve injury.[18,19]

Whilst sound anatomical knowledge is pivotal and will help to reduce the risk and potential of nerve-induced trauma, practitioners should acknowledge that anatomical variations do exist.

If a patient presents with paralysis or weakness following an aesthetic procedure, it is vital that a full face-to-face consultation, medical history analysis and examination of ocular and perioral musculature is sought, as this will greatly assist in the effective and appropriate management of onward secondary care referral.



Figure 1: 56-year-old female patient at baseline in 2019, and at 2022 following botulinum toxin treatment

Facial paralysis caused by dermal fillers is extremely rare, and in my 12 years of aesthetic practice, I have never encountered this complication. Studies in this area are limited, and it would be beneficial for it to be recorded in the future. To ensure the safety of the patient, it is important to have a reliable referral system in place. The use of ultrasound scanning can provide valuable information about the placement of dermal fillers, which can be shared with emergency services if immediate treatment is needed.[20] If the clinician lacks relevant experience or cannot provide treatment, it is necessary to refer the patient for emergency treatment via the NHS Emergency Department or with a complications management specialist.

The facial nerve is a vital structure for emotion and communication, and impairment can cause a substantial decline in a patient's quality of life.[14] The impact of the inability to smile and express emotion is the main distressing aspect of facial palsy, and such individuals fear being negatively evaluated by others, which has a detrimental impact on their social interactions.[21]

Aesthetics as a treatment for facial paralysis

The administration of botulinum toxin can play a crucial role in improving quality of life in facial palsy patients. A recent study showed that a single dose of botulinum toxin administered on the unaffected side of 18 patients with acute facial paralysis generated momentous improvement in facial symmetry four weeks post-treatment.[21] Individualised botulinum toxin injection patterns are critical for optimal unilateral synkinesis and contralateral hyperkinesis success. It is important to note that synkinesis treatment aims to target accurate, viable synkinesis muscles and not stimulate flaccid muscles.[21]

When it comes to individualising treatment for patients with facial paralysis, it is crucial that the clinician is well-trained and highly experienced. They should have received ample training and gained experience by shadowing other specialist practitioners who regularly treat facial palsy. In addition to having a thorough understanding of facial anatomy, clinicians should also take a holistic approach to treatment and be familiar with various options such as surgery, therapy, rehabilitation and more. If a clinician is not experienced in treating facial paralysis, referring the patient to a specialist practitioner or back through their NHS pathway is recommended.

Those seeking to expand their knowledge can refer to courses like 'A Multidisciplinary Approach to the Management of Facial Palsy' developed by Catriona Neville (ESP Physiotherapist at Queen Victoria Hospital NHS Foundation Trust) and Sally Glover (Clinical Specialist Physiotherapist, University Hospitals Birmingham NHSFT).[22]

Botulinum toxin can be administered into the non-paralysed facial muscles for successful hyperkinesis treatment to help relax the activity and improve symmetry. Clinicians must carefully consider the precise injection location, depth and angle of treatment, as unnecessary side effects can harm such patients and further exacerbate facial asymmetry. To help minimise such risks, under-correction is essential in the initial treatment plan, as additional injections can be made during the review appointment.[23]

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Figure 2: 35-year-old female patient at baseline, after botulinum toxin treatment in 2023 and after EMFACE treatment in 2023.

Case study one

This case looks at a 56-year-old female patient. The patient has attended my clinic for regular treatment over the past four years. She has Ramsay Hunt syndrome, and had previously accessed toxins for palsy from the NHS. Free NHS treatment is limited, so additional treatment at my clinic has been used to maintain results in between. Following a recent appointment with her NHS consultant, she was highly dissatisfied with the results, noting that the results seemed to emphasise asymmetry. The patient's wedding was imminent and following successful treatment at my clinic in the past, she returned to discuss possible options before her big day.

A consultation was conducted before treatment to assess suitability and manage the patient's expectations. It was explained that a conservative approach with a view to subsequent top-ups would be the best approach, as in patients with facial palsy, higher doses of botulinum toxin can lead to difficulty talking, eating and drinking.[24]

Treatment

Botulinum toxin type A (Azzalure from Galderma) was injected into the depressor anguli oris (5 Speywood units) and the upper horizontal fibres of the platysma (20 s.U) on the contralateral side to the facial palsy to decrease the tone of the muscle and improve symmetry. This reduced the downward force of zygomaticus major, zygomaticus minor, levator labii superioris and levator labii superioris alaeque nasi, and provided an elevation of the tissue.

Azzalure was also injected into the mentalis (10 s.U) to enable oral commissure elevation, and the orbicularis oculi (20 s.U) and corrugator supercilia (20 s.U) on the unaffected side to improve symmetry and balance. Vivacy Stylage dermal filler was combined with botulinum toxin to improve zygomaticus function and balance as well as improve lip symmetry at rest. Stylage S (1.2ml) was used to augment the lip and soften perioral lines on the hyperactive side. Stylage M (1.3ml) was used to soften and reduce static line activity in the nasolabial fold areas and to support oral commissure elevation.

Results

The patient results show facial balance and harmony have been restored (**Figure 1**), and she reported that her wellbeing had significantly improved. Aftercare advice was general for any patient undergoing toxin and dermal filler treatment; no aftercare specific to facial paralysis was necessary. The patient will next attend the clinic four months after treatment for a new assessment and potential continued treatment.

Case study two

This case looks at a 35-year-old female patient. She suffered facial palsy due to nerve damage from surgical operations on the jaw. Her wellbeing was deeply affected by the physical effects of facial paralysis, meaning she was sometimes withdrawn from society.

Treatment

Initially, toxin was chosen as the management plan to relax unwanted muscle activity on the unaffected side. Azzalure was injected into the corrugator supercilia (20 units s.U), frontalis (15 units s.U) and orbicularis oculi (15 units s.U) on the unaffected side to achieve symmetry and facial harmony by reducing unwanted tension and hyperactivity due to synkinesis. Four months following toxin treatment, we utilised this patient as part of a small study using EMFACE technology. The patient underwent four sessions of EMFACE, each session one week apart. In EMFACE, three facial applicator pads simultaneously emit both synchronised radiofrequency and high intensity facial electromagnetic stimulation (HIFES) energies, causing stimulation on the elevators of the facial muscles – the frontalis, the zygomaticus major and minor and the risorius muscles.[25] The treatment resulted in significant improvements in facial symmetry even after one session.

Results

The patient results show facial balance and harmony have been restored (**Figure 2**), and she reported her wellbeing and mental health had significantly improved. Aftercare advice was general for any patient undergoing toxin or EMFACE treatment; no aftercare specific to facial paralysis was necessary. Toxin results typically last around four months, so the patient will next attend the clinic in four months for a new assessment for toxin management.

Improving patient wellbeing

When carrying out aesthetic treatments, sound anatomical knowledge is required to minimise the risk of nerve injury/neurapraxia, which can be linked to dermal fillers and thread administration, resulting in facial palsy. When it comes to facial palsy patients, whether the condition is related to Bell's palsy, Ramsay Hunt Syndrome etc., experienced clinicians can play a pivotal role in improving patients' quality of life through the successful administration of botulinum toxin and other aesthetic treatments.



Michelle McLean is the founder and medical lead for Aesthetically You, a 'good' rated CQC clinic in the Northwest of England. She has more than 12 years of experience in the industry and is a regional leader for the BACN. McLean is currently completing a second Master's in Cosmetic Medicine.
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Simultaneous Emission of Synchronized Radiofrequency+ and HIFES for Non-invasive Submental Volume Reduction: The Mechanism of Action

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Abstract

An EMFACE submentum applicator is revolutionizing the non-invasive treatment of the submental area. Utilizing the simultaneous emission of Synchronized RF+ and HIFES, the submental applicator targets three layers in the submental region; HIFES selectively tones the strategic submental muscles, and simultaneously RF heating induces lipolysis of the fat depots in the region and tightens fascias and the overlying skin. With two energies targeting all layers from muscle to skin, this novel EMFACE submentum applicator promises a new and strategic approach in improving the appearance of the submental region.

Keywords: HIFES, Radiofrequency, Synchronized RF+, Simultaneous, Application, Supramaximal, Contraction, Muscle, Fat, Reduction, Hypertrophy, Face, Lift, Double chin, Pseudo-double chin, Digastric muscle,

Introduction

The submental region is one of the most critical areas regarding the overall aesthetic of the face. Both aging and lifestyle can be reasons for changes in submental volume, making it a problem for people of all ages. Submental fullness affects how others perceive us. The holy grail of measurement determining submental aesthetics is the angle formed by the submental and cervical planes. This angle is called the submental-cervical angle. Studies reported that the submental appearance is considered attractive and youthful when the submental-cervical angle is between 90°-105°.[1] When below this range, the aesthetic look is perceived as unnatural. When the angle is above this "ideal" range, the submental region is perceived as too volumized and unattractive.

From the anatomical standpoint, the submental region is a multilayered unit where each layer significantly contributes to the degree of the submental-cervical angle. The uppermost layer is the skin covering the subcutaneous fat layer, under which is located the thin platysma muscle. Under the platysma is usually a thin layer of subplatysmal fat that covers the muscles of the submandibular triangle. The outermost muscle of the submandibular triangle is the digastric muscle, which keeps and elevates the position of the hyoid bone as well as all other submandibular muscles.[2,3]

A change in one of these layers affects the submental-cervical angle. However, during aging all of these layers undergo changes, leading to a large impact on the overall submental appearance.

Submental skin layer

As in all body areas, the skin of the submental region undergoes age-related changes due to the continual loss of collagen and elastin.[4,5] Due to the loss of these crucial skin proteins, the skin loses its elastic properties and firmness, which inevitably leads to skin sagging and the formation of wrinkles. However, submental skin experiences sagging more than wrinkles. Gravity pulls lax skin down, and this downward repositioning thus increases the submental-cervical angle. Skin sagging is the predominant submental concern for older patients but can also result from rapid fat loss in the region, either because of weight loss or by aesthetic procedures not followed by skin tightening. [6,7]

Submental fat layer

An increase in the volume of the submental region is often the first noticeable change and is commonly called "double chin." One of the reasons for increased volume is the accumulation of submental fat formed superficially over the platysma. Importantly, there is also fat located under the platysma.[3] Aesthetic treatments target the superficial compartments, which Larson et al. reported as the location where the majority of the fat is located and which highly affects the submental cervical angle.

Submental muscles' relation to the submental cervical angle

Weakened submental muscles are another reason for increased submental volume and have long been neglected. To truly comprehend the muscle contribution to the submental volume it is necessary to understand the anatomy of the submental region.

The muscles of the anterior upper neck, including the submandibular and submental triangle, are arranged in two layers separated by fat. The superficial muscular layer is formed by the platysma, a muscle of facial expression, whereas the deep muscular layer is formed by the suprahyoid muscles which contribute to swallowing and head movement. The platysma muscle covers the entire anterior and lateral neck region and extends from its attachments at the mandible to its continuation with the superficial fascia of the chest; the transition from muscle to fascia occurs approximately at the clavicles. Age-related features of the platysma include platysmal banding, which is visible at rest and is referred to clinically as Turkey neck deformity. This age-related feature must be differentiated from platysmal bands that are visible only during muscular contractions and can be treated with neuromodulator injections, which were shown to decrease the appearance of contraction-related banding and improve lower face and neck contouring.[8–11] In addition to the inhibition of the platysma muscle to reduce platysma bands, there are surgical options for aesthetic improvement of the submental-cervical angle through platysma manipulation, such as a "neck-lift". During this procedure, the platysma muscle is repositioned upward, contributing to the elevation and support of the underlying tissues in the submental cervical area.[12–15]

The deep muscular layer of the upper neck consists of two muscles, which together form the submandibular triangle. A pair of anterior bellies of the digastric muscle, which creates borders of the submandibular triangle and the mylohyoid muscle located deep to the anterior bellies of the digastric, form the floor of the submental area. Both of these muscles most likely undergo a process termed sarcopenia which results potentially in a reduction of their baseline tone and maximal contraction strength.[16] However, only the anterior bellies of the digastric muscle are deemed to significantly contribute to the submental fullness due to their more superficial position and place of attachment.[17,18]

It has been observed that the anterior belly of the digastric muscle might "bulge" more anteriorly therefore increasing the submental cervical angle. The etiology of this problem was previously

incorrectly labeled as digastric muscle hypertrophy. Multiple surgical interventions were designed to target the "bulky" digastric muscle. However, recent MRI findings do not support the theory of muscular hypertrophy with aging but rather indicate muscle laxity of the digastric muscle that affects submental fullness. [16,19]

The most likely explanation of this phenomenon is that the weakened digastric muscle loses its muscle tone resulting in its increased laxity. In conjunction with changes in the surrounding tissue, the lax digastric muscle allows for the movement of the surrounding fat compartments in a downward direction, making the digastric muscle "bulge out" consequently increasing the submental-cervical angle. This condition is called the pseudo-double chin (Figure 1). A weak digastric muscle is unable to hold the weight of accumulated fat and reposition itself inferior and anterior, thus changing the aesthetic appearance of the neck as a whole.[16,20]

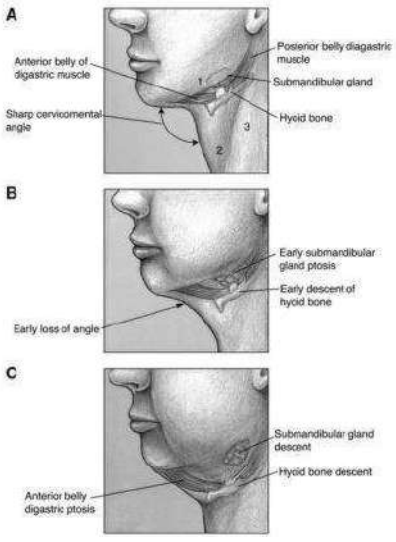


Figure 1: Progression of pseudo double chin (Ptosis of the anterior belly of Digastric m.)A - Ideal Digastric m., B - Erly stage of ptosis of anterior belly Digastric muscle, C - Anterior belly of Digastric m. ptosis (Source: DeFatta and Ducic 2007)

The aging of the digastric muscle is well known to plastic surgeons who commonly suture the weak anterior bellies of the digastric muscle together and suspend them to the mylohyoid muscle. The reason is that although the mylohyoid muscle does lose its tone, it is immune to sagging due to its flat structure and long insertion along the mandible and thus provides good support to the sutured digastric.[2,20–23]

Age-related digastric sagging is not the only concern associated with the digastric muscle. Because the anterior and posterior bellies of the digastric muscle are attached to the hyoid bone, they also have a significant role in keeping the hyoid bone in place. While other bones are directly articulated with other bones the hyoid bone does not have such articulation, and its position is solely given by attached muscles, ligaments, and fascias.[24]

Weakening and laxity of the digastric muscle both create an imbalance in the forces maintaining the hyoid position, which gradually leads to its descent and thus to an increase in the submental-cervical angle. [24–27]



Figure 2: Low-laying hyoid bone (Source: Dedo 1980)

Digastric muscle ptosis and laxity, together with a consequent descent of the hyoid bone, might most likely play a major role in the creation of the so-called pseudo-double chin. The issue is well known to plastic surgeons who attempt to resolve the issue via surgery. However, up to date, there is

no non-invasive way to modulate the digastric muscle to regain its condition and thus its ability to maintain a low submental-cervical angle. Noninvasive aesthetic approaches focused on the submental region should aim at digastric muscle condition to prevent or resolve this issue.

Multiple layer approach

As explained above, the submental layers age differently; nevertheless, they are still part of one submental unit and can mutually influence one another. Due to the complexity of the submental unit, patients may experience an increase in submental volume involving one or multiple layers (see Figure 3), yet there is no non-invasive solution that would be able to target three layers that contribute to the submental fullness.



Figure 3: Profile of a patient with increased skin laxity, fat accumulation, and Digastric muscle weakness

EMFACE submentum applicator

The EMFACE submentum applicator is the first non-invasive solution designed to address all submental layers, skin, fat, and muscle tissues. Addressing these three complex targets simultaneously provides a novel solution for enhancing the submental appearance. The applicator uses two technologies, HIFES and Synchronized Radiofrequency plus (Synchronized RF+) to affect all three tissues.

HIFES submental stimulation

EMFACE placed in a submental area is the first device that can address submental muscle aging. HIFES is placed over the mylohyoid nerve which innervates the anterior bellies of Digastric m. and, through neuromuscular stimulation, provides supramaximal contraction. This mechanism of action has been proven to stimulate muscles to increase their tone.[30,31] By increasing the tone of digastricus m. it is tightened, thus decreasing its ptosis and preventing it from bulging out. As a result, the toned digastric muscle can hold the hyoid bone in the right position at C4 thus improving the submental-cervical angle.

HIFES stimulation occurs in the midline of the submental region. This design is crucial to specifically target the Digastric muscle and not the platysma muscle which has more lateral innervation. As previously described the platysma muscle and Digastric m. need a completely different approach to treating signs of aging. Platysma muscle treatment can consist of botulinum toxin-based muscle inhibition to treat platysma bands. However, inhibition of the Digastric m. in this way could lead to dysphagia. The Digastric m. is already weakened by aging and therefore needs to be stimulated to regain strength and reverse ptosis.. [32–34]

Synchronized RF+

Synchronized RF+ is a high power Synchronized RF technology used in other EMFACE applicators that is exclusively implemented in submental applicator. RF+ is simultaneously emitted with HIFES and provides homogenous heating over the whole submental area. Synchronized RF+ increases the temperature in the fat layer to induce apoptosis levels while simultaneously keeping the therapeutic temperatures in the skin to induce neocollagenesis and neoelastinogenesis.

Additionally, tissue heatings might enhance HIFES toning abilities, as has been demonstrated in numerous skeletal muscle studies, which is the

group that also includes Digastric. It is well known that heating-stimulated muscle increases the expression of heat shock proteins and satellite cells, both of which are necessary for muscle remodeling and development.[35–38]

Clinical evidence of submental applicator

The efficacy of Submental applicator has been validated in pilot studies on animal subjects showing a significant increase in the fat apoptotic levels by 4.8 times. Furthermore, skin histology showed an increase in collagen and elastin content by 33% and 113%, respectively.

The results seen in animal studies were replicated in human testing, where histology, MRI, 3D photos, and Ultrasound were used to evaluate treatment efficacy. Histology shows a significant increase in apoptotic cells. MRI evaluation on a 1-month follow-up showed a decrease in submental fat volume by 25%. Furthermore, this study also incorporated the cheeks applicators with Synchronized RF, and MRI evaluation showed no significant decrease in cheek fat volume thus proving the important difference between Synchronized RF and Synchronized RF+ effect on adipose tissue. In addition to the volume of the fat layer the, area of "double-chin" with all layers was identified and evaluated. This approach emphasizes the importance of the multimodal approach to submental volume reduction with a volume reduction of the "double-chin" by 31%. This reduction was reflected by 3D photo evaluation with a reduction of 5.78 ml in the submental area.

Summary

As stated in the introduction the submental area is a complex problem that needs to be addressed by a complex and cohesive solution. A non-invasive, multiple-modality approach that would lead to significant changes in all anatomically relevant layers was missing until now. The Synchronized RF+ and HIFES together yield the combined effects needed for complex double chin reduction. When these two modalities are used in conjunction, the reduction effect is amplified. In this way, the connective tissue is rejuvenated, the fat layer is reduced, and the muscle is toned, thus lifting the whole submental area with a reduction of muscle bulging.

Conclusion

EMFACE submentum applicator is the first non-invasive device that affects the submental area problems by incorporating two modalities with effects on skin, fat, and muscle.

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Check for updates

Received: 13 October 2023 | Revised: 9 February 2024 | Accepted: 28 February 2024

DOI: 10.1111/jocd.16273

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Treatment with synchronized radiofrequency and facial muscle stimulation: Histologic analysis of human skin for changes in collagen and elastin fibers

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Abstract

Background: Skin's exposure to intrinsic and extrinsic factors causes age-related changes, leading to a lower amount of dermal collagen and elastin.

Aim: This study investigated the effects of a novel facial muscle stimulation technology combined with radiofrequency (RF) heating on dermal collagen and elastin content for the treatment of facial wrinkles and skin laxity.

Methods: The active group subjects ($N=6$) received four 20-min facial treatments with simultaneous RF and facial muscle stimulation, once weekly. The control subject ($N=1$) was untreated. Skin biopsies obtained at baseline, 1-month and 3-month follow-up were evaluated histologically to determine collagen and elastin fibers content. A group of independent aestheticians evaluated facial skin appearance and wrinkle severity. Patient safety was followed.

Results: In the active group, collagen-occupied area reached $11.91 \pm 1.80 \times 10^6\,\mu m^2$ (+25.32%, $p<0.05$) and $12.35 \pm 1.44 \times 10^5\,\mu m^2$ (+30.00%, $p<0.05$) at 1-month and 3-month follow-up visits. Elastin-occupied area at 1-month and 3-month follow-up was $1.64 \pm 0.14 \times 10^5\,\mu m^2$ (+67.23%, $p<0.05$), and $1.99 \pm 0.21 \times 10^5\,\mu m^2$ (+102.80%, $p<0.05$). In the control group, there was no significant difference ($p>0.05$) in collagen and elastin fibers. Active group wrinkle scores decreased from 5 (moderate, class II) to 3 (mild, class I). All subjects, except the control, improved in appearance posttreatment. No adverse events or side effects occurred.

Conclusion: Decreased dermal collagen and elastin levels contributes to a gradual decline in skin elasticity, leading to facial wrinkles and unfirm skin. Study results showed noticeable improvement in facial appearance and increased dermal collagen and elastin content subsequent to simultaneous, noninvasive RF, and facial muscle stimulation treatments.

KEYWORDS
collagen, elastin, radiofrequency, rejuvenation

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1 | INTRODUCTION

Facial aging is a complex process that is a result of alterations in multiple layers of the face: the skin, subcutaneous fat, superficial musculoaponeurotic system (SMAS), muscle, and bone.[1,2] The facial muscles tend to lose their resting tone, especially when affecting the elevator muscles such as zygomaticus major muscles or frontalis muscles, leading to the repositioning of facial tissue. The elevator's inability to hold the overlying tissue in place inevitably results in soft tissue sagging. The skin and SMAS are affected by the loss of collagen and elastin, the principal structural and connective tissue proteins. Depletion of these proteins leads to wrinkle formation, reduced elasticity, and sagging appearance. Additionally, thinning of the SMAS layer contributes to laxity and jowling.[3,4] As such, when approaching facial aging, it is necessary to take into account all of the factors and ideally target all involved components. However, current noninvasive approaches focus solely on treating the skin or artificially providing facial volume to compensate for the repositioned tissue or inhibiting certain muscles to balance the loss of tone in others.

Yet, recently a novel approach has been introduced, a novel device using a noninvasive applicator that administers HIFES technology and synchronized radiofrequency (RF) simultaneously has been proposed to enhance the facial appearance.[5] HIFES selectively stimulates the elevator muscles by inducing supramaximal, involuntary, muscle contractions by generating strong electrical currents.[1] The electrical current depolarizes the motor neurons' membrane creating a signal for the muscle to contract. The recruited heat shock proteins and satellite cells can support muscle microprotein structure alterations.[6] Studies have shown that repeated application of HIFES induces muscle protein synthesis, which may result in an increase in muscle tissue density and overall enhancement of muscle tissue together with increasing the resting tone of carefully selected facial muscles in the forehead (frontalis muscle) and cheeks (zygomaticus major, zygomaticus minor, and risorius muscles).[7–10] The monopolar RF is an oscillating electrical current that is partially absorbed by the tissue, where it creates heat. The heating for a period of time is able to increase fibroblast activity and unwind the H-bonds to denaturate the collagen. After the heating stimuli stops, the body starts to induce normal regenerative process, which lead to the neocollagenesis and neoelastinogenesis. With repetition the collagen and elatine is rebuilded repeatedly.[11]

This study includes histological examination of facial skin tissue collected from the foreheads and cheeks of patients who underwent treatment using the non-invasive HIFES and RF applicator. The study objective was to assess changes related to the connective tissue structural proteins—collagen and elastin—and to evaluate the effectiveness of this combined treatment modality in enhancing the structural integrity of the skin (as shown in previous animal model studies)[12,13] and aesthetic facial appearance.

2 | MATERIALS AND METHODS

2.1 | Study design and subject population

This prospective, single-center, interventional, two-arm, open-label design study enrolled seven (7) female subjects interested in participating in a clinical study with a device intended for noninvasive facial rejuvenation. Six (6) subjects in the active group [39–62 (55.83 ± 8.56) years old, BMI 22.73–38.59 (27.65 ± 5.87) kg/m^2, Fitzpatrick skin types I to IV], received active treatment with simultaneous HIFES + RF to the cheeks and forehead. One (1) subject served as a control and was not treated [62 years old, BMI 36.9 kg/m^2, Fitzpatrick skin type IV].

The subjects from the Active group ($N = 6$) received four 20-min facial treatments, 1 week apart, with single-use, self-adhesive, noninvasive applicator electrodes (EMFACE device BTL Industries Ltd., Boston, MA). The whole face (i.e., forehead and cheeks simultaneously; see Figure 1 for applicator placement) was treated. Subjects

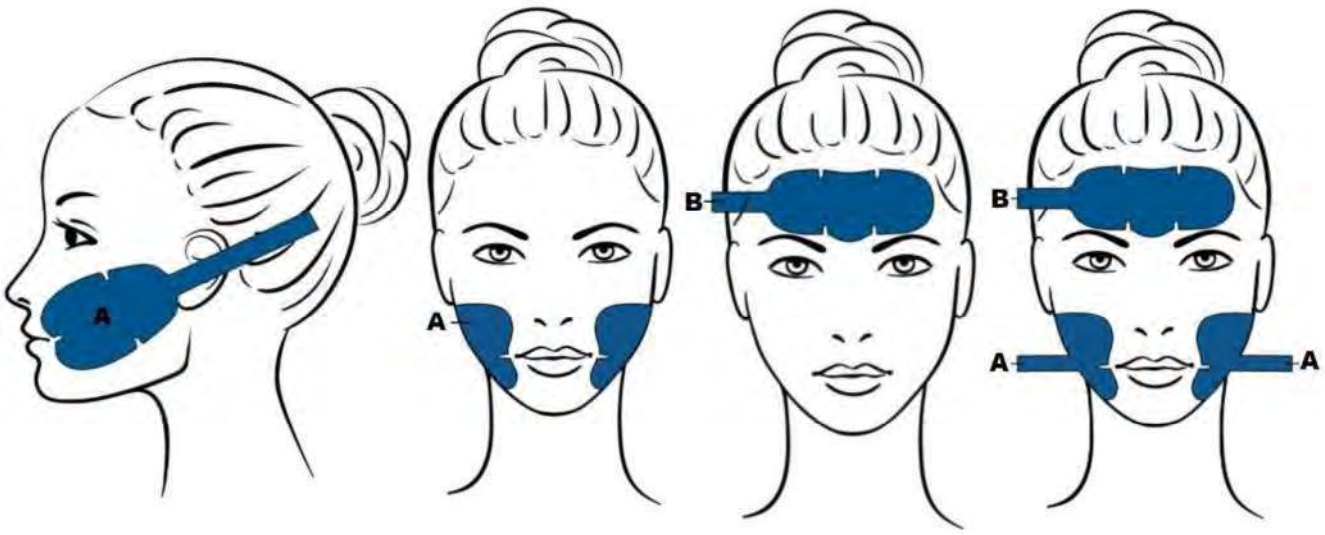


FIGURE 1 Illustration of the noninvasive, self-adhesive, hands-free device applicator placement during the therapy (A = cheek, B = forehead). The patient is treated in the supine position. The forehead and both cheeks are treated simultaneously for a 20-min duration.

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were in a supine position, anesthesia was not required. Both energy intensities (HIFES and RF) were individually set according to patients' feedback and tolerability on a scale of 0%–100%. Jewelry and prominent hair were removed from the face and the skin before the treatment.

Punch biopsies of the skin tissue from the periauricular area were performed at baseline, followed by 1-month and 3-month follow-up visits. All biopsies, 3 mm in diameter (Kruse Buster), were obtained full-thickness (approximate depth 2.0–3.0 mm) at the investigator's site. Local anesthetic was used to numb the biopsy collection area. The biopsy wounds were subsequently closed and disinfected, and the healing process was monitored throughout the study. Participants received detailed instructions for home wound care to ensure proper healing. Inclusion criteria were healthy subjects aged over 21 years, with clearly visible wrinkles on the cheeks and forehead (face) when relaxed, who were willing to abstain from any facial treatments other than the study procedure during study participation. Exclusion criteria prohibited subjects with any active psoriasis, eczema, local infection in the treatment, neurological disorders, or electroanalgesia. The study was IRB approved and registered on clinicaltrials.gov (NCT05524662).

2.2 | Histological evaluation

The obtained skin tissue samples were processed for histological examination. All samples were correctly labeled using subject ID and the description of the corresponding visit—pretreatment (baseline) and posttreatment (1-month and 3-month follow-up visits). The samples were sliced, and the sections were then stained to visualize and examine collagen and elastin under a microscope.

A clinical histologist analyzed the stained samples to evaluate the changes in the tissue, including any pathological changes to rule out potential skin damage resulting from treatment with HIFES and RF noninvasive electrode applicators.

The staining process employed conventional Masson's trichrome procedure, which enables a detailed visual assessment of collagen and the general tissue structure. Collagen fibers developed a green color. Orcein staining was used to specifically visualize elastin in the samples. The elastin fibers developed a brown-dark color. The stained samples were mounted to microscopy slides.

The slides were observed and photographed using an automated slide scanning microscope (Hitachi Axio Scan.Z1, Carl Zeiss AG, Germany; 20×/0.8NA Plan-Apochromat objective) in a bright field. Collagen and elastin quantification was performed with the Image J software based on semi-automatic segmentation in the HSB (Hue-Saturation-Brightness) color system. The appropriate threshold differentiating the collagen and elastin fibers from the background was identified in the selected regions of interest (ROI = 1800 × 1200 μm; $2.16 \times 10^6\,\mu m^2$) at a defined scale, allowing for the quantification of the area covered by collagen and elastin within the tissue sections. After selecting the collagen and elastin fibers, their densities were expressed as the occupied area (square micrometers) encompassed by the fibers in the evaluated images' in the ROI.

Statistical analysis Student's *t*-test and Friedman's one-way repeated measures ANOVA test were performed with significance level set at $\alpha = 0.05$. Post hoc Tukey HSD test was done for multiple comparisons.

This process was repeated for the seven subjects included in this two-arm study design, which consisted of one control subject and six active treatment subjects. The changes in the average areas representing elastin and collagen content before and after treatment were compared for the active group subjects and the control subject.

2.3 | Aesthetic improvement and wrinkle severity

Subjects had digital photographs of their faces taken before treatment (baseline) and at the follow-up visits. Three reviewers, independent of each other and the clinic, evaluated the facial skin appearance according to the Global Aesthetic Improvement Scale by comparing the before and after photos marked by follow-up visit.

A different trio of evaluators received the same set of photographs and evaluated the extent of skin wrinkles and lines (wrinkle severity) according to the Fitzpatrick Wrinkle Elastosis Scale (FWES). The evaluators were blinded to the follow-up stage (i.e., the photos were not labeled according to the follow-up visit and the order in which the evaluators were shown the photos was randomized). Each evaluator assigned a FWES grade per photograph.

2.4 | Safety

The occurrence of treatment or study-related adverse events and side effects was followed/monitored during the course of the trial.

3 | RESULTS

3.1 | Collagen

In the Active group, the average area occupied by collagen was $9.50 \pm 1.77 \times 10^5\,\mu m^2$ at baseline. The average collagen-occupied area increased to $11.91 \pm 1.80 \times 10^6\,\mu m^2$ ($p < 0.05$) and $12.35 \pm 1.44 \times 10^5\,\mu m^2$ ($p < 0.05$) at the 1-month and 3-month follow-up visits. Compared to baseline, in the active group, the average collagen amount increased ($p < 0.05$) at both posttreatment follow-ups. In the control group, there was no significant difference ($p > 0.05$) in collagen fibers, since the collagen content fluctuated in the range of $9.68 \pm 0.45 \times 10^5\,\mu m^2$–$9.51 \pm 0.23 \times 10^5\,\mu m^2$ throughout the study. There was a significant difference ($p < 0.05$) in the collagen-occupied sample area at both the 1-month (+25.32%) and 3-month (+30.00%) follow-ups (see Figure 2) in the treated (active) group.

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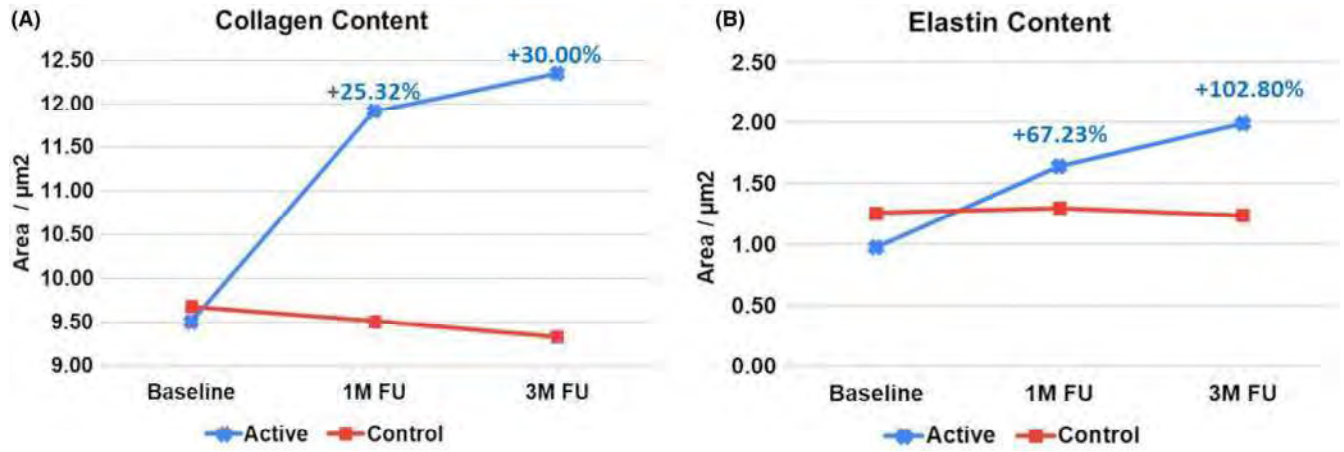


FIGURE 2 Bright-field visualization of collagen fibers by Masson's Trichome method. In the active group, the collagen fibers (A) and elastin fibers (B) increased significantly ($p < 0.05$) and occupied a greater area after 3 months follow-up compared to baseline. No significant change occurred in the Control group. (1M FU: 1-month follow-up; 3M FU: 3-month follow-up).

3.2 | Elastin

In the Active group, the mean elastin-occupied area at baseline was $0.98 \pm 0.34 \times 10^5\,\mu m^2$. At the 1-month follow-up, the average elastin amount was $1.64 \pm 0.14 \times 10^5\,\mu m^2$. At the 3-month follow-up, the area encompassed by elastin increased further to $1.99 \pm 0.21 \times 10^5\,\mu m^2$. Compared to baseline, the average elastin-occupied area increased at both follow-ups ($p < 0.05$). At the 1-month (+67.23%) and 3-month (+102.80%) follow-ups, the amount of elastin was significantly different ($p < 0.05$) comparing the active and control group (Figure 2). In the control group, there were no significant changes ($p > 0.05$) in elastin density at the follow-up points, elastin content ranged between $1.26 \pm 0.16 \times 10^5\,\mu m^2$–$1.30 \pm 0.12 \times 10^5\,\mu m^2$.

Exemplary samples of the collagen (Figure 3) and elastin (Figure 4) microscopic evaluation results of the Active group are shown below (Figure 5).

3.3 | Safety

No adverse events or side effects related to the treatment occurred. Histopathological analysis of the biopsy sample did not reveal any complications or unwanted and unexpected effects.

3.4 | GAIS & FWES results

Overall, the average score of the GAIS evaluation reported that all subjects, except the control, had an improved appearance post-treatment.

The average scores of the active group decreased by 2 grade points on the FWES and GAIS from 5 (moderate, class II wrinkles) to 3 (mild, class I fine lines). The evaluators did not find any change in the control subject's appearance.

Detailed results of the GAIS and FWES independent reviewers' evaluations can be found in Tables 1 and 2.

4 | DISCUSSION

This study demonstrates that noninvasive facial treatment with simultaneous HIFES and RF can induce collagen and elastin expression. In this study, a significant increase ($p < 0.05$) of collagen (+30%) and elastin (+103%) content was observed in dermal biopsy analysis 3 months posttreatment.

The observed increase in elastin content surpasses that of collagen by a factor of around three, marking a noteworthy finding. Upon initial observation, one might perceive the response to changes in elastin levels as deviating from the usual. However, upon examining the baseline data of the active group, it becomes apparent that the levels of elastin are significantly diminished, accounting for approximately 3.5% of the total cross sectional area. In contrast, typical physiological levels of elastin typically fall within the range of 5%–10%. Following the administration of the therapies, there was a twofold increase in elastin levels, resulting in the occupation of 7% of the slice area. This observation indicates a restoration of skin elastin levels to a state consistent with healthy physiological levels.[14–16] Additionally, as SMAS is a tissue that is intertwined with the rest of the facial structures and is made of collagen and elastin, we believe the SMAS layer was also affected and helped with the results.[17] Furthermore, the observed outcomes should not be regarded as a malfunction (e.g., flawed staining process) or an uncommon occurrence. This is supported by the findings of a study conducted by Kinney et al., which examined the effectiveness of HIFES+RF technology on an animal model. In their study, they reported a significant 110.8% increase in elastin levels, which aligns with the outcomes of our own investigation. A similar trend is observed in the case of collagen, as reported by Kinney et al., where there was a notable increase of 26.3%.[5]

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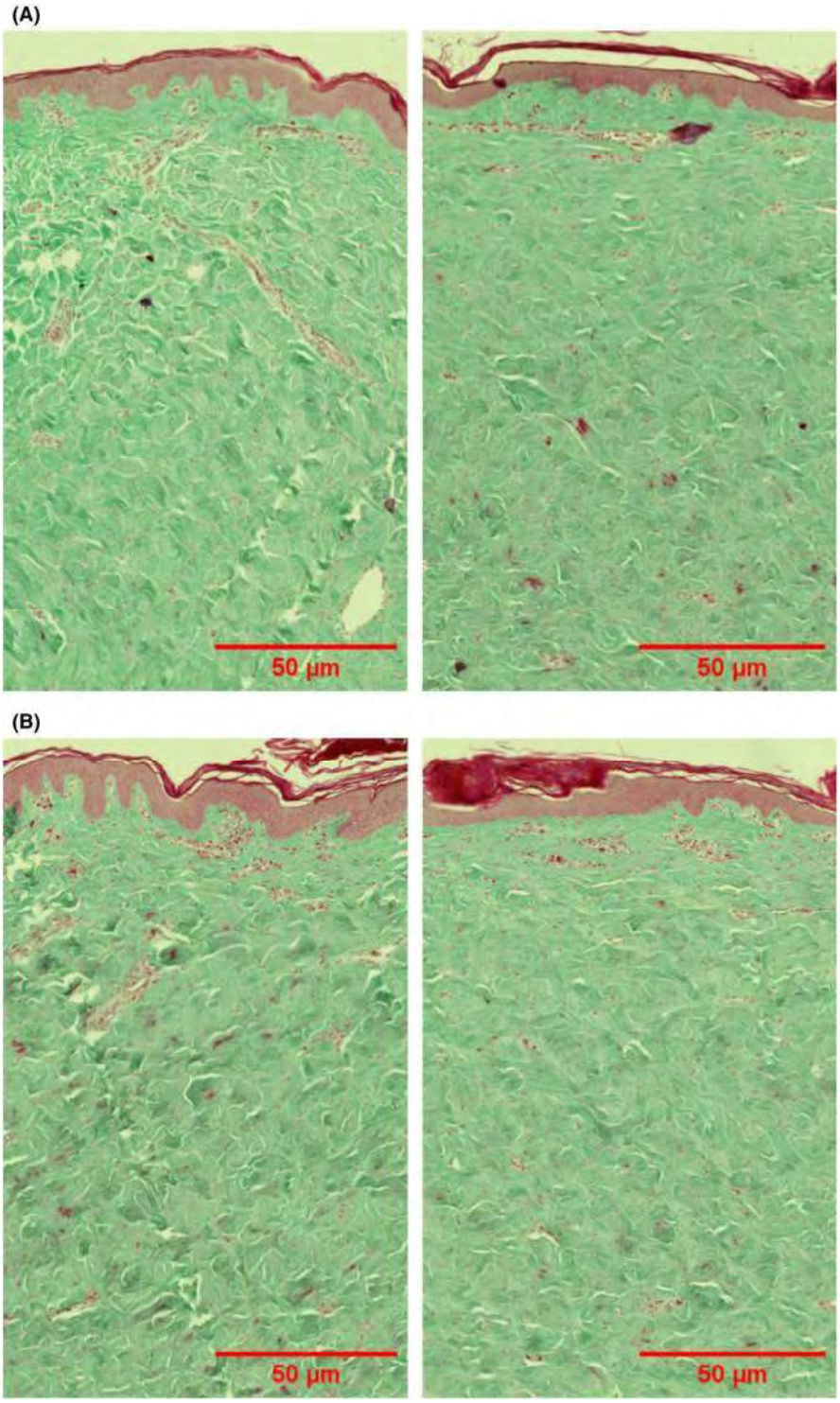


FIGURE 3 Bright-field visualization of collagen fibers stained by trichrome stain, active group samples of two patients (A, B). The collagen fibers appear in green color. At the 3-month follow-up (right), the collagen fibers are noticeably denser, occupying a greater area when compared to the baseline (left).

The substantial increase in the production of elastin and collagen could be attributed to the multimodal approach of the HIFES+RF technology. The application of RF energy has been found to elicit a thermal response in fibroblasts, whereas the HIFES technology induces muscle contractions that mechanically stimulate the skin. These processes have been shown to cause similar responses in fibroblast cells.[18–21] The findings of the study demonstrate a consistent elevation in the concentrations of collagen and elastin, which reached their highest point after a period of 3 months. This aligns with existing understanding on the time it takes for fibroblasts to react to external stimuli of this nature. However, additional research is required to examine the longevity of such an increase.

Besides histological methods, this study further incorporates FWES and GAIS evaluations (by six qualified, independent, clinical aestheticians), all objective basis. As such, the objective evaluation of patient appearance provides insight on significant increase in crucial skin components, namely elastin and collagen. The results

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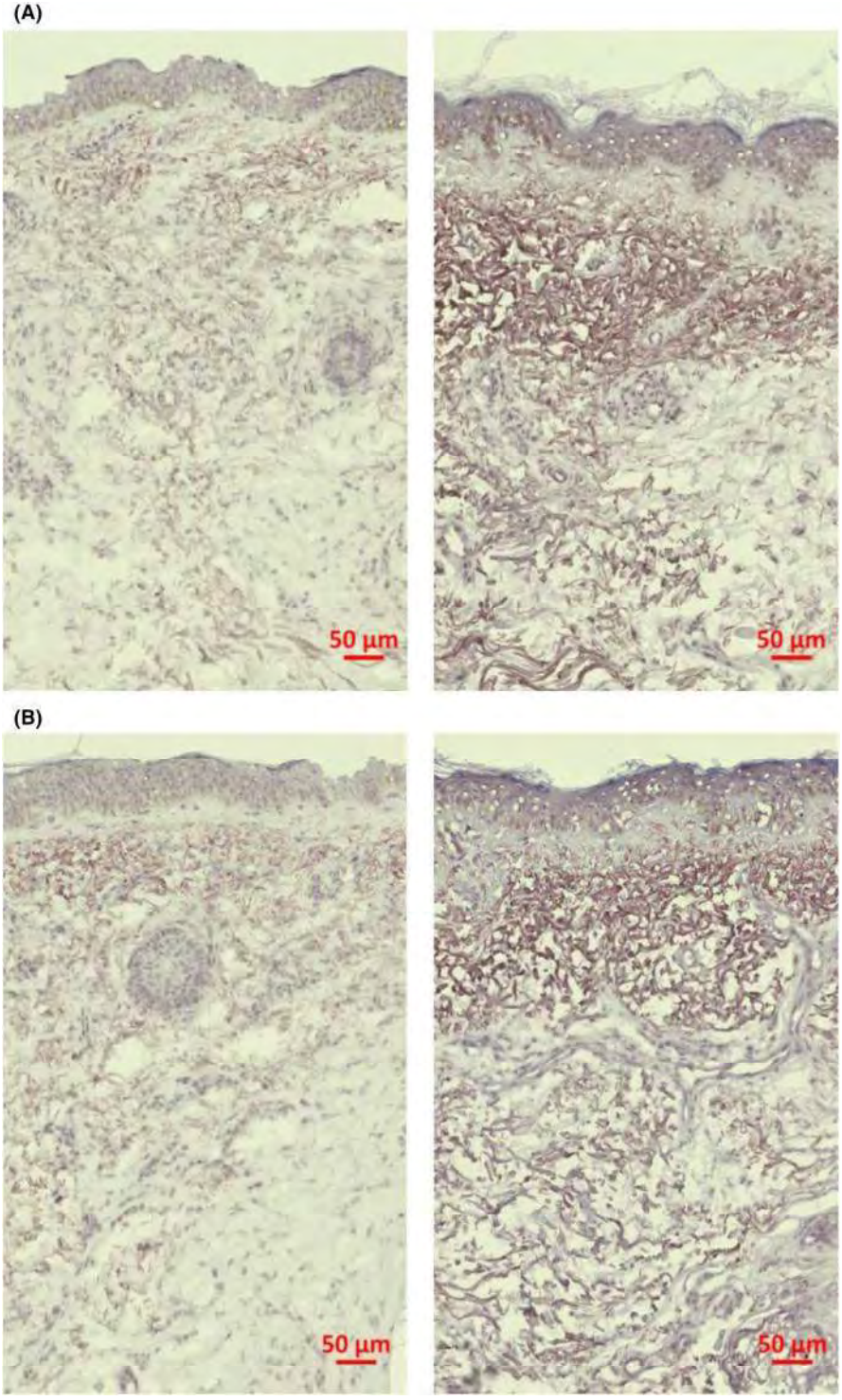


FIGURE 4 Bright-field visualization of elastin fibers by Orcein staining (active group samples of two patients, A and B). The baseline sample (left) has noticeably fewer elastin fibers, observed as dark/brown filaments, than the 3-month follow-up (right). 3-month follow-up shows elastotic fibers replaced with new, longer elastic fibers.

of both evaluation scales indicate a substantial enhancement in the active group, but the control group exhibited no change. These findings provide empirical support for the rejuvenation effect of the HIFES+RF modality.

This objective evaluation approach exhibited a favorable outcome. The findings from the Facial Wrinkle Evaluation Scale (FWES) demonstrate that patients who had scores of 6 or above, indicating moderate to severe wrinkles, experienced more substantial improvements (see Table 1). Comparable results have been observed when comparing the FWES findings to the Global Aesthetic Improvement Scale (GAIS), (Table 2). In contrast, subject number 2, who had only minor wrinkles at the baseline, did not have a major improvement according to the FWES. However, evaluators rated this subject best possible score on the GAIS. The observed discrepancy indicates that the involvement of facial muscles in the aging process holds considerable importance in the context of face rejuvenation, as outlined in the introductory section. The findings of this study may indicate that the utilization of both modalities (RF and HIFES) in combination is

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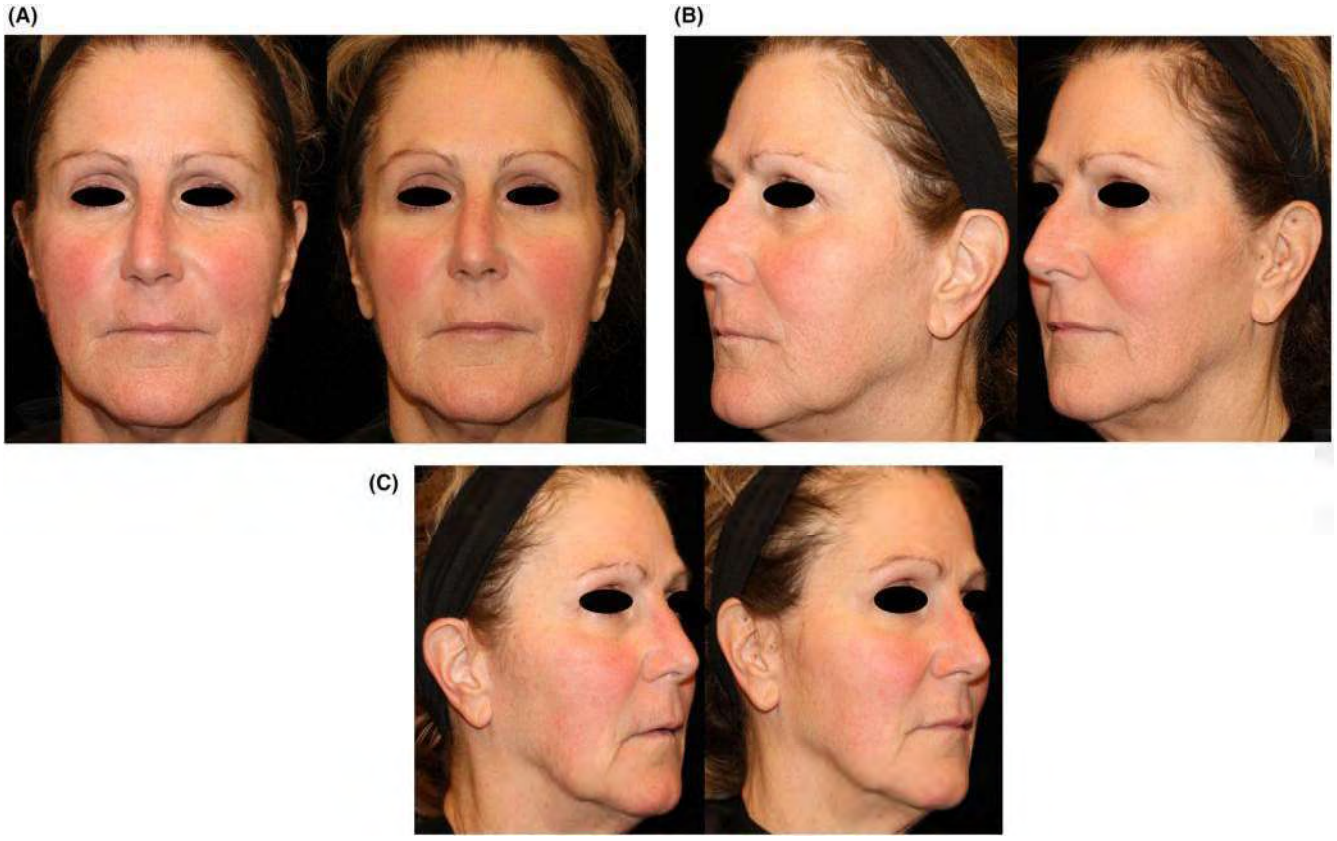


FIGURE 5 Female patient (Skin Type I, 60 years old, BMI 22.6 kg/m^2) at baseline (left) versus 3 months (right)—frontal view (A), left (B) and right (C) lateral oblique angles. The fine lines around the eyes present at baseline have reduced in severity and are less prominent, as well as lifted brows are visible after the treatments. GAIS score = 2 (i.e., much improved), FWES score decreased from 6 (moderate, class II) at baseline to 4 (moderate, class II) at 3-month follow-up.

TABLE 1 Fitzpatrick Wrinkle Elastosis Scale evaluation.

Subject ID	EV 1	EV 2	EV 3	Average	EV 1	EV 2	EV 3	Average
Subject 1	6	5	6	6	4	3	4	4
Subject 2	3	2	2	2	2	1	1	1
Subject 3	4	4	5	4	3	3	4	3
Subject 4	5	5	5	5	4	4	4	4
Subject 5	6	6	6	6	3	3	3	3
Subject 6	7	6	7	7	4	5	4	4
Subject 7[a]	6	5	6	6	6	5	6	6
	Average of active group			5	Average of active group			3

[a]Control subject.

more effective compared to therapies that solely incorporate either one of them.

Furthermore, the study device's practicality increases the comfort for both the operator and patient. The hands-free, self-adhesive applicator provides a significant enhancement in terms of safety and comfort aspects. Operator fatigue is eliminated, and the patients underwent the facial rejuvenation procedures without recovery time or impact to their daily routine. Adverse effects common with some facial rejuvenation therapies such as hyperpigmentation, dyschromia, hematoma and nerve damage did not occur in this study.[22–24]

This clinical study was limited due to the low subject count. Despite that the all-female patient set is also a limiting factor, it must be considered that real-world data have shown women as the vast majority seeking facial cosmetic and rejuvenation procedures.[25] This may be driven by an increased interest and diversity of the patients motivated to undergo treatments aimed at regenerating the body in a more natural way, as opposed to augmentative and

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TABLE 2 Global aesthetic improvement score evaluation.

Subject ID	EV 1	EV 2	EV 3	Average
Subject 1	2	2	2	2
Subject 2	3	3	2	3
Subject 3	1	1	1	1
Subject 4	1	2	2	2
Subject 5	3	3	3	3
Subject 6	3	3	2	3
Subject 7[a]	1	0	0	0

[a]Control subject.

invasive procedures, which provide a different less appealing result. Nonetheless, further in-vivo investigations of this method are warranted to expound the clinical aspects.[26]

5 | CONCLUSION

The cumulative effects of reduced collagen and elastin, lead to an overall loss of skin elasticity, resulting in skin laxity or loose skin. This is especially noticeable in the face, where laxity leads to sagging, the formation of wrinkles and fine lines, and a generally "aged" appearance. This study histologically evaluated facial skin tissue samples for collagen and elastin content pre and post-treatment with the simultaneous HIFES and RF noninvasive. Results demonstrated increased levels of dermal collagen and elastin at the 3-month follow-up.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The study was conducted in line with Good Clinical Practice and the Decalaration of Helsinki. The study protocol and informed consent form were approved by the Advarra IRB institutional review board on the 3rd of May 2022 (reference number Pro00063141). Prior to enrolment, subjects provided voluntary written informed consent (date and signature). Subjects further provided voluntary written consent (date and signature) to have photographs of their face taken for the study records, publication and marketing purposes.

CONSENT STATEMENT

Prior to enrolment, subjects provided voluntary written informed consent (date and signature) to have photographs of their face taken for the study records and publication.

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How to cite this article: Goldberg DJ, Lal K. Treatment with synchronized radiofrequency and facial muscle stimulation: Histologic analysis of human skin for changes in collagen and elastin fibers. *J Cosmet Dermatol*. 2024;00:1-9. doi:10.1111/jocd.16273

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EMFACE in Asian Population

Evaluating the Efficacy and Safety of Combined Synchronized Radiofrequency and HIFES Stimulation for Facial Lifting in Asians: A 6-Month Analysis

Woraphong Manuskiatti, M.D.

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Presented at the American Society for Laser Medicine and Surgery (ASLMS), Baltimore, Maryland, April 11, 2024

Highlights

- 15 Asian subjects (skin types III-V) received four 20-min treatments (EMFACE Forehead & Cheeks)
- Results were evaluated using 2D and 3D imaging techniques, cutometer as well as patients' self-assessments at 1M, 3M and 6M post-treatment
- Results show significant lifting of the eyebrow, forehead, and cheeks up to 2.14 mm
- Results were maintained for up to 6 months



93%

Patients Reported Improvement at 6 Months

81%

Skin Firmness Improvement at 6 Months

Results after 4 treatments show a significant lifting effect

Baseline



1 Month



Long-Term Efficacy of EMFACE

Evaluation of Synchronized RF and HIFES Efficacy One Year Post-Treatment: A Case Study

Yael Halaas, M.D., FACS

New York, NY, USA

Highlights

- 3 subjects (skin types II-IV) evaluated
  1 year after their original series of four 20-min treatments
  (EMFACE Forehead & Cheeks)
- 3D camera imaging was used to calculate volumetric changes
- All 3 patients maintained post-treatment volume changes at 1Y FU



68%

Maintained Improvement of the Original 3-Month Follow-up

+2.6 ml

Volume Improvement in Upper Cheeks Compared to Baseline

-2.7 ml

Volume Reduction in Jowls Compared to Baseline

Patients Demonstrated Volume Shift Towards Upper Cheek One Year Post-Treatment







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CORE TO FLOOR STUDY: IMPROVED QUALITY OF LIFE IN ELDERLY PATIENTS

THE IMPROVEMENT IN QUALITY OF LIFE AND CORE MUSCLE STRENGTH IN ELDERLY PATIENTS BY SIMULTANEOUS APPLICATION OF HIFEM WITH SYNCHRONIZED RADIOFREQUENCY: PRELIMINARY DATA

Diane Duncan, M.D., FACS[1], David Kent, MD[2], Evan Appelbaum, M.D., FAAC[3]

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Presented at American Society of Dermatologic Surgery Annual Meeting 2022, Denver, CO

HIGHLIGHTS

- 39 patients were enrolled (60–79 years, 19.7–33.9 kg/m^2, skin type I-V)
- Four HIFEM+RF procedures (once a week over abdomen) and six standalone HIFEM procedures (twice a week over pelvic floor) were administered
- The biofeedback pressure measurements showed an increase in core muscle strength by **+55.9%** at a 3-month follow-up
- The average reduction in waist circumference was **-2.4 cm**
- Three months after the last treatment, on average:
  - **92%** of patients were satisfied with the treatment outcomes
  - **90%** of patients could get up easily from a sedentary position
  - **90%** of patients felt that their core is stronger
  - **84%** of patients felt improvement in overall body movement
  - **76%** of patients were able to perform their daily activities better

RESULTS

BASELINE

AFTER THE 4TH TREATMENT

1 MONTH FOLLOW-UP



Digital photographs of a 60 years old female patient with a BMI of 22 kg/m^2 at baseline (left), after the 4th treatment (middle), and 1-month follow-up (right; -2.54 cm in circumference). At 3 months the core muscle strength increased by +55.6%. Courtesy of: David Kent, M.D.

BASELINE

AFTER THE 4TH TREATMENT

1 MONTH FOLLOW-UP



Digital photographs of a 65 years old female patient with a BMI of 21.1 kg/m^2 at baseline (left), after the 4th treatment (middle), and 1-month follow-up (right; -2.06 cm in circumference). At 1 month, the core muscle strength increased by +21.4%. Courtesy of: Diane Duncan, M.D.

CORE TO FLOOR STUDY: IMPROVED QUALITY OF LIFE IN FEMALES AFTER CHILDBIRTH

THE IMPROVEMENT OF QUALITY OF LIFE IN FEMALE PATIENTS AFTER CHILDBIRTH BY HIFEM WITH SYNCHRONIZED RADIOFREQUENCY FOR THE STRENGTHENING OF CORE MUSCLES

Julene B. Samuels, M.D., FACS[1], Andrea Pezzella, M.D., FACOG, FPMRS[2], JD. McCoy, NMD[3],

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Accepted at American Society of Dermatologic Surgery Annual Meeting 2022, Denver, CO

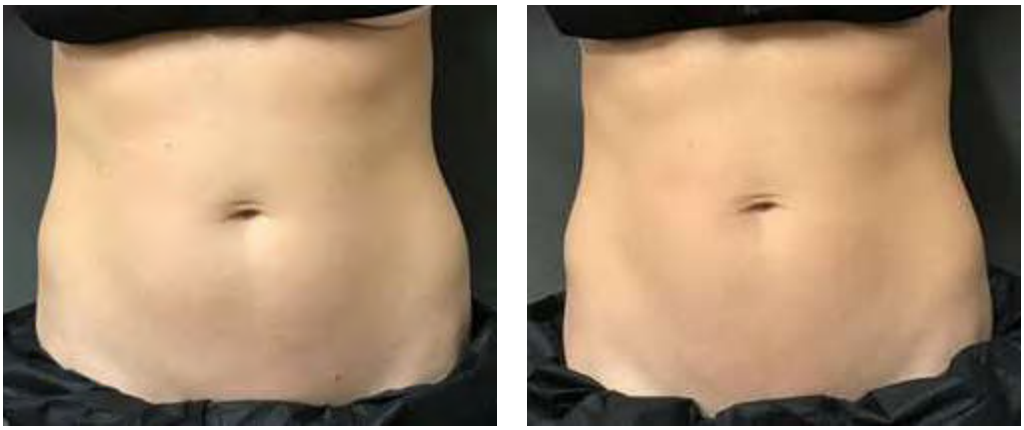
HIGHLIGHTS

- 36 women (27-44 years, 19.4-34.5 kg/m^2, skin type I-V) within the time frame of 6-60 months after their last childbirth, were enrolled
- Four HIFEM+RF procedures (once a week over abdomen) and six standalone HIFEM procedures (twice a week over pelvic floor) were administered
- The biofeedback pressure measurements showed an increased core muscle strength by **+25.2%** at a 1-month follow-up
- The average reduction in waist circumference was **-4.6 cm**
- Three months after the last treatment, on average:
    - **97%** of patients were satisfied with the results and would recommend the treatment to friends and relatives
    - **100%** of the patients reported that they could perform their daily activities without any issues and spend quality time with their children after the treatments
    - **97%** of the patients reported that their core feels stronger, and they could get up easily from a lying down position after the treatments
    - **94%** of the patients reported that their pelvic floor feels stronger after the treatments
    - **85%** of the patients reported that they feel more youthful after the treatments
    - **70%** of the patients reported an improvement in their back discomfort after the treatments

RESULTS

BASELINE

3 MONTH FOLLOW-UP

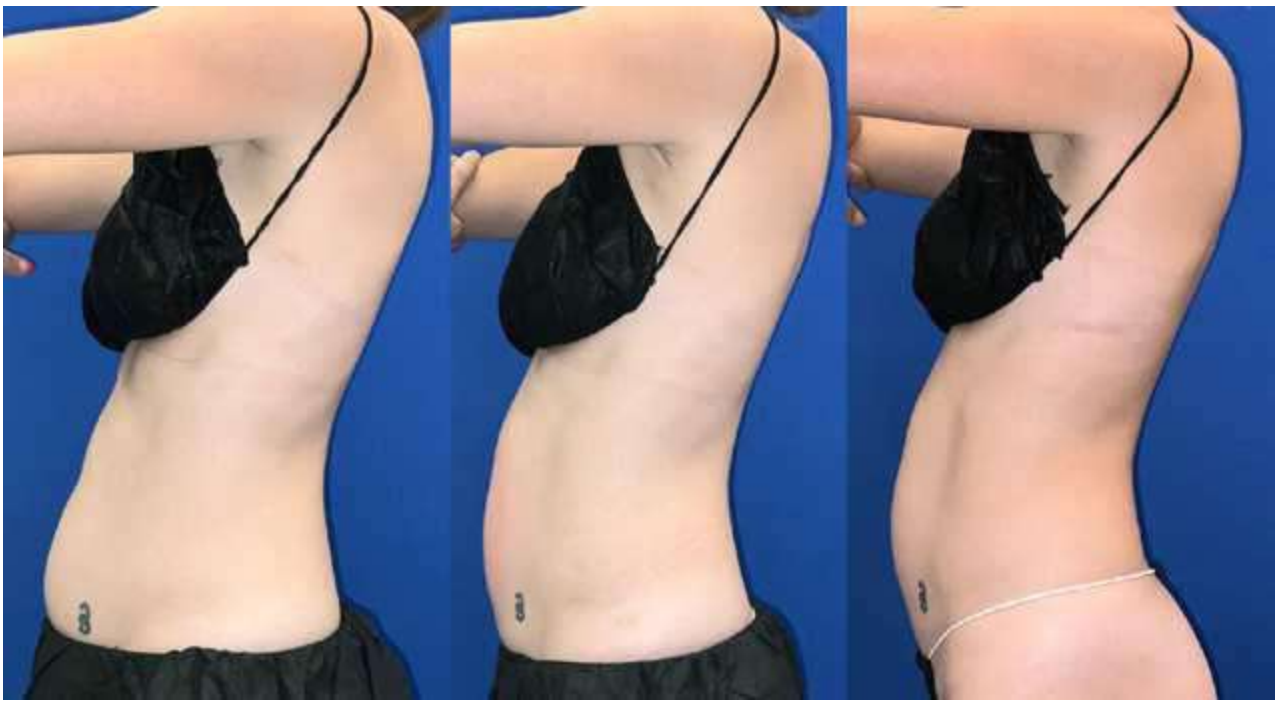


Digital photographs of a 33 years old female patient with a BMI of 24.2 kg/m^2 at baseline (left) and 3-month follow-up (right). At 3 months, the core muscle strength increased by 53.9%.
Courtesy of: Julene B. Samuels, M.D., FACS

BASELINE

AFTER THE TREATMENTS

1 MONTH FOLLOW-UP



Digital photographs of a 38 years old female patient with a BMI of 20.8 kg/m^2 at baseline (left), after the treatments (middle), and at the 3-month follow-up (right, waist reduction of -6.3 cm).
At 3 months, the core muscle strength increased by 21.5%.
Courtesy of: JD. McCoy, NMD

CORE TO FLOOR STUDY: IMPROVEMENT IN THE SYMPTOMS OF SARCOPENIA

CONSECUTIVE APPLICATION OF STANDALONE HIFEM PROCEDURE WITH SIMULTANEOUS APPLICATION OF HIFEM AND SYNCHRONIZED RADIOFREQUENCY FOR SARCOPENIA TREATMENT

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Presented at the 5th Annual Global Aesthetics Conference 2022, Miami, FL

HIGHLIGHTS

- **Sarcopenia** is a gradual age-related loss of muscle mass and strength that can occur as early as at the age of 30. The loss of muscle mass and strength contribute to a decline in muscle function, reduced mobility, and decreased quality of life.
- **30 patients** were enrolled (26-75 years old, BMI of 19.7-33.5 kg/m^2)
- Four HIFEM+RF procedures (once a week over abdomen) and six standalone HIFEM procedures (twice a week over pelvic floor) were administered
- Evaluation included **five standard tests to assess sarcopenia**, InBody and DEXA measurements
- Patients over 60 years old (n=16) showed **balance** improvement by **30.3%**, and comfortable **gait speed** (the time one takes to walk a specified distance comfortably) improved by **45.6%**
- **The TUG (Time Up & Go) test** showed a 20.6% improvement for patients above 60 years (p-value<0.001). TUG, which correlates to balance and fall risk, is the amount of time to stand up from a chair, walk a certain distance at your normal pace, turn and walk back to the chair, and sit down again.

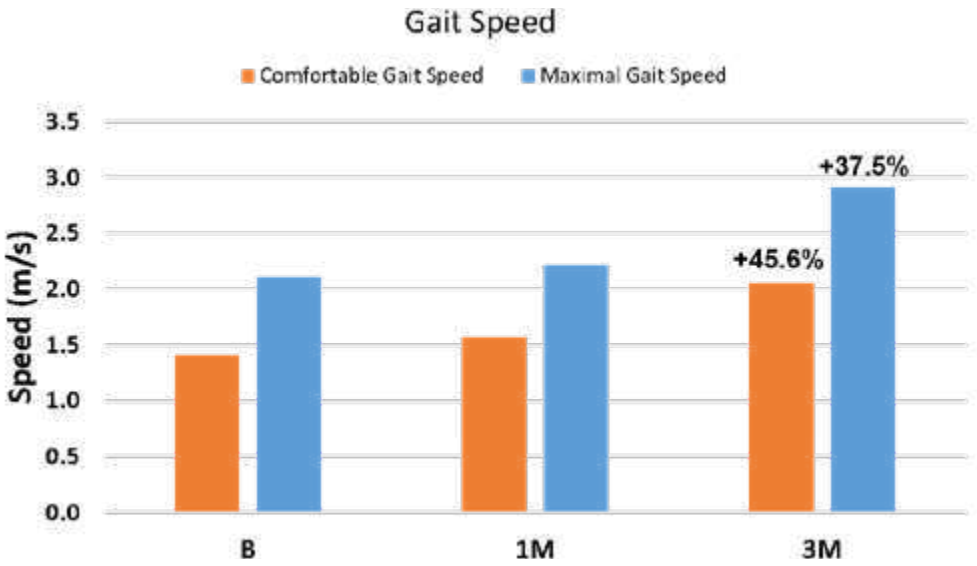


Figure 1: The bar chart shows the gradual improvement in comfortable and maximal gait speed in elderly subjects from baseline (B), peaking at 3 months.

HIFEM™ TECHNOLOGY CAN IMPROVE QUALITY OF LIFE OF INCONTINENT PATIENTS

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Background:
Urinary incontinence (UI) represents one of the most prevalent female intimate health issues negatively affecting a patients' quality of life (QoL). Current treatment options require a combination of pelvic floor muscles exercising and intravaginal electrostimulation or drug treatment with side effects. Women seek non-invasive and efficacious solutions for UI.

Aim:
The aim was to investigate the effect of High-Intensity Focused Electromagnetic technology (HIFEM) on QoL of incontinent patients.

Methods:
30 women (mean age 53.05 years) with stress, urge and mixed type of UI took part in the pilot study. They attended 6 therapies scheduled 2x a week. QoL was assessed through King's Health Questionnaire (KHQ). The number of used hygienic pads and patients' subjective feedback were recorded. Data was collected pre-, post-treatment, during 3- and 6-month follow-ups. KHQ scores were statistically evaluated through t-test ($p<0.05$). Number of used hygienic pads and patients' subjective feedback were evaluated through frequency of occurence.

Results:
After 6 treatments, 95 % of treated patients improved their QoL according to the scores of the KHQ. These results were maintained during the 3- and 6-month follow-ups. 67 % of the treated patients reduced or totally eliminated the use of hygienic pads in day-to-day life. 100 % of patients reported better awareness of the pelvic floor muscles.

Conclusion:
Results suggest that the tested device significantly improves the QoL of incontinent patients.

Keywords:
urinary incontinence, hygienic pads, King's Health Questionnaire, Quality of Life, HIFEM technology, FDA

1. INTRODUCTION

1.1. Definition of the problem

Urinary incontinence (UI) is involuntary loss of urine, which objectively and subjectively represents a social, psychological and hygienic problem. It is estimated that 1 in every 4 women aged between 30 and 59 years has experienced a problem with urinary leakage. Estimation of worldwide UI prevalence is around 40 % of the female population. However, a vast majority of the patients is reluctant to discuss this intimate issue with their medical doctors. National Association for Incontinence (NAFC) reports that 4.5 out of 10 patients do not seek help. (1, 11)

1.2. Types of urinary incontinence

UI can be divided into 3 types according to its' etiology. Clinical symptoms of stress urinary incontinence (SUI) usually involve involuntary leakage of urine when events with increased intra-abdominal pressure are performed (e.g. coughing, sneezing, laughing and lifting). The cause of SUI is due to a loss of support of urethra and deconditioned pelvic floor musculature (PFM), which is usually a consequence of damage to the pelvic support structures. SUI is strongly associated with vaginal childbirth and menopausal hormonal changes (1). The second UI type is associated with a strong desire to void and pathological contractions of the bladder, so-called urge incontinence. Urge incontinence is a neuromuscular dysfunction commonly treated with pharmacotherapy. Urge incontinence is usually a symptom of an underlying problem (e.g. diabetes mellitus). The third UI type is mixed urinary incontinence (MUI) and involves a combination of the SUI and urge incontinence symptoms (1).

1.3 Treatment options for urinary incontinence

The choice of treatment for UI depends on its' type and severity. In the case of SUI, treatment options range from pelvic floor muscle exercising, intravaginal electrotherapy up to surgical intervention. Surgical intervention is recommended usually only in severe cases of SUI, whereas drug treatment of urge incontinence is common. A vast majority of patients use hygienic pads and their quantity depends on the severity of UI and leakage episodes (13, 15).

2. HIFEM technology

2.1. Mechanism of Action

High-intensity Focused Electromagnetic technology (HIFEM) triggers intense pelvic floor muscles contractions by targeting neuromuscular tissue and inducing electric currents. Electric currents depolarize neurons resulting in concentric contractions and lift up of all pelvic floor muscles. Key effectiveness is based on focused electromagnetic energy, in-depth penetration, and stimulation of the entire pelvic floor area. The HIFEM technology brings deep PFM stimulation and restoration of the neuromuscular control. The HIFEM passes non-invasively through pelvic floor area. Therefore, it represents a non-invasive solution for incontinent patients, who remain fully clothed during the therapy (2-10, 12, 14-19).

- *H0: Course of treatments with the HIFEM technology will not lead to any improvement of QoL of incontinent patients.*
- *H1: Course of treatments with the HIFEM technology will lead to significant improvement of QoL of incontinent patients.*
- *H2: Course of treatments with the HIFEM technology will reduce the use of hygienic pads.*

3.2. Patients

All patients were enrolled in the pilot study after their voluntarily agreement and signed written informed consent. 30 women aged 36-76 years (mean age 53.05±11.74) with SUI, urge and MUI were included in the pilot study. UI resulted out as a consequence of vaginal childbirth, hormonal changes (menopause) or through obesity.

3.3. Exclusion criteria

Women with pacemakers, metal implants, blood coagulation disorders, tumors, fever, menstruation and pregnant women were not included in this study.

3.4. HIFEM technology tested device

In this pilot study, FDA approved device for female urinary incontinence treatment BTL EMSELLA (BTL EMSELLA, BTL Industries Inc.) was used.

3.5. Methods

The effect of HIFEM technology on QoL of incontinent

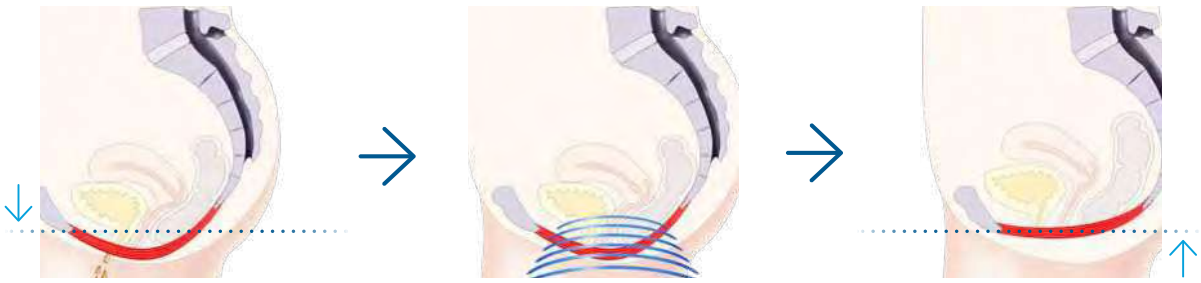


Figure 1: HIFEM™ technology

3. MATERIALS AND METHODS

3.1. Aim

The aim was to investigate the effect of HIFEM technology on QoL of incontinent patients. For such purpose 3 hypotheses were created:

patients was assessed through the King's Health Questionnaire (KHQ). The KHQ detects incontinence impact in patients' socio-emotional life and activities of daily living (ADL) (13). Additionally, number of used hygienic pads and patients' subjective feedback were recorded.

4. COLLECTING THE DATA

4.1. Data collection

Data was collected pre-, post-treatment and during 3- and 6-month follow-ups.

4.2. BTL EMSELLA therapy protocol

All women absolved 6 therapies scheduled 2x a week. Therapy was performed by medical personnel, who positioned the patient into a comfortable sitting position, feet on the floor, hip, knee and ankle joints perpendicularly flexed. 30-minute duration for each treatment session.

4.3. Therapy parameters

Frequency range 20-30 Hz with trapezoid intensity modulation was used to achieve gradual motor unit recruitment. Relative intensity (in %) was gradually increased from patients' motor up to above the motor threshold.

4.4. Statistics

Data of 30 patients was collected and statistically evaluated. During the course of treatment no adverse events occurred and therapy was well tolerated. KHQ scores were calculated and tested for statistical significance by means of Student's t-test at statistical significance level $p<0.05$. Improvements were compared as follows: between pre-treatment and post-treatment data, between pre-treatment and 3- and 6-month follow-ups data. Patients' reports of the number of used hygienic pads were calculated as statistical frequency of occurrence between pre-treatment and post-treatment data, between pre-treatment and 3- and 6-month follow-ups data. Additionally, subjective feedback was collected from all patients. The frequency of answer occurrence was calculated.

5. RESULTS

5.1 The King's Health Questionnaire results

The KHQ has two parts – Part 1 reports about the general health perception; Part 2 reports about the incontinence impact on the patient's life. The scores are calculated separately. The research results proved/disproved following hypotheses and are discussed in the text below:

- *H0: Course of treatments with the HIFEM technology will not lead to any improvement of QoL of incontinent patients.*

H0 hypothesis disproved. All patients (n=30) have improved their QoL after a course of treatment with the HIFEM technology, which was proved by H1.

- *H1: Course of treatments with the HIFEM technology will lead to significant improvement of QoL of incontinent patients.*

H1 hypothesis proved. After the course of treatment with the HIFEM technology, 95 % of treated patients reported improvement in the QoL according to the scores of the KHQ. Before the therapy, the average score of the KHQ-Part 1 was 82.08 points. After course of treatment with the HIFEM technology, the average score of the KHQ-Part 1 was 51.67 points, which decreased to 45.42 points during 3 months and to 48.33 points during 6 months, respectively. These improvements are demonstrated as 37%, 42% and 38% levels of improvement in general health perception ($p<0.05$).

Before the therapy, the average score of the KHQ-Part 2 was 187.50 points. After a course of treatment with the HIFEM technology the average score of the KHQ-Part 1 was 103.75 points, which decreased to 81.11 points during 3 months and further to 74.44 points during 6 months, respectively. These improvements are demonstrated as 37%, 55% and 57% levels of improvement ($p<0.05$).

5.2 The results of use of hygienic pads

- *H2: Course of treatments with the HIFEM technology will reduce the use of hygienic pads.*

H2 hypothesis proved. In this study, 12 patients wore hygienic pads during the day and night. Before the therapy, average number of used hygienic pads was 1.1 pad per day and night. After a course of treatment, 67 % (n=9) of treated patients totally eliminated or decreased the average number of used hygienic pads decreased to 0.45 pad per day and night. The results were maintained during the 3- and 6-month follow-ups.

5.3. The patients' subjective evaluation of the therapy

Additionally, patients answered the question *'What is the major difference you noticed after the BTL EMSELLA therapies?'*

40 % of patients reported that they are able to perform proper contraction of the PFM; 28 % of patients were able to contract PFM selectively; 20 % of patients reported better muscle firmness and 12 % of patients reported that the period between micturition is longer. Additionally, all patients (n=30; 100 %) reported better awareness of pelvic floor muscles.

Parameter	KHQ Part 1	KHQ part 2
KHQ score pre-treatment (Mean±SD)	**82.08±29.53**	**187.50±119.24**
KHQ score post-treatment (Mean±SD)	**51.67±33.62**	**103.75±83.07**
KHQ score, 3-month follow-up, (Mean±SD)	**45.42±26.83**	**81.11±64.94**
KHQ score, 6-month follow-up, (Mean±SD)	**48.33±23.66**	**74.44±58.03**
Level of improvement, Pre/Post-treatment	**37%**	**37%**
Level of improvement, Pre-treatment/3-month follow up	**42%**	**55%**
Level of improvement, Pre-treatment/6-month follow- up	**38%**	**57%**

Figure 2: Results of the KHQ score
SD = standard deviation

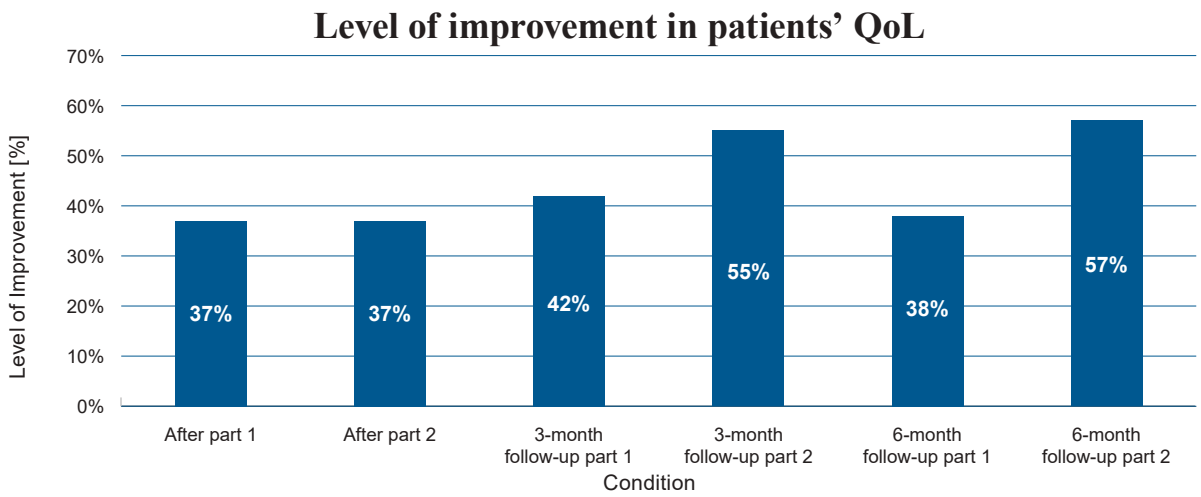


Figure 3: Level of improvement in the patients´ QoL according to the KHQ scores

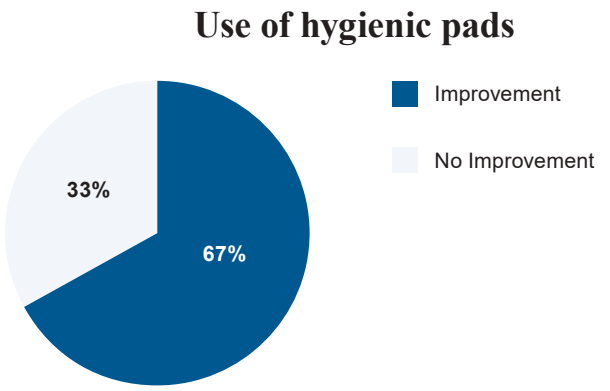


Figure 4: Use of hygienic pads

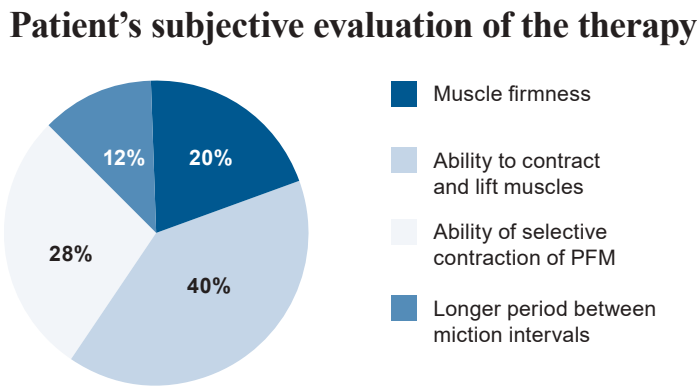


Figure 5: Patients subjective evaluation of the therapy

6. DISCUSSION

To regain continence, regular pelvic floor muscles exercising is required. Normally, 300-500 contractions of the pelvic floor muscles should be performed to begin to develop a new motor pattern, whereas 3,000-5,000 contractions are required to erase and correct poor motor pattern. During 1 session using HIFEM technology, thousands PFM contractions are performed. This method is extremely important to PFM re-education as the patients are not able to perform this high-repetition rate pattern due to PFM weakness and an inability to consistently contract this muscle group. After 6 therapeutic sessions with HIFEM therapy, patients developed the new motor pattern needed to better control pelvic floor muscles and also regained muscle strength and continence control (3-9, 12-16).

7. CONCLUSION

UI represents a significant psycho-socio-economical healthcare problem that has a major negative impact on today's modern lifestyles. The majority of patients are not satisfied with the current treatment methods offered, which include surgical intervention, drug therapy, pelvic floor muscles exercising (Kegel) or minimally invasive intravaginal procedures. This latest research, as well as, previous studies suggest that HIFEM technology leads to significant improvement in QoL of incontinent patients, maintains a patient's privacy all while avoiding more invasive approaches.

8. CONFLICT OF INTEREST

Authors declare that no conflict of interest exists.

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HIFEM® TECHNOLOGY – A NEW PERSPECTIVE IN TREATMENT OF STRESS URINARY INCONTINENCE

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Presented at 38th American Society for Laser Medicine and Surgery Annual Conference on "Energy-based Medicine and Science", April 11-15, 2018

ABSTRACT

Background:
Stress urinary incontinence (SUI) is a prevalent condition among women and negatively affects their quality of life (QoL). The aim of the study was to assess the effect of High-Intensity Focused Electromagnetic (HIFEM) technology in the treatment of SUI.

Study Design/Materials and Method:
30 women from two clinics (United States, Bulgaria) with SUI were delivered a treatment course with HIFEM technology. Patients attended 6 therapies scheduled 2x a week. QoL was assessed through King's Health Questionnaire (KHQ). Data was collected pre-, post-treatment, at 3- and 6-month follow-up visits. All patients reported the number of used hygienic pads. Scores of questionnaires were calculated and statistically evaluated through t-test ($p<0.001$). Number of used hygienic pads was calculated as average.

Results:
Course of the treatment with the HIFEM technology significantly improved QoL of all women. This was demonstrated as 77% level of improvement in incontinence impact according to the KHQ scores during 6-month follow-up. 95% of patients decreased the use of hygienic pads to 2.0 pads per day and night post-treatment. 71% of patients significantly decreased the use of hygienic pads to 1.33 pad per day and night during 6-month follow-up.

Conclusion:
Results suggest that HIFEM technology is an efficacious therapy for treatment of SUI.

1. INTRODUCTION

1.1. Medical background of stress urinary incontinence

Urinary incontinence (UI) is a prevalent condition manifested as involuntary urine leakage and represents a hygienic and a social problem. UI may be classified as stress, urge or mixed type. The stress urinary incontinence (SUI) is usually caused by stress applied over the pelvic floor muscles and bladder, where in the common case this stress is led by coughing, sneezing, laughing or physical activities. In women, the reasons for SUI include events such as condition after childbirth, hormonal changes in menopause, physical inactivity, obesity, aging or pelvic organ prolapse (cystocele, rectocele, uterine prolapse). Further concomitant effects in sexually active women, such as decreased gratification during intercourse and other related dysfunctions, could also be present. In the majority of the cases, patients with SUI, evaluate their QoL as affected in a negative manner due to their condition.

1.2. Current treatment methods for SUI

Therapeutic approaches for SUI depend on the underlying causes of the problem and involve medications, pelvic floor muscles exercising and re-education or surgical interventions.

1.2.1. Drug treatment

The most used drugs for SUI are Alpha-adrenergic agonists, anticholinergic and antispasmodic agents. However, their effectiveness is not always certain and wide range of side-effects are present.

1.2.2. Pelvic floor muscles exercising

The Agency for Healthcare Research and Quality suggests rehabilitation techniques such as vaginal weight training or Kegel exercises with a biofeedback. Vaginal weight training involves intravaginal approach pertruding patient's privacy and comfort. On the other hand, non-invasive Kegel exercises are hard to perform in patients with SUI, because of the decreased level of the pelvic floor muscle awareness and inability to contract these muscles selectively. The conventional muscle strengthening and re-education include intravaginal electrostimulation, which is discomfortable for the patient and risk of tissue burn is still present.

1.2.3. Pelvic floor surgery

The surgical intervention involves procedure that increases urethral outlet resistance – Transobturator Vaginal Tape (TVT). TVT are in the common case carried out only after all other approaches took place.

1.2.4. Behavioral changes

Benefits for improving the condition, to some extent, may be provided by behavior changes such as quitting smoking, avoiding alcohol, losing excess weight, avoiding physical activities (e.g. jumping, running etc.).

As discussed, the SUI condition is prevalent and finding more effective and non-invasive method addressing SUI appears essential for the female intimate health.

2. HIFEM technology

2.1. Mechanism of action

HIFEM technology uses high-intensity focused electromagnetic fields, which are generated by a coil positioned inside a chair applicator. High-intensity focused electromagnetic fields interact and depolarize the pelvic floor motoneurons. Fields deliver focused electromagnetic energy into whole pelvic floor area, which results in selective and supramaximal pelvic floor muscles contractions.

2.2. Supramaximal pelvic floor muscles contractions

For its myostimulative effect, the method is used in pelvic floor muscles strengthening in order to adress the SUI. The patient affected by the SUI is not able to contract pelvic floor muscles selectively, therefore HIFEM represents targeted pelvic floor muscles strengthening and re-education. As the electromagnetic field passes through human body non-invasively, therapy is delivered to the patients whilst they remain fully clothed throughout the whole therapy.



Figure 1: HIFEM technology mechanism of action

3. MATERIALS AND METHODS

3.1. Aim

The aim of the study was to assess the effect of HIFEM technology in treatment of SUI.

3.2 Subjects

30 women with SUI (classified as SUI type 0-2a), aged between 38-75 years (Mean±SD= 57.99±10.36) were voluntarily comprised in this study.

3.3. Inclusion and exclusion criteria

Women with diagnosed SUI were the main inclusion criterium. Women with pacemakers, metal implants, blood circulation disorders, tumors, fever, menstruation and pregnant women were excluded from the study.

3.4. BTL EMSELLA™ device

FDA approved device for female urinary incontinence treatment BTL EMSELLA (BTL EMSELLA, BTL Industries Inc.) was used in the course of treatments.

3.5. Used methods

The effect of the course of treatments with the HIFEM technology was assessed through the King's Health Questionnaire (KHQ). The questionnaire detects the general health condition and incontinence impact in day-to-day life. Additionally, patients were asked to report the number of used hygienic pads.

4. DATA COLLECTION

4.1. Data collection

Data was collected pre- and post-treatment. The long-term effect was evaluated during 3- and 6-month follow-ups.

4.2 Therapy protocol

All patients were delivered the course of treatments consisted of 6 therapies scheduled 2x a week. Patients sat on the BTL EMSELLA chair, feet on the ground, hips, knees and ankles were perpendicularly flexed. Throughout the procedure all patients remain fully clothed. Therapy duration was set to 28 minutes; frequency range between 20-30 Hz with trapezoid intensity modulation were used to achieve gradual motor unit recruitment. Intensity (in %) was set according to patients' feedback and comfort to trigger supramaximal pelvic floor muscle contractions.

4.3. Statistical evaluation

Data of 30 patients was collected and statistically evaluated. During the course of treatment no adverse events occured and therapy was well-tolerated by all patients. KHQ scores were calculated through Student's t-test ($p<0.001$). Results were compared between pre- and post-treatment, pre-treatment and 3- and 6-month follow-ups data. Patients' reports about the use of hygienic pads were calculated as average pre-, post-treatment, and 3- and 6-month follow-ups.

5. RESULTS

5.1. The KHQ results

The results are discussed in the text below (See Figure 2).

5.1.1. KHQ Part 1 results

Pre-treatment average score of the KHQ-Part 1 was 97.78±34.67 points. Post-treatment average score of the KHQ-Part 1 decreased to 65.83±29.31 points. During 3-month follow-up average score further decreased to 59.72±30.25 points, and to 55.00±35.12 points during 6-month follow-up. These scores are calculated as 28%, 34% and 39% levels of improvement of general health perception ($p<0.001$).

5.1.2. KHQ Part 2 results

Pre-treatment average score of the KHQ-Part 2 was 284.91±147.08 points. Post-treatment average score of the KHQ-Part 1 decreased to 110.19±115.66 points. During 3-month follow-up the score further decreased to 85.00±119.72 points. During 6-month follow-up the score decreased to 71.02±122.34 points. These scores are calculated as 61%, 70% and 77% levels of improvement of decreased negative incontinence impact ($p<0.001$).

Parameter	KHQ Part 1	KHQ part 2
Score pre-treatment (Mean±SD)	**97.78±34.67**	**284.91±147.08**
Score post-treatment (Mean±SD)	**65.83±29.31**	**110.19±115.66**
Score 3-month follow-up (Mean±SD)	**59.72±30.25**	**85.00±119.72**
Score 6-month follow-up (Mean±SD)	**55.00±35.12**	**71.02±122.34**
Level of improvement pre- and post-treatment (%)	**28%**	**61%**
Level of improvement pre-treatment and 3-month follow-up (%)	**34%**	**70%**
Level of improvement pre-treatment and 6-month follow-up (%)	**39%**	**77%**

Figure 2: Results of the KHQ score
Legend: SD = standard deviation; KHQ = King's Health Questionnaire

5.2. Hygienic pads results

Pre-treatment, patients used on average 2.43 hygienic pads per day and night. Post-treatment, all patients decreased the use to 2 pads per day and night. All patients completed 3- and 6-month follow-up. During 3-month follow-up patients used 1.4 pad per day and night. During 6-month follow-up patients used 1.33 pad per day and night (See Figure 3).

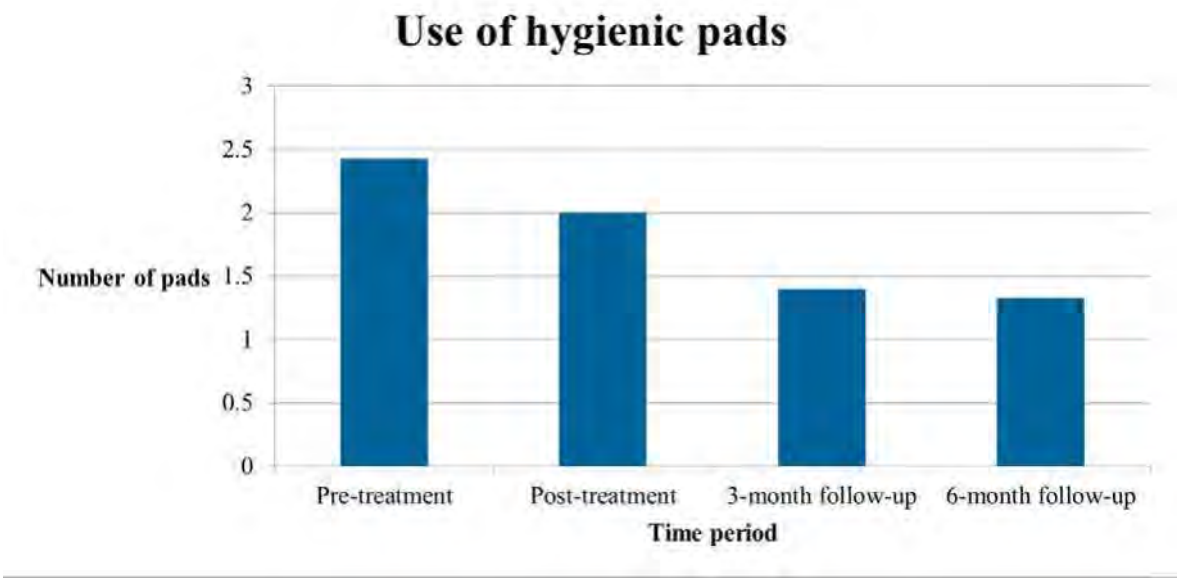


Figure 3: Use of hygienic pads

6. DISCUSSION

Prior to undergoing the treatment, the majority of patients described, according to the answers in the KHQ, that their overall health condition is affected and role, social and emotional limitations are present, which signifies affected QoL. Improvement in patients' QoL was observed in short- and long-term period according to the results of KHQ and decreased use of hygienic pads. Evidence for effectiveness of this method in addressing SUI is available from previous research. These results are explained through intense stimulative effect of the entire pelvic floor area by using high-intensity focused electromagnetic fields.

7. CONCLUSION

The results obtained from this study suggest the HIFEM technology is promising approach for pelvic floor muscles stimulation that further improves the quality of life among SUI patients.

8. CONFLICT OF INTEREST

Authors declare that no conflict of interest exists.

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HIFEM TECHNOLOGY – THE NON-INVASIVE TREATMENT OF URINARY INCONTINENCE

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Presented at 38th American Society for Laser Medicine and Surgery Annual Conference on "Energy-based Medicine and Science", April 11-15, 2018

Background:
Urinary incontinence (UI) has a prevalence of 30-40% in post-partum and menopausal women. Women may be reluctant to discuss UI with their healthcare providers as well as the degree to which it may negatively impact their quality of life (QoL) for numerous reasons including embarrassment and fear associated with treatment options. Women consistently express the preferred desire to address UI in a non-surgical and discreet manner. This study sought to report on results of a novel non-surgical treatment that may provide an affordable and discrete solution to this common problem.

Study Design/Materials and Method:
This is a retrospective two-site study investigating the effectiveness of the treatment using quantified data, as well as the impact on QoL of incontinent women using a High-Intensity Focused Electromagnetic Technology (HIFEM) device.
20 women, 45 to 77 years (58.63±SD=9.86) who presented with urinary incontinence including stress, urge and mixed UI, were included in a pilot study. All patients completed a total of 6 treatments performed twice weekly for 3 consecutive weeks. Twenty patients completed King's Health Questionnaire (KHQ) pre- and post-treatment. The same data was collected during 3 and 6-month follow-up as well. Additionally, patients reported the frequency of urinary leakage episodes and pad usage. Scores of the KHQ were calculated and statistically evaluated through t-test ($p<0.05$). The frequency of urinary leakage episodes and number of used hygienic pads were calculated through frequency of occurrence.

Results:
Treatment with the HIFEM technology significantly improved QoL scores in all patients. There was a 60% improvement in both parts of the KHQ which were maintained through the 6-month follow-up ($p<0.05$). Nearly 75% of patients significantly decreased urinary leakage or achieved total dryness and maintained these results through follow-up. Pre-treatment, 16 patients used on average 2 hygienic pads per 24 hour period. During 3-month follow-up, 6 patients used 0.6 pads, 10 patients were completely dry. Twenty patients completed the 6-month follow-up, with eleven patients completely dry and 5 patients used 0.5 pads per 24 hour period. The vast majority of the patients decreased usage of hygienic pads to a minimum or totally eliminated usage.

Conclusion:
Results suggest that HIFEM technology significantly improves the QoL and reduces UI in post-partum and menopausal female patients who present with all types of UI. This study confirms that further investigation is warranted.

1. INTRODUCTION

1.1. Prevalence of urinary incontinence

Urinary incontinence (UI) is defined as an involuntary loss of urine affecting mainly the female population. It is estimated that prevalence in young women is 20-30%, in mid-aged women 30-40%, whereas in elderly women prevalence rises to 50%.

1.2. Cause and consequence of urinary incontinence

The pelvic floor muscles (PFM) support pelvic organs and help control continence. Due to physiological changes such as body aging, childbirth or hormonal changes, PFM decondition and do not provide sufficient support for pelvic organs and continence control. This leads to PFM dysfunction with direct consequence toward incontinence.

1.3. Types of urinary incontinence and treatment options

There are 3 types of UI comprising stress urinary incontinence (SUI), urge incontinence and mixed urinary incontinence (MUI).

1.3.1. Stress urinary incontinence

Clinical symptoms of SUI are associated with involuntary urinary leakage during increased intra-abdominal pressure (e.g. coughing, sneezing, laughing, lifting etc.). The cause of the SUI is discoordination among weakened PFM and increased abdominal pressure. SUI is often associated with vaginal delivery, studies have shown 78.5 % of women were unable to contract pelvic floor muscles properly 1 year after delivery. SUI occurs as well in the post-menopausal period. Weakening of the pelvic floor muscles is caused by reduced estrogen level. In the case of SUI, treatment options range from PFM exercising (e.g. Kegel), intravaginal electrotherapy, hormone therapy, in addition to surgical intervention. Surgical intervention is recommended usually only in severe cases of SUI and a vast majority of female patients are reluctant to undergo surgical intervention, especially due to adverse events such as bleeding, development of urge incontinence due to inability to empty the bladder fully, and decreased sexual satisfaction.

1.3.2. Urge urinary incontinence

Urge incontinence is associated with an intense desire to void, during which the bladder pathologically contracts without cause. It is a neuromuscular dysfunction, typically representing a symptom of an underlying disease (e.g. diabetes mellitus). Traditional treatment of urge incontinence usually involves drug treatment.

1.3.3. Mixed urinary incontinence

A third type – mixed urinary incontinence (MUI) usually includes combination of stress and urge incontinence symptoms. MUI treatments usually involve a combination of PFM exercises and drug therapies. (1, 2)

1.4. Disadvantages of current treatment options

There are disadvantages to current treatment methods. In the case of SUI, one of the main problems in the case of pelvic floor exercising is the patients' inability to selectively contract their pelvic floor muscles and to maintain an exercise routine. Kegel exercises are the most common form of PFM excercise, yet lack proof of efficiency as an effective solution. Another available treatment is intravaginal electrotherapy and biofeedback. A common concern of intravaginal electrostimulation is the electrode placements, which can cause patient's discomfort. Adverse events can include bleeding, localized pain or irritation of the tissue under the patch electrodes. Surgical interventions are invasive and can also include adverse events. Pharmacotherapy is non-targeted, and side-effects such as dry mouth, bowel constipation and indigestion can occur. Today, both physicians and their patients seek a solution that meets the criteria of providing an effective clinical outcome via a non-invasive modality.

2. HIFEM technology

2.1. HIFEM technology Mechanism of Action

High-intensity Focused Electromagnetic technology (HIFEM) uses focused electromagnetic field with its intensity measured in Tesla. Such an intense electromagnetic field passes non-invasively through the pelvic floor area, interacts with PFM motoneurons and subsequently triggers supramaximal PFM contractions due to the action potential.

2.2. Supramaximal pelvic floor muscle contractions

Maximal voluntary contraction (MVC) is the greatest



Figure 1: HIFEM technology mechanism of action

amount of tension that could be developed and held physiologically by the PFM for a few seconds. Contractions with a tension higher than MVC are defined as supramaximal. HIFEM triggers supramaximal PFM contractions and holds them for multiple seconds (see Figure 2). Supramaximal contractions are independent of brain function and target directly the motoneurons in the pelvic floor area. This phenomenon cannot normally be achieved by voluntary muscle action (e.g. Kegel exercise).

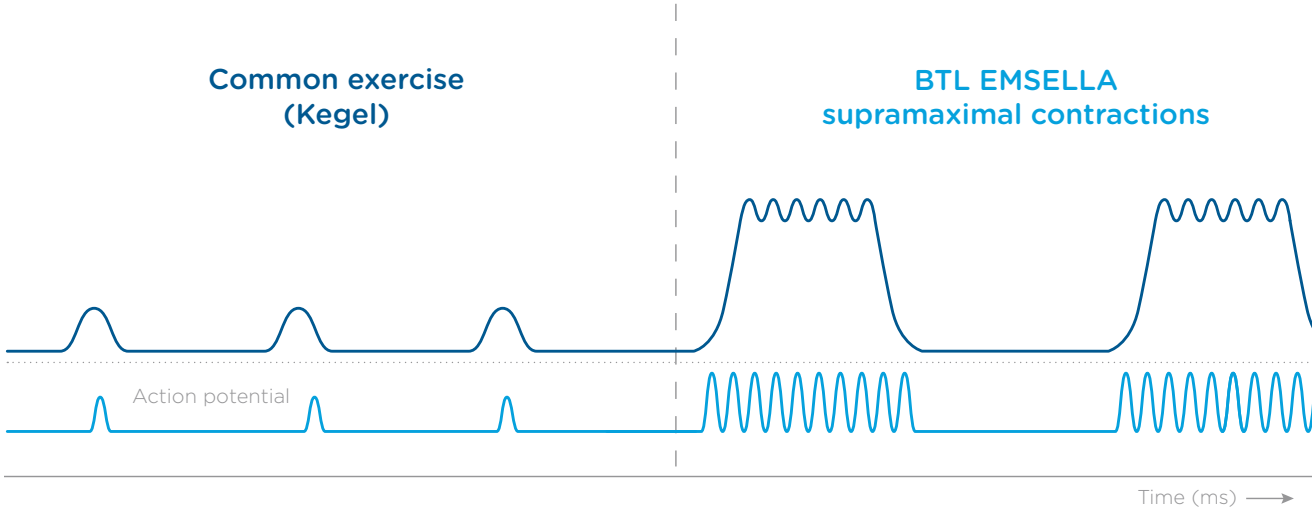


Figure 2: Supramaximal contractions caused by BTL EMSELLA device

2.3. HIFEM muscle re-education

During a normal treatment session, thousands of PFM supramaximal contractions are performed. This is extremely important to PFM re-education, as the patients are typically not able to perform these high-repetition rate contractions due to PFM weakness.

3. MATERIALS AND METHODS

3.1. Aim

We aimed to investigate the impact of the course of treatment on QoL of incontinent patients through a device based on HIFEM technology.

3.2. Hypotheses

We hypothesized as follows:

H0: Course of treatments with the HIFEM technology will not improve the QoL of incontinent patients.

H1: Course of treatments with the HIFEM technology will significantly improve the QoL of incontinent patients.

H2: Course of treatments with the HIFEM technology will reduce the frequency of urine leakage episodes and number of used hygienic pads.

3.3. Subjects

Subjects were enrolled after their voluntary agreement and signed written informed consent. 20 women, 45 to 77 years (58.63±SD=9.86) with SUI, urge incontinence and MUI were included in the pilot study. According to the patients' history, UI was a consequence of vaginal delivery, sudden weight change, obesity or post-menopausal status.

3.4. BTL EMSELLA device

FDA cleared device for female urinary incontinence treatment. BTL EMSELLA (BTL Industries, Marlborough, MA) was used in the course of treatments.

3.5. Inclusion and exclusion criteria

The main inclusion criteria were female patients with diagnosed stress, urge or mixed UI. Women with pacemakers, metal implants, blood circulation disorders, tumors, fever, menstruation and pregnant women were excluded from the study.

3.6. Used methods

The effect of the course of treatments with the HIFEM technology on the QoL of incontinent patients was assessed through the King's Health Questionnaire (KHQ). KHQ helps to observe the general health condition and incontinence

impact on day-to-day life. Additional questions inquired regarding the number of used hygienic pads and frequency of urinary leakage.

4. DATA COLLECTION

4.1. Data collection

Data was collected pre- and post-treatment. The long-term effect was tested during 3- and 6-month follow-ups.

4.2. Therapy protocol

All patients completed 6 therapy sessions, 2 times per week. Patients were instructed by medical personnel to sit on the BTL EMSELLA chair with their spine straight, feet on the ground, hips, knees and ankles perpendicularly flexed. Throughout the procedure patients remained fully clothed. Therapy duration was set at 28 minutes; frequency range between 20-30 Hz with trapezoid intensity modulation were used to achieve gradual motor unit recruitment. Intensity (in %) was set according to patients' feedback and comfort to achieve supramaximal PFM contractions.

4.3. Statistical evaluation

Data from the 20 patients were collected and statistically evaluated. During the course of treatment, no adverse events were recorded, and therapy was well-tolerated by all patients. KHQ scores were calculated ($p<0.05$). Results were compared between pre- and post-treatment, pre-treatment and 3- and 6-month follow-up data. Patients reported frequency of the urinary leakage episodes and use of hygienic pads, this data was then calculated as frequency of occurrence between pre- and post-treatment, as well as between pre-treatment and 3- and 6-month follow-ups.

5. RESULTS

5.1. The KHQ results

The results and hypotheses are discussed in the text below.

- H0: *Course of treatments with the HIFEM technology will not improve the QoL of incontinent patients.*

H0 hypothesis disproved. All patients (n=20) experienced improved QoL after course of treatment with the HIFEM technology, which was further proved by H1.

- H1: *Course of treatments with the HIFEM technology will improve the QoL of incontinent patients.*

H1 hypothesis proven.

5.1.1. KHQ Part 1 results

Pre-treatment average score of the KHQ-Part 1 was 92.22 points. Post-treatment average score of the KHQ-Part 1 decreased to 66.94 points. During 3-month follow-up, average score further decreased to 60.56 points, and to 37.04 points during 6-month follow-up, respectively. These scores are demonstrated as 50%, 51% and 60% levels of improvement in general health perception ($p<0.05$).

5.1.2. KHQ Part 2 results

Pre-treatment average score of the KHQ-Part 2 was 194.63 points. Post-treatment average score of the KHQ-Part 1 decreased to 154.44 points and was maintained during 3-month follow-up. During 6-month follow-up the score decreased to 90.59 points. These scores are demonstrated as 53%, 61% and 60% levels of improvement ($p<0.05$).

Parameter	KHQ Part 1	KHQ part 2
Score pre-treatment (Mean±SD)	**92.22±36.09**	**194.63±107.34**
Score post-treatment (Mean±SD)	**66.94±34.91**	**154.44±104.23**
Score 3-month follow-up (Mean±SD)	**60.56±27.68**	**154.63±87.42**
Score 6-month follow-up (Mean±SD)	**37.04±34.44**	**90.59±90.79**
Level of improvement pre- and post-treatment (%)	**50%**	**53%**
Level of improvement pre-treatment and 3-month follow-up (%)	**51%**	**61%**
Level of improvement pre-treatment and 6-month follow-up (%)	**60%**	**60%**

Figure 3: Results of the KHQ score
Legend: SD = standard deviation; KHQ = King's Health Questionnaire

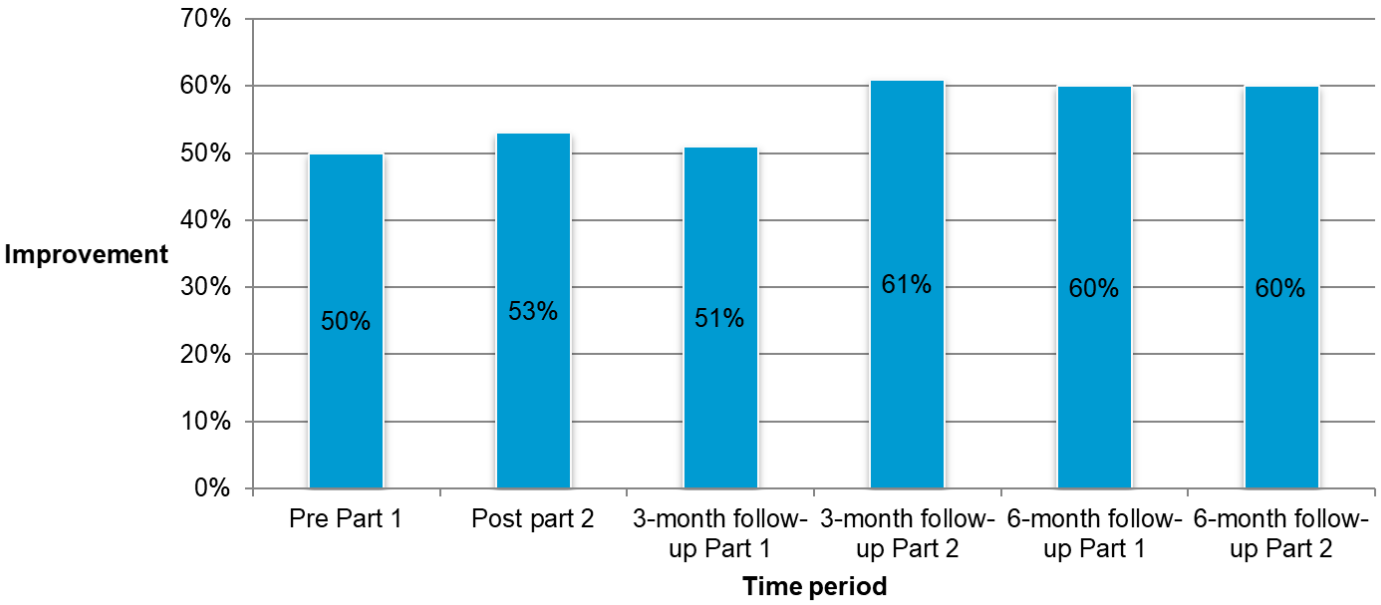


Figure 4: Level of improvement in the patients' QoL according to the KHQ scores

5.2. The urinary leakage episodes and use of hygienic pads

- *H2: Course of treatments with the HIFEM technology will reduce the frequency of urine leakage episodes and number of used hygienic pads.*

H2 hypothesis proven.

5.2.1. Urinary leakage episodes

Pre-treatment, all patients reported urine leakage in different severity (See Figure 6). Post-treatment, in 7 patients urine leakage episodes decreased to 1-3x a day, whereas 4 patients were completely dry. During 3-month follow-up, 7 patients decreased episodes to 1-3x a day, and another 11 patients to 1-3x a week, while 5 patients were completely dry. 20 patients completed the 6-month follow-up. 3 patients decreased episodes to 1x a day, whereas 12 decreased episodes to 1-3x a week, while 5 patients were completely dry.

5.2.2. Use of hygienic pads

Pre-treatment, 16 patients used on average 2 hygienic pads per 24 hour period. Post-treatment, 12 patients decreased use to 0.8 pad per 24 hour period, whereas 4 patients were completely dry. During 3-month follow-up, 6 patients were using 0.5-0.6 pad per 24 hour period, whereas 10 patients remained completely dry. At the 6-month follow-up, 5 patients were using 0.5-0.6 pad per 24 hour period, whereas 11 patients remained completely dry (See Figure 6).

Frequency/number of patients	5x a day	3x a day	2x a day	1x a day	3x a week	2x a week	1x a week	Never
Pre-treatment	3	3	2	4	2	2	4	0
Post-treatment	2	2	2	3	3	3	1	4
3-month follow-up	0	0	2	2	2	5	4	5
6-month follow-up	0	0	0	3	2	4	6	5

Figure 5: Frequency of leakage episodes

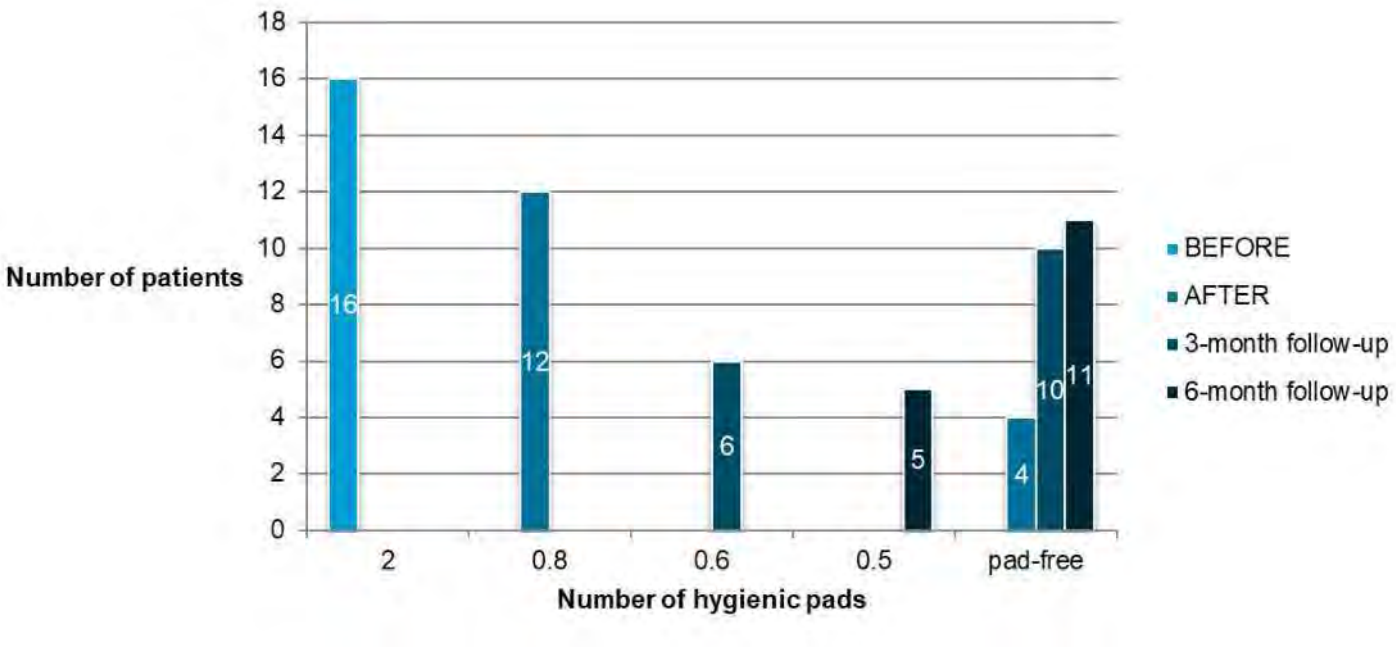


Figure 6: Use of hygienic pads

6. DISCUSSION

The results suggest that the treatment with HIFEM technology significantly decreases the negative impact incontinence has in patients' day-to-day life. This improvement was observed in both short- and long-term results by KHQ, decreased frequency of urine leakage episodes, and decreased use of hygienic pads. The results are explained through myostimulation of the pelvic floor area by using high-intensity focused electromagnetic fields therapy, which trigger supramaximal PFM contractions. A single session brings thousands of PFM contractions. This is extremely important in PFM re-education helping the patients to regain PFM strength and bladder control.

7. CONCLUSION

UI represents an important healthcare problem with high prevalence and negative impact on patients' QoL. As most of the patients are not suitable for current treatment methods, this study as well as previous research, suggest that UI can be treated non-invasively through HIFEM technology.

8. LIMITATIONS

The limitations of this study were the small number of patients and absence of a control group, such that a control randomized study with larger number of patients should take place in further research.

9. CONFLICT OF INTEREST

Authors declare that no conflict of interest exists.

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Journal of Women's Health Care

Hlavinka et al., J Women's Health Care 2019, 8:1
DOI: 10.4172/2167-0420.1000455

Research Article Open Access

The Use of HIFEM Technology in the Treatment of Pelvic Floor Muscles as a Cause of Female Sexual Dysfunction: A Multi-Center Pilot Study

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Received date: November 14, 2018; **Accepted date:** March 2, 2019; **Published date:** March 11, 2019

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Abstract

Introduction: Pelvic Floor Muscles (PFM) supports the pelvic floor organs, control continence and is crucial for adequate genital arousal and attainment of an orgasm. Due to the aging process, post-delivery condition or menopause, the PFM weaken. Therefore, they do not provide sufficient support to pelvic organs, bladder control, and they may negatively affect intimate satisfaction.

Aim: We aimed to investigate the High-Intensity Focused Electromagnetic (HIFEM) technology for strengthening of PFM in women with impeded sexual functioning.

Methods: 30 women (average age 36.41 ± 5.62) with limited arousal, ability to achieve orgasm and painful intercourse participated in the study. Patients underwent 6 treatments (28 minutes each) scheduled twice a week. Standardized Female Sexual Function Index (FSFI) questionnaire was used pre-, post-treatment, and at the 3-month follow-up visit. FSFI scores were statistically evaluated through student´s t-test (α=0.05). Subsequently, Pearson correlation coefficient was calculated for sections arousal/lubrication, lubrication/orgasm, orgasm/satisfaction, and pain/desire.

Results: The average total FSFI score significantly ($p<0.001$) increased from 20.06 ± 6.55 to 30.69 ± 7.55 post-treatment and to 30.29 ± 7.37 during the 3-month follow-up. A significant improvement was observed in all FSFI sections. The most significant change at the 3-month follow-up was observed in desire (76%), satisfaction (76%) and orgasm (60%) items. The overall FSFI score was improved in 93% (n=28) of patients post-treatment. All patients (n=30; 100%) showed improvement during the 3-month follow-up.

Conclusion: Our initial experience shows that HIFEM technology is a promising method in addressing women's decreased sexual satisfaction through the strengthening of PFM.

Keywords: HIFEM; FSFI; Sexual dysfunction; Pelvic floor muscles; Myostimulation

Introduction

Healthy sexual function is an essential component of life. Sexual dysfunction can, therefore, have a negative impact on female well-being [1]. Female Sexual Dysfunction (FSD) is age-dependent and highly prevalent in premenopausal and menopausal women. Available studies report on the prevalence of sexual dysfunction in the female population to be ranging between 25% and 63% [2-9]. The incidence in women younger than 25 years was found to be approximately 20% while in women aged 55-74 years the incidence was up to 80% [7].

Pelvic floor and its functioning are closely linked to a healthy female sexual cycle. It is formed by several pelvic muscles which support the pelvic organs and maintain their normal function by keeping these organs in their anatomical position. Pelvic Floor Muscles (PFM) also play an important role in pregnancy parturition, attainment of orgasm [10-12] and are responsible for adequate genital arousal [13,14]. Firmer muscle tone adds intensity to the muscle contractions during orgasm and enables a woman to identify, isolate, and command PFM [14].

Any insult to the pelvic floor can potentially lead to denervation of the female erectile tissues followed with sexual dysfunction [10,15,16]. The main cause for the development of Pelvic Floor Disorder (PFD) occurs when the PFM and connective tissue weaken. Weak or deconditioned muscles may provide insufficient activity necessary for vaginal friction or blood flow, and thus inhibit orgasmic potential [13,14]. Therefore the initial approach for the treatment of PFD and FSD is to start with the strengthening of PFM [11,12,17].

Non-invasive addressing of PFM should be the first treatment option prior to any surgical intervention. A novel approach for non-invasive targeting of PFM is a treatment based on High-Intensity Focused Electromagnetic (HIFEM) technology. The HIFEM technology triggers intense PFM contractions by depolarizing motoneurons and inducing electric currents in the pelvic floor area. The focused electromagnetic energy penetrates into the depth of up to 10 cm into the pelvic floor area where it induces supramaximal and brain-independent contractions at high repetition rates [18,19].

Due to the intense repetitive muscle stimulation combined with the vasodilating effect of electromagnetic fields and restoration of the muscle tonus, we assume that HIFEM may positively affect female intimate health and sexual functions. The subject of the study is a device based on HIFEM technology (BTL EMSELLA, BTL Industries Inc., Boston MA), which is FDA cleared for strengthening of pelvic floor muscles in the treatment of female urinary incontinence (UI).

Previous studies [18,19] investigating the HIFEM technology for UI proved that female patients reported a significant decrease in incontinence symptoms as well as a reduction in usage of incontinence pads. As the HIFEM technology impacts the PFM due to its myostimulatory effect, it could be beneficial not only in bladder control, but also in improvement of intimate life and sexual functions.

We aimed to investigate the myostimulatory effect of a High-Intensity Focused Electromagnetic (HIFEM) technology on PFM in women who reported impeded sexual functioning. We hypothesized that HIFEM can strengthen PFM and as a consequence will improve the quality of intimate life.

Method

Study design

This was a retrospective single-arm study of the patients who had been admitted to our department between 2017-2018. A total of 30 female patients (average age 36.41 ± 5.62) were enrolled. The inclusion criteria included initial impeded sexual functioning through limited arousal, impaired ability to achieve orgasm and increased intercourse pain.

Patients with pregnancy, metal implants, tumor, blood coagulation disorder, and vaginal infectious disease were excluded from the study. Before the treatments, all subjects received informed consent about the treatment procedure and signed written consent.

The patients received a treatment procedure applied to the PFM using the BTL EMSELLA device (BTL Industries Inc., Boston MA) based on HIFEM technology. The device consists of a control unit and a cable connecting the unit to a chair with an in-built circular coil. During the treatment, the device generates a focused electromagnetic field with intensities of up to 2.5 T and penetrating into depths of up to 10 cm.

The treatment protocol consisted of six treatments scheduled twice a week with a single treatment lasting for 28 minutes. The treatment protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki adopted by the General Assembly of the World Medical Association (1997-2000) and by Convention on Human Rights and Biomedicine of Council of Europe (1997).

During the treatment, patients were seated on the chair and remained fully clothed. Prior to the therapy, each of the patients received verbal instructions about the course of the therapy and about the principles of supramaximal PFM contractions. Contractions are supposed to help them to identify, isolate and command their PFM.

After the instructions, the patients were positioned on the chair and the optimal position for inducing muscle contractions was identified. Then, the therapy was initiated with low intensity which was continuously adjusted during the treatment in accordance with patient tolerance threshold [18,19].

Data collection

As a standard part of the treatment procedure, all of the 30 enrolled subjects reported patient's feedback in the form of the standardized Female Sexual Function Index (FSFI) questionnaire pre- and post-treatment, and during the 3-month follow-up visit [20]. Obtained feedback was statistically analyzed by comparing the pre- and post-intervention patients' condition.

A normal data distribution has been assumed (0.05 significance level), therefore the parametric Student t-test was used to calculate the significance of FSFI full-scale scores and individual FSFI sections. Furthermore, Pearson correlation coefficient was calculated for paired items Arousal/Lubrication, Lubrication/Orgasm, Orgasm/Satisfaction, and Pain/Desire. Bonferroni correction was applied according to the number of the carried tests. Finally, the percentage of improved patients was calculated according to the FSFI full-scale score.

Results

The analysis of the pre-treatment FSFI questionnaires showed an average full-scale score of 20.06 ± 6.55, which according to the predefined cut-point of 26.5 indicates sexual dysfunction. The post-treatment average full-scale score significantly increased to 30.69 ± 7.55 and was maintained during 3-month follow-up at the level of 30.29 ± 7.37 ($p<0.001$). The total FSFI scores are shown in Figure 1.

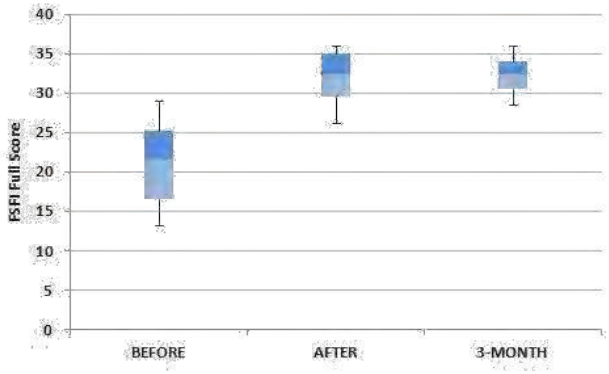


Figure 1: Changes in FSFI full score in treated patients. Data are visualized in box plots; blue rectangles contain 50% of data (interquartile range). Whiskers indicate the variability of the results.

The spread of whiskers and Interquartile Range (IQR) in the Figure 1 indicate the variability of the results obtained at the baseline. Before the treatments, there were patients with substantially lower FSFI score indicating moderate sexual function issues.

After the procedure consisting of 6 treatments the score significantly increased and also the variability of the data was reduced. At the 3-month follow-up, these results sustained showing no shift in the average, while the patient's scores were spread closely around the median.

The level of average improvement in the FSFI score, expressed in percentage, was on average 53% after the last treatment and was maintained at 51% ($p<0.001$) during the 3-month follow-up. Immediately after the 6th treatment, an improvement in FSFI score was

observed in 28 (93%) subjects. During the follow-up appointment, all of the patients (n=30, 100%) reached a certain degree of improvement.

The improvement was observed in all individual sections of the FSFI questionnaire, while the most prominent average improvement was seen in sexual satisfaction (+76%), in sexual desire (+76%) and in orgasm (+60%). The scores of individual sections can be seen in Table 1.

Timing	FSFI Score Mean ± SD (Median)					
	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain
Before	2.79 ± 0.63 (3.00)	3.41 ± 1.2 0 (3.30)	3.42 ± 1.89 (1.60)	3.20 ± 1.33 (3.20)	3.01 ± 1.05 (2.80)	4.24 ± 1.72 (4.80)
After	4.91 ± 0.93 (5.40)	5.24 ± 1.4 3 (5.70)	4.92 ± 1.7 3 (6.00)	5.13 ± 1.50 (6.00)	5.29 ± 1.25 (5.60)	5.20 ± 1.46 (5.60)
3-Month follow-up	4.87 ± 0.82 (4.80)	5.24 ± 1.4 2 (5.40)	4.68 ± 1.5 7 (4.80)	5.06 ± 1.46 (5.60)	5.20 ± 1.38 (5.60)	5.25 ± 1.48 (6.00)

Table 1: A detailed description of FSFI items scores.

The analysis of relationships between the changes in different sections was performed to assess potential correlations. A highly significant correlation was observed in the case of before-after and before-follow-up for pairs Lubrication/Orgasm and Orgasm/Satisfaction (Table 2). The strong correlation ranged between 0.65-0.71 and was statistically significant. The correlation between the differences in Arousal and Lubrication score showed to be insignificant with weak correlation coefficients. No correlation was found between the pair Pain/Desire. Calculated correlations for investigated pairs can be found in Table 2.

Correlations				
Timeline	**Arousal and Lubrication**	**Lubrication and Orgasm**	**Orgasm and Satisfaction**	**Pain and Desire**
Difference before-after	r=0.34	r=0.65*	r=0.68*	r=0.13
Difference before-follow-up	r=0.15	r=0.66*	r=0.71*	r=0.03

Table 2: Statistically significant (Bonferroni correction, alpha less than 0.006) correlations are marked with an asterisk symbol (*).

Discussion

The results suggest that the treatment procedure with HIFEM technology leads to significant improvement of the intimate life in female patients with FSD. The improvement was observed in all sections of the FSFI questionnaire in both short- and long-term results.

We contribute this improvement to well-structured intense pelvic floor workout delivered through HIFEM, induced supramaximal PFM contractions consequently accompanied with increased blood flow [21]. The correlation analysis showed a positive strong relationship between lubrication and orgasm, indicating that the treatments improved the vaginal lubrication of the patients which then was reflected in the increased ability to achieve orgasm.

Similarly, strong correlation was found between the orgasm and satisfaction. This indicates that the patients were able to reach orgasm easily which was logically reflected in their sexual satisfaction. On contrary, no correlation was found between the pain and the desire even though it could be assumed that reduced pain would lead to increased sexual desire [22,23].

The importance of PFM strength during intercourse was described by the previous authors [10-17,24-28] whose results correlate with our findings. Piassarolli et al. concluded that increased EMG activity of PFM muscles was associated with the improvement in all FSFI items [25]. Kanter et al. found that among sexually active women (n=370), a strong pelvic floor was associated with higher scores in the FSFI orgasm domain [11].

The results of our study correlate with this research as the most significant improvement was observed in sexual satisfaction, desire, and orgasm domain. Similar results were reported by Martinez et al. where women with stronger PFM scored higher in the domains: desire, excitement, orgasm and also reported higher levels of FSFI score [26]. Authors also reported a moderate correlation between PFM strength and sexual satisfaction as well as between lubrication and PFM strength. This was also supported by findings from Lowenstein et al. stating that women with strong or moderately strong PFM scored significantly higher on the FSFI orgasmic and arousal domains than women with weak PFM [27].

The duration of PFM contraction was correlated with FSFI orgasmic domain and sexual arousal. Their finding suggests that both the orgasm and arousal function are related to better PFM function. Furthermore, Aydın et al. reported that Vaginal Electrostimulation (VES) treatment leads to improvement of total FSFI score, particularly in arousal, desire, orgasm, and satisfaction sections [29]. They observed no significant changes in pain or lubrication domains. Comparing to our study, pain was the part where we observed the lowest level of improvement. However, we would like to highlight that the VES includes an intravaginal probe which is not comfortable for the patient, while the BTL Emsella procedure is performed fully clothed and without a need of intravaginal probe.

The results show the importance of PFM in female intimate life and the fact, that they can be addressed in a non-invasive way. Both sexual dysfunctions and incontinence are strongly affected by the actual condition of PFM and as such, these two indications frequently accompany each other. The treatments are ideal for improving both aspects in patients with weak pelvic muscles and are thus an alternative not only to women who experience leakage issues but also to those who feel their sexual satisfaction is impeded and could be improved.

Conclusion

The obtained FSFI data showed a significant improvement in female sexual function through the strengthening of PFM. The data suggest BTL EMSELLA as an effective tool for improving patient's sexual life satisfaction and as such, it is a promising alternative to existing treatment options and deserves further investigation.

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Safety and Efficacy of a Non-Invasive High-Intensity Focused Electromagnetic Field (HIFEM) Device for Treatment of Urinary Incontinence and Enhancement of Quality of Life

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Background and Objectives: Urinary incontinence is a common and distressing condition which interferes with everyday life. Patients frequently experience discomfort related to urine leakage and the subsequent need to use absorbent pads. Since the continence mechanism is primarily maintained by a proper function of pelvic floor muscles (PFM), many treatment methods focused on strengthening of the PFM have been introduced in the past. The aim of this study was to evaluate the safety and efficacy of a high-intensity focused electromagnetic technology (HIFEM) for treatment of urinary incontinence with emphasis on effects on prospective patients' quality of life.
Study Design/Materials and Methods: The study followed an institutional review board approved protocol. A total of 75 women (55.45 ± 12.80 years, 1.85 ± 1.28 deliveries) who showed symptoms of stress, urge, or mixed urinary incontinence were enrolled. They received six HIFEM treatments (2 per week) in duration of 28 minutes. Outcomes were evaluated after the sixth treatment and at the 3-month follow-up. The primary outcome was to assess changes in urinary incontinence by the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and changes in the number of absorbent pads used per day. The secondary outcome was subjective evaluation of the therapy and self-reported changes in quality of life. The statistical analysis was conducted by paired *T-test* and Pearson correlation coefficient ($\alpha = 0.05$).
Results: After the sixth session, 61 out of 75 patients (81.33%) reported significant reduction of their symptoms. The average improvement of 49.93% in ICIQ-SF score was observed after the sixth treatment, which further increased to 64.42% at the follow-up (both $P < 0.001$). Individually, the highest level of improvement was reached in patients suffering from mixed urinary incontinence (69.90%). The reduction of absorbent pads averaged 43.80% after the sixth treatment and 53.68% at 3 months (both $P < 0.001$), while almost 70% of patients (30 out of 43) reported decreased number of used pads. At the follow-up, a highly significant medium correlation ($r = 0.53$, $P < 0.001$) was found between the ICIQ-SF score improvement and the reduction in pad usage. A substantial decrease in the frequency of urine leakage triggers was documented. Patients reported no pain, downtime or adverse events, and also reported additional beneficial effects of the therapy such as increased sexual desire and better urination control.
Conclusions: This study demonstrated that HIFEM technology is able to safely and effectively treat a wide range of patients suffering from urinary incontinence. After six treatments, an improvement in ICIQ-SF score and reduction in absorbent pads usage was observed. Based on subjective evaluation, these changes positively influenced quality of life. Lasers Surg. Med.
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Key words: HIFEM; pelvic floor muscles; urinary incontinence

INTRODUCTION

Urinary incontinence (UI), defined as involuntary loss of urine [1], is a chronic condition which may negatively affect quality of life (QOL). On the basis of its etiology and

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Accepted 6 May 2019
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.23106

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pathophysiology it is classified as stress (SUI), urge (UUI), or mixed UI (MUI) [2,3]. According to clinical research performed on large population samples, its prevalence was reported to range between 25 and 45% [4,5] with the maximum prevalence quoted as high as 69% [6]. These studies revealed that severity of UI symptoms increases predominantly with age. In addition, it was found that factors such as higher body mass index [7,8], parity [8], or certain medical comorbidities [9] are also associated with development of UI. In general, the continence mechanism is mainly associated with the pelvic floor muscles (PFM). The pelvic skeletal muscles support the urinary bladder, the urethra and other pelvic organs, and thus maintain the optimal urethral closure pressure that prevents involuntary urine leakage. In the case of PFM weakening, the pressure balance is disrupted, which results in UI [10,11].

Due to the discomfort and inconvenience caused by urinary leakage, incontinent patients are usually forced to change their habits regarding their personal and professional lives, which may result in lowered self-esteem. Depression and anxiety [12], negative impact on work productivity [13,14] or diminished sexual desire and activity [15,16] are only a few of the possible negative consequences. To deal with urine leakage, patients often use absorbent pads. However, this passive solution does not improve UI symptoms, and despite the advancements in pad composition, there is still a risk of incontinence-associated dermatitis (IAD), an inflammation of the skin caused by the contact of urine with the perineal or perigenital skin [17].

To increase patient's QOL by reduction of UI severity, many treatment methods addressing the weakened PFM via its (in)voluntary stimulation were introduced in the past. These include Kegel exercise [18], PFM exercise with bio-feedback [19], surface and intravaginal electrotherapy [20] and vaginal cones [21], however all these techniques have limitations. It was estimated that 30–50% of women do not perform PFM exercises properly [22,23], and a common issue with electrical stimulation is the discomfort caused by the electrodes and the risk of vaginal infections [20]. Finally, there has been documented evidence which supports non-invasive laser therapy as an effective modality for SUI treatment by the thermal action on the vaginal mucosa, resulting in the rejuvenation processes [24–28].

Most recently, the high-intensity focused electromagnetic (HIFEM) stimulation [29] was introduced to address UI problems. HIFEM technology is known for its simulative effects. The electromagnetic field passes in a non-invasive manner through the neuromuscular tissue where induced electric currents depolarize neuronal cells and initiate action potentials [30]. The high frequency of action potentials then leads to selective and supramaximal muscle contractions. Previous research documented that HIFEM technology is able to affect abdominal [31] as well as pelvic muscles, and that it may be an effective and safe modality in treatment of UI [32,33]. However, further investigation should result in more evidence of how strengthening of PFM by HIFEM reduces UI symptoms and improves QOL.

The aim of this study was to objectively evaluate the efficacy and safety of the BTL EMSELLA device (BTL Industries Inc., Boston, MA) utilizing the HIFEM technology for treatment of UI with emphasis on QOL enhancement.

MATERIALS AND METHODS

Subjects and Ethics

This was a prospective, multi-center, open-label, single-arm study. In total, 75 adult women (mean age 55.45 ± 12.80 years, on average 1.85 ± 1.28 deliveries) who showed signs of SUI, UUI, or MUI urinary incontinence and who expressed an interest in treatment were enrolled (for detailed patient data see Tables 1 and 2). The study was conducted in accordance with ethical standards stated in the Belmont Report and followed the institutional review board approved protocol. At study initiation, patients underwent medical history examination, and a written informed consent was obtained from all participants. Enrolled subjects were required to meet the following inclusion criteria: age > 22 years, weight ≤ 300 lb, were medically stable, and reported UI symptoms. The exclusion criteria were: metal implants, a recent surgical procedure, pregnancy, any concurrent treatment of UI and any contraindication listed in the investigational device manual. Additionally, women with childbearing potential underwent a urine pregnancy test prior to their enrollment and were asked to re-test prior any subsequent exposure.

Investigational Device

BTL EMSELLA generates a rapidly changing, high-intensity focused electromagnetic field that interacts with the motor neurons and triggers stimulation and toning of PFM. The electromagnetic field is produced by a flat spiral-shaped coil which reaches intensities up to 2.5 T. The coil is situated within a seat of a uniquely designed

TABLE 1. Demographic Data of Enrolled Subjects

Data	*N* (%)
Age	
22–29	2 (2.67)
30–39	6 (8.00)
40–49	14 (18.67)
50–59	22 (29.33)
60–69	21 (28.00)
70–79	8 (10.67)
80–89	2 (2.67)
Diagnosis	
SUI	37 (49.33)
MUI	30 (40.00)
UUI	8 (10.67)
Deliveries	
Vaginal	104 (74.82)
C-section	35 (25.18)

MUI, mixed urinary incontinence; SUI, stress urinary incontinence; UUI, urge urinary incontinence.

TABLE 2. Number of Deliveries

	Patients	
Number of deliveries	*N*	%
0	13	17.33
1	13	17.33
2	31	41.33
3	12	16.00
4 or more	6	8.00

chair, externally supplied by the power from the main unit. The electromagnetic energy is directed vertically upward from the center of the seat, while the chair design ensures that the patient's perineum is centered when sitting.

Treatment Protocol

Subjects received six treatments at a frequency of two sessions per week and were required to complete the 3-month follow-up evaluation. Each therapy consisted of a 28-minute treatment session, during which the patient sits straight in the center of the chair seat. To ensure adequate PFM stimulation, the operator confirmed the patient's chair posture throughout the treatments and adjusted the intensity of stimulus as high as tolerated by patient, usually at 100%. Patients received the treatments at a discounted price to minimize dropouts.

Outcomes and Evaluation

The primary outcome was the evaluation of improvement in UI with an emphasis on QOL. To assess a patient's continence, the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was used. The questionnaire consists of three questions designed to quantify the frequency of leakage, the amount of urine leaked, and the level of interference with daily life, with the total score ranging from 0 (no interference) to 21 (severe involuntary urination interfering with the subject's QOL). At least a 50% [34–36] overall improvement in the total score was expected. The fourth ICIQ-SF question relates to urine leakage triggers and was assessed separately. Subjects were asked to indicate the listed answers that pertained to them, and changes in their answers in time were evaluated. In regard to patient's QOL, the usage of absorbent pads (per 24-hour cycle) was monitored via a pad usage questionnaire.

The secondary outcome was a voluntary subjective evaluation of the therapy. This also served as feedback for the operator and a subjective evaluation of changes in patient's QOL. The evaluation consisted of the following questions: "What would you praise (+) or reproach (–) regarding the therapy" and "Specify if there were any other positive/negative changes in QOL after the therapy."

The primary outcome data was acquired before the first therapy, after the sixth therapy, and at the 3-month follow-up appointment. The subjective evaluation was performed only at the follow-up visit. Adverse events (AE) were monitored throughout the entire study. Only subjects who report an AE that is deemed unsafe for continued participation in the study, should be immediately excluded. The observation of side effects in the treated area included evaluation of: muscular pain, temporary muscle spasm, temporary joint or tendon pain, local erythema or skin redness.

Statistical Analysis

Results were analyzed for statistical significance. The null hypothesis was formulated as: "The treatments caused no difference in patients score." To evaluate the significance of differences caused by the treatments (alternative hypothesis) we used Student's paired t test and Wilcoxon signed-rank test for small sample sizes at the significance level $\alpha = 0.05$. The sample size of 75 subjects was considered as sufficient for purposes of this single-arm prospective study to reveal clinically relevant improvement [29,34,35]. Possible association between measured variables was verified by Pearson correlation coefficient ($\alpha = 0.05$).

RESULTS

The patient group was composed mostly of menopausal and postmenopausal women as there were approximately only 10% of subjects below the age of 40. Almost 90% of patients suffered from SUI or MUI symptoms. Medical examination revealed there were seven (9.33%) women who had undergone hysterectomy in the past, which was the most common procedure stated during the anamnesis when considering the treatment area. Some patients had received a urethral/bladder sling surgery or vaginal rejuvenation (both $N = 4$, 5.33%), hernia repair ($N = 2$, 2.67%), abdominoplasty, removal of ovaries, appendectomy, endometrial ablation, interstitial cystitis surgery, or vaginoplasty (all $N = 1$, 1.33%).

Generally speaking, after the sixth session, 61 out of 75 patients (81.33%) reported significant improvement of their symptoms. Their average ICIQ-SF score at baseline was 10.57 ± 4.22 (ranging 2–18) which declined to 5.33 ± 3.97 after six sessions, and further improved to 4.16 ± 4.04 points at the 3-month follow-up. The ICIQ-SF score improvement thus averaged 49.93% ($P < 0.001$) after six sessions, and 64.42% ($P < 0.001$) at the 3 months. At the end of the study, there were 31 (50.82%, $P = 0.028$) patients who further improved at follow-up compared to immediate post-treatment evaluation. Zero ICIQ-SF score was observed in 13 (21.31%) subjects after the sixth session and in 21 (34.43%) subjects at follow-up. Summarization of ICIQ-SF results is shown in Table 3.

When evaluating ICIQ-SF score separately according to the symptoms we found that SUI patients reached improvement of 54.64% (5.83 ± 3.62 points) after six treatments and 66.98% (6.66 ± 3.45) at 3-month follow-up. Similarly, the MUI patients showed before-after difference score of 52.00% (5.38 ± 4.34 points) which further improved to 69.90% (6.67 ± 3.66 points) at

TABLE 3. Summarization of ICIQ-SF and Pad Usage Data

Parameter	ICIQ-SF	*P* value	Absorbent pads	*P* value
Number of evaluated subjects	61		43	
Baseline	10.57 ± 4.22		2.47 ± 2.25	
After sixth Tx	5.33 ± 3.97		1.35 ± 1.74	
Difference Before & After	5.25 ± 4.02	<0.001	1.12 ± 1.80	<0.001
Average improvement	49.93%	<0.001	43.80%	<0.001
Zero score after sixth Tx (%)	13 (21.31%)		15 (34.88%)	
3 Months Follow-Up	4.16 ± 4.04		1.19 ± 1.91	
Difference Before & Follow-Up	6.41 ± 3.75	<0.001	1.28 ± 1.83	<0.001
Average improvement	64.42%	<0.001	53.68%	<0.001
Zero score after Follow-Up (%)	21 (34.43%)		19 (44.19%)	

ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form.

follow-up. Results of both SUI and MUI patient group were highly statistically significant ($P < 0.001$). The patients who experienced UUI symptoms initially do not respond to the treatments well; as they reported mild yet significant improvement of 26.54% (4.00 ± 4.74 points; $P < 0.05$) after the sixth treatment. However, at the follow-up examination, they showed a substantially greater level of improvement, reaching 54.11% (7.00 ± 5.24 points, $P < 0.05$).

According to the baseline evaluation, patients most frequently reported they had been experiencing leakage about one time per day. At the 3-month follow-up, most of them mentioned that leakage occurred only about once a week or less. A similar shift was observed when evaluating interference of UI with everyday life. Patients in general improved from "moderate interference" (median score 5 out of 10) to "almost no interference" (median score 1 out of 10) at the 3-month follow-up.

Initially, there were 43 patients who had been using one or more absorbent pads per day, with the average number of used pads 2.47 ± 2.25 daily. After the sixth treatment, a significant improvement of 43.80% ($P < 0.001$) was observed as the average number of used pads decreased to 1.35 ± 1.74 per day. Similarly, to ICIQ-SF evaluation, the improvement at the follow-up was even more significant as the average pad usage further decreased to 1.19 ± 1.91 per day which resulted in an average 53.68% ($P < 0.001$) improvement (see Table 3). The therapy course also allowed some patients to completely get rid of pads. After the sixth treatment, 15 (34.88%) subjects reported they were not using pads anymore, and at the 3 months this number increased to 19 (44.19%) subjects. In total, 29 out of 43 patients (67.44%) reported a reduction in used pads after the sixth treatment, and this increased to 30 out of 43 patients (69.77%) at the follow-up.

A medium, significant and positive correlation ($r = 0.43$, $P < 0.01$) was found between the improvement in ICIQ-SF questionnaire score and the reduction in absorbent pads after the sixth treatment. At the follow-up this correlation was even more profound ($r = 0.53$, $P < 0.001$). Any other possible relations such as between age, the number of pads or ICIQ score, and the number of deliveries were found insignificant with weak correlation coefficients (<0.30).

Evaluation of urine leakage triggers revealed a gradual improvement. At the follow-up, 54.05% fewer patients reported leakage before they could reach the restroom, 64.29% fewer patients who experienced leakage while

TABLE 4. Analysis of Urinary Incontinence (UI) Causes and Frequency of Patients' Answers

Question	Baseline	After sixth Tx (impr. in %)	3 Months Follow-Up (impr. in %)
Never—urine does not leak	2	11 (550.00)	10 (500.00)
Leaks before you can go to the toilet	37	26 (29.73)	17 (54.05)
Leaks when you cough or sneeze	54	38 (29.63)	32 (40.74)
Leaks when you are asleep	14	7 (50.00)	5 (64.29)
Leaks when you are physically active/exercising	45	24 (46.67)	19 (57.78)
Leaks when you have finished urinating and are dressed	21	10 (52.38)	9 (57.14)
Leaks for no obvious reason	14	9 (35.71)	8 (42.86)
Leaks all the time	5	3 (40.00)	3 (40.00)
Total frequency of answers	192	128 (33.33)	103 (46.35)

asleep, and 57.78% fewer patients who experienced leakage during physical activity/exercise. Detailed results are shown in Table 4.

Patients were satisfied with the therapy and treatment results. We observed no AE related to the treatment and only minor side effects such as "muscle fatigue" were documented. Patients described that the therapy was easy and very tolerable as there was no pain, downtime or negative effects. In total, 43 out of 75 patients answered the voluntary section of the questionnaire focused on their subjective satisfaction with the results. They described beneficial changes in QOL as a response to the treatment mostly as: better control over urination throughout the day and night ($N = 17$) a reduced number of pads and incidents of involuntary urination ($N = 10$), a reduced number of visits to the toilet ($N = 6$), much better urine flow ($N = 4$), an improved vaginal and pelvic floor tone ($N = 3$), increased sexual desire and more intense orgasms ($N = 3$).

DISCUSSION

According to results documented in this study, the PFM training by HIFEM stimulation proved to be effective in treatment of a patient group demonstrating multiple types of UI and differing degrees of severity (ICIQ-SF scores at baseline ranging from 2 to 18). The improvement in UI severity measured by ICIQ-SF standardized questionnaire and pad usage questionnaire (showing a medium correlation) was associated with an enhanced QOL according to the patient subjective evaluation. As a result of the treatment, UI interfered less with one's everyday life and/or these symptoms completely disappeared which enabled patients to regain self-confidence. The statistically significant differences in ICIQ-SF score at the 3-month follow-up implies that results were gradually improving over time. Data describing causes of leakage are also a useful indicator of patients QOL, and as shown in Table 4, we observed a substantial suppression of the urine leakage triggers at the follow-up when patients indicated fewer responses that applied to them.

It is suggested that PFM training increases the tone of pelvic muscles and causes hypertrophy and strengthening of the muscle fibers. This should lead to elevation of the levator plate and restoration of protective continence mechanisms [37]. To effectively achieve motor and PFM re-education, hundreds of correctly performed contractions are required. Various training programs have been examined in the past to determine the most effective elements of a training regime [38]. However, when treated subjects perform the exercise, they must be individually educated on the anatomy of the pelvic floor, lower urinary tract and continence mechanism, and also supervised by a skilled physiotherapist. Furthermore, a number of additional education sessions necessitate inclusion, especially in case of individual, self-monitored exercises in the patient's home [39]. The advantage of the HIFEM technology over such traditional approach is its mechanism of a rapidly changing electromagnetic field which initializes thousands of supramaximal contractions during one therapy, something that cannot be achieved by any conventional training program. The high intensity and frequency of the stimuli ensure that PFM are targeted properly. Each contraction is then repeated identically while the outcome of regular exercise may be limited by the inability of patients to perform contractions consistently. Moreover, regular exercise is more time-consuming (multiple studies reported treatment duration of 12 weeks and longer [40]) in comparison to a 3-week duration for each patient who receives the HIFEM treatments.

Patients' overall improvement by 64.42%, as well as 34.43% of cured subjects (zero score at the follow-up) is comparable to previously published literature on the effects of electromagnetic stimulation for PFM strengthening [36,41,42], despite the fact that our patients received fewer treatment sessions than in the referenced studies. Our data showed slightly higher level of improvement in SUI ($N = 37$; 66.98%) and MUI ($N = 30$; 69.90%) patients which may be contributed to the limited size of UUI patient group ($N = 8$). Additionally, the number of subjects who improved in absorbent pads usage (70%) was similar to what was previously documented by Galloway et al [43]. Our results also correspond to observations from other modalities such as exercising [34] or electrical stimulation [44,45] where the reported improvement usually ranged between 50 and 90%. Nevertheless, exact comparison of various modalities and treatment outcomes throughout the literature is complicated due to utilization of a range of different standardized and non-standardized methods of UI evaluation, as well as patient self-evaluation or QOL assessment. Previous studies also vary in terms of methodology and composition of the patient group which could substantially influence the outcomes and conclusions. It can be assumed that these circumstances are responsible for the diversity of published results [40,46,47].

The therapy was well tolerated, and subjects provided positive feedback about the procedure, its non-invasive manner and its low-risk profile. Patients reported additional benefits of the therapy as improvement in sexual satisfaction which was also documented by other authors who investigated effects of electromagnetic stimulation [48].

A limitation of this study was the lack of any control group which received sham treatments, however we believe the statistical significance of our results is sufficient to overcome this limitation. We did not establish a sham treatment group due to the likelihood that patients would be aware they were not receiving a full electromagnetic treatment if they perceived a lowered intensity of stimulus or an otherwise adjusted treatment protocol. Another major limitation was a relatively short follow-up interval of 3 months. Documented results seem to be promising in terms of the continuing improvement over time, however it would be necessary to follow patients in a future study for 6–12 months in order to establish appropriate re-treatment intervals for maintenance of continence results. Furthermore, the subjective

evaluation of patient satisfaction should be more comprehensively designed in future studies, as the results obtained by voluntary questionnaire indicate there might be other interesting benefits associated with HIFEM therapy. It would be also beneficial to recruit a greater portion of UUI patients to provide sufficient sample for analysis of treatment outcomes.

CONCLUSION

This study demonstrated that HIFEM technology can safely and effectively treat stress, urge and mixed urinary incontinence by pelvic floor muscle strengthening in a wide demographic of patients. Subjects benefited from a decreased severity of UI symptoms and a reduced usage of absorbent pads which positively influenced their quality of life. On the basis of the subjective evaluation, patients also reported additional effects of the therapy such as a better control of urination as well as an increased sexual satisfaction.

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ISSN: 2577 - 8005

Research Article

Medical & Clinical Research

Safety And Preliminary Efficacy of Magnetic Stimulation of Pelvic Floor with Hifem Technology in Urinary Incontinence

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Submitted: 01 May 2018; **Accepted**: 10 May 2018; **Published**: 07 June 2018

Abstract

Introduction: *BTL EMSELLA™ utilizes High-Intensity Focused Electromagnetic technology (HIFEM) to cause deep pelvic floor muscles stimulation and restoration of the neuromuscular control. Key effectiveness is based on focused electromagnetic energy, in-depth penetration and stimulation of the entire pelvic floor area. A single BTL EMSELLA™ session brings thousands of supramaximal pelvic floor muscle contractions, which are extremely important in muscle re-education of incontinent patients.*

Objective: *Prospective study to evaluate the safety and preliminary effectiveness of the use of BTL EMSELLA magnetic stimulation in urinary incontinence.*

Method: *Thirty-two patients with light and moderate urinary incontinence were recruited to perform 6 sessions of BTL EMSELLA during three weeks of initial treatment. Follow-up after three months. The patients received sessions lasting 28 minutes, completing the different treatment protocols. Initially the patients underwent a quality of life test before and after treatment, evaluation with advanced ultrasound using elastography to measure the initial tissue's elasticity and be able to compare after treatment, clinical functional evaluation and urodynamic test.*

Results: *No adverse reactions were observed. All the patients finished the treatment sessions. Two patients reported increased pain after treatment in the first session corresponding to a VAS scale greater than 5 with duration greater than three hours. The treatment was highly satisfactory in 84,4% of the patients. After the first three months the improvement was maintained in 77% of the patients. No muscle injuries were observed. Elastographic changes and improvement of muscle tone were detected by advanced ultrasound (elastography) in 100% of patients.*

Conclusions: *BTL EMSELLA is safe, well tolerated and effective for the treatment of mild and moderate urinary incontinence. The observed elastographic changes demonstrate the improvement of pelvic floor muscle tone after treatment. A reduction in the symptoms of urinary incontinence was demonstrated.*

Recommendations: *Continue increasing the number of cases for research and increase the variables that we have decided to incorporate in the next research section such as MRI and pressure calculation.*

Introduction

Urinary incontinence (UI) is a health problem that affects the quality of life of patients who suffer from it and the impact is different depending on the severity, the type of UTI and the woman's experience of this problem. The diagnosis and treatment and treatment of UI in women is presented in the form of algorithms with accompanying notes that incorporate existing evidence and assigned a level of evidence (NE) and a grade of recommendation (GR) [1].

The algorithms are divided into two parts: algorithms for the initial treatment and algorithms for specialized treatment referring to diagnostic techniques and treatments that should only be used by specialists with specific training to establish personalized treatment behavior.

According to the National Observatory of Incontinence (ONI) it is estimated that in Spain could be affected by urinary incontinence about six million people [2].

In the studies carried out on women in Spain, although there are regional variations, the estimated average prevalence for women is

24%, increasing to 30-40% in middle-aged women and up to 50% in elderly women [2,3].

Types of Incontinence

1. Stress incontinence Supposedly due to urethral hypermobility and / or intrinsic Urethral Dysfunction.
2. Mixed incontinence
3. Hyperactive bladder with or without Urinary Incontinence supposedly due to detrusor overactivity

Initial Clinical Evaluation

The most important aspect in the diagnosis in the initial clinical evaluation. The most important variables are: Evaluation of the general condition, assessment of urinary symptoms (including voiding diary and validated questionnaires), impact of UI on quality of life, desire of the patient to receive treatment, urinalysis with or without culture, measurement of residual volume (Table 1).

N 32	First Visit					
	+++	++	+	no	% Positive	% Negative
	King's -	Health -	Questionnaire			
Pain	1	4	2	25	21,8 %	75,2 %
Nocturia	2	4	3	23	28,1 %	71,9 %
Infections	1	2	1	28	12,5 %	87,5 %
Urgency	2	5	6	19	40,6 %	59,4 %
Sexual problem	1	1	6	24	25,0 %	75,0 %
Stress incontinence	2	11	6	13	59,3 %	40,7 %
Physical and social limitations	1	9	14	8	75,0 %	25,0 %

Degree of affectation: --no, + mild, ++ moderade, +++ server (Cidranes & Estrada 2018 CIMEG MADRID)

Pelvic and Perineal Examination

It is one of the most important parts to define diagnosis and behavior. The advanced examination of pelvic floor should serve to rule out associations to prolapses of pelvic organs. The evaluation of the pelvic floor musculature is essential as well as the evaluation of vulvovaginal disorders due to urigenital atrophy. In complex cases and with recurrent UTI, interdisciplinary evaluation will be useful and necessary [4].

HIFEM Technology (The BLUE CHAIR EMSELLA)

EMSELLA™ utilizes High-Intensity Focused Electromagnetic technology (HIFEM) to cause deep pelvic floor muscles stimulation and restoration of the neuromuscular control. Key effectiveness is based on focused electromagnetic energy, in-depth penetration and stimulation of the entire pelvic floor area. A single BTL EMSELLA™ session brings thousands of supramaximal pelvic floor muscle contractions, which are extremely important in muscle reeducation of incontinent patients [5-7].

Material and Method

Thirty-two patients with light and moderate urinary incontinence were recruited to perform 6 sessions of BTL EMSELLA during three weeks of initial treatment. Follow-up after three months. (Figure 1) The first session lasted 7 minutes, (Figure 2) the second session 14 minutes to achieve a dose of priming and adequate muscle adjustment assessed in real time by elastography of muscles and fascias. (Figure 3) The patients received four sessions lasting 28 minutes, completing the different treatment protocols. Initially the patients underwent to quality of life test before and after treatment, evaluation with advanced ultrasound using elastography to measure the initial tissue's elasticity and be able to compare after treatment, clinical functional evaluation and urodynamic test.



Figure 1: Emsella CIMEG MADRID / Key Points

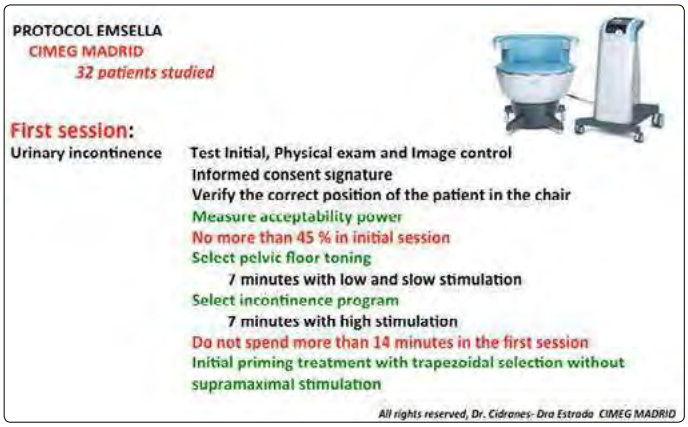


Figure 2: Emsella Protocol Cimeg Madrid First Session

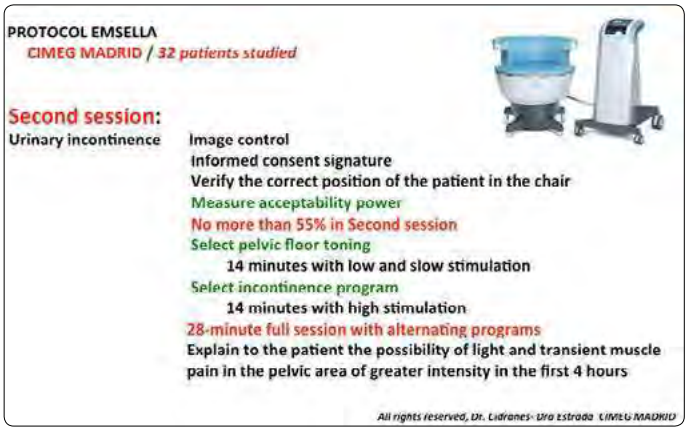


Figure 3: Emsella Protocol Cimeg Madrid , Second Session, Urinary Incontinence

Data Collection

The impact of HIFEM Emsella in our patients has been evaluated through the Spanish version of King's Health Questionnaire 1993

obtaining demographic, subjective, objective variables as well as quality of life. (Table 1) The urinary incontinence questionnaire ICIQ-SF (International Consultation of Incontinence Questionnaire) was carried out. (Table 2) We value in all patients the degree of tissue elasticity through advanced ultrasound and elastography using ESAOTE technology.

ICISF / n 32	0	1-3	4-6	7-10	Total % Positive
Frequency of urine loss	0	19	11	2	100 %
Amount of urine lost according to patient	0	22	8	2	100 %
Escaping urine and affecting daily life	2	19	7	4	93,75 %
When do you lose urine? Small activities to big activities	2	10	13	7	93,75 %

Degree of affectation: 0 no, 1-3 mild, 4-6 moderade, 7-10 server ICIQ-SF Positive greater than 1
(Cidranes & Estrada 2018 CIMEG MADRID)

Results

No adverse reactions were observed. All the patients finished the treatment sessions. Two patients reported increased pain after treatment in the first session corresponding to a VAS scale greater than 5 with duration greater than three hours. The degree of improvement after three months was already remarkable and maintained. (Table 3). The treatment was highly satisfactory in 84,4% of the patients. (Figure 4) After the first five months the improvement was maintained in 75% of the patients. No muscle injuries were observed. Elastographic changes and improvement of muscle tone were detected by advanced ultrasound (elastography) in 94 % of patients. (Table 4). After 5 months the degree of satisfaction of patients reaches 84.4% and 75% have solved the problem that generated their urinary incontinence.

N 32	After three months					
	+++	++	+	no	% positive	% Negative
	King's -	Health -	Questionnaire			
Pain	0	2	1	29	09,3 %	90,7 %
Nocturia	1	3	1	27	15,6 %	84,4 %
Infections	0	0	0	32	0,00 %	100 %
Urgency	1	3	3	26	21,8 %	79,2 %
Sexual problem	0	0	4	28	12,5 %	87,5 %
Stress incontinence	0	2	2	28	12,5 %	87,5 %
Physical and social limitations	0	2	4	28	18,7 %	81,5 %

Degree of affectation: --no, + mild, ++ moderade, +++ server (Cidranes & Estrada 2018 CIMEG MADRID)

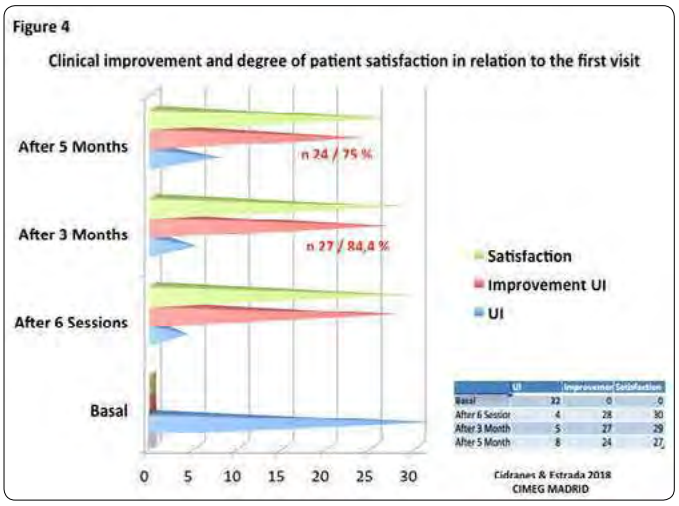


Figure 4: Clinical improvement and degree of patient satisfaction in relation to the first visit

N 32	First Visit		After three months		After five months	
	Positive	Negative	Positive	Negative	% Positive	% Negative
Elastography	30	2	7	25	3 / 09,3 %	29 / 90,6 %
Strain Rate	30	2	9	23	7 / 21,8 %	25 / 78,2 %
Urogynecological ultrasound Findings	14	18	12	16	3 / 09,3 %	29 / 90,6 %
MRI	9	23	5	27	2 / 09,3 %	30 / 93,7 %
Uroflowmetry	17	15	2	30	2 / 0,9,3 %	30 / 93,7 %
Urethrocytoscopy	4	28	4	28	4 / 12,5 %	28 / 87,5 %
Clinical Improvement	-	-	27 84,4 %		24 75 %	-

Positive: Pathological findings, Negative Non Pathological (Cidranes & Estrada 2018 CIMEG MADRID)

Conclusion

BTL EMSELLA is safe, well tolerated and effective for the treatment of mild and moderate urinary incontinence. The observed elastographic changes demonstrate the improvement of pelvic floor muscle tone after treatment. A reduction in the symptoms of urinary incontinence was demonstrated.

Recommendations

Continue increasing the number of cases for research and increase the variables that we have decided to incorporate in the next research section such as Fusion Image and pressure calculation.

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OPEN

A Comparative Study on the Effects of High-Intensity Focused Electromagnetic Technology and Electrostimulation for the Treatment of Pelvic Floor Muscles and Urinary Incontinence in Parous Women: Analysis of Posttreatment Data

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Objectives: Pelvic floor muscles (PFMs) weakening and urinary incontinence (UI) represent health issues that have a negative impact on daily life. This study compares the immediate efficiency of high-intensity focused electromagnetic (HIFEM) therapy and electrostimulation for the treatment of weakened PFMs, accompanied by the UI.

Methods: Ninety-five parous women were considered for the study. Symptomatic patients received either HIFEM or electrostimulation treatment. Treated patients completed 10 therapies scheduled 2 to 3 times per week (HIFEM) or every other day (electrostimulation). Patients underwent examination by 3-dimensional transperienal ultrasound at the baseline and posttreatments. Levator-urethra gap, anteroposterior diameter, laterolateral diameter of levator hiatus, and hiatal area were measured. In addition, Pelvic Floor Disability Index 20 questionnaire and subjective evaluation of patient's intimate health were assessed.

Results: Enrolled patients were divided into group I (n = 50, HIFEM), group II (n = 25, electrostimulation), and group III (n = 20, control) according the indication and treatment modality. Three-dimensional ultrasounds showed positive changes in dynamics of the pelvic floor posttreatment (decreased anteroposterior diameter, laterolateral diameter, and hiatal area). However, the significant ($P < 0.05$) changes of pelvic floor integrity were observed only in group I. In addition, group I achieved greater level of improvement in Pelvic Floor Disability Index 20 questionnaire compared with group II (52% and 18% respectively; $P < 0.001$). Substantially fewer patients in group I reported urine leakage after treatments.

Conclusions: Posttreatment results suggest that HIFEM technology is suitable for treatment of PFMs weakening and showed to be more effective when compared with electrostimulation in short-term. Therefore, we recommend HIFEM as treatment option for weakened PFMs and UI.

Key Words: pelvic floor, ultrasonography, urinary incontinence

(*Female Pelvic Med Reconstr Surg* 2019;00: 00–00)

The pelvic floor is highly complex, consisting of skeletal and striated muscles. It plays an important role in the maintenance of continence mechanism. For its proper functioning, strong and well-conditioned pelvic floor muscles (PFMs) are required,[1] ensuring the pelvic viscera's integrity.[2] Weakening of the PFMs may promote a wide range of health issues, such as pelvic organ prolapse or bladder dysfunction manifested as urinary incontinence (UI). Symptoms associated with UI directly affect the patient's quality of life.[3]

Between 4% and 8% of the human population suffer from UI as implied by the data released by Global Forum of Incontinence.[4] Prevalence of UI tends to increase with age[5] and can be triggered by risk factors such as surgical intervention or childbirth (especially vaginal delivery).[6,7] These may have a negative impact on the pelvic floor muscle's activity and morphology.[8] The deconditioning of PFMs accompanied with UI often influences the patient's mental and physical health. Fortunately, there are both surgical and nonsurgical methods of treatment available for such conditions. However, the nonsurgical approach should be always recommended as first-line therapy.[9]

Pelvic floor muscles can be treated with either monotherapy or combination therapy, which includes a combination of available treatment modalities to enhance treatment outcomes.[10–12] In general, nonsurgical approaches for the correction of pelvic muscle dysfunction include biofeedback therapy,[12] Kegel exercises (and its modifications),[13] magnetic stimulation,[14,15] and a wide range of electrostimulation methods.[16] Lately, a novel noninvasive technology utilizing the high-intensity focused electromagnetic (HIFEM) field was introduced for treating PFMs.[17,18] The HIFEM field depolarizes membranes of peripheral motoneurons and initiates muscle contraction.[19] High repetition rate of stimulation ensures that pelvic muscles reach nonvoluntary contractions of great intensities, referred to as "supramaximal" contractions. Although the effectiveness of HIFEM therapy was described earlier,[17,18] comparative assessment with other treatment modalities is still lacking.

The changes of the function of PFMs with regards to the UI are often assessed by the subjective standardized questionnaires, in particular with Pelvic Floor Impact Questionnaire or Pelvic Floor Disability Index (PFDI).[20] These are designed to allow patients comprehensively describe their perception of their pelvic area. This serves as a powerful tool for the practitioners when used in combination with some objective evaluation (magnetic resonance, ultrasound imaging, or electromyography).[21,22] Especially, the 3-dimensional (3D) transperineal ultrasonography of the pelvic floor has become widely used due to its ability to promptly assess essential parameters of pelvic floor integrity.[23,24]

The goal of this pilot study is to investigate and compare the immediate efficiency of HIFEM technology and electrical stimulation, for the treatment of weakened PFMs accompanied by UI.

MATERIALS AND METHODS

Inclusion Criteria and Ethical Principles

Between the 2018 and early 2019, 95 postpartum women in reproductive age referred to the Hospital Lapino (MD Medical

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The authors have declared they have no conflicts of interest.

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DOI: 10.1097/SPV.0000000000000807

Group) were considered for the study. The present study is a retrospective analysis of all the short-term data, which were gathered during their pretreatment and posttreatment examination.

The inclusion criteria were age 18 to 45 years and history of vaginal childbirth (not earlier than 6 months ago). The exclusion criteria included the following: pelvic organ prolapse; pregnancy at the time of therapy initiation (urinary pregnancy test was done in both groups at the baseline); the presence of metal implants in the area of lumbosacral spine, pelvis, or hip joints or intrauterine device, which includes any metal components, cardiac pacemaker, or other inner electronic devices; and general contraindications for physiotherapy. All the patients signed a voluntary informed consent.

Treatment Protocol

Patients who showed PFMs weakness and continence issues received either therapy with the BTL EMSELLA (BTL Industries Inc, Boston, MA) or BioBravo (MTR+ Vertriebs GmbH, Germany) device. BTL EMSELLA uses HIFEM technology for PFM strengthening and reduction of UI. The device is consisted of a power generator and a circular coil mounted in the seat of the chair. During the treatment, the patient is fully clothed and seated on the center of the chair while the alternating magnetic fields with intensities of up to 2.5 T have been penetrating the pelvic area. In total, 10 HIFEM treatments (for 28 minutes each) with frequency 2 to 3 sessions per week were delivered to match the electrostimulation protocol.

BioBravo portable low-frequency stimulator is used for self-administered PFMs stimulation to treat urinary/fecal incontinence symptoms (approved by European Union conformity mark, not Food and Drug Administration cleared or approved). Patients performed a course of 10 procedures at home (every other day or, at least, 3 times a week) with BioBravo device, after they passed preliminary training. Time of each BioBravo session was set to 28 minutes to mirror the duration of Emsella's treatment.

Evaluation of Study Outcomes

Various methods for documentation of treatment outcomes were used. The first (baseline) visit consisted of medical anamnesis, gynecological examination, and 3D transperineal ultrasound of the pelvic floor area by Voluson E10 device (RIC6-12-D transducer). During the examination, patients were placed in the dorsal lithotomy position with both hips symmetrically flexed, legs abducted, and knees flexed. The transducer was located on the perineum between the mons pubis and the anal margin. In particular, measured biometric indices of pelvic floor integrity included anteroposterior diameter (LH-AD) and laterolateral diameter (LH-LD) of levator hiatus and hiatal area (HA). In addition, levator-urethra gap (LUG) was studied before the first treatment (pelvic prolapse detection due to the levator ani avulsion). The ultrasound examination was repeated after the prescribed course of treatments.

Treated women were also asked to complete PFDI-20 standardized questionnaire to assess the degree of PFM functioning and continence issues. These patients also evaluated their intimate health on bimodal basis (yes/no), according to following questions: Q1 — Are you experiencing vaginal laxity during intimacy? Q2 — Are you experiencing changes of vaginal topography? Q3 — Does the water or air enter the vagina during swimming and exercise? Q4 — Are you experiencing stress UI symptoms (eg, involuntary urine leakage during physical activity, when coughing or sneezing or before you can visit the toilet)? After the successful completion of all treatments, the patients reevaluated their continence and PFM functioning.

Safety and comfort of the patients were monitored (any possible adverse effects or adverse events, for example, pain, muscle fatigue, or bruising induced by therapies). Patients who performed treatments at home were instructed to record any inconveniences caused by electrotherapy.

There was a large number of patients to provide sufficient sample for statistical analysis, further verified by G-power 3.1.9.2 software.[25] Gathered results were statistically analyzed using Statistica version 6 software (StatSoft Inc, Tulsa, OK) using the paired t test and 2-way analysis of variance followed by least significant difference post hoc test. Level of significance α was set to 5%. Assumption of normality was tested by Kolmogorov-Smirnov and Lilliefors tests.

RESULTS

All 95 patients were recruited. In total, 75 women reported PFMs weakness and incontinence issues. Symptomatic patients were divided into 2 groups. Group I (n = 50, mean ± SD age of 31.1 ± 5.4 years) received therapy with the EMSELLA device. Group II (n = 25, mean ± SD age of 32.0 ± 7.7 years) was treated with BioBravo stimulator. The remaining patients marked as a group III (n = 20, mean age of 27.2 ± 4.3 years) were classified as healthy participants and were used only as control for 3D ultrasound measurements.

Each patient from groups I and II finished the prescribed course of treatments. No adverse events or pain were reported. None of the patients experienced prolapse of pelvic floor, which can be seen in Table 1. Thickness of LUG on both sides of the pelvis did not exceed the cutoff value of 25 mm as stated in literature,[26] and thus, both treated groups met the inclusion criteria. The minor differences in LUG thickness within the groups were insignificant.

3D Ultrasounds of Pelvic Floor

The rest of the parameters obtained by 3D ultrasounds are documented in Table 2. Before the treatment, significantly higher values were documented in all studied indices against the control group. After the last therapy, the initially high values of LH-AD, LH-LD, and HA were significantly reduced only in group I ($P < 0.05$), approaching the averages of group III. Results of group II showed similar yet insignificant trend ($P > 0.05$). Such difference indicates the significant effect only in patients treated by HIFEM technology.

The examples of 3D ultrasounds obtained before and after HIFEM treatments are visualized on the Figure 1. There is visible improvement in LH-AD and HA parameters. Thickness of LH--AD was decreased by 2.6 mm, which is comparable with mean difference of whole group I (−3.12 mm on average). In addition, HA showed more profound reduction of 1.83 cm^2 that exceeds the group I average difference (−1.38 cm^2) of almost 0.5 cm^2.

TABLE 1. Examination of LUG Thickness for Determination of Levator Ani Avulsion as Sign of Pelvic Organ Prolapse

Levator Avulsion	LUG Right Side, Mean (SD), mm	LUG Left Side, Mean (SD), mm
Group I	20.94 (3.22)	21.76 (3.14)
Group II	20.96 (2.49)	21.48 (2.68)
Group III	20.70 (2.68)	20.85 (2.94)

Data are expressed as mean with SD.

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TABLE 2. Three-dimensional Ultrasound Examination of Intervention (I and II) and Control (III) Groups

	LH-AD, Mean (SD), mm		LH-LD, Mean (SD), mm		HA, Mean (SD), cm^2	
PFM Integrity	**Before**	**After**	**Before**	**After**	**Before**	**After**
Group I	51.10 (6.80)†	47.98 (6.25)*	41.44 (6.43)†	38.40 (6.03)*	14.47 (1.72)†	13.09 (1.78)*
Group II	52.52 (5.75)†	51.36 (5.36)†	46.60 (6.70)†	45.56 (6.41)†	14.77 (1.82)†	14.69 (1.79)†
Group III	46.60 (2.30)	N/A	35.40 (2.50)	N/A	11.59 (0.35)	N/A

Data are expressed as mean with SD. Group III was measured only at the baseline as a reference, therefore values after treatment are not available.
*Statistically significant differences against baseline ($P < 0.05$).
†Statistically significant differences against control.
N/A, not available.

PFDI-20 Standardized Questionnaire

No difference in the baseline PFDI-20 score was found. Although the baseline score was slightly higher in group II, this tendency showed to be insignificant ($P = 0.45$). The more profound change has been achieved by group I. After the HIFEM treatments, patients improved by 31.45 points (52%, $P < 0.001$). On the contrary, group II showed lesser yet significant mean difference of 11.70 points (18%, $P < 0.001$). The comparison of results obtained after the last treatments revealed also significant difference between the group I and II mean scores ($P < 0.001$; Table 3).

Patient's Self-Evaluation

Results of the patient's subjective bimodal evaluation are summarized in Table 4. The percentages describe a portion of patients who answered questions Q1 to Q4 positively (yes). After the treatments, the percentage of answers regressed in both groups; however, group I showed substantially greater differences in comparison with group II. On average, the subjective assessment revealed that patient self-reported 2 times greater results after HIFEM treatment. Especially remarkable improvement was observed in questions Q1 (laxity) and Q4 (incontinence). In group I, the differences reached up to 30% (Q1) and 44% (Q4), respectively, whereas group II reported much lower change of 16%.

Sample Size and Verification of Power

Using G-power software, we calculated the minimal sample size to reveal statistical significance in gathered data as 16 patients for both 2-tailed t test ($\alpha = 0.05$; power, 0.95; effect size, 1) and analysis of variance ($\alpha = 0.05$; power, 0.95; 3 groups; effect

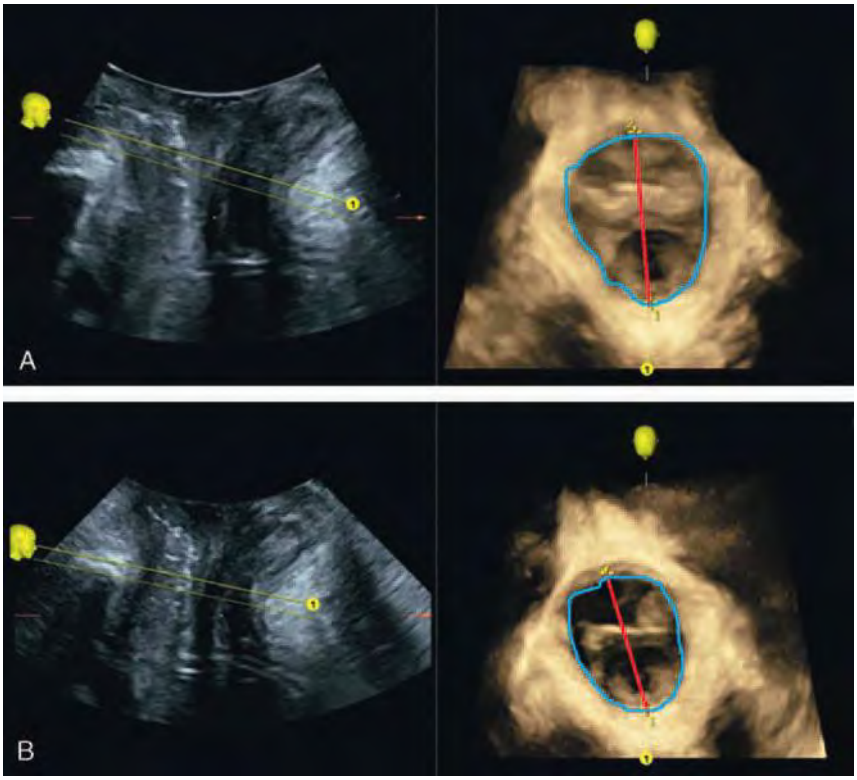


FIGURE 1. A 39-year-old patient, 1 childbirth. Visualization of ultrasound measurements (Voluson E10, equipped with RIC6-12-D transducer) before (A) and after (B) HIFEM treatments. Midsagittal plane on the left, axial rendered volume on the right. Red line indicates LH-AD dimensions. Area of HA is bordered by blue line. Direction of view in 3D is indicated by yellow lines and ❶ mark.

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TABLE 3. Mean Scores of the Standardized PFDI-20 Questionnaire Including the 95% CIs

PFDI-20	Baseline Score (CI)	After Tx Score (CI)	*P*
Group I	60.22 (50.62–69.82)	28.77 (20.74–36.81)	<0.001
Group II	66.21 (54.08–78.34)	54.51 (43.92–65.11)	<0.001
P value	0.45	<0.001	

Data were gathered at baseline and after treatments (After Tx).
CI, confidence interval;Tx, treatment.

size, 1). In addition, the power of conduced statistical analysis was verified post hoc and showed to be equal to 0.99.

DISCUSSION

According to the documented results, we suggest that HIFEM therapy was more effective method for treatment of weakened pelvic floor than electrostimulation in short-term. Apparently, based on the evaluation by both subjective (questionnaires) and objective (3D transperineal ultrasound) methods, HIFEM therapy produces more profound improvement in PFMs and UI posttreatment.

Besides the magnetic resonance, one of the most reliable methods for examination of pelvic area is diagnostic ultrasound. Because of the complex manner of structures forming the pelvic floor, 2-dimensional image may not always provide proper visualization. Hence, the examination should be combined with 3D analysis.[23] The use of such technology in routine practice may help to reveal pelvic floor muscles weakening even if the patient does not have any subjective complaints. Early diagnosis helps start timely treatment, as the 3D reconstruction of pelvic floor allows to obtain specific parameters of its integrity (LUG, LH-AD, LH-LD, and HA).

Recent research demonstrated that LUG is strongly associated with puborectalis avulsion, and the cutoff threshold for its diagnosis appears to be 25 to 27.5 mm.[23,26] Our initial gynecological examination showed no levator avulsion, which would exclude patients from the study. Levator-urethra gap ranged from 20.70 to 21.76 mm (Table 1), and thus, no pelvic organ prolapse was diagnosed because measured values showed to be substantially lower than cut-off threshold.

The biometric indices of control group are comparable with the results reported in literature for nuliparous women at rest.[27] It was found that LH-AD in healthy patients ranges from 45.2 to 48.4 mm, LH-LD from 32.8 to 37.5, and HA from 11.3 to 12.0 cm^2, which corresponds to our observations in healthy parous women (group III). However, both treated groups at the baseline showed significantly higher LH-AD, LH-LD, and HA in comparison with the group III. As a result of the treatments, these indices decreased toward the control values. Nonetheless, significant changes of the pelvic floor anatomy were demonstrated only in patients treated by HIFEM technology (Table 2; Fig. 1).

The presented data showed an enhanced functioning of PFMs with reduction of UI severity and impact on the quality of life has been achieved (Tables 3 and 4). Differences in PFDI-20 mean scores were found to be highly statistically significant. Both treatment modalities proved to be effective in treating PFMs weakness accompanied with UI. However, our observations indicate significantly more profound efficiency of the HIFEM technology in comparison with the electrostimulation after a course of 10 treatment sessions. Based on the questionnaire data, it was proved ($P < 0.001$) that group I reached a higher level of improvement (2.68 times) after a series of 10 treatments. Patients treated by HIFEM technology showed mean difference in PFDI of over 50%. On the contrary, group II was only able to reach an average improvement of 18%.

The patient's subjective bimodal assessment revealed greater results in group I, which reported reduced incontinence symptoms after the treatments, when compared with group II. In addition, those who received HIFEM therapy noticed a substantial reduction in vaginal laxity symptoms. Modest improvement of incontinence and laxity issues was seen in group II, probably attributed to the less recognizable improvement of PFM functioning. Conversely, the greater results observed in patients from group I correlate to their significant change in pelvic floor integrity and PFDI-20 score.

For PFM strengthening, the strong contractions with interposed rest periods should be involved to deliver sufficient load.[28] If the muscles are properly stimulated, both endurance and strength are regained.[29] Superior results after HIFEM therapy in our study may be explained by the deep penetration of high-intensity electromagnetic field into the pelvic area, resulting in uniform activation of PFMs. On the contrary, electrical devices may not be able to involve whole pelvic floor with sufficient intensity of the stimuli. Because of its superficial application, the electrostimulators lost the largest portion of emitted energy on the surface, and only its fraction reaches deep-lying tissues.[30] Although some positive effects of electrostimulation on PFM strengthening was documented in the past, there is still not sufficient evidence to determine whether it is more effective than traditional exercise.[20,31,32]

In this study, the treated postpartum patient groups were consisted of relatively young women of average age 31.1 ± 5.4 years and 32.0 ± 7.7 years. However, we assume that our findings are applicable also in the older postmenopausal patients who would probably show symptoms of greater severity because of the estrogen deficiency. Samuels et al,[33] for instance, was able to reach similar degree of immediate posttreatment improvement after the series of 6 HIFEM treatments in patient group aged 55.5 ± 12.8 years. Almost identically aged group (55.2 ± 12.8 years) was established also by Castro et al[34] who described significant and continuous results of electrostimulation therapy.

TABLE 4. Subjective Examination of Patient's Intimate Health Obtained at the Baseline and After Treatments (After Tx)

	Group I			Group II		
Question	Baseline	After Tx	Difference	Baseline	After Tx	Difference
Q1	48%	18%	−30%	44%	28%	−16%
Q2	36%	12%	−24%	36%	24%	−12%
Q3	34%	16%	−18%	48%	36%	−12%
Q4	74%	30%	−44%	72%	56%	−16%

The percentages express the portion of patients who answered *yes*.
Tx, treatment.

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Continuity of results after noninvasive pelvic floor stimulation is still being investigated in the literature. Based on the long-term observation of treatment outcomes after magnetic and electrical stimulation, it is assumed that beneficial effect of induced PFM strengthening may be sustained up to 1 year.[14,35] However, after this period of time, the relapse may occur and maintenance session should be considered in some patients.

Although the presented data are based on the short-term observation of patient cohort, the discovered findings showed to be sufficient to identify contrast in efficacy between the HIFEM technology and electrostimulation. Future research should verify the persistence of herein published results and further tendencies in patient's PFMs and UI management as well as retreatment period. Treatment groups of at least 16 patients should be established when the great effect of intervention is observed. Otherwise, the higher number of patients might be required.

It was demonstrated that HIFEM technology was able to significantly improve biometric indices of pelvic floor integrity and UI symptoms. Therefore, we recommend HIFEM for a widespread uses in practice as the treatment of weakened pelvic muscles and continence issues.

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SEXUAL MEDICINE ORIGINAL RESEARCH

Electromyographic Evaluation of the Pelvic Muscles Activity After High-Intensity Focused Electromagnetic Procedure and Electrical Stimulation in Women With Pelvic Floor Dysfunction

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ABSTRACT

Introduction: Impaired coordination, relaxation, and atrophy of pelvic floor muscles (PFMs) may cause various health issues referred to as pelvic floor dysfunction (PFD). In recent years, electromagnetic noninvasive stimulation of the pelvic floor was successfully used to treat PFD symptoms.

Aim: This study aims to compare the effectiveness of electrical and magnetic noninvasive stimulation for the treatment of PFD in postpartum women.

Methods: 2 intervention groups treated with high-intensity focused electromagnetic ([HIFEM]; G1) procedure and electrical stimulation (G2) were established along with the control group (G3). Patients received 10 therapies delivered at the hospital (G1; 2−3 times per week) or self-administered at home (G2; every other day) after initial training. The protocol was identical for both modalities. Functionality of the PFM was examined by surface electromyography measurements (maximal voluntary contraction [MVC]; mean MVC; muscle activity at rest; endurance of contraction) while patient's subjective perception of pelvic floor functionality was assessed by Pelvic Floor Impact Questionnaire−Short Form 7 (PFIQ-7) standardized questionnaire. Changes in electromyography values and PFIQ-7 scores were statistically evaluated from baseline to after all treatments.

Main Outcome Measure: The main outcome measure was enhancement of PFM activity.

Results: In total, 95 patients (G1 = 50; G2 = 25; G3 = 20) participated in the study. The MVC, mean MVC, and endurance were lowered in symptomatic patients. After the treatments, these parameters significantly increased ($P < .001$) and moved toward the values of healthy population. Electrogenesis at relaxation revealed divergent tendencies in the G1 and G2 groups. PFIQ-7 scores significantly improved in treated patients ($P < .001$). In general, superior results were documented in the HIFEM group as it reached improvement of electromyography parameters from 48% to 59% (electrical stimulation from 7% to 36%) and similarly the improvement of PFIQ-7 score by 57% (electrical stimulation by 32%).

Conclusion: This study documented that the HIFEM procedure was significantly more effective than electrical stimulation in treatment of PFD in postpartum women. Both the objective and subjective evaluation indicates more profound effects of magnetic stimulation. **Elena S, Dragana Z, Ramina S, et al. Electromyographic Evaluation of the Pelvic Muscles Activity After High-Intensity Focused Electromagnetic Procedure and Electrical Stimulation in Women With Pelvic Floor Dysfunction. Sex Med 2020;XX:XXX−XXX.**

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Key Words: Electrical Stimulation; Electromyography; HIFEM Procedure; Pelvic Floor Dysfunction; Pelvic Floor Muscles

Received September 7, 2019. Accepted January 10, 2020.

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https://doi.org/10.1016/j.esxm.2020.01.004

INTRODUCTION

Electromyography (EMG) is a method frequently used for examination of electrical activity of muscle tissue. Although this technology is relatively new, it is assumed to be reliable and objective, while causing minimal or no discomfort to patients. Essentially, EMG uses the surface or intramuscular electrodes to record the intensity of signals which propagate in the muscle

fibers during the contraction because muscle tissue conducts electrical potentials similar to the nerves. Results of the measurements are expressed as a function of voltage over the time. Except single-fiber EMG,[1] measured values represent a sum of all signals originated from the muscle tissue of certain body area.[2–4]

Besides ultrasound,[5,6] magnetic resonance,[7] manometers,[8] dynamometers,[9] or simple palpation combined with observation,[10] surface EMG (sEMG) is one of the possible objective methods for monitoring resting level, strength, and endurance of the pelvic floor muscles (PFMs). The pelvic floor consists of 3 main compartments—anterior (bladder and urethra), middle (vagina and uterus), and posterior (rectum). Furthermore, there are morphologically complex multilayers of anatomical structures such as pelvic diaphragm (composed of levator ani and coccygeus muscles), urogenital diaphragm (composed of connective tissue, perineum, bulbospongiosus, and ischiocavernosus muscles), and urethral/anal sphincters. All of these tissues are arranged in the pelvic area and have multiple attachments to the surrounding structures.[11] Under normal circumstances, the PFM prevents multiple disorders such as incontinence (urinary/fecal), sexual dysfunction, or pelvic organ prolapse accompanied with pain and discomfort. However, the atrophy and relaxation of PFMs may promote manifestation of these heath issues, collectively referred as pelvic floor dysfunction (PFD),[10–12] occurring naturally with aging or as a consequence of childbirth.

Recording of sEMG in women who showed certain symptoms of PFD was reported previously by multiple authors. It has been found that EMG is a suitable method for investigation of PFM functioning among healthy subjects and women with signs of urinary incontinence or PFM weakness.[13–21] Despite the various protocols and electrode configurations used, in general, there is a clear relationship between the characteristics of the EMG signal and PFD. In comparison with the healthy and asymptomatic subjects, postmenopausal and even premenopausal women affected by some form of PFM impairment, show distinctively lower EMG values. The intensity of maximum voluntary contraction (MVC) is reduced because the PFMs are weakened and endurance of contraction and muscle activity during rest are affected as well.[13,14,18–20] Aside from sEMG, various subjective questionnaires (Pelvic Floor Disability Index, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, Pelvic Floor Impact Questionnaire, International Consultation on Incontinence Questionnaire - Vaginal Symptoms or Pelvic Floor Bother Questionnaire) were also used to document strengthening and reeducation of the PFM which helped patients to improve their symptoms.[22,23]

Besides the regular exercise,[24] the function of the weakened PFM can be enhanced by noninvasive PFM stimulation. Along with well-established electrical stimulation,[25,26] high-intensity focused electromagnetic (HIFEM) technology is being more frequently used in recent years.[27–29] Both technologies deliver electric currents into the pelvic floor to depolarize membranes of motoneurons to elicit action potential and achieve brain-independent muscle contractions when the action potential of sufficient strength reaches the neuromuscular junction.[30] However, despite the direct flow of electric charge through electrode-tissue surface, the HIFEM induces electrical currents selectively in the PFM by mechanism of electromagnetic induction.[31] As magnetic field passes any medium without attenuation of the energy, the induced contractions may be achieved at greater depths and intensities[32] to possibly provide better outcomes.

Based on the rationale mentioned previously, the aim of this study is to investigate and compare treatment outcomes of the HIFEM procedure and electrical stimulation in women suffering from PFD. The expected changes in PFM activity would be examined by subjective (questionnaire) and objective (sEMG) methods. The measured values will be compared with asymptomatic subjects.

MATERIALS AND METHODS

Patient's Recruitment Criteria

The inclusion criteria were specified as follows: women of age 18–45 years, who had vaginal delivery, and who already stopped lactation. There were 3 patient groups. The symptomatic patients who reported PFD symptoms related to weakened PFM as lower urinary tract or bowel symptoms (incontinence) and/or sexual dysfunction (dyspareunia, vaginal laxity, decreased sensitivity during intimacy, inability to achieve orgasm—anorgasmia), were randomly (2:1) divided into the G1 group treated by HIFEM and G2 group which received electrical stimulation. The third group G3 consisted of healthy postpartum patients, to obtain sEMG values of normal population. Exclusion criteria were presence of any metal implants or devices which include metal components, pregnancy, malignant tumor, history of surgical procedure in the pelvic region, presence of pelvic organ prolapse of stage II-IV as per the Pelvic Organ Prolapse Quantification classification, and all general contraindications for physiotherapy. Patients were asked to perform pregnancy test before the first treatment and then retest on a regular basis.

Ethical Considerations

This study was approved by the local ethics committee of Hospital Lapino (MD medical group). It complied with ethical principles stated in the Declaration of Helsinki, Convention on Human Rights and Biomedicine, and International Ethical Guidelines for Health-related Research Involving Humans, and it completely excludes impairment of patients' interests and damage to health. All of the subjects were informed about the potential risks and possible benefits of the study, and all participants provided written informed consent.

Treatment Protocol

Both intervention groups received 10 treatments in total addressing the stimulation of PFM. The G1 group was treated using a BTL EMSELLA (BTL Industries Inc, Boston, MA) device, which uses HIFEM technology for noninvasive PFM

stimulation and reeducation based on the principle of electromagnetic induction. The device consists of a generator connected to the chair where the stimulation coil is located. The coil emits focused magnetic field of intensities up to 2.5 Tesla, responsible for induction of muscle contraction up to depths of 10 cm. Each therapy with the BTL EMSELLA device lasted 28 minutes, and it was administered under the supervision of a skilled physician at the Lapino Hospital. Patients were seated in a chair, and the intensity of the stimulus was modulated on the scale of 0−100% (0−2.5 Tesla) in accordance with their feedback up to maximum tolerable threshold, when patients felt a strong muscle contraction but without pain or discomfort. All patients have achieved 100% intensity during the first or second procedure. Treatments with HIFEM were addressed 2−3 times per week for a duration of 4 weeks. The sessions were planned to suffice this interval as per the patient/device availability. 2 consecutive treatments were spaced at least 48 hours apart to prevent muscle fatigue.

The G2 group performed home-based and self-administered procedures with a BioBravo (MTR+ Vertriebs, GMBH, Germany) electrical stimulation device. First, the patients were comprehensively trained how to safely and effectively use a BioBravo stimulator. Then, they were instructed to finish treatments at home by repeating therapy every other day. The protocol of stimulation was identical for both groups because the settings of the BioBravo device have been adjusted to reflect those used by the BTL EMSELLA device. Finally, group G3 did not receive any treatment.

sEMG Measurements

The primary outcome of the study was to perform sEMG measurements to determine activation of the PFM in symptomatic and asymptomatic patients and to document the hypothesized changes caused by muscle strengthening. At first, by using a Myomed 632 myofeedback device (Enraf-Nonius B.V., Netherlands), the patients were instructed how to correctly perform contractions of the PFM without (voluntary) involving the muscles of the anterior abdominal wall and gluteal or hip region. When performing contractions, patients were lying in the supine position. During the examination, they were requested to repeat 3 specified PFM activations which consisted of the following: 5 short (quick flick) contractions at maximum intensity with an interval of 10 seconds, followed by sustained contraction and relaxation (both 10 seconds long, 5 repetitions) and finally the sustained contraction held as long as possible to determine PFM endurance.[33]

The sEMG recordings were performed by the Myomed 632 device at the baseline (all groups) and after the patient's last treatment (only G1 and G2). To isolate the signal originated in the PFM, 2 types of superficial electrodes were used: first was applied on the anterior abdominal area (served as reference), and the second (vaginal) electrode was mounted on the intravaginal probe. Neutral gel was always applied on the sensor introduced into the vagina. An experienced physiotherapist confirmed the correct placement of intravaginal probe and PFM contractions. Concurrent registration of muscular electric potential by using the vaginal and skin electrodes allowed differentiating PFM contractions. During the sEMG examination, myofeedback (in a form of graph) was displayed on the device's monitor and the external monitor unit which was additionally connected to the device to enlarge the graphic output. The sEMG measurements were performed automatically by the Myomed device, following the pattern of PFM activations described higher. These parameters were acquired for each patient during each visit: MVC, mean MVC, mean activity at rest/resting level (all in μV), and endurance of contraction (in seconds).

Standardized Questionnaire

The secondary outcome was to assess subjective changes in perception of PFD by the PFIQ-7. This standardized questionnaire was used to determine the impact of PFD on the patient's quality of life as it showed to be psychometrically valid and reliable in previous research.[34] Patients from groups G1 and G2 were given the PFIQ-7 at baseline and after the last treatment. Based on their answers, the PFIQ mean scores (on a scale from 0 = no distress to 300 = maximal distress) were calculated and compared against baseline and between the both groups.

Safety

The safety of treatments and sEMG measurements and possible adverse events (AEs) were monitored. Patients were also asked to report any signs of discomfort or pain during the therapies or caused by the positioning of the intravaginal electrode.

Statistical Analysis

All variables were checked for normality by the Kolmogorov-Smirnov test. Descriptive statistics were estimated by the sample mean with 95% confidence interval. The differences between groups were tested using analysis of variance test followed by Least Significant Difference post hoc tests. Levene's test of homogeneity of variance was run before analysis of variance to verify the equal variances in groups. Paired variables were tested by a student's t-test. All statistical tests were 2-tailed. Whole statistical analysis was conducted with Statistica v.6 (StatSoft Inc, Tulsa, OK), and the significance level was set as default to 0.05 (5%). Initially, the minimum sample size was verified by using Statistica software. At least 19 subjects must have been included in each of the 3 tested groups, to achieve a power of 80% with $\alpha = 5\%$.

RESULTS

Patient Group Characteristics

In total, 95 patients were recruited during 2018 and early 2019 in accordance with the specified criteria and current state of patients in the clinic: G1 (n = 50), G2 (n = 25), and G3 (n = 20). See Table 1 for detailed characteristics of patient groups. All of the recruited patients from the G1 and G2 groups finished a prescribed

Table 1. Characteristics of patient groups at the time of recruitment (mean followed by 95% confidence interval)

Group	Age (years)	BMI ($kg \cdot m^{-2}$)	Vaginal deliveries	PFD symptoms (% of patients)
G1 (n = 50)	31.12 (1.52)	23.27 (0.76)	1.76 (0.22)	Urinary incontinence (74%); decreased sexual desire (36%); decreased sensitivity during intimacy (70%); dyspareunia (26%); hypo/anorgasmia (52%)
G2 (n = 25)	31.96 (3.20)	24.32 (3.70)	1.56 (0.27)	Urinary incontinence (72%); decreased sexual desire (44%); decreased sensitivity during intimacy (44%); dyspareunia (24%); hypo/anorgasmia (40%)
G3 (n = 20)	27.20 (2.02)	22.40 (1.27)	1.25 (0.21)	-

BMI = body mass index; PFD = pelvic floor dysfunction.

number of treatment sessions. 8 patients who reported zero PFIQ-7 score at the baseline (G1 = 5, G2 = 3) were excluded from the questionnaire evaluation. No AEs were observed in regard to the delivered treatments or sEMG measurements. Subjects seldom reported only mild discomfort when recording sEMG using an intravaginal electrode.

Quantification of the EMG Signal

The results of sEMG measurements are summarized in Table 2. In general, there are significant differences between the symptomatic groups in comparison with healthy patients. On the other hand, the changes in the measured values after the HIFEM or electrical stimulation were highly statistically significant ($P < .001$) in comparison with the baseline, showing that stimulation of the PFM modifies the muscle (electrical) activity.

At baseline, measured peak intensity of the MVC signal was significantly higher in healthy patients by approximately 22 μV on average, when compared with that in the G1 or G2 group. At the same time, there was no change between the intervention groups. At the end of study, the G1 group showed significantly higher EMG values than the G2 group ($P < .001$), reaching an average change of 10.58 μV (57.29%) and 1.44 μV (7.34%), respectively. Although the HIFEM treatment considerably increased the PFM activity, the G1 group still showed lower values than control.

Similar findings were observed in case of average MVC. As expected, the average MVC magnitudes are lower in each group. The more profound increment was also observed in the G1 group (6.65 μV, 58.69%) compared with the modest increase of the G2 group (0.91 μV, 6.81%). There were also significant differences between G1 and G2 groups after treatments ($P < .05$). Despite the observed improvement, asymptomatic subjects still showed greater EMG values.

Interestingly, the examination of muscle activity at rest revealed divergent tendencies. Initially, only the G1 group showed significantly different (higher) values from control ($P < .05$) while after the last therapy, the G1 average resting level decreased at the level of G3 (2.08 μV and 1.90 μV, respectively). Conversely, the average resting level of the G2 group had risen from 2.42 μV to 3.94 μV. In conclusion, the G2 subjects manifested significantly higher EMG values than the control and G1 group at the end of study ($P < .001$).

In terms of endurance, there were observed significant differences between both the symptomatic groups and either control group at the baseline and after the treatments (see Table 2). The measurement of the G3 group showed that healthy patients were able to hold contraction of the PFM on average for 62.25 s. Furthermore, we observed a significant increase in endurance of PFM contraction by 48.24% in the G1 group because the patients have been able to hold a contraction by 13.44 s longer after their treatments, reaching 41.30 s in total. The G2 group improved by 36.26%, and PFM contraction was prolonged on average by 6.60 s.

Pelvic Floor Impact Questionnaire—Short Form 7

Patient's subjective evaluation is summarized in Table 3 and Figure 1. The minimal variation in the baseline score of both symptomatic groups was insignificant. Nonetheless, after the last treatment, there was an observed significant difference in the PFIQ score between the G1 and G2 group ($P = .01$). Although both treatment modalities resulted in highly significant subjective improvement, the patients treated with HIFEM experienced greater outcomes. In addition, 16 patients (35.56%) from the G1 group reached a score of zero after the HIFEM treatments (meaning 100% improvement against the baseline). Contrary to this, only 3 patients (12.00%) from the G2 group, who underwent electrical stimulation, reported zero score at their last visit.

The shift in PFIQ scores is visualized in Figure 1. As can be seen, the relative frequency of scores was remarkably changed in the G1 group while almost 90% of patients fall into the low-score categories (0—10 or 10—20) after the treatments. In addition, the scores more than 50 were entirely eliminated from patient's responses. The G2 group showed only minimal changes in distribution of patient's PFIQ scores, corresponding to a moderate average improvement of 5.15 points (see Table 3).

DISCUSSION

Our examination of PFM electrogenesis in patients, who showed signs of PFD, revealed a significant reduction of the

Table 2. Results of the sEMG measurements at the baseline and after the last therapy for both treated groups (G1 and G2) and control subjects (G3) presented as mean followed by 95% confidence interval in brackets

Group	Peak MVC (μV)		Average MVC (μV)		Resting level (μV)		Endurance (s)	
	Baseline	After	Baseline	After	Baseline	After	Baseline	After
G1 (n = 50)	19.49† (2.31)	30.06†,*** (3.75)	11.33† (1.54)	17.99†,* (2.50)	3.83†,* (0.82)	2.08 (0.38)	27.86†,** (4.17)	41.30†,*** (5.21)
G2 (n = 25)	19.56† (2.93)	21.00† (2.82)	13.39† (2.46)	14.30† (2.42)	2.42 (0.45)	3.94†,*** (0.60)	18.20† (2.85)	24.80† (3.12)
G3 (n = 20)	41.96 (2.51)	-	32.69 (1.88)	-	1.90 (0.63)	-	62.25 (3.68)	-

EMG = electromyography; MVC = maximal voluntary contraction; sEMG = surface electromyography.
Significantly different results ($P \leq .002$) against control are depicted by† and * denotes significantly higher EMG values for comparison of G1 and G2.
*$P < .05$, **$P < .01$, ***$P < .001$.

generated EMG signal in comparison with the asymptomatic patients at baseline (MVC, mean MVC, and endurance). The results of intervention groups G1 and G2 denote that noninvasive PFM strengthening is able to positively influence the activity of the PFM. As seen in Table 2, the sEMG measurements obtained after therapies with the BTL EMSELLA device or electrical stimulation showed increased values of maximum possible voluntary contraction and endurance. It suggested that at the end of study, patients were capable of stronger and more complex PFM contractions resulting in reduction of PFD symptoms (whether incontinence or sexual based), demonstrated also by significant decrease in the PFIQ-7 score.

In contrast to sEMG measurements, which demonstrated considerable PFM weakening in the G1 and G2 group at baseline, the PFIQ resulted in relatively low scores in both groups. We attribute this to perhaps a less specific grading system of the PFIQ, when evaluating patients who showed a various range of PFD-related symptoms of different severity. In future studies, it might be beneficial to focus on the evaluation of particular patient's symptoms by using condition-specific questions evaluated by a visual analogue scale or 5- to 7-point Likert scale for instance to enhance grading possibilities.

Comparison of the Magnetic and Electrical Stimulation

Significantly, greater improvement in EMG values was observed in the G1 group, treated by HIFEM technology. In comparison with electrical stimulation, the BTL EMSELLA device showed to be substantially more effective in restoration of muscle strength as the MVC, mean MVC, and endurance parameters uniformly increased ranging from 48 to 59% after HIFEM treatments. On contrary, electrical stimulation induced only mild changes in MVC (7.34%) or mean MVC (6.81%) while reaching mild to moderate improvement (36.26%) of endurance.

The sEMG measurements coincide with the results of the PFIQ. Patient's subjective evaluation showed more pronounced improvement in the G1 group (57.16%) than in the G2 group (32.18%), which corresponds to the improvement rate in EMG values. The HIFEM procedure also resulted in substantial reduction of high PFIQ scores after the last therapy session (see Figure 1).

PFM Electrical Activity and sEMG Measurements

Given the specific patient group and scarce evidence in literature, control group G3 was established to obtain normative EMG values, valid for the studied sample. In general, herein presented results coincide with the previously published findings. It has been documented by numerous authors[13–15,17,18,20] that women who are suffering from PFD show lower MVC and endurance values because of the impairment of the PFM. By the proper stimulation of the PFM, patients are able to produce

Table 3. Results of the PFIQ-7 for the both treated groups (G1 and G2) presented as mean followed by 95% confidence interval in brackets

	PFIQ-7 average score		Improvement		
Group	Baseline	After	Absolute	Relative	*P*-value
G1 (n = 45)	24.68 (6.81)	9.67 (3.38)	15.01	57.16%	<.001
G2 (n = 22)	26.04 (8.69)	20.89 (8.04)	5.15	32.18%	<.001
P-value	.81	.01	-	-	-

Absolute and relative differences against baseline were calculated.

greater voluntary contractions for longer durations. In addition, the muscle activity at rest is influenced by the PFD as the PFMs are less electrically active. However, the evaluation of the PFM resting level revealed significant differences between both modalities in our study. Although the G1 group after treatments reached similar EMG values as healthy population, patients from group G2 showed altered muscle activation with relatively high electromyogenesis at rest (3.94 μV on average, see Table 2). This indicates that G2 patients cannot properly relax their PFM after treatments because they are not able to isolate and control the appropriate muscle activation patterns, which was then reflected by the lower MVC amplitudes. The correct activation pattern during PFM contraction is associated with increased activation of the PFM and lower transverse abdominal wall with markedly less activation of the upper abdominal and chest wall. The inappropriate activation refers to an increased level of abdominal and chest wall activation while PFM activation decrease,[16] resulting in lessened strength (MVC amplitude) of contraction.

Showing high test-retest reliability,[13,14] the sEMG measurement is a useful tool for detection of PFM activity. For recording of PFM electrical activity, we used an intravaginal electrode with a large surface to obtain EMG signals of sufficient amplitude with high sensitivity.[2,3] Fortunately, the PFM encompasses only a partial amount of subcutaneous tissue which may possibly further attenuate the amplitude of EMG.[35] To prevent any systematic error during measurements, insertion and the position of the measuring electrode was supervised by the skilled physiotherapist. The normalization of data was not considered necessary as we assessed the same muscle group during one measurement session without removal of the active electrode.[3]

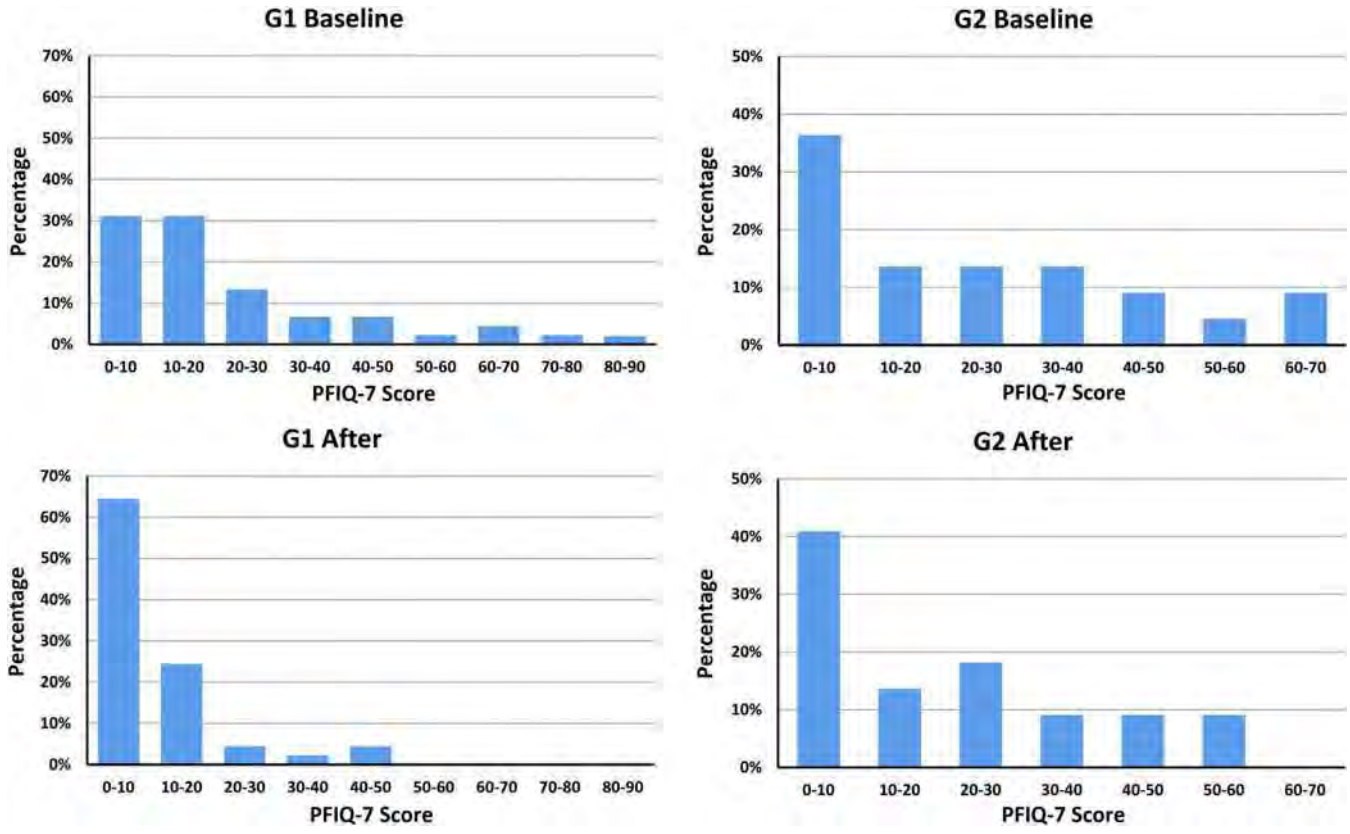


Figure 1. The comparison of PFIQ-7 scores per group and appointment. The relative frequencies of scores reported by the patients of group 1 (G1) and group 2 (G2) are plotted in the graphs. There is a substantial shift toward the lower PFIQ-7 scores in the G1 group after the treatments.

The selectivity of measured values was accomplished by the reference electrode, placed on the abdomen. The signal obtained by the abdominal electrode was subtracted from the recording site to eliminate common components, and received EMG values thus represented summation activity of the whole PFM. To achieve an even greater degree of selectivity, the specific design of the vaginal electrode is required. For instance, Voorham-van et al[14] have been able to successfully measure and compare the activity of selected pelvic muscles (pubococcygeus, puborectalis, bulbospongiosus and ischiocavernosus) by using experimental intravaginal probe with a matrix of 24 electrodes.

Study Limitations

Still, a sEMG measurement faces various challenges. The nature of the recorded electrical signal (amplitude, frequency or noise) is influenced by several factors, such as composition of measured muscle along with structure and position, or placement of electrodes.[35] The core and skin temperature[36] or different humidity of measured environments may also influence the signal parameters. Because of the moisture and temperature within the vaginal lumen, it is difficult to ensure identical conditions at each visit during the intravaginal measurements. Especially, the moisture between the electrode and tissue may lead to decreased EMG amplitude. Furthermore, the electrode positioning is crucial for reliability of sEMG measurement. Therefore, the operator must insert the intravaginal probe consistently with respect to the measured muscles as the power of the signal is affected by the electrode orientation.[37] In addition, the intravaginal probes should be designed in such a way to minimize any impact on the PFM by its insertion to avoid cross talk and motion artifacts.[14]

Indisputably, the appropriate planning of treatments is essential to achieve desired results. Unlike the electrical stimulation, HIFEM is relatively new technology which is still being investigated to some extent. In our study, the HIFEM treatments were administered at least 48 hours apart (2−3 per week) to maximize treatment outcomes but also to avoid muscle fatigue, caused by overtreatment of the PFM, as the therapy with maximum settings produces intense muscle contractions. Presumably, the results would differ because of changes of the treatment frequency; however, this should be verified by future studies.

CONCLUSION

Electromyographic measurement of PFM activity proved to be a valid method for examination of patients with PFD (suffering from urinary incontinence and/or accompanied with sexual dysfunction) treated with HIFEM and electrical stimulation. Surface EMG of the PFMs showed more profound muscle activation after HIFEM treatments along with improved relaxation and enhanced endurance. As well, the PFIQ indicates greater effect of HIFEM procedure based on the significant change of score reported by patients. Documented outcomes imply that the HIFEM procedure is substantially more effective in restoration of PFM strength and treatment of PFD when compared with the electrical stimulation, applied correspondingly in postpartum women.

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Conflict of interest: None.

Funding: None.

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HIFEM PROCEDURE ENHANCES QUALITY OF LIFE OF ELDERLY MEN WITH POST-PROSTATECTOMY INCONTINENCE

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ABSTRACT

Background: Post-prostatectomy incontinence (PPI) is a common and bothersome side effect of the surgery which may be persistent. Aim of this pilot study is to document the change in quality of life (QoL) of subjects with PPI treated by High-Intensity Focused Electromagnetic (HIFEM) procedure.

Materials and methods: Ten male subjects (72.90±3.90 years) with history of prostatectomy accompanied by persistent PPI were recruited. They received six 28-minute HIFEM treatments spaced two treatments per week. Change in subject's QoL was monitored by using standardized King's Health Questionnaire (KHQ) at the baseline, after the last therapy, at 1 month, and 3 months. The usage of absorbent pads was assessed by 24-hour Pad Usage questionnaire. Data was statistically analyzed and tested for normality (α=5%).

Results: All patients showed improvement of QoL after HIFEM treatments. KHQ score decreased significantly in both parts of questionnaire (30.8 points in Part I, P=0.002; 107.5 points in Part II, P=0.001) revealing that subjects improved most in the domains: incontinence impact (23.3 points; P=0.01), social limitations (21.1 points; P=0.01), emotions (18.9 points; P<0.001), role limitations (18.3 points; P=0.03), and sleep/energy (13.3 points; P=0.04). All of the differences in domain scores exceeded the minimally clinically important difference of 5 points. The 1-month and 3-month data showed further improvement in subject's QoL. All ten subjects were using absorbent pads at the baseline. Post-treatment, they reported average reduction of 1.0 absorbent pad per day. Also, two subjects were pad free after the last therapy. HIFEM procedure was safe and no adverse event was found.

Conclusion: The first use of HIFEM procedure for the treatment of PPI in men showed that HIFEM can significantly improve QoL immediately after the last treatment and this improvement may be sustained. In future research, it is necessary to identify longevity of achieved outcomes.

INTRODUCTION

Surgical removal of prostate referred as radical prostatectomy is one of the most common therapeutic options for patients with localized prostate cancer[1–3]. Despite the latest advancements in surgical techniques and therapeutic approaches, still post-prostatectomy incontinence (PPI) is a commonly reported side effect of the operation with prevalence reaching up to 60%[2]. Although patients may recover from PPI in one year post surgery, as much as 65% of them continue to experience incontinence symptoms beyond 12 months[4,5].

During surgery the prostatic segment of urethra is being removed with occasional intraoperative damage to intrinsic and striated urethral sphincters along with impairment of detrusor contractility, triggering the PPI[1,6,7]. Urodynamic examination revealed that vast majority of incontinent men after prostatectomy tend to describe symptoms consistent with stress urinary incontinence (SUI)[8]. There are also several risk factors which increase the subjects predisposition to develop PPI, including pre-existing abnormalities of bladder function, high body mass index, and advancing age[2,9].

PPI is a clinically significant and distressing condition. It has a high impact on quality of patient's life (QoL)[3], negatively affects mental health and subsequently leads to social isolation[10]. Nevertheless, due to the similar etiology of PPI and SUI, the non-surgical strengthening of pelvic floor muscles (PFM) may be effectively used to recover subject's continence and self-esteem.

Continence in men depends on the contribution of urethral constriction by striated muscles which maintains its activation during urine storage and prevents urine leakage when intra-abdominal pressure is suddenly raised during physical activities[6]. To enhance muscular control of urinary incontinence (UI), patients are recommended to perform pelvic floor muscle training (PFMT) by teaching an accurate voluntary PFM contractions timed against increases in intra-abdominal pressure[2]. However, the conventional PFMT faces the difficulty to selectively engage the PFM and patients may not be able to sustain the intensity of contractions.

We hypothesized that High-Intensity Focused Electromagnetic (HIFEM) procedure may be a promising alternative for a non-invasive PPI treatment. It utilizes time-varying magnetic fields of great intensities which selectively targets neuromuscular tissue to induce supramaximal PFM contractions. In contrast to voluntary contractions, the supramaximal contractions are of higher tension and they can be easily sustained, therefore the muscles are encouraged to improve its strength and function. The efficacy of HIFEM procedure for UI treatment and QoL changes in women has been established by the recent research[11–14], nonetheless its effectiveness in men is not clear yet.

The aim of this pilot study is to document changes in quality of life following HIFEM procedure in male population suffering from persistent PPI.

MATERIALS AND METHODS

Ten elderly men with average age of 72.90±3.90 years were recruited. All of them had a history of radical prostatectomy (2014-2017) accompanied with continuous PPI symptoms. At the time of enrollment, they were examined for medical history and eligibility with inclusion/exclusion criteria listed in the manual of investigated device. The study was carried out with respect to generally accepted ethical standards stated in Declaration of Helsinki and all subjects signed informed consent prior to the treatments.

In the course of three weeks the subjects were required to undergo six 28-minute HIFEM procedures (2 sessions per week). Treatments were performed over the pelvic area by utilizing EMSELLA device (BTL Industries Inc., Boston, MA; see Figure 1), capable of inducing supramaximal PFM contractions. EMSELLA uses flat spiral coil to generate HIFEM fields which may be modulated according to the patient's tolerability on the scale from 0-100% (2.5 Tesla). As the proper positioning is necessary to maximize therapy outcomes, subject's posture was supervised by the therapist and verified by using device's positioning system to achieve optimal PFM contractions.



Figure 1: Subject device. The spiral coil is embedded in the center of the therapeutic chair and connected to the main unit which supplies the whole system with power and allows operator to adjust therapy settings.

The evaluation of change in subject's QoL was assessed by the standardized King's Health questionnaire (KHQ, Part I and Part II) and 24-hour Pad Usage questionnaire at baseline and after completion of the treatments. The 1-month and 3-month follow-up visits have been scheduled as optional. Subjects were monitored throughout the whole study for occurrence of any adverse events.

Obtained results were compared to baseline and statistically analyzed by two-tailed paired t-test with level of significance set as 5%. Normality of data was verified by the Shapiro-Wilks test for normality.

RESULTS

All subjects successfully finished the treatments while three subjects completed also the 1-month and 3-month non-mandatory visits. The KHQ showed significant improvement in QoL of all treated patients. The total baseline KHQ score was significantly reduced from 426.9±117.5 to 288.6±133.4 points. The improvement was seen in both parts of questionnaire. Score of Part 1 (general health perception and incontinence impact) decreased on average from 114.2±24.2 to 83.3±26.4 points (-27.0%; P=0.002) post treatment, whereas Part II (role limitations, physical limitations, personal relationships, emotions and sleep/energy, severity measures) showed even more pronounced improvement from 312.8±98.1 to 205.3±93.9 points (-34.4% P=0.001).

The change in score divided according the particular KHQ domains is shown in Figure 2. Detailed analysis revealed that subjects improved most in sleep/energy domain (-13.3 points, 53.3%; P=0.04), emotions (-18.9 points, 42.5%; P<0.001) and social limitations domain (-21.1 points, 42.2%; P=0.01) which indicated a significant shift in subject's QoL. The greatest absolute improvement in score was observed in the incontinence impact domain, as subjects reported reduction of 23.3 points (-30.4%; P=0.01). Also, the role limitations domain, which refers to limitations of daily activities, showed substantial improvement of 18.3 points (31.4%; P=0.03). In general, all of the differences in domain scores exceeded the minimal clinically important difference (MCID) of 5 points, suggested by Kelleher et al[15].

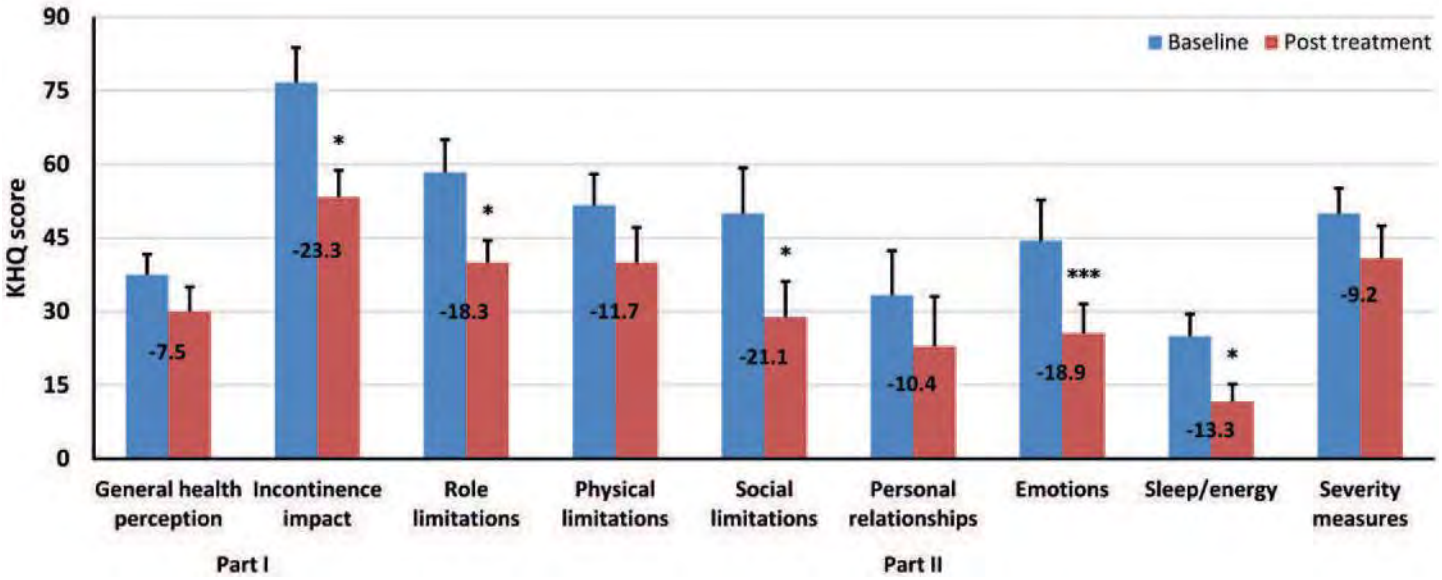


Figure 2: Difference in mean KHQ score achieved in particular KHQ domains (mean ± standard error). Maximum score of each domain is 100 points. Lower scores indicate patient wellbeing and higher scores mean that the QoL is severely affected by the PPI. The statistical significance of difference in score is highlighted by the asterisk (*P<0.05; ***P<0.001).

Further improvement was seen at 1 month in those subjects (N=3) who referred to their follow-up visits (see Table 1). Documented results suggest that effect of HIFEM procedure may improve in time as the examined patients showed a decrease in Part I and Part II scores at 1 month. Subject No. 5 even reached zero score in Part I of the KHQ, meaning that incontinence did not affect his life and he also rated his health condition as "*very good*". Results of subject No. 5 persisted up to 3 months followed with noticeable improvement in Part II of the questionnaire, leading to overall score of 16.7 points (reported in physical limitations domain). Similar tendency was observed in subject No. 8, who also showed continuous improvement of QoL at 1 month which persisted at 3 months. Nonetheless, subject No. 6 was not able to sustain treatment-induced changes at 3 months and reported slight elevation of score in both parts of KHQ, since he returned to his post-treatment values.

24-hour Pad Usage questionnaire revealed that all of the subjects were using absorbent pads at baseline with an average use of 2.5 pads per day. In addition, four subjects reported they wore pads at night due to the nocturia. After the treatments the whole patient group reduced pad usage on average by 1.0 pad (1.5 pads per day on average). Furthermore, two subjects reported to be pad free and two out of four subjects achieved complete reduction of pads used during the sleep.

DISCUSSION

Post-prostatectomy incontinence considerably compromises men's quality of life. As health-related QoL is a multidimensional construct, it involves all aspects of human wellbeing including health status in general, physical activities, psychological state and social interactions[16]. Therefore, many individuals are seeking for an effective treatment options, hoping that they no longer have to worry about the inability to control their bladder during their day-to-day activities. This study documented that HIFEM procedure may be effectively used for treatment of PPI.

The present results showed clinically significant decrease in all KHQ domains which also corresponds with reduced usage of absorbent pads. The procedure was safe and no adverse event was documented.

Previous studies have described that impact of PPI can be reduced by PFM strengthening by the means of pelvic floor muscle exercises or electromagnetic stimulation[2,5]. Majority of the papers studied the evolution of UI and QoL in the 12-month post-treatment period or evaluated effects

This study documented significant improvement in QoL after only six HIFEM treatments. Presumably, adding additional two to four treatments according to the severity of subject's symptoms may result into more noticeable improvement. At baseline subjects achieved highest KHQ score in the incontinence impact domain, followed by the role limitations, physical limitations, social limitations, emotions and severity measures domains, which in general corresponds to severe post-operative UI[19]. The greater is the urinary loss, the greater impact it has on these domains of QoL.

ID	Part I score (range 0-200)				Part II score (range 0-700)			
	Baseline	Post treatment	1 month	3 months	Baseline	Post treatment	1 month	3 months
5	83.3	33.3	0.0	0.0	244.4	83.3	41.7	16.7
6	116.7	116.7	58.3	91.7	233.3	194.4	186.1	222.2
8	91.7	83.3	58.3	58.3	275.0	202.8	113.9	113.9

Table 1: KHQ score (Part I and Part II) of subjects at 1 month and 3 months.

of pre-operative PFMT on male continence as the PPI is iatrogenic, therefore predictable and perhaps preventable[17]. Although it was found that patients with stronger PFM need less time to be continent after the surgery, and at the same time they report higher QoL levels, the evidence is still limited due to the lack of randomized controlled trials[2,18,19]. Also the exercise protocols may possibly fail to properly target the muscles that control continence in men or do not target the aspect of function that needs to be trained[6].

The PPI is associated with impaired functioning of striated urethral sphincter, pubovisceralis, bulbocavernosus, and levator ani muscles which cannot fully compensate the prostate removal, thus control urethral pressure and prevent descent from excessive abdominal pressure[20,21]. Therefore, it is hypothesized that optimal treatment strategy should aim to target these particular muscles. HIFEM procedure utilizes non-invasive and painless electromagnetic stimulation of pelvic floor. It selectively activates motor neurons[22] that innervate striated muscles. The high repetition rate of stimulation forces muscles to perform intense supramaximal contractions which lead to enhanced strength, endurance[23], and re-education. Due to the great penetration, depth, and zero attenuation of magnetic field in biological tissues[24]; the HIFEM procedure is able to effectively stimulate the muscles involved in the male continence mechanism, treat incontinence and consequently improve QoL.

As the severity of incontinence symptoms decreased after the treatments, patients showed uniform improvement in all KHQ domains accompanied with a reduced number of pads used. The examination showed that elderly subjects with persistent PPI appreciated that they were less limited in their social life (being able to visit relatives without being afraid of urine leakage) or when performing daily/physical activities and they also slept better. Emotions domain showed that patients did not feel depressed due to the PPI after the treatments and in general, they reported a more pro-active life style.

We see the strength of our study in detailed analysis of KHQ which is complex, highly reliable, and validated questionnaire that covers important aspects of patient's QoL. On the other hand there are several limitations in this pilot research. The sample size of ten subjects is relatively small and enables only basic statistical analysis. Furthermore, this study lacks solid follow-up data, since only three subjects referred to their 1-month and 3-month follow-ups. In future studies it would be mandatory to observe prolonged effect of HIFEM procedure on QoL similarly to Yamanishi et al[19], as the individual results of subjects 5,6, and 8 suggest that outcomes may considerably improve over time. This coincides with the findings of Frontera et al[25], who observed significant and continuous muscle changes in an elderly man in a 12-week period (approximately 3 months) after the strength training

program. Results may be also influenced due to the specific patient group consisting of elderly men (average age of almost 73 years), where muscle response is mediated through a combination of hypertrophy and neural adaptation[26], and strength gains (although substantial), may be less than in young individuals. Moreover, the male urinary incontinence is being often associated with erectile dysfunction[27]. Since sexual function is also an integral part of QoL, later studies should consider assessing its changes as well.

CONCLUSION

This pilot study documented the first use of HIFEM procedure for the treatment of persistent post-prostatectomy incontinence in men. The achieved results imply that HIFEM is able to significantly improve quality of life of incontinent elderly men, and this improvement may be sustained. Future studies should verify documented outcomes and determine the longevity of achieved changes to establish HIFEM as a convenient first-line modality for treatment of male incontinence.

CONFLICT OF INTEREST

The authors have declared they have no conflicts of interest.

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HIFEM PROCEDURE AND PELVIC FLOOR EXERCISES COMPARISON IN URINARY INCONTINENCE TREATMENT

RANDOMIZED TRIAL ON HIFEM PELVIC FLOOR STIMULATION DEVICE COMPARED WITH PELVIC FLOOR EXERCISES FOR TREATMENT OF URINARY INCONTINENCE: 12-MONTH ANALYSIS

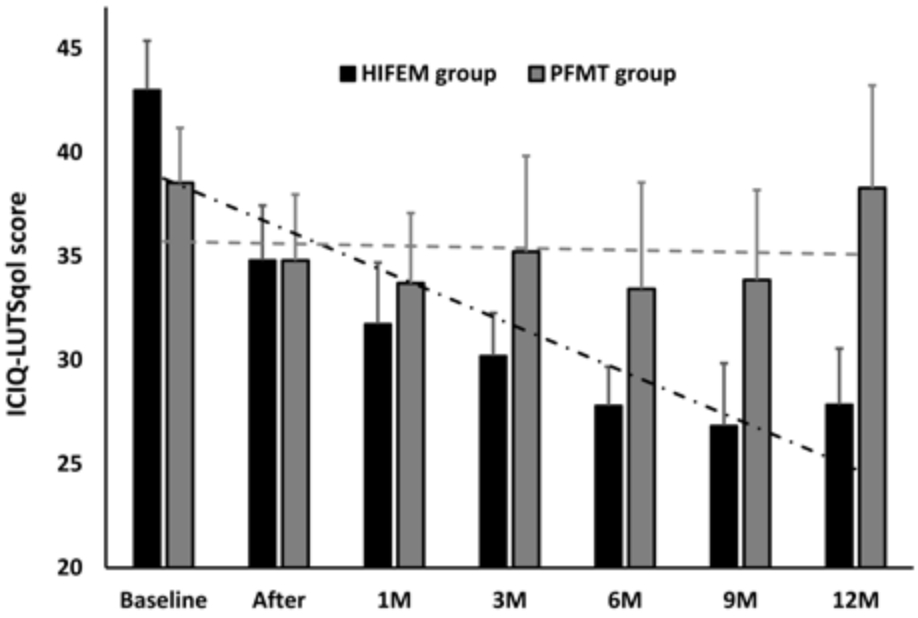
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Presented at 41st Annual Meeting of the American Society for Laser Medicine and Surgery, 2022; San Diego, CA

HIGHLIGHTS

- Forty-seven women (27-66 years) received 6 treatments of either HIFEM or pelvic floor muscle training (PFMT).
- Significant (**-15.2 points**, p<0.001) improvement of ICIQ-LUTSqol score in incontinent subjects was found in the **HIFEM group, but not in the PFMT** group (-5.1 points, p>0.05).
- Urine urgency symptoms were reduced considerably in the **HIFEM group (34%)** when compared to PFMT (5%).
- Pad-using patients reported an improvement of **-1.7 pad per day** in the HIFEM group.
- At 1 year, **86% of patients** in the HIFEM group reported less urine leakage and frequency.



ICIQ-LUTSqol score improvement in the HIFEM (black) and PFMT group (grey) during the whole follow-up including linear trendlines.

FEMALE URINARY INCONTINENCE AND SEXUAL FUNCTION AFTER THE **HIFEM®** PROCEDURE

HIFEM PROCEDURE FOR IMPROVEMENT OF URINARY INCONTINENCE AND FEMALE SEXUAL FUNCTION: 9-MONTH PERSPECTIVE

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2. Hillcroft Medical Clinic, Sugar Land, TX, USA

Presented at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2021

HIGHLIGHTS

- **33 females** (49.2 ± 9.8 years) who showed a **decreased interest in sexual activity accompanied by UI,** were enrolled in this prospective one-arm study.
- Subjects' **continence and sexual function** have been significantly improved.
- The Improvement in UI and sexual function **peaked at 3 months:**
    - **ICIQ-UI SF** score decreased on average by **61% (-6.8 points)**
    - **FSFI** showed significant increase by **33% (+7.3 points)**
    - **PISQ-12** score increased significantly by **24% (+7.9 points)**
- The data suggest that **treatment efficacy was maintained for 9 months.**
- Patients also benefited from increased sexual desire, improved lubrication, desire and orgasmic response.

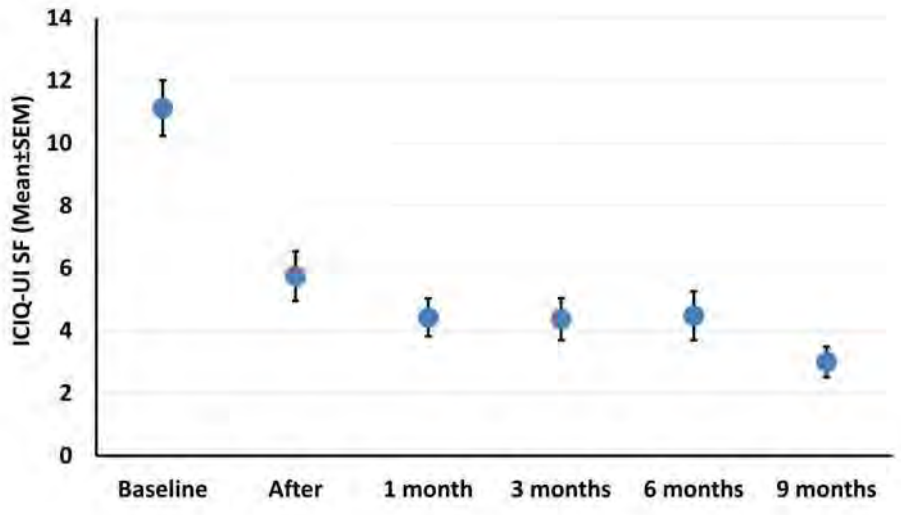


Figure 1: ICIQ-UI SF score has significantly decreased. The level of improvement was stabilized at 1 month and maintained up until 9 months (-8.1 points)

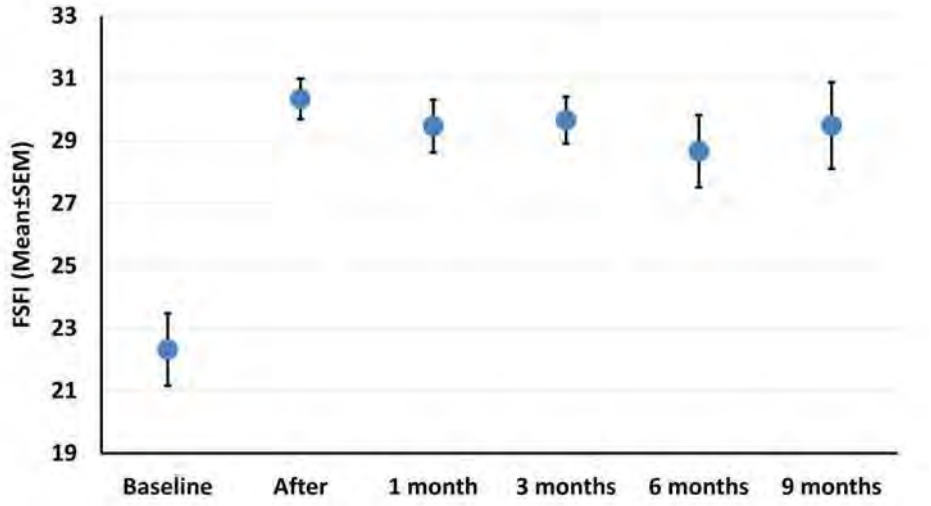


Figure 2: FSFI score significantly improved by +7.1 points at 1 month, exceeding the threshold for female sexual dysfunction (26.55 points). No significant decline in score was seen after the 1 month.

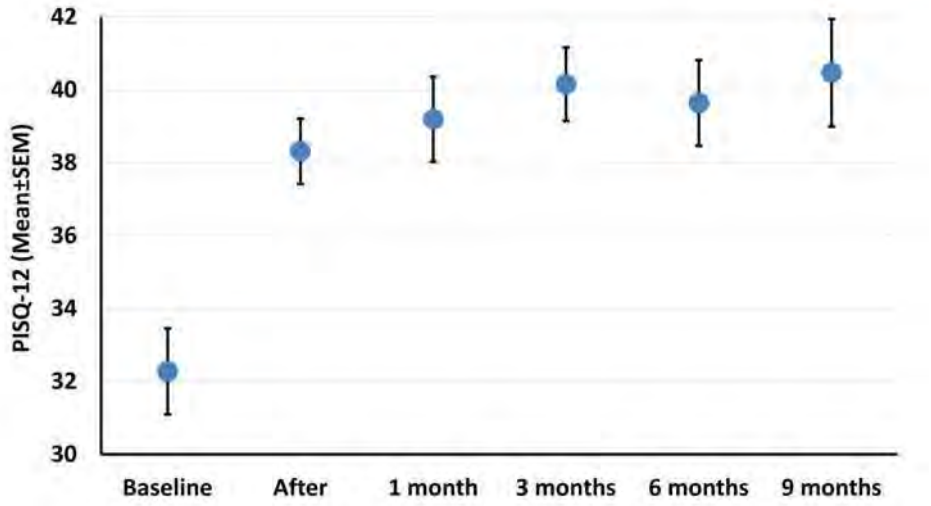


Figure 3: PISQ-12 score was continuously improving, while peaking at 3 and 9 months (+7.9 and +8.2 points, respectively). Subjects reported more frequent orgasm, increased desire and sexual excitement.

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HIFEM TREATMENT OF URINARY INCONTINENCE (UI) IN WOMEN POST GENITOURINARY SURGERY

HIFEM PROCEDURE FOR TREATMENT OF PERSISTENT URINARY INCONTINENCE POST PELVIC ORGAN PROLAPSE AND ANTI-INCONTINENCE SURGERY

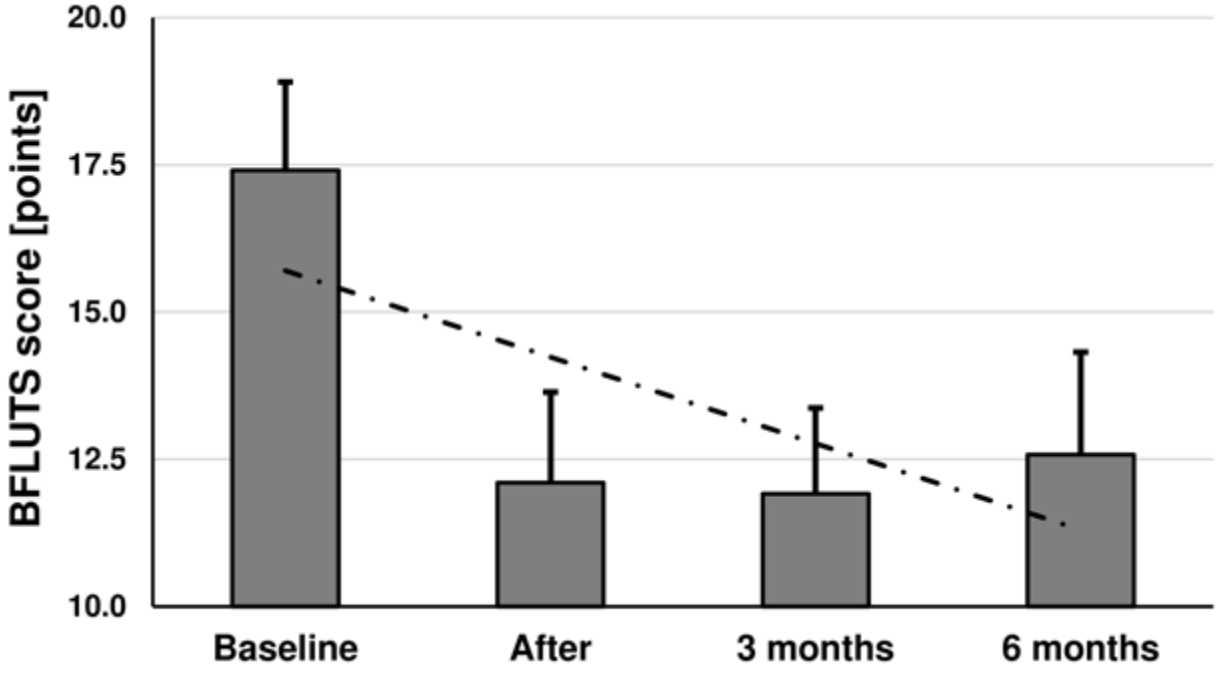
Manish Gopal, M.D., MSCE[1]

1. Center for Urogynecology and Reconstructive Pelvic Surgery, NJ, USA

Presented at 41st Annual Meeting of the American Society for Laser Medicine and Surgery, 2022; San Diego, CA

HIGHLIGHTS

- Fifty females (60.1±12.3 years), with **pelvic organ prolapse (POP) and anti-UI surgery**, received six HIFEM procedures for UI treatment.
- The combined **BFLUTS-SF score decreased significantly** ($p<0.05$) at 3 and 6 months to 11.9±10.2 (-5.5 points) and 12.6±11.7 (-4.8 points).
- The greatest decrease was observed in the **Incontinence domain (-2.0 points**, $p<0.001$), Filling domain (-1.4 points, $p<0.001$) and QoL domain (-1.5 points, $p<0.01$).
- There was a significant improvement in filling, voiding, and incontinence domains regardless of the severity of prolapse.



A decrease in BFLUTS score after the treatment and at all follow-up visits including a linear trendline.

HIFEM® FOR IMPROVEMENT OF SEXUAL FUNCTION

THE NON-INVASIVE HIFEM PROCEDURE FOR IMPROVEMENT OF WOMEN'S SEXUAL FUNCTION

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Presented at IMCAS annual world congress in Paris: January 30, 2020

HIGHLIGHTS

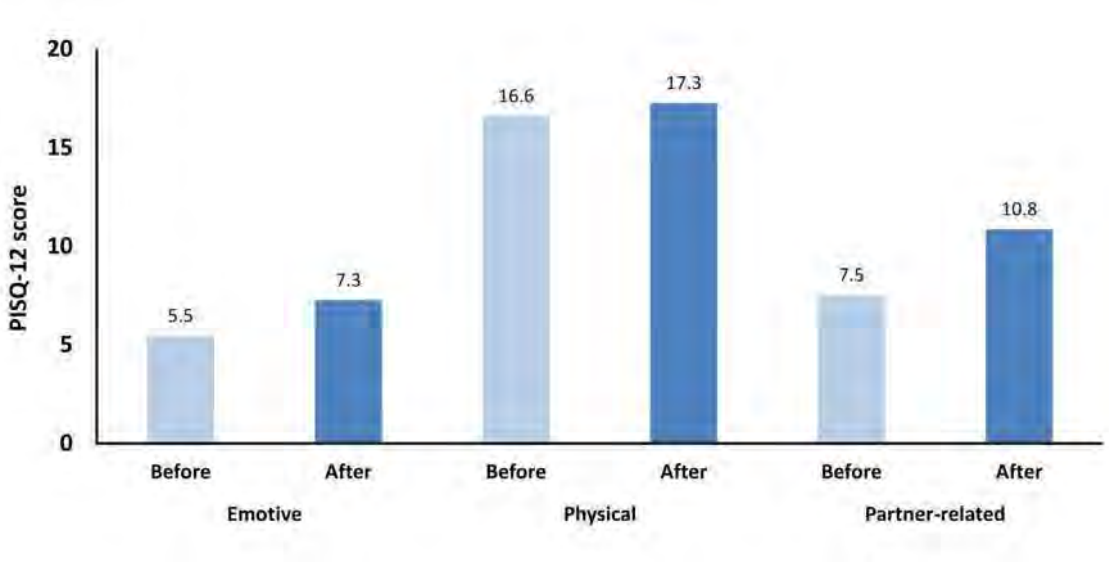
- **HIFEM** procedure **enhanced sexual function** of all treated women after the course of six treatments.
- **PISQ-12** score showed **clinically** and **statistically significant** improvement.
- Subjects reported **more intense** and **frequent orgasm** along with **greater sexual desire** and **excitement**.

DESIGN AND METHODOLOGY

- **Fifteen women** (on average 46.9±14.0 years) were recruited.
- All subjects received **six** 28-minute **HIFEM treatments** to enhance their sexual function.
- Therapies were scheduled **twice a week for three consecutive weeks**.
- **Intensity** of the treatments (0-100%) was **modulated** according to the subject's feedback.
- Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form **(PISQ-12)** was used for **analysis of sexual function** at baseline and at 1 month.
- **Cronbach's** coefficient **alpha** was used to verify **internal consistency** and **reliability** of the data.
- **Safety** of the procedure was **monitored**.

RESULTS

- **Each subject** showed an **improvement** in PISQ-12 total score **when compared** to baseline with minimum improvement of 3 points (range 3-14).
- The mean **score increased** by **5.8 points** (+19%; P<0.001) from 29.6±5.6 to 35.4±5.1.
- The **greatest change** was observed in **partner-related domain** (+3.3 points, P<0.001) mainly due to the **considerable improvement** in subject's **orgasm intensity**.
- Additionally, subjects reported **greater sexual desire** and **excitement**, as they were **more satisfied** with the variety in their sexual life and were more likely to **attain orgasm**.
- The subjects with **lower** PISQ **scores** at the baseline **benefited most** from the treatment, showing that **HIFEM procedure** is able to **improve sexual function** in **women** who are substantially **dissatisfied** with their sexual life.
- **Results** were found to be both **statistically and clinically significant**, since the change in score **highly exceeded** generally accepted level of **MCID** (minimal clinically important difference).
- **HIFEM** procedure was **safe** with no adverse events or side effects.



Mean PISQ-12 score before and after the treatments divided according to the domains. Improvement was found to be statistically significant in each domain (P<0.05).

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HIFEM® FOR MALE URINARY INCONTINENCE

HIFEM PROCEDURE ENHANCES QUALITY OF LIFE OF ELDERLY MEN WITH POST-PROSTATECTOMY INCONTINENCE

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2. Male Sexual Medicine and Rejuvenation Center, San Ramon, CA, USA

HIGHLIGHTS

- Post-prostatectomy incontinence (PPI) is a commonly reported side effect of the radical prostatectomy with prevalence reaching up to 60%[a].
- HIFEM procedure significantly **enhanced quality of life** of men with PPI.
- **All subjects** achieved **improvement** after six HIFEM treatments.
- In general, subjects were **less limited** in their social life, daily activities, physical activities and reported improvement in sleep quality.
- Average pad usage was reduced by **1.0 pad/day**.

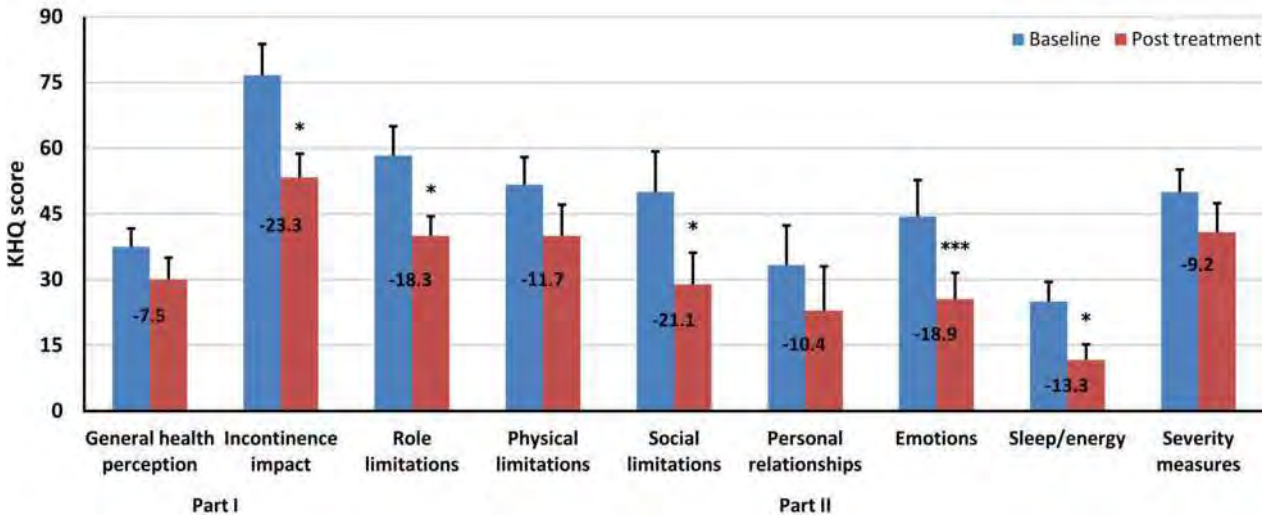
DESIGN AND METHODOLOGY

- Ten **elderly men** (72.9±3.9 years) with a recent history of **radical prostatectomy** accompanied with PPI were recruited.
- They underwent six HIFEM treatments scheduled twice a week for three weeks.
- Subject's **Quality of Life** (QOL) was assessed by King's Health Questionnaire (KHQ) at baseline and post-treatment; 1 and 3-month follow-up were optional.
- 24-hour **Pad Usage** questionnaire was used to identify any changes in the frequency of wearing absorbent pads.
- **Adverse events** were monitored throughout the study.

[a]Anderson CA, Omar MI, Campbell SE, Hunter KF, Cody JD, Glazener CM. Conservative management for postprostatectomy urinary incontinence. Cochrane Incontinence Group, ed. Cochrane Database Syst Rev. Published online January 20, 2015

RESULTS

- **Each subject** achieved favorable **changes** in the QOL after the treatments by reason of reduction in various domain scores of KHQ.
- Baseline **KHQ score** was **significantly reduced** post-treatment.
    - o KHQ Part I from 114.2±24.2 to 83.3±26.4 points (-27%; P=0.002)
    - o KHQ Part II from 312.8±98.1 to 205.3±93.9 points (-34%; P=0.001)
- Subjects reported the highest improvement in the following **domains**: *sleep/energy* (-53.3%; P<0.001); *emotions* (-42.5%; P<0.001); *social limitations* (-42.2%; P=0.01); *role limitations* (-31.4%; P=0.03) and *incontinence impact* (-30.4%; P=0.01).
- In general, all differences in domain scores **exceeded** minimal **clinically important** difference (MCID) of 5 points.
- Individual patients' results at 1-month and 3-month follow-up visits showed **further improvement** of QOL.
- **Pad usage** decreased on average by 1.0 pad from 2.5 pads/day at baseline to 1.5 pads/day after the treatments while two subjects reported to be **pad free**.
- Two out of four subjects who wore pads at night due to **nocturia** achieved **complete reduction of pads** during the sleep.
- No adverse events were found.



Difference in mean score of KHQ domains (mean ± standard error). Maximum score of each domain is 100 points and lower scores indicate patient wellbeing. The statistical significance is highlighted by the asterisk (*P<0.05; ***P<0.001), reduction in score by 5 points indicates clinical significance.

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Journal of Women's Health Care

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Research Article

Randomized Trial of HIFEM Pelvic Floor Stimulation Device Compared with Pelvic Floor Exercises for Treatment of Urinary Incontinence

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ABSTRACT

Objective: The pelvic floor muscles (PFM) are essential for structural support for the pelvic organs. Loss of PFM function can lead to urinary incontinence (UI), a common condition in parous women. This study investigated the efficacy of High-Intensity Focused Electromagnetic (HIFEM) compared to conventional pelvic floor muscle training (PFMT) for the improvement of UI in women.

Methods: Thirty-eight women (27-66 years) underwent six treatments scheduled twice a week for three weeks with either a HIFEM procedure or a standardized pelvic floor exercise. Follow-up visits were performed at 1, 3, 6, 9, and 12 months after the final treatment session. Outcome measures included quality-of-life questionnaires (ICIQ-BD, UDI-6, ICIQ-LUTSqol), pad usage, therapy satisfaction, and therapy comfort.

Results: Analysis of ICIQ-LUTSqol at 6 months showed significant UI improvement in the HIFEM group (-15.2 points, 35%, p=4.4·10-10) but not in the PFMT group (-5.1 points, 13%, p=1.8·10-1). The HIFEM group maintained significant improvement over baseline at 12 months (24%, p=3.4·10-2) while the PFMT group's score regressed (3%, p=9.3·10-1). ICIQ-BD demonstrated greater improvement in urgency symptoms in the HIFEM vs. PFMT group (32% vs. 5%) at 12 months. 86% of HIFEM subjects reported less leakage at 12 months compared to 71% of PFMT subjects. Pad usage decreased by -1.7/day in the HIFEM group vs. -1.0/day in the PFMT group.

Conclusion: The HIFEM procedure appears to be safe and effective for improving female continence and quality of life to 1-year.

Keywords: Electromagnetic Procedure, Incontinence, Leakage, Bladder Diary, Pad Usage

INTRODUCTION

Urinary incontinence (UI) is defined as a complaint of any involuntary and uncontrolled leakage of urine occurring more than twice a month, with the most common forms noted to be stress (SUI; loss of urine on effort, physical exertion, or sneezing or coughing) and urge (UUI; the immediate urge to urinate) [1-3]. The combination of SUI and UUI is present in over 30% of incontinent women and is described as mixed urinary incontinence (MUI) [4-6]. UI symptoms are highly prevalent among adult women (nearly 50% may experience UI[2,7]), negatively impacts the quality of life, and are associated with considerable personal and societal economic impact [7-9]. The prevalence of UI increases with age but is not a normal part of healthy aging. Significant risk factors include childbirth, hormonal changes, and chronic medical conditions such as diabetes, hysterectomy, obesity, and sedentary behaviour [10-12]. All these factors consequently can result in weakening or trauma to the pelvic floor muscles (PFM), increasing the probability of UI. Pelvic floor muscle training (PFMT), commonly known as Kegel exercises is considered first-line therapy [13-14]. However, the efficacy of PFMT relies on patient compliance and physical ability to perform proper PFM contractions [13,15]. Furthermore, biofeedback training with a physical therapist using a vaginal or rectal probe as well as the addition of passive electrical

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Received: 21-Aug-2023, Manuscript No. JWH-23-26283; **Editor assigned:** 25-Aug-2023, PreQC No. JWH-23-26283 (PQ); **Reviewed:** 30-Aug-2023, QC No. JWH-23-26283; **Revised:** 08-Sep-2023, Manuscript No. JWH-23-26283 (R); **Published:** 16-Sep-2023, DOI: 10.35248/2167-0420.23.12.680

Citation: Guerette N, Molden S, Gopal M, Kohli N (2023) Randomized Trial of HIFEM Pelvic Floor Stimulation Device Compared with Pelvic Floor Exercises for Treatment of Urinary Incontinence. J Women's Health Care. 12(9):680.

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stimulation (ES) may be more effective than PFMT alone [16]. A novel technology to strengthen and improve the function of the PFM using High-Intensity Focused Electromagnetic Therapy (HIFEM) has recently been developed. HIFEM utilizes an alternating magnetic field passing through the tissue, inducing brain-independent contractions. These contractions are of higher tension and frequency than can be achieved with voluntary contractions or biofeedback during PFMT and are, therefore, defined as supramaximal. Moreover, since the magnetic field penetrates living tissues without attenuation, the induced contractions achieve greater depth and intensity [17,18]. The purpose of this study is to compare the efficiency of PFMT with biofeedback to the HIFEM procedure for the treatment of female UI.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

This study included adult female subjects diagnosed with UI (either SUI, UUI, or MUI). Inclusion criteria were as follows: female aged 25-70 years, voluntarily signed informed consent, abstinence from any additional treatment of UI including a two-week wash-out period from any prior UI treatment. Exclusion criteria were any contraindication to either HIFEM or PFMT, inability to consent to the protocol or inability to comply with the protocol.

Ethical Consideration

The study design and treatment protocol was approved by the Advarra Institutional Review Board (ClinicalTrials.gov identifier: NCT03969368), and the study adhered to the ethical principles of the 1975 Declaration of Helsinki.

Randomization

This is a prospective randomized multi-center open-label (no masking) double-arm study. Subjects were recruited from the Investigators' existing pool of patients and were randomly distributed into two study groups – HIFEM and PFMT by a computer-generated list.

Treatment Protocol

At the baseline visit, medical history was reviewed and the diagnosis of UI from either SUI, UUI, or MUI was confirmed. Additional causes such as medications, urinary tract infections, and urinary retention were ruled out.

HIFEM Group

Six 28-minute standardized treatments were delivered twice a week, over three consecutive weeks by BTL EMSELLA (BTL Industries Inc., Boston, MA) device. A fully clothed patient was correctly positioned to sit straight in the center of the chair applicator. The device administered an alternating magnetic field of 2.5 Tesla by stimulation coil, to provide non-invasive electromagnetic stimulation of pelvic floor musculature. The stimulation intensity (0-100%) was adjusted according to the patient's feedback based on maximum tolerance.

PFMT Group

A standardized biofeedback protocol adopted from Beth Israel Deaconess Medical Center Physical Therapy department was implemented at all sites. Six treatment visits were delivered twice a week, over three consecutive weeks. During treatment, a vaginal probe was inserted or palpation was performed to monitor therapy and the subject performed the therapy in the supine position with legs straight and slightly abducted.

All patients were required to complete all treatments and five follow-up visits at 1, 3, 6, 9, and 12 months. The occurrence of adverse events was monitored by an investigator while patients were also asked to report any sign of adverse event pain, injury, or discomfort during treatments.

Main outcomes Evaluation and Data collection

Standardized questionnaires were administered to assess symptoms at baseline and at each additional data point. UDI-6 (Urinary Distress Inventory) provided a brief assessment of the impact of symptoms of urinary incontinence (frequency of urination, urine leakage related to physical activity, bladder emptying, and pain or discomfort in the lower abdominal or genital area). ICIQ-LUTSqol (International Consultation on Incontinence Questionnaire Lower Urinary Tract Symptoms Quality of Life Module) evaluated the impact of urinary symptoms on physical activities, social activities/relationships, and mood associated with the interference of UI with the patient's everyday life. The evaluation of pelvic floor muscle strength was conducted through the palpation assessment (in the distal one-third of the vagina) according to the Oxford Grading system.

ICIQ-BD (International Consultation on Incontinence Questionnaire–Bladder Diary) was a three-day patient-completed record for documentation of the drinking habits, micturition (to determine urine frequency per 24 hours), bladder sensation (range 0-4; 0-no sensation of needing to pass urine, but passed urine for "social reasons", 1-normal desire to pass urine and no urgency, 2-urgency but it had passed away before you went to the toilet, 3-urgency but managed to get to the toilet, still with urgency, but did not leak urine, 4-urgency and could not get to the toilet in time so you leaked urine), and pad usage. In addition, a Pad Usage Questionnaire was also utilized to document the number of hygienic pads used by subjects per day. The Subject Satisfaction Questionnaire (SSQ) evaluating patients' satisfaction with the therapy outcomes was designed as two open-ended questions for summarising the patients' experiences during the therapy and after the treatment. Therapy Comfort Questionnaire (TCQ; 5-point Likert scale) recorded the patients' comfort during treatments.

Statistical Methods

The descriptive statistic was calculated (mean, standard error of the mean). All data were analysed for normality (Shapiro-Wilk test). Based on the paired and independent variables measured at multiple time points, parametric tests (paired T-test, One-way Repeated measures ANOVA) and their non-parametric alternatives (Wilcoxon test, Friedman test), were used. The significance level was set to α=0.05 (5%). The analysis was performed using the Microsoft Excel and Real Statistics Resource Pack add-in [19].

RESULTS

Out of the forty-nine patients recruited, thirty-eight (27-76 years old) completed the study, HIFEM (N=23) and PFMT (N=15) as shown in [Figure 1].

ICIQ-LUTSqol, UDI-6, and Palpation examination

a) HIFEM group

The ICIQ-LUTSqol score improvement [Figure 2] was observed after the last treatment (-8.2 points, p=7.2·10-3, N=21) compared with ICIQ-LUTSqol baseline value (43.0±2.4 points), and continued improvement to 6-months with improvement of 35% (-15.2 points, p=4.4·10-10, N=15). Improvement (N=7) was maintained

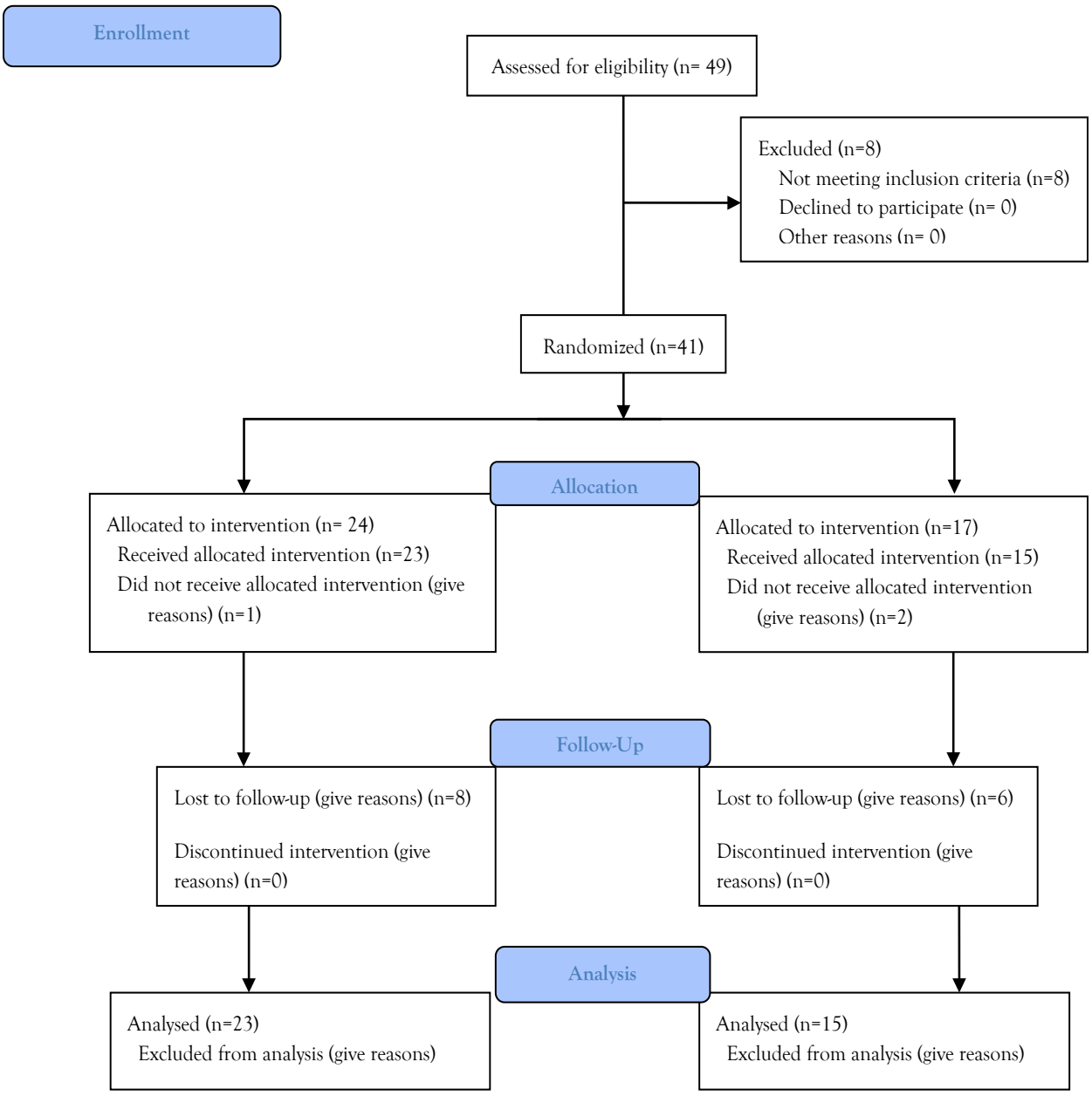


Figure1. Consort Flow Diagram.

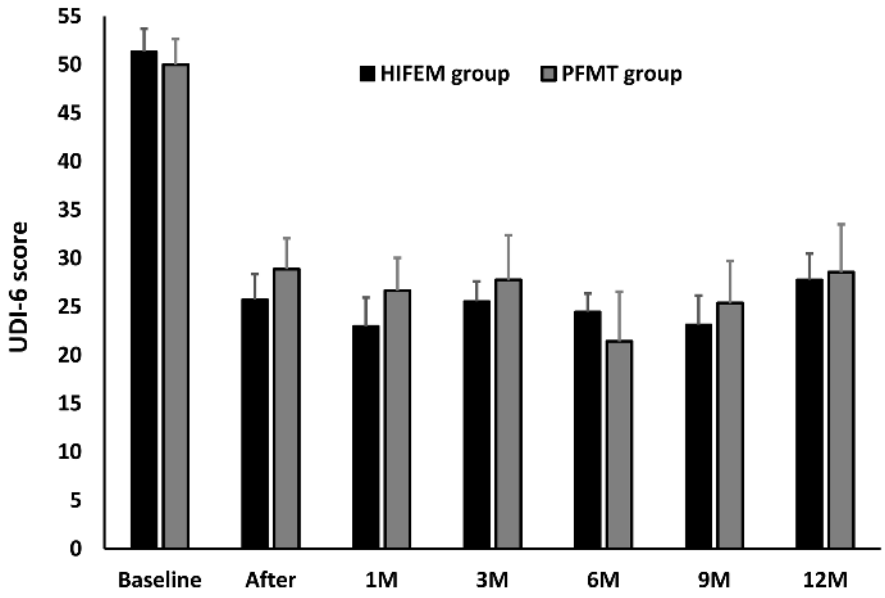


Figure 2: UDI-6 score improvement in the HIFEM (black) and PFMT group (grey) during the whole follow-up

to 12 months with an average value of 27.9±2.7 points (p=3.4·10-2). For the ICIQ-LUTSqol questionnaire, the HIFEM group, patients showed a 34% (-32.8 points, p=2.6·10-3) improvement in bother score immediately after the treatment compared to a baseline of 95.5±10.0 points, and a 68% (-65.1 points, p=1.2·10-8) improvement at 6 months, which was maintained (43%) with a slight decline at 12 months as well.

The UDI-6 [Figure 3] showed an average score of 51.3±4.1 points at baseline which significantly decreased to 25.7±3.7 points (N=19, p=6.3·10-5) and was maintained to 6 months (24.5±3.5 points, N=16) with a 52% improvement (p=1.5·10-6). The improvement in the UDI-6 score was maintained at 12 months (27.8±4.7 points, N=7, p=2.2·10-2).

The average palpation value using the Oxford scale in HIFEM-treated subjects showed a significant improvement of +1.2 points at the first follow-up (73%, p=6.8·10-4, N=18).

b) PFMT group

ICIQ-LUTSqol score and bother rate did not show a statistically significant change (p>5.0·10-2) at any follow-up period as shown in Fig. 2. The baseline value of 38.5±2.6 points declined the most at 6 months by -5.1 points (13%, N=7). The bother rate decreased immediately after the treatment from a baseline value of 94.2±12.6 points to 59.9±14.3 points and was maintained at 67.0±26.2 points 6 months post-treatment (-27.2 points, 29%, p=8.1·10-1). The UDI-6 score significantly decreased exact time by -21.1 points (42%, N=15, p=1.9·10-2), and was maintained to 6 months (-28.6 points, N=7, p=3.0·10-6). At 12 months, the changes in UDI-6 did not achieve statistical significance. Palpation using the Oxford scale achieved a significant improvement value of +1.1 points at the first follow-up (64%, p=7.4·10-3, N=15).

ICIQ-BD & Pad usage questionnaire

The micturition frequency (per 24 hours, the sum of day and night urine micturition frequency) and average bladder sensation were assessed from the ICIQ-BD questionnaire showing the improved trends following both investigated modalities. The averaged ICIQ-BD records for both groups are shown in [Table 1].

The micturition frequency (per 24 hours) decreased in both groups. This was true for both nocturia and daytime micturition. Improvement was observed in both groups from 8-9 voids per day to a normal frequency of 7-voids per day. Nocturia was reduced from 0.8 to 0.5 points (PFMT group) and 0.9 to 0.5 points (HIFEM group).

In the HIFEM group, average bladder sensation decreased from a baseline value of 2.0±0.1 to 1.4±0.1 points after the last treatment (N=15). This level of improvement was maintained to 1 year, peaking at 9 months post-treatment (1.3±0.1, N=7) with a 34% change against the baseline. In the PFMT group, a minor treatment effect on decreasing average bladder sensation improvement was observed as shown in Tab.2. The highest change was achieved at 1 month (N=5) showing a 17% decrease. The effect then regressed at later follow-ups, returning and even exceeding the baseline values.

The number of hygienic pads used for protection during urine leakage was documented by ICIQ-BD and Pad usage Questionnaire. Pad records from ICIQ-BD and Pad usage questionnaires were merged and averaged to obtain usage per 24 hours at respective follow-ups [Table 2]. The number of pads declined after the last

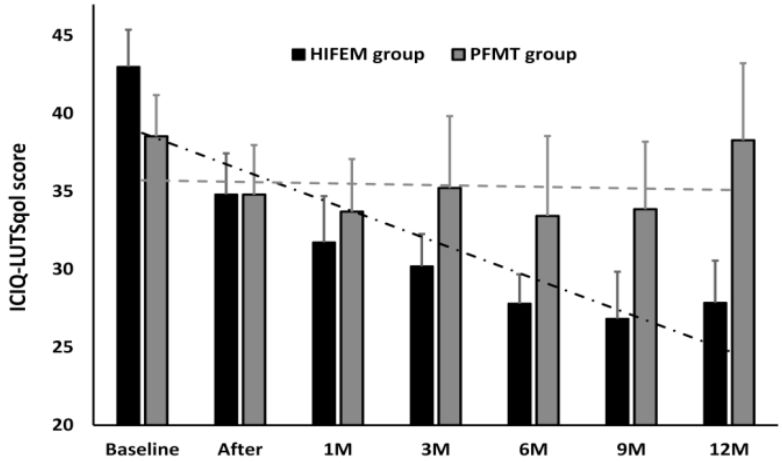


Figure 3: ICIQ-LUTSqol score improvement in the HIFEM (black) and PFMT group (grey) during follow-up including linear trendlines

Table 1: Averaged ICIQ-BD records for HIFEM and PFMT groups. Each visit is an average of the subject's three-day records. The average bladder sensation was counted by dividing the summary score of bladder sensation (assigned to the urgency of each micturition) in a day by Frequency per 24 hours

PFMT group	Baseline	After	1M	3M	6M	9M	12M
Frequency per day	8.0	7.0	6.8	6.8	6.9	6.9	6.9
Frequency per night	0.8	0.5	0.5	0.3	0.5	0.5	0.5
Frequency 24 hours	8.8	7.5	7.3	7.2	7.2	7.4	7.4
Average bladder sensation	1.8	1.7	1.5	1.7	1.9	1.8	1.9
HIFEM group	**Baseline**	**After**	**1M**	**3M**	**6M**	**9M**	**12M**
Frequency day	7.5	6.7	6.9	6.8	6.7	5.6	6.8
Frequency night	0.9	0.7	0.3	0.4	0.5	0.4	0.5
Frequency 24 hours	8.3	7.4	6.9	7.3	7.1	6.0	7.3
Average bladder sensation	2.0	1.4	1.3	1.3	1.4	1.3	1.4

Table 2: Average numbers of hygienic pads (average+SEM) used for protection from urine leakage during the whole study.

	Baseline	After	1M	3M	6M	9M	12M
HIFEM group	3.0±0.4	1.9±0.5	1.5±0.4	1.4±0.2	1.3±0.3	1.4±0.4	1.3±0.5
PFMT group	2.8±0.6	2.3±0.7	2.0±0.6	2.2±1.1	1.8±1.4	1.8±1.1	1.8±1.1

treatment in both groups. Baseline values of HIFEM=3.0±0.4 pads and PFMT=2.8±0.6 pads. In the HIFEM group (N=15), 86.7% reported an improvement in pad use at 6 months (p=8.4·10-3). The average improvement showed a decrease of 1.7 pad/24 hours, and this effect was maintained for up to 1 year (p=1.7·10-3). In the PFMT group (N=8), 62.5% decreased their pad usage. Significant improvement in the PFMT groups was observed only after 9 months (p=4.2·10-2) and was maintained up to 1 year (p=4.2·10-2) with -1.0 pad/24 hours.

Therapy Comfort and Satisfaction evaluation

Therapy comfort questionnaire showed on average 3.0±0.4 points in the HIFEM group and 2.2±0.4 points in the PFMT group. Throughout the subjective experiences from two open-ended questions for satisfaction evaluation, 86.4% of patients from the HIFEM group (N=22) reported less urine leakage and frequency. In addition, 63.6% noted less urgency, and the ease of therapy was appreciated by 54.5% of patients. In the PFMT group (N=14), 78.6% of patients endorsed the effect of PFM exercise, 71.4% noted less urine leakage and its frequency, and 64.3% declared that they are more informed about UI symptoms and treatment than before concerning adjustment of their liquid input.

Minimal Clinically Important Difference (MCID)

A MCID analysis was performed for ICIQ-LUTSqol and UDI-6. Previous studies identified the MCIDs for the ICIQ-LUTSqol questionnaire as a difference of 4-6 points[20] and for UDI-6 as 11 points[21]. Considering the formerly inferred threshold values, it can be concluded that the improvement achieved in the HIFEM group was clinically significant, due to sufficient differences in both questionnaires (minimal difference of ICIQ-LUTSqol=8.2 points and UDI-6=25.6 points). In the PFMT group, the MCID was achieved for UDI-6 (21.1 points), however, this was not the case for changes in the ICIQ-LUTSqol with a maximum change of 5.1 points.

DISCUSSION

Pelvic Floor Therapy with or without biofeedback as reported by [22, 23, 24] has traditionally been considered the standard for pelvic floor rehabilitation. This modality, however, has significant limitations. Most women with poor pelvic floor control have, by definition, poor muscle and nerve function. Any therapy requiring the patient to engage neurologically compromised and traumatized muscles can be challenging. Electrical stimulation has been used to overcome this limitation; however, it predominantly stimulates the muscles in close proximity to the electrodes, limiting the efficacy of this method due to the dependence on the electrode placement. The HIFEM technology overcomes this limitation by creating an electromagnetic field encompassing the entire pelvic area and engaging all pelvic floor and accessory musculature. Further, the HIFEM is supraphysiologic, engaging the muscles more intensely and more rapidly than is otherwise possible. Prior single-arm studies have supported HIFEM's success, demonstrating significant improvement in continence and quality of life to 6 months post-treatment [17,18,25,26] reported on HIFEM compared to electrical stimulation for UI treatment using electromyographic measurements and 3D transperineal ultrasonography of the pelvic floor with the HIFEM group demonstrating superior results. This evidence also provided further insight to support the earlier findings [25, 26].

This study was designed to prospectively compare PFMT with biofeedback to HIFEM for improvement in female urinary continence. The study results demonstrated a significant improvement in the ICIQ-LUTS qol score in the HIFEM group. The improvement achieved statistical significance at the first follow-up and was maintained to 12 months. A peak improvement of 35% was noted at 6 months. Conversely, the PFMT group subjects did not show a statistical improvement in ICIQ-LUTSqol scores at any follow-up interval. The UDI-6 indicated improvement in both the HIFEM and PFMT groups up to 52% and 42% respectively to 12-month follow-up. Of particular note is the ICIQ-LUTSqol bother rate evaluation. In this analysis, the HIFEM group achieved about 2.4 times higher improvement ($P<0.01$) in QoL than in the PFMT group ($P>0.05$) at the 6-month follow-up interval.

Evaluation with the ICIQ-BD indicated the micturition frequency per 24 hours decreased in both groups from 8-9 times per day to 7 times per day. Bladder sensation improvement was seen only in the HIFEM group and was most prominent at 9 months (-34%). PFMT appeared to have minimal effect on bladder sensation.

Regarding pad usage and SSQ, in the HIFEM group, 86.7% of subjects reported an improvement in pad use at 6 months, and 86.4% of patients reported less leakage and frequency. In the PFMT group, 62.5% of subjects reported improvement in pad usage and 71.4% reported less leakage and frequency. Quantitatively, the HIFEM group reduced pad usage by 1.7 pads/24 hours and the PFMT group reduced pad usage by 1.0 pad/24 hours. This was maintained for 1 year. The clinical significance of results was demonstrated in the HIFEM group for the ICIQ-LUTSqol but not in the PFMT group. UDI-6 scores initially demonstrated clinically significant improvement in both groups but the PFMT group did not show significant ($P>0.05$) improvement at 12 months compared to the HIFEM group.

The strengths of this study were the randomized prospective multi-center design and standardization of both therapy arms. This is the first study to evaluate PFMT and HIFEM in a prospective comparative way. There were also limitations to the study. The most significant was the drop-out rate exacerbated by the COVID-19 pandemic. This may have led to certain aspects of the study being underpowered. Numerous key measures, however, achieved statistical significance.

CONCLUSION

The HIFEM procedure appears to be a safe and effective modality for improving female continence and related quality of life to 1-year. When compared to the conventional pelvic floor exercise, the HIFEM procedure may be more effective and better tolerated. Larger, higher-powered studies are warranted.

DECLARATION OF INTEREST

The authors have declared they have no conflicts of interest

ACKNOWLEDGEMENT

None

FUNDING STATEMENT

This IRB-approved study (ClinicalTrials.gov Identifier: NCT03969368) was sponsored by BTL Industries.

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Study Book

EXION™



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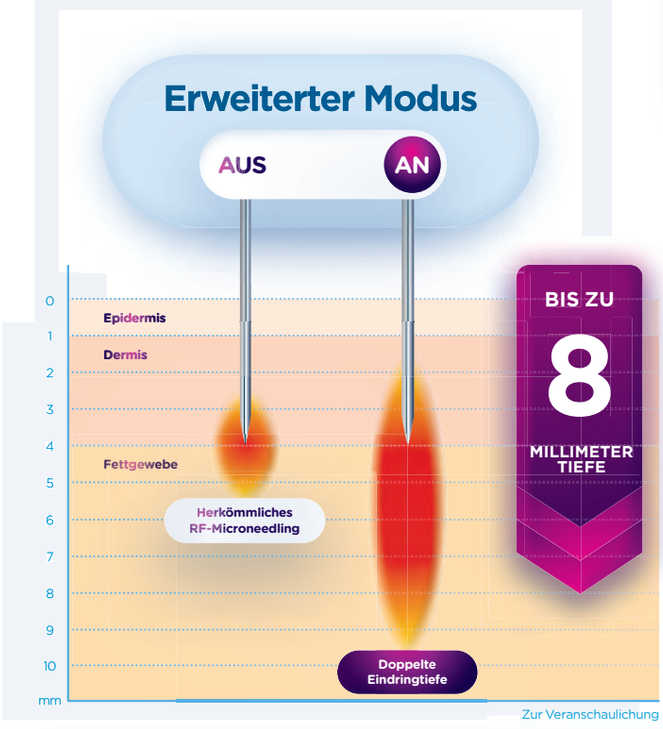
EXION™ Radiofrequenz-Microneedling

WIRKMECHANISMUS

RF-Microneedling ist eine minimal-invasive ästhetische Behandlung, die das Erscheinungsbild der Haut durch kontrollierte thermische Mikroverletzungen in den tieferen Schichten der Dermis verbessert. Erreicht wird dies durch den Einsatz feiner Mikronadeln, die zusätzlich Radiofrequenzenergie abgeben. Während der Behandlung wird das Zielgewebe auf Temperaturen zwischen 60 bis 80 °C erhitzt, was zu einer Koagulation und Denaturierung alter Kollagen- und Elastinfasern führt.[1–4]

Allerdings weisen bestehende Technologien einen Nachteil in der Komfortabilität der Behandlung auf. Dieses Unbehagen schreckt oft Patienten davon ab, weitere Behandlungssitzungen aufzusuchen. Die Schmerzen werden durch das Eindringen der Nadeln und die RF-Energie im Gewebe verursacht, insbesondere bei subdermalen Behandlungen, die tiefe Nadelpenetrationen erfordern. Das Schmerzempfinden steigt mit der Eindringtiefe der Nadeln, was mit der Aktivierung mehrerer Arten von Mechanorezeptoren in der Dermis zusammenhängt, einschließlich Schmerzrezeptoren.[5,6].

Die EXION™ Fractional RF-Microneedling-Technologie bietet ein komfortableres Erlebnis, indem sie eine einzigartige Kombination aus monopolarer Radiofrequenz und KI-gesteuerter Energieabgabe verwendet, die eine tiefe Gewebepenetration ohne vollständige Nadelinsertion ermöglicht. Die EXION™ Fractional RF-Technologie überwindet das intensive Schmerzempfinden, indem sie die Nadel nur 4 mm tief einführt und darunter einen zusätzlichen thermischen Gradienten von 4 mm erzeugt. Auf diese Weise werden die tiefen mechanischen Schmerzrezeptoren umgangen, und das subdermale Gewebe kann bis zu einer Tiefe von 8 mm behandelt werden.



Zur Veranschaulichung

Ohne tiefgehendes Wissen könnte man annehmen, dass ohne vollständiges Einführen der Nadel oder mehrfache Durchgänge “microneedling-ähnliche” Ergebnisse nicht erzielt werden können. Die klinischen Studien deuten jedoch auf das Gegenteil hin.

Unter anderem Duncan sowie Clark-Loeser & Halaas führten Studien zur Single-Pass Anwendung im Gesicht bzw. zur Behandlung am Körper durch. Beide Studien umfassten drei Therapiesitzungen und zeigten beeindruckende Ergebnisse mit hoher Patientenzufriedenheit. Clark-Loeser berichtete, dass 82% der Probanden die Behandlungen als angenehm empfanden und es eine 41%ige Reduktion von Aknenarben gab, wie durch 3D-Fotoanalyse nachgewiesen wurde. Die zweite Studie zeigte, dass 90% der Probanden selbst eine signifikante Verbesserung ihres Erscheinungsbildes meldeten, bei lediglich leichtem Schmerzempfinden und 98% äußerten Zufriedenheit mit den Ergebnissen. [7,8].



3 MONATE NACH DER LETZTEN BEHANDLUNG; MIT FREUNDLICHER GENEHMIGUNG VON: DIANE DUNCAN, M.D.

EXION™ Fractional RF ist eine bahnbrechende Technologie, die die Wahrnehmung von mikronadelbasiertem Radiofrequenz-Microneedling als schmerzhaftes Verfahren verändert. Sie verbessert das Empfinden der Patienten hinsichtlich der Behandlung und erzielt gleichzeitig hervorragende Ergebnisse bei der Behandlung von Dehnungsstreifen, Aknenarben und insgesamt bei der Hautverjüngung sowie bei der subdermalen Remodelierung.

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ACNE SCARS SMOOTHING AND TEXTURE IMPROVEMENT

EFFICACY AND SAFETY OF NOVEL AI-CONTROLLED FRACTIONAL RADIOFREQUENCY FOR ACNE SCARS TREATMENT AND SKIN TEXTURE IMPROVEMENT

L. R. Clark-Loeser, M.D.[1], Y. Halaas, M.D., FACS[2]

1. Precision Skin Institute, Davie, FL, USA, 2. Yael Halaas, MD, New York, NY

Presented at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2022

Highlights

- 34 patients (30 women, 4 men)
- **3 single-pass FRF treatments**, 7-14 days apart
- All patients attended 1-month and 3-month follow-ups
- The efficacy of the treatment was analyzed using the **GAIS evaluation** as well as **3D skin analysis**

41%

Improvement in acne scars

82%

Patients reported comfortable treatment



Acne scar improvement on a 26-year-old patient at baseline (left) and 6-month follow-up visit (right)

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STIMULATION OF COLLAGEN PRODUCTION VIA RF MICRO-NEEDELING

INVESTIGATION OF HISTOLOGICAL CHANGES INDUCED BY A NOVEL FRACTIONAL RADIOFREQUENCY DEVICE FOR SKIN REJUVENATION IN PORCINE SKIN TISSUE

MVDr. J. Bernardy Ph.D.[1]

1. Veterinary Research Institute, Brno, CZ

Presented at ODAC Dermatology Conference 2023, Orlando, FL

Highlights

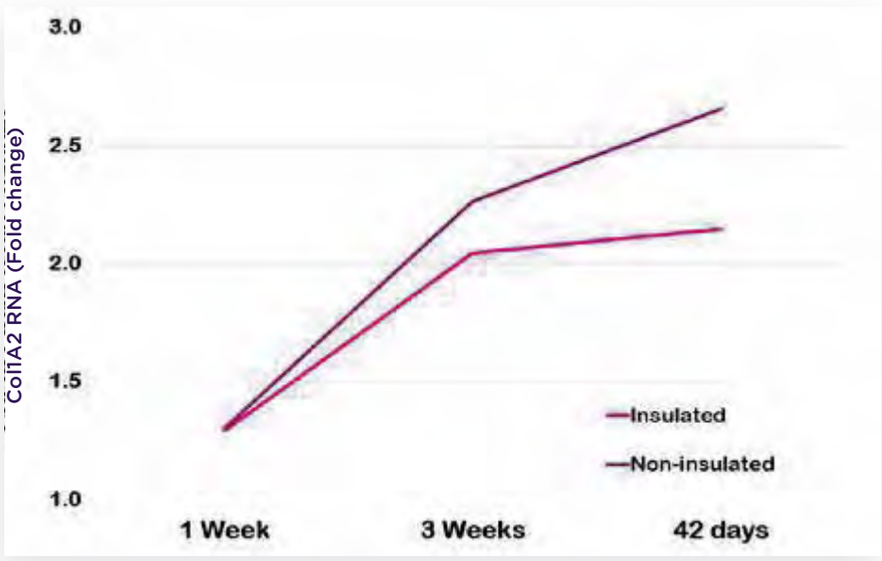
- Three swines were treated (on average 5 years old)
- The goal of this study was to evaluate **effects of insulated** and **non-insulated needles on skin texture**
- Samples were collected 1 week, 3 weeks, and 42 days post-treatment and evaluated by **PCR assessment of collagenases**
- **Both needle types induced a strong neocollagenesis response**

2.5x

More collagen with NON-INSULATED tips

2x

More collagen with INSULATED tips



Change in the skin collagen content following treatment by insulated and non-insulated microneedle tips

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INNOVATIVE RF MICRONEEDLING WITH MINIMAL DISCOMFORT

EVALUATING THE EFFICACY OF FRACTIONAL RADIOFREQUENCY TREATMENT FOR FACIAL ACNE SCARS AND WRINKLES: PRELIMINARY DATA

Diane Duncan M.D., FACS[1]

1. Plastic Surgery Associates, Fort Collins CO, USA

Presented at the American Society for Laser Medicine and Surgery (ASLMS), Phoenix, Arizona, April 13-16 2023

Highlights

- 14 patients (13 women and 1 man) received facial or body treatment
- **3 single-pass FRF treatments** spaced 7-14 days apart
- The results were analyzed using **comfort and pain assessment** as well as **GAIS evaluation**
- All patients attended a 1-month and 3-month follow-up

93%

Patients reported improved appearance in the treated area

98%

Satisfaction with the results



Acne scars improvement in a 22-year-old patient
during 3-month follow-up visit (right) compared to baseline (left)

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Revolutionary Fractional RF Microneedling Enables Deep Tissue Penetration Without Full Needle Insertion for Skin Rejuvenation and Fat Reduction.

L.R. Clark-Loeser, M.D.[1] and Y. Halaas. M.D., FACS.[2]

1. Precision Skin Institute, 3501 S. University DR, Suite 5, Davie, FL, USA

2. Yael Halaas, MD, New York, NY

Abstract

The Exion Fractional RF applicator is a new technology used in RF microneedling, a minimally invasive cosmetic treatment that improves the skin's appearance. The applicator uses a unique combination of monopolar radiofrequency, AI-controlled energy delivery, and Extended mode allowing for both deep tissue penetration without needle insertion and a single pass procedure. This technology overcomes intense pain sensation associated with traditional RF microneedling by creating a thermal gradient below the needle to affect subdermal tissue up to 8 mm in depth. Clinical studies have shown that this breakthrough technology yields great results in treating stretch marks, acne, acne scars, as well as overall skin rejuvenation and fat reduction. It improves the patient's perception of the treatment while providing impressive results with high patient satisfaction rates.

Keywords: AI-controlled energy delivery, Deep tissue penetration, Single pass procedure, Thermal gradient, RF microneedling

Introduction

RF microneedling is a minimally invasive aesthetic procedure without significant downtime or serious complications. In the last few years, microneedling procedures have seen the highest growth among other skin rejuvenation treatments. Standard non-energetic microneedling has been rapidly replaced by fractional radiofrequency, which brings significant benefits to patients and provides the ability to treat a wider range of indications [1,2].

Generally, RF microneedling uses the application of radiofrequency energy through a set of small needles that are inserted into the skin. This treatment is designed to improve the appearance of the skin by inducing controlled thermal damage in the deeper layers of the dermis or subcutaneous fat tissue; in addition to mechanical damage via the penetrating needles.

When the needles penetrate into the deep layers of the skin, they create microchannels in the tissue to which the RF energy is delivered. The RF is used to generate heat of up to 60-80°C which leads to controlled thermal damage in the dermis. Such intense heating results in coagulation and denaturation of old collagen and elastin fibres. This process stimulates the body's natural healing response, leading to the formation of new collagen and elastin fibres [3–6].

Although the microneedling RF has become a widely popular procedure yielding great results, the major drawback of existing technologies lies in high treatment discomfort. Due to the needles penetrating the skin and the RF heating the treatment is often perceived as very painful even when using numbing creams. The painful and uncomfortable perception is further enhanced by treatments requiring multiple passees, when the already micro injured skin is again penetrated with

needles and RF. Pain perception is especially associated with bodily treatments, where it is desired to treat subdermal layers, thus requiring deep needle penetrations of up to 8 mm. It is not uncommon that patients refuse to come for additional treatments after a single session[7].

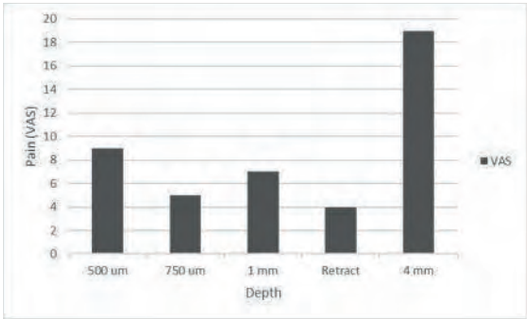
Exion Fractional RF

Exion Fractional RF technology has been designed to revolutionise this approach by tackling the major drawbacks to provide the major benefits of the microneedling RF but with significantly more comfortable experience. A unique combination of monopolar radiofrequency and AI controlled energy delivery has enabled deep tissue penetration without requiring full needle insertion, allowing for a single pass procedure.

Deep tissue treatment without full needle insertion

The depth of needle penetration during microneedling RF procedures is directly related to the intensity and frequency of pain experienced; the deeper the penetration, the greater the sensation of pain. Which is logical, because the pain receptors are present throughout all layers of the skin, thus with deeper penetration more pain receptors are stimulated along the needle. Such needle insertion generates a potent mechanical stimulus that triggers the activation of several types of mechanoreceptors located in the dermis, including pressure-sensitive Ruffini endings, movement-sensitive hair follicle receptors (Pacinian corpuscles), and mechanoreceptors innervated by single nerve endings [8–10].

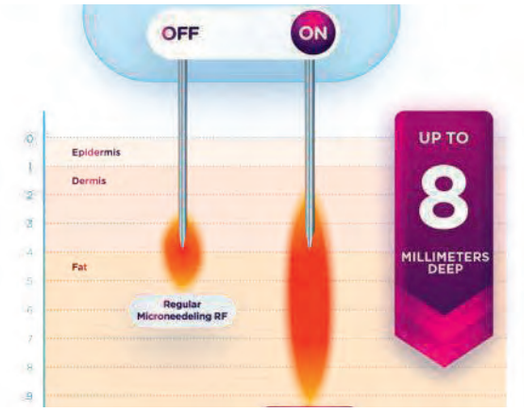
Although the pain sensation generally increases with needle penetration depth, there is a significant escalation in perceived pain intensity when needles are inserted to depths of 4 mm or greater.. The induction of heightened pain sensation is primarily attributed to the nerve pain receptors rather than superficial receptors[7]. These are highly concentrated at the subcutaneous and dermal layers. Local anaesthetics are able to block impulses from the superficial receptors but their effect is very limited on larger nerve endings localised in the depth at around 4 mm [11].



The absolute VAS pain scores associated with the insertion of microneedles into the skin indicate a significant difference in pain perception intensity when inserting needles to depths of 4mm or more[7].

Exion Fractional RF addresses the issue of intense pain sensation associated with deep tissue treatments by limiting needle penetration to 4 mm and creating a thermal gradient extending 4 mm below the needle. This approach bypasses the deep mechanical pain receptors enabling the subdermal tissue to be affected up to a depth of 8 mm.

The generation of thermal gradient is linked to the AI controlled energy delivery and monopolar nature of used radiofrequency, which requires the use of a neutral electrode located in the back of the patient. Therefore, when a long enough RF pulse is brought to the needle tip, the RF energy is directed towards the neutral electrode and as the energy passes through the tissue, it creates an additional thermal gradient below the needle. The built-in AI adjusts the pulse duration and power delivery automatically, optimising the energy flow to create the thermal gradient. This approach enables treatment of deep subdermal tissue without requiring full insertion of the needles.



The Extended mode delivers RF energy up to 4 mm beyond the needle tip, allowing for greater depth and tissue penetration without the need for physical puncturing of the tissue.

AI for Single pass treatment

However, such deep penetration may not be desired for facial treatments or when only skin remodelling is desired since it requires precise energy delivery. While deep tissue penetration is desirable in some treatments, facial treatments, and skin remodelling procedures require precise energy delivery rather than deep penetration. To ensure this precision, the device offers the option to switch off the Extended mode and provide greater control over energy delivery to the targeted depth.

When the mode is turned off, the device generates RF pulses that are of higher intensity but shorter duration , which physically does not allow energy to be directed towards the neutral electrode. The energy is localised only along the needles without a deep thermal gradient below the needle tip, which resembles traditional FRF devices that have been used for many years.

However, unlike any other currently available microneedling RF technologies, Exion Fractional RF has been enhanced with an AI pulse control system, eliminating the need for multiple passes during treatment. Since the skin parameters differ from patient to patient and even from one body area to another, the AI retrieves impedance measurement from every single needle and during each pulse, when the skin and needles come into contact. Then, the AI evaluates this information and uses it to adapt the major pulse parameters to optimise the energy delivery for highest efficacy.

Many parameters are automatically set for each pulse of the device including the RF power, pulse length, and delivery rate. The technology ensures that the required energy is delivered during each pulse and from each needle based on individual needs of each patient and treatment area. The AI guarantees consistency and homogeneity of the delivered energy, which eliminates the need for repeating the application on already treated areas.

This single pass approach avoids excessive micro-injuries and prevents irritation of once-injured spots which significantly increases the comfort perception of the treatment. [12]

Increased comfort does not mean less results

Without in-depth knowledge it could be assumed that without full needle insertion or multiple passes it is not possible to achieve the “microneedling-like” results, however, the clinical studies suggest otherwise.
Duncan et al. assessed the effectiveness of single pass therapy on the face and the thermal gradient treatment on the body. The study involved three therapy sessions, and the results are impressive. 90% of subjects self-reported improved facial appearance. Also 98% expressed their satisfaction with the results [13].

Clark-Loeser & Halaas reported that 82% of subjects found the treatments comfortable, and there was a 41% reduction in acne scars, as shown through 3D photo analysis. The efficacy of the treatment on the cellular level has been confirmed in a study by Bernardy et al. who showed significantly increased levels of collagen, which was elevated by 2.5 times [14].



53-years old female at 1 months after facial wrinkle treatment.



53-years old male at 3 months after facial treatment.

Solution For All Skin Types

To take into account the skin specifics related to skin types, the Exion Fractional RF is compatible with two types of needle tips: non-insulated and insulated microneedles tips. Non-insulated microneedles deliver energy along the entire length of the needle during one insertion, resulting in a more profound clinical effect along the entire microchannel wound. This approach affects the entire skin layer. However, this may not be suitable for higher skin types, where irritation of the upper layer of the skin may lead to hypo- or hyperpigmentation.
Insulated microneedles were thus designed to deliver the energy only at the needle tip, allowing the physician to target specific depths of the dermis while protecting the epidermis from heat and thermal damage. This approach is compatible with all skin types (I-VI) and allows for procedures that are less aggressive and safe from pigmentation changes [15].

The availability of both treatment approaches and the adjustable needle depth from 0.5 to 4 mm provides high versatility for the operator allowing to tailor the treatment according to the various conditions and their severity and also to fit the patient's expectations.

What happens in tissue?

During the microneedling RF treatment the affected tissue is heated to temperatures of 60-80°C leading to coagulation and denaturation of old collagen and elastin fibres. Mechanical and thermal injuries trigger a successive wound healing cascade of inflammation, proliferation, and remodelling of the skin's collagen and elastin fibres [3,16].

The healing process starts with a release of potassium and proteins that alter intracellular resting potential. The first phase of the cascade is the inflammation phase, which begins shortly after the injury with the release of chemotactic factors from platelets; resulting in invasion of other platelets, neutrophils, and fibroblasts. Thus shortly after the application; the skin erythema and edema can be observed at the place where the needles penetrated the skin.

In the second phase, proliferation phase, monocytes replace neutrophils and change into macrophages with subsequent release of numerous growth factors, including platelet-derived growth factor, fibroblast growth factor (FBF), and transforming growth factors; stimulating the fibroblasts to synthesise new fibrous structures. Keratinocytes then start to re-establish the basement membrane by enhancing the production of laminin and collagen types IV and VII. The studies have also shown up-regulation of a cytokine that prevents aberrant scarring, increased gene

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expression for collagen type I, and elevated levels of vascular endothelial growth factor. The levels of metalloproteinases, which are crucial for long-term remodelling, showed an increase in correlation with histological findings.

The last phase, the remodelling phase, which is mainly achieved by the fibroblasts, continues for months after the injury, and collagen is formed in the upper dermis over a period of a year or longer. After the cutaneous injury, a fibronectin network is created, providing a matrix for collagen type III deposition, which is eventually replaced by Type I collagen. This transition occurs over several weeks, resulting in clinical skin tightening and rhytide reduction. Over the next several months a more gradual tightening effect, called "secondary tightening" is observed, which translates into increased dermal thickness, density, firmness and elasticity, and even epidermal thickness [2,12,17,18].

Multiple clinical and histological studies investigating the synergy effects of RF and microneedling on skin have shown significant effects not only for skin tightening, reduction of wrinkles, or improving skin tone and texture, but they have also found improvement of conditions such as hyperhidrosis [19], acne, acne scars, body scars, stretch marks and many more indications are being investigated [20–28].

In conclusion

Exion Fractional RF is a breakthrough technology in the field of microneedling RF as this is the first approach that allows treating deep subdermal layers without full needle insertion. The technology uses advanced artificial intelligence to achieve consistent results with a single pass technique, without the need for additional passes. Designed to change the paradigm of microneedling being a horrifyingly painful procedure it improves the patient's perception of the treatment, while yielding great results when treating both the face and body.

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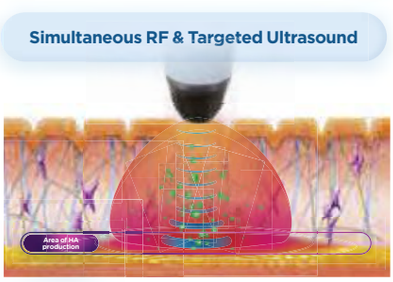
EXION™ Face & Body Applicators

MECHANISM OF ACTION PAPER

Not many know that the first signs of aging are often due to a shortage of hyaluronic acid rather than changes in collagen or elastin. Hyaluronic Acid creates volume and provides structural support, intense hydration, and plumping effects to the skin.[1] Unfortunately, its concentration decreases as we age. At age 60, our skin has 50% less hyaluronic acid than when we were in our 40s.[2] Thus, aestheticians counter the hyaluronic acid depletion by delivering manufactured HA into the skin through topical solutions, injectable dermal fillers, and oral remedies, which may substitute the natural function of skin cells but do not encourage the body to produce more HA on its own.[1]

Specialized cells called fibroblasts produce HA, as well as collagen and elastin. However, with age, their activity decreases which leads to the continuous depletion of all three components. Yet, it has been shown that the fibroblast activity can be rebooted by exposure to external stress, such as mechanical or heat stress. Studies documented that heat or mechanical stimulation is able to enhance collagen and elastin levels. However, the hyaluronic acid levels remained intact.[3] The studies also found slight variations in the responses to different types of stress. Therefore it has been proposed that inducing the two types of responses simultaneously could be the key to restarting the production of hyaluronic acid as well. For this purpose, a new technology has been developed. It combines monopolar radiofrequency and targeted ultrasound to provide the two required stress factors and it has indeed been shown to effectively boost the production of all skin components, including hyaluronic acid. [4–8]

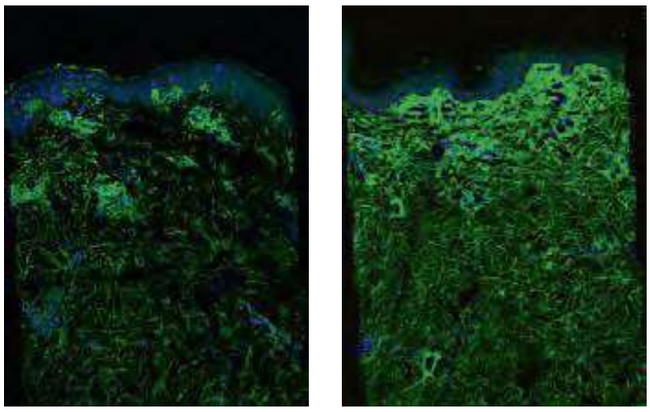
The monopolar radiofrequency homogeneously heats the entire dermis to 40-42°C which induces therma stress on fibroblasts and targets aged and rigid collagen and elastin fibers in the dermis.[10] The thermal energy triggers collagen coagulation and rapid skin tightening, evoking the restorative process, which promotes the production of new collagen and elastin. This allows for improvement in the dermal structure resulting in skin improvement through neocollagenesis and neoelastinogenesis.[9]



Targeted ultrasound directs high-frequency mechanical waves to the reticular dermis, where the most active fibroblasts reside. The mechanical stimulation caused by the ultrasound waves induces vibrations in the tissues, including the fibroblasts, resulting in an energy buildup within the reticular dermis that leads to the heating of the tissue up to 42°C. Ultrasound waves activate cell receptors, causing changes in gene expression and protein synthesis within fibroblasts. This enhances their responsiveness to radiofrequency waves, which can disrupt the cellular environment and increase the production of hyaluronic acid, collagen, and elastin fibers.[3]

Multiple clinical studies showed that directing the ultrasound to the reticular dermis is absolutely crucial for increasing the concentration of HA in the skin, as demonstrated by Duncan et al., who found that only targeted ultrasound and RF resulted in increased HA production, while the RF with general non-targeted ultrasound did not yield any significant changes. The group treated by RF + targeted ultrasound showed up to a 224% increase in HA concentration.[4] Similarly, Fritz et al. showed that RF+TUS led to a significant increase in hyaluronic acid levels in porcine skin samples, while radiofrequency alone did not have the same effect, highlighting the importance of targeted ultrasound in altering tissue composition.[6] Findings from the animal studies were confirmed by Goldberg et al.´s study on human subjects.[7] Kent et al.'s porcine study then documented that this technology can significantly increase collagen (by 47%) and elastin (by 50%).[8] The improvement in skin structures translated into an overall improvement in skin appearance, as evidenced by Chilukuri&Boyd's study showing increased skin hydration (by 23%) and improved skin texture (by 41 %).

BEFORE AFTER



Confocal microscopy images show that at the 2-month follow-up, the network in the dermis of the RF+TUS group appears denser with more green fibers compared to the baseline on the left

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BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 29

ANIMAL HISTOLOGY STUDY EVALUATING HYALURONIC ACID PRODUCTION

INCREASED LEVELS OF HYALURONIC ACID IN SKIN AFTER MONOPOLAR RADIOFREQUENCY AND TUS TREATMENT: PORCINE ANIMAL STUDY

Diane Duncan, M.D., FACS[1], MvDr. Jan Bernardy PhD[2], MVDr. Nikola Hodkovicova PhD[2], PharmDr. Josef Masek PhD[2]

1. Plastic Surgery Associates, Fort Collins, CO, USA, 2. Veterinary Research Institute, Brno, CZ

Presented at the American Society for Laser Medicine and Surgery (ASLMS). San Diego, California, 27 April 2022

Highlights

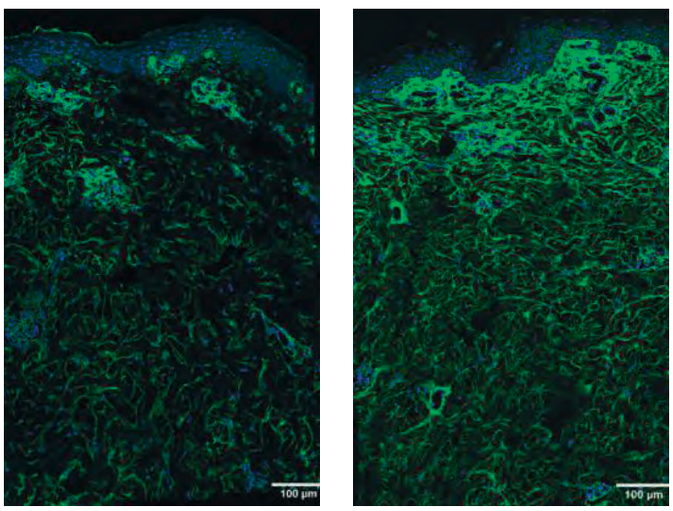
- 12 swines had four treatments of 30 minutes on each side of the abdomen
  - 6 treated by **RF + Targeted Ultrasound (TUS)**
  - 6 treated by **RF + Non-Targeted Ultrasound**
- 252 samples collected and analyzed using three different evaluation methods **(PCR, MALDI-TOF, and Confocal Microscopy)**
- Study shows that the use of **Targeted Ultrasound is essential** for stimulating the **HA production**, whereas the **RF+US** had **no significant effect**

RF+TUS Group

224% MORE HYALURONIC ACID

RF+Non-Targeted Ultrasound

NO SIGNIFICANT CHANGE IN HA



Confocal microscopy images show that at the 2-month follow-up, the network in the dermis of the RF+TUS group appears denser with more green fibers compared to its baseline on the left.

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IMPROVED SKIN HYDRATION AND SKIN TEXTURE BY RF+TUS

THE SIMULTANEOUS APPLICATION OF MONOPOLAR RADIOFREQUENCY AND TARGETED ULTRASOUND FOR IMPROVEMENT OF SKIN HYDRATION AND SKIN TEXTURE

Suneel Chilukuri, M.D., FAAD, FASDS[1], Charles M. Boyd, M.D., MBA,FACS [2]

1. Refresh Dermatology, Houston, TX, USA, 2. Boyd Beauty, Birmingham, Michigan, USA

Presented at the Annual Meeting of the Vegas Cosmetic Surgery, 2022

Highlights

- **41 subjects** (26-77 years) received four treatments 7-14 days apart
  - Group A: **RF+Targeted Ultrasound (TUS)**
  - Group B: **RF only**
- **3D Skin Analysis & Hydration Measurements** were conducted
- **RF+TUS** group achieved **superior improvement** of skin elasticity **compared to RF only group**
- **95% satisfaction rate** at 3-month follow-up in the RF+TUS group

41%

Improvement in skin texture

23%

Increase in skin hydration



52-year-old patient from the RF+TUS group at baseline (left) and at 3-month follow-up (right)

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 26

HUMAN HISTOLOGY: ENHANCED HYALURONIC ACID PRODUCTION

A NOVEL TECHNOLOGY TO BOOST NATURAL PRODUCTION OF HYALURONIC ACID IN THE SKIN TISSUE: HUMAN HISTOLOGY STUDY

David J. Goldberg, M.D., J.D.[1]

1. Skin Laser and Surgery Specialists, a Division of Schweiger Dermatology, Hackensack, NJ

Presented at the Annual Meeting of the American Society for Laser Medicine and Surgery, 27 April 2022

Highlights

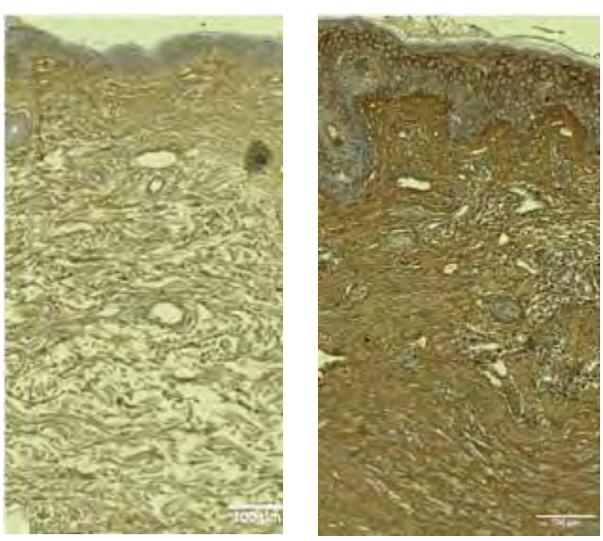
- 7 patients divided into 3 groups received four treatments one week apart
  - Three subjects **(RF alone)**
  - Three subjects **(RF+Targeted Ultrasound)**
  - One control subject
- Biopsy samples were taken for analysis of HA levels by semi-automatic segmentation

1.67x HIGHER HA DENSITY

In RF+TUS group

NO SIGNIFICANT CHANGE IN HA

In RF only group



Histology visualizes an increased amount of hyaluronic acid (shown as dark brown color) in the RF+TUS group, both at baseline (left) and at the 3-month follow-up (right)

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 34

OPEN FORUM

Cosmetic Medicine

The Superior Effect of Radiofrequency With Targeted Ultrasound for Facial Rejuvenation by Inducing Hyaluronic Acid Synthesis: A Pilot Preclinical Study

Diane Duncan, MD, FACS; Jan Bernardy, PhD; Nikola Hodkovicova, PhD, PharmD; Josef Masek, PhD, MS; Marketa Prochazkova, PhD, MSc; and Rea Jarosova, PhD

Aesthetic Surgery Journal Open Forum 2024, 1–8
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https://doi.org/10.1093/asjof/ojae005
www.asjopenforum.com

OXFORD UNIVERSITY PRESS

Abstract

Background: The level of dermal hyaluronic acid (HA) can be depleted by 75% at age 70. HA provides dermal hydration, volume, and thickness, making it a major component of the extracellular matrix. Restoration of dermal and epidermal HA can be achieved by combining radiofrequency (RF) energy and targeted ultrasound (TUS). The monopolar RF generates heat, with the TUS stimulating HA production. The heat induces a regenerative response in the skin, increasing the fibroblast activity and producing various extracellular matrix compounds, including HA.

Objectives: To investigate the effect of the simultaneous application of RF + TUS or RF + US on the stimulation of HA production.

Methods: Twelve animals underwent 4 treatments. Six were treated with transcutaneous RF + TUS and 6 with the combination RF + US. The opposite untreated side served as a control. Punch biopsies of the skin were taken at baseline, immediately posttreatment, 1 month, and 2 months posttreatment. The tissue was evaluated with real-time quantitative polymerase chain reaction (RT-qPCR), matrix-assisted laser desorption (MALDI) and time of flight (TOF), and confocal microscopy.

Results: The RT-qPCR focused on assessing the production of *has1* and *has2*, enzymes responsible for HA synthesis. RT-qPCR results of the RF + TUS group revealed a +98% and +45% increase in hyaluronic synthetase (HAS) 1 and HAS2 production after the treatments, respectively. The MALDI–TOF revealed a +224% increase in measured HA 2 months after the treatments. The changes were also visible in the confocal microscopy. The control group showed no significant ($P > .05$) results in either of the evaluation methods.

Conclusions: Concurrent application of RF and TUS significantly enhances the natural regenerative processes in skin tissue.

Level of Evidence: 5



Editorial Decision date: January 11, 2024; online publish-ahead-of-print January 30, 2024.

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The skin mirrors our age, and therefore, the major feature of the antiaging process is skin rejuvenation. The intrinsic and extrinsic processes of skin aging share similar molecular mechanisms, such as the reactive oxygen species that are involved in both processes and affect the ability of fibroblasts to produce all components of the extracellular matrix (ECM), therefore enhancing the signs of aging.[1] The first sign of aging may be caused by the absence of hyaluronic acid (HA) instead of changes in collagen and elastin.[2] HA is the major glycosaminoglycan present in the human skin and the key contributor to moisture retention. It creates an interface between collagen and elastin fiber and thus fills the ECM, improves mechanical support in the skin, and scavenges free radicals.[1] With sufficient levels of HA, the skin is healthy, elastic, filled, and retains a young appearance, but HA is constantly being turned over in the body and degraded inside the lysosomes by hyaluronidases encoded by *hyal1* and *hyal2* genes.[3-6]

The depletion of hyaluronic is currently treated by rejuvenating-rich moisturizers, wrinkle creams, or injections containing HA, and vitamins. These methods directly deliver HA or vitamins in the skin tissue and substitute the function of fibroblasts, but are unable to restore the body's natural ability to produce HA. Radiofrequency (RF) and ultrasound (US) energies were used, aiming to restore the synthesis of HA, yet, as standalone procedures were "only" found to stimulate the production of collagen and elastine.[2,7]

A novel technology simultaneously emits monopolar RF and targeted US (TUS) to utilize the benefits of synergistic effects of both technologies when applied simultaneously. RF causes the temperature to increase by oscillating electrical current to the treated tissue, where it drives collisions between charged molecules and ions, converting this kinetic energy into heat, while US is a mechanical compression wave that stimulates the tissue through both mechanical and thermal mechanisms.[8,9] Although both modalities contribute in providing heat and mechanical stress, TUS is focused similar to the way magnifying glass focuses light, creating a smaller yet concentrated area of effect that allows for deeper and more accurate targeting. This enables higher temperatures without causing undesired effects within the reticular dermis, the location with the most active dermal fibroblasts.[9-11] These are mechanically stimulated, leading to additional thermal increments and mild intracellular vibrations in this layer.

It is hypothesized that combining the thermal and mechanical stress of the fibroblasts may trigger processes that may not lead only to enhanced collagen and elastin production but may actually boost the natural synthesis of HA as well.

This study aims to determine the effects of the simultaneous use of RF and TUS treatment on the production of HA and the importance of targeting the energy to the reticular dermis for the best possible outcomes. Thus, the study will compare the technology combining RF with TUS with a technology combining RF with general non-TUS.

METHODS

This investigational, single-center, 2-arm animal study was approved by the Institutional Animal Care and Use Committee and the Ethics Committee for Animal Protection of the Ministry of Agriculture. The study took place between June and October 2020. It was supervised and performed by the Veterinary Research Institute (VRI, Brno, CZ), a holder of the Good TUSultrLaboratory Practice Authorisation. Animals were stabled at the VRI during the study duration, with the certified veterinarian and veterinary staff handling the animal care to secure animal well-being.

Twelve sows (*Sus scrofa f. domestica*, 60-80 kg) were divided into 2 groups. Both groups underwent four 20 min treatments 2 to 3 days apart delivered to the abdomen. The treatment area was approximately 25 cm^2. One group ($n = 6$) was treated with a small applicator that simultaneously emits RF and TUS (Exion, BTL Industries Inc., Boston, MA), with the second ($n = 6$) treated with RF and non-TUS (BTL Exilis System, BTL Industries Inc. Boston, MA). All utilized energies were set to 100%. The untreated side of the abdomen served as a control.

Animals were kept under general anesthesia during the treatment procedure and sample collection. The anesthetic (Propofol 2% MCT/LCT Fresenius, dosing 1-2 mg/kg) was delivered to the pig's system by an intravascular cannula placed into the ear's vein. All animals were preventively intubated and monitored by electrocardiogram (EKG) with a certified veterinarian overseeing the vital signs, together with assessing study-related adverse events and side effects. The animals were euthanized by an analgesic overdose (T61 a.u.v. inj., Intervet International B.V./MSD AH) administered by a veterinarian after the study completion.

Six tissue samples (3 from the treated side and 3 from the untreated side) were taken by a 6 mm punch biopsy needle at baseline, after the last treatment, and 1 and 2 months after the last treatment. Overall, 252 samples were taken and used for analysis. Upon the biopsy extraction, the sample site was numbed by injecting local anesthetic (Lidocaine 2% a.u.v. inj., Fatro s.p.a., dosing 2 mL per biopsy) to relieve the pain upon waking up. The sampling wound was disinfected, enclosed by 2 clamps, and covered by an Aluminium Silver Spray Skin Care.

The effect of the procedures was evaluated by real-time quantitative polymerase chain reaction (RT-qPCR), mass spectrometry separation technique based on molecular weight (MW) using matrix-assisted laser desorption (MALDI) in combination with a time-of-flight (TOF) analyzer, and Confocal microscopy. RT-qPCR is a very sensitive

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technique that allows the amplification of a specific segment of DNA and makes copies of DNA fragments or genes, which allows the identification and quantification by size and charge of gene sequences using visual techniques.[12] To support the data obtained by RT-qPCR analysis, the HA within the skin tissue was evaluated using the MALDI–TOF method, which is an analytical method that reflects the presence and amount of HA in the organism based on its MW.[13,14] Confocal microscopy is a broadly used visualization technique to resolve the detailed structure of specific objects. Various components of cells or tissue sections can be specifically labeled using immunofluorescence. HA is visualized by green color and the cell nucleus by blue color.[15]

RT-qPCR Analysis

Skin tissue samples were fixed in RNA later (Thermo Fisher Scientific, Waltham, MA), left for 24 h at 4°C, and then stored at −80°C until RNA extraction.

Skin tissue samples were individually removed from RNAlater, dried, cut into smaller pieces with sterile scissors, and homogenized on the MagNaLyser (Roche, Basel, Switzerland) in 0.75 mL of TRI Reagent RT (Molecular Research Center, Cincinnati, OH). Total RNA free of DNA contamination was further purified using the RNeasy Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. According to the manufacturer's instructions, the RNA was reversely transcribed to messenger RNA using the LunaScript RT SuperMix Kit (New England BioLabs Inc., Ipswich, MA). The individual sample RNA was diluted with RNase-free water (Qiagen, Hilden, Germany) to obtain the same resulting RNA concentration for all samples, that is, 1 μg. The control samples were included and prepared as recommended by the manufacturer. The resulting 20 μL reaction was heated at 25°C for 2 min to ensure primer annealing, followed by 55°C for 10 min when the complementary DNA (cDNA) was synthesized and the reaction was inactivated by 95°C for 1 min. For reverse transcription, the Engine Thermal Cycler (Bio-Rad, Hercules, CA) tool was used. The samples of cDNA, including the controls, were stored at −20°C until RT-qPCR, which can record the amount of DNA throughout the cycle, was performed.

Biopsy samples were evaluated by molecular biochemistry through gene expression of markers that are involved in HA production processes such as *tgfb1*, *fgf1*, *has1*, *has2*, *has3*, and membrane receptor *cd44*. Hyaluronan synthases (HASs) are enzymes synthesizing molecules of HA, there are 3 types of HAS based on the molecular dimension of synthesized molecules of HA—HAS1, HAS2, and HAS3.[5,16] HAS2 synthesized large-size molecules of HA (2×10^6 Da); therefore, it plays a major role in the syntheses of HA in fibroblasts, myofibroblasts, and most importantly in the dermis itself,[3,17] while HAS1 facilitates the formation of both large and small molecules, synthesized by HAS3.[17-19] Transforming growth factor beta 1 (TGF-β1) is a major regulator of biosynthesis in the ECM, throughout the activation of signaling pathways that regulate ECM genes and induce collagen, fibronectin, and elastin production in the dermis.[1] TGF-β signaling pathway is essential for maintaining structural and mechanical integration of dermal connective tissue by increasing ECM production. TGF-β1 controls proliferation and cell differentiation.[1,7,20] An acidic fibroblast growth factor 1 (FGF1) plays a role in the regeneration and proliferation of fibroblast cells, which produce collagen and elastin, and leads to HAS expression and synthesis of HA.[19,20] CD44 is a major receptor for HA.[5] After the interaction with HA, several biological processes are activated such as endocytosis, cell migration, differentiation (specialization), and proliferation (cell formation).[16] HA in conjunction with CD44 supports skin tightening, hydration, and elasticity. CD44 also regulates the expression of proteins based on corneocyte and keratinocyte differentiation, so it might be assumed that the treatment may target not only the dermis but also, to some extent, epidermis as well.[17]

Sequences for primers were designed using the NCBI primer-blast design tool available online. The obtained data were analyzed using the LightCycler 480 SW 1.5 program (Roche, Basel, Switzerland) within the comparative 2Δ threshold cycle (Ct) method. The HPRT gene was chosen as an optimal reference gene for data normalization using the NormFinder software (MOMA, Aarhus, Denmark). The relative expression was calculated according to the formula: [1/(2Ct of gene)]/[1/(2Ct HPRT)].[21] In each run, cycling conditions were as follows: initial denaturation at 95°C for 15 min; 45 cycles of denaturation at 95°C for 15 s, primer annealing at 58°C for 30 s, and extension at 72°C for 30 s. Melting analysis was performed at 60 to 95°C.

Matrix-Assisted Laser Desorption Time of Flight (MALDI–TOF)

A novel application of MALDI–TOF MS Autoflex speed (Bruker Daltonics, Billerica, Massachusetts) was used in positive linear mode with laser energy of 80%, frequency of 2000 Hz, and a sum of spectra 10,000. Calibration of the MS instrument was done with Protein standard II in the range of 20 to 80 kDa with extrapolation for higher masses. 2,5-Dihydroxybenzoic acid, a saturated solution in organic solvent (MeCN with 1% trifluoroacetic acid), was used as a matrix. Samples for measurement were prepared by extraction to acetone, 0.5 M NaCl, and ethanol.

Samples tissues were put to the 0.5 mL of acetone and left in solution in 1.5 mL Eppendorf tube overnight (for tissue breakdown). After 24 h acetone was removed and samples of tissues were put into the 0.25 mL of 0.5 M NaCl aq. solution and shook in a 1.5 mL Eppendorf tube in the shaker at 800 rpm for 2 h. Samples of tissues were removed and put into the mixture of glycerol and 0.5 M

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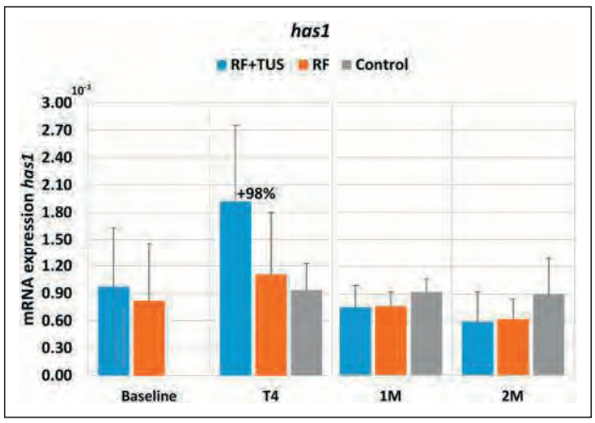


Figure 1. The bar chart of *has1* concentration evaluated by real-time quantitative polymerase chain reaction. 1M, 1-month follow-up; 2M, 2-month follow-up; RF, radiofrequency; energy; T4, last (fourth) treatment; TUS, targeted ultrasound.

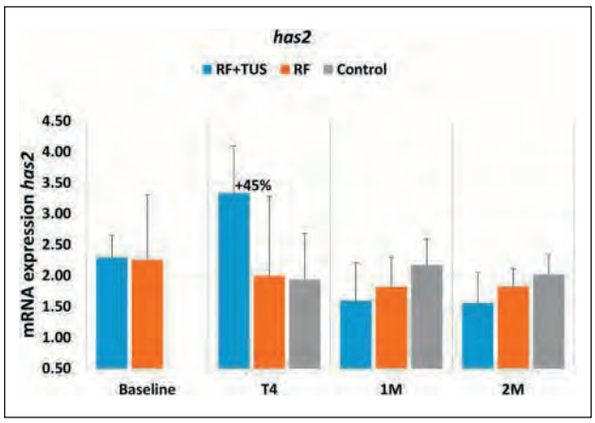


Figure 2. The bar chart of *has2* concentration evaluated by real-time quantitative polymerase chain reaction. 1M, 1-month follow-up; 2M, 2-month follow-up; RF, radiofrequency; energy; T4, last (fourth) treatment; TUS, targeted ultrasound.

NaCl aq. (v/v, 1:1) and put in the freezer (−40°C) for keeping and the possibility of next usage. Sample extracts were mixed with ethanol in the range sample extract/ethanol, v:v, 1:5. It means mixing the 0.25 mL of the sample extract in 0.5 M NaCl aq. solution with 1 mL of ethanol. Immediately after mixing samples with ethanol, extracts were put in the fridge and left at 7°C for 16 h (for the formation of a precipitate of the HA and its separation from the lower molecular proteins). Sample precipitates were centrifuged at 14,000 rpm for 20 min, after centrifugation, the supernatant was removed, and the precipitates were completely dissolved in 100 µL of ultrapure water. After the dissolution of the precipitates, 75 µL of ethanol were added to each sample (for the precipitation of the high-molecular proteins). Samples were then centrifuged at 14,000 rpm for 20 min, and surfactants were used for MALDI–TOF MS measurements. Then, a direct application of each sample to the plate and dripping of the matrix were proved immediately before MALDI–TOF measurement.

Confocal Microscopy

Each collected sample was vertically cut into 5 µm thick slices, then fixated in a fixative consisting of 3.7% formaldehyde-PBS, 70% ethanol, and 5% glacial acetic acid. A 1:100 dilution of biotinylated hyaluronan-binding protein solution was used to bond with HA and was left to incubate for 12 to 16 h in 4°C. After the incubation, slides carrying the samples were washed, stained with streptavidin conjugated with a fluorescent label (Alexa 488), and left to incubate for 1 h in the dark. Samples were then washed again and to mount, VectaShield with DAPI (Vector Laboratories, Newark, CA) was used. The samples were sealed with nail polish around the edges of the coverslip. The images of the prepared samples were conducted through Leica Microsystem, LAS X 3.5.1.18803 (Wetzlar, Germany), at a wavelength of 580 nm and magnification of 63×. Protocol from the National Heart, Lund and Blood Institute under award number PO1HL107147 inspired this process.[22]

Statistical Analysis

The statistical analysis was done by using the Real Statistics Resource Pack software for Microsoft Excel.[23] The difference between the individual measurements was tested by the Friedman test. The significance level α was set at 5%.

RESULTS

All 12 animals underwent 4 treatments and collection of samples at baseline, after the treatment, 1-month, and 2-month follow-up visits. The 252 collected samples were divided into 3 groups, 1 for each evaluation method with a control. The control samples were evaluated together regardless of group.

RT-qPCR Results

RF + TUS

The production of *has1* and *has2* peaked after the treatment, with *has1* and *has2* showing a 98% and 45% increase ($P < .001$), respectively. The production of *has1* and *has2* slowly decreased at 1-month and 2-month follow-ups. *has3* production peaked at a 1-month follow-up with an 85% increase, and similarly to *has1* and *has2*, the value measured at a 2-month follow-up slightly decreased. The *fgf1* and *fgfb1* peaked at 1-month follow-up with a 113%

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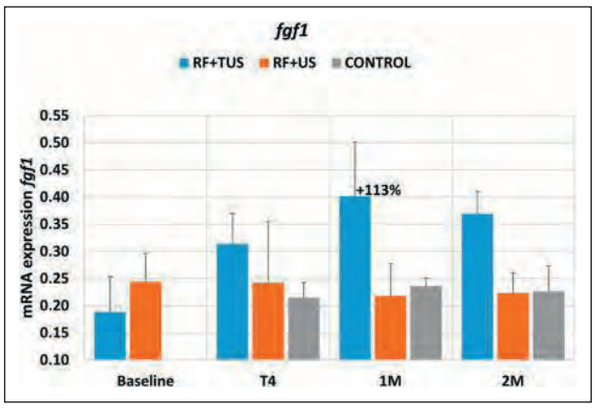


Figure 3. The bar chart of *fgf1* concentration evaluated by real-time quantitative polymerase chain reaction. 1M, 1-month follow-up; 2M, 2-month follow-up; RF, radiofrequency; energy; T4, last (fourth) treatment; TUS, targeted ultrasound.

and 31% increase ($P < .001$), respectively. The last measured marker, the receptor *cd44* for HA peaked at a 2-month follow-up with a 27% increase. Figures 1-3 represent a graphical visualization of the changes.

RF + US and Control

The RT-qPCR evaluation discovered no change in the measured parameters in Group B or in the control samples.

MALDI–TOF

The analysis of the MW of molecules in the samples showed a peak between 66 and 68 kDa, which corresponds with the MW of HA, due to the extrapolation for higher masses.

RF + TUS

Based on the MALDI–TOF evaluation, the amount of HA in the sample showed a gradual increase by 79% at the 1-month follow-up and by 224% at the 2-month follow-up ($P = .022$).

RF + US and Control

Group B showed no clear trend in the HA changes as the results fluctuated between 14% at the 1-month follow-up, and 11% at the 3-month follow-up when compared with baseline. However, those changes were not statistically significant in either Group B ($P = .1353$) or the control group ($P = .3173$).

Confocal Microscopy

After the marker-detecting techniques, the presence of HA was visualized through confocal microscopy. Figure 4 shows the different intensities of colors representing HA (green) and cell nucleus (blue), where the top row (A-D) represents RF + TUS, while the bottom row (E-H) represents RF + US. The apparent intensification of the color green in the samples shows the continuous improvement in the production of HA in the RF + TUS group while showing no change in the RF + US group. The pictures of the RF + TUS group show deeper and more lasting HA production. The green color appears brighter in the epidermis, where the keratinocytes are densely placed and produce the HA, while in the dermis, HA is produced by fibroblasts, which are separated by an ECM and collagen fibers, and the brightness seemingly fades.

DISCUSSION

This present study aimed to compare the technology combining RF with TUS with a technology combining RF and general non- TUS in their ability to alter the natural processes leading to the synthesis of HA in the skin. The obtained data documented the changes occurring in the skin of 12 sows 2 months after receiving four 20 min treatments. No study-related adverse events or side effects were observed in the animals or samples obtained.

Approximately, 50% of the body's deposit of HA is located in the skin.[24] HA is an extremely hydrophilic molecule that is able to retain up to 100 times its weight in water[25] with a very dynamic turnover of approximately 24 h. In lower HA concentrations, the turnover is accelerated.[26] Apart from moisture retention, HA functions in the framework for blood vessel formation and the framework through which cells migrate, wound healing, and tissue repair.[27] HA also has the ability to stretch the fibroblasts and stimulate collagen and tubulin production.[28,29] As the variability of HA use in the body is so vast, reminding the dermal fibroblasts of HA production may improve the skin's overall health.

The presented study provided novel information on the noninvasive stimulation of HA production, as both quantification and visualization methods indicate the superior results of the simultaneous application of RF + TUS to RF + US. All of the methods demonstrated highly significant changes ($P < .001$) in the RF + TUS group, while no statistically significant changes ($P > .05$) were observed in the RF + US group or the control, indicating the importance of stimulating the deep dermal layer reachable only by the TUS.

Fibroblasts, under specific circumstances, can initiate increased elastin production contingent upon the presence of sufficient TGF-β and FGF.[30] Moreover, in response to certain external conditions, fibroblasts may engage in the production of HA, involving a complex biosynthetic cascade orchestrated by various enzymes and cofactors such as TGF-β, epidermal growth factor, and platelet-derived growth factor.[31] We hypothesize that the mentioned impact of heat and mechanical stress on

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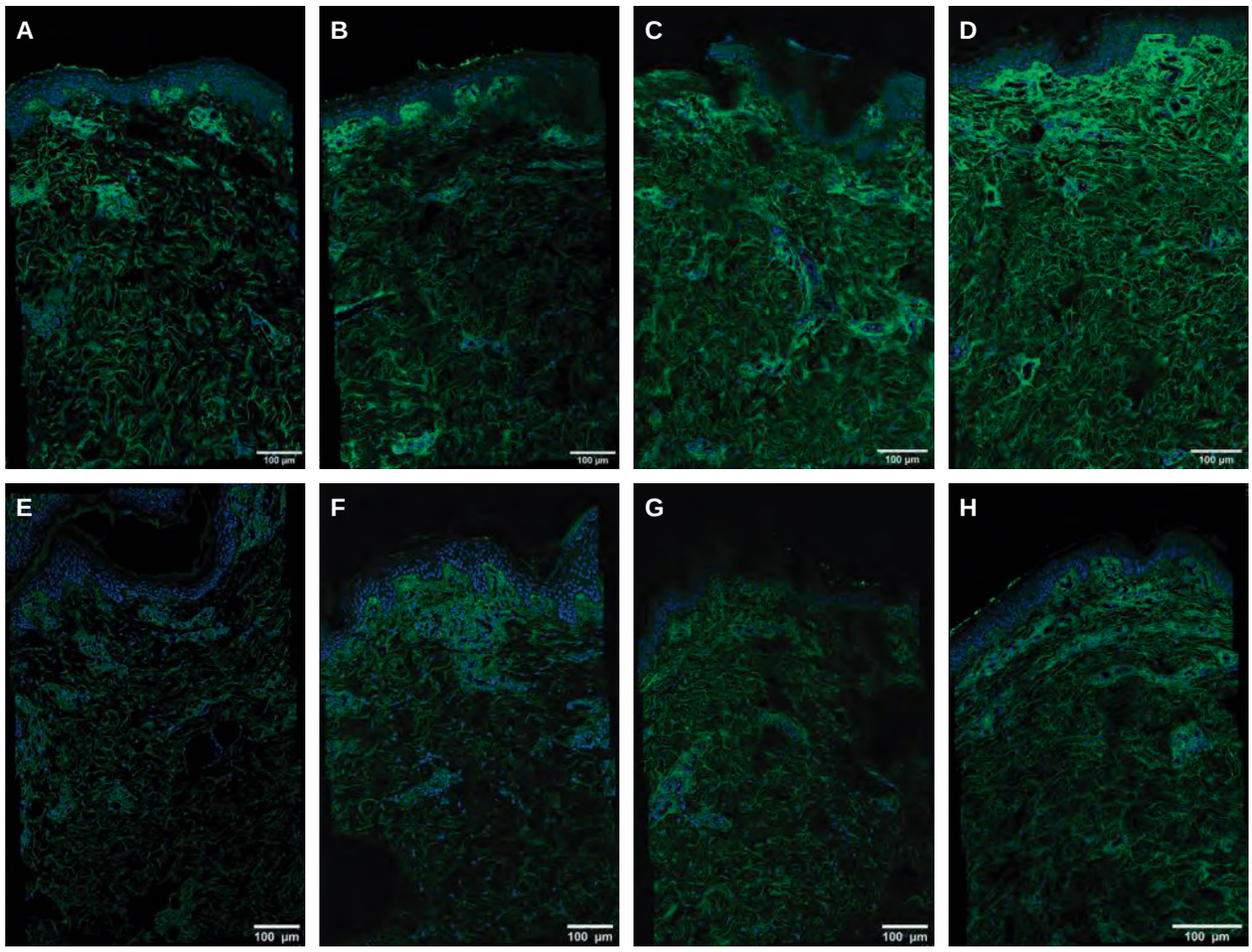


Figure 4. The visualization of hyaluronic acid through confocal microscope, magnification of 63×, radiofrequency (RF) + targeted ultrasound (TUS): (A) baseline, (B) after the last treatment, (C) 1-month follow-up, (D) 2-month follow-up; RF + US: (E) baseline, (F) after the last treatment, (G) 1-month follow-up, (H) 2-month follow-up.

fibroblast metabolism contributes to this cascade, creating favorable conditions for HA synthesis.

First, the samples were proceeded by RT-qPCR analysis which revealed the changes connected to the RF + TUS therapy. Immediately after the treatments, the expression of genes for enzymes synthesizing the HA peaked (*has1* + 98%, *has2* + 45%), with the last enzyme peaking at a 1-month follow-up (*has3* + 85%). This has been followed by a subsequent decrease in the synthases levels, most likely due to the negative feedback regulation of enzymes, where the product limits its production when reaching a certain amount and aims to restore homeostasis after enough HA-synthesizing enzymes were produced,[32] leading to increased production of *tgfb1* gene, which is an ECM biosynthesis regulator (+31% at 1-month follow-up). HA also influences the fibroblast proliferation[33]; therefore, the increase in HA leads to an increase in *fgf1*, a fibroblast growth factor, production (+113% at 1-month follow-up). The last measured marker, *cd44*, a membrane receptor, showed a gradual increase as it was adapting to the increasing amount of HA in the skin while peaking 2 months after the treatments (+27%). After the RT-qPCR evaluation, which measured genes involved in HA or fibroblast production and interaction, MALDI–TOF measured the amount of HA in the sample. The amount of HA peaked at the 2-month follow-up which represented an increase of +224%. As all 3 HASs were activated, we can assume that HA of all MW was synthesized. However, the most detected HA in the sample is low-molecular-weight (LMW) HA, which is depolymerized from high MW HA.[34] LMWHA is an important molecule that is biologically active and affects cellular behavior, including wound care, fibroblast, and endothelial cell migration and activation.[34] The prevailing presence of LMWHA may be one of the reasons for such a complex ECM response.

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These results of quantification methods are supported by the confocal microscopy pictures, which visualized the increased amount of HA in the skin after the RF + TUS, which filled the ECM (Figure 4).

The first limitation of this study is the sample size; although even with 6 animal cases per group, the statistical analysis found significance in the observed markers. Due to the physiological similarities between pig and human skin, in addition to the invasive nature of sample collection, we believe that the use of an animal model was necessary and an adequate first step into acquiring insights into this previously undescribed phenomenon. However, a small sample size poses limitations to statistical analysis and its potency. In order to minimize the stress induced on animals, the last sample was obtained 2 months posttreatment. In order to verify the efficacy of these findings, the study warrants a longer follow-up as well as advancement to human trials in a statistically meaningful population.

CONCLUSIONS

This pilot animal histology study suggests that the simultaneous use of RF + TUS treatment is able to enhance the natural production of HA through stimulation of fibroblasts, while RF + US treatment is not. If confirmed by further studies, this method could present a shift in the rejuvenation field as it restores the cells ability to produce the major skin components. As such this could become a viable tool for facial rejuvenation.

Disclosures

Drs Duncan and Bernardy are consultants for BTL (Boston, MA). Drs Hodkovicova, Masek, and Prochazkova are associates of VRI. All authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding

BTL Industries (Boston, Mass) was the sponsor of this study and provided the study device. However, no funding for authorship or publication of this article was provided. The authors thank the Ministry of agriculture of the Czech Republic for Institutional Support No. MZE-RO0523.

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Research Article

Radiofrequency *vs.* Synchronized Radiofrequency and Targeted Ultrasound Technology for Enhanced Skin Hydration

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ABSTRACT

Objective: Skin aging is characterized by significant changes including the loss of collagen, elastin, and Hyaluronic Acid (HA), impacting skin moisture, elasticity, and overall health. Radiofrequency (RF) and Ultrasound (US) are well-recognized modalities, typically utilized as independent procedures. Due to the novel device allowing simultaneous delivery of both energies in a single applicator, this study compares the effects of RF as a standalone treatment to simultaneous RF and Targeted Ultrasound (TUS) treatment

Methods: A prospective multi-center, two-arm study was conducted with forty-one (41) subjects (3 males, 38 females, 26-77 years, skin types I-VI), randomly allocated into two groups: Group A (N=21) treated with monopolar Radiofrequency+Targeted Ultrasound (RF+TUS), and Group B (N=20) treated with monopolar RF only. In each group, subjects received four (4) full-face treatments delivered once per week. Skin hydration was measured with a moisture meter following the final treatment session. Digital photographs were scored by three independent evaluators using the Global Aesthetic Improvement Scale (GAIS scale) and 3D analysis was performed. Additionally, subject satisfaction and therapy comfort were assessed.

Results: At 3 months, group A achieved a marked improvement in the GAIS scale by +1.3 ± 0.1 points. 3D photographs demonstrated more profound results in Group A, achieving a skin texture improvement of +7.3 points (41.6%, $p<0.05$) at 3 months *vs.* Group B by +5.3 points (28.5%). While almost all subjects found both treatments comfortable, treatment satisfaction outcomes were higher in the RF+TUS group. The study demonstrated the synergistic effects of RF and TUS in enhancing skin hydration and overall quality, with no adverse events reported.

Conclusion: Analysis of facial skin hydration, and skin quality showed that simultaneous RF+TUS treatment has significantly better outcomes than single modality RF for improving the overall facial appearance. The results suggest that this novel treatment offers a potential non-invasive approach to skin rejuvenation, with implications for broader application in dermatological and aesthetic practices. However, further research addressing limitations like subject variability and long-term hydration effects is necessary to validate and expand upon these findings.

Keywords: Skin hydration; Radiofrequency; Ultrasound; Healthy skin; Radiofrequency; Skin rejuvenation; Facial aging

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Received: 04-Jan-2024, Manuscript No. JCEDR-24-29327; **Editor assigned:** 08-Jan-2024, Pre QC No. JCEDR-24-29327 (PQ); **Reviewed:** 22-Jan-2024, QC No. JCEDR-24-29327; **Revised:** 29-Jan-2024, Manuscript No. JCEDR-24-29327 (R); **Published:** 05-Feb-2024, DOI: 10.35841/2329-9509.24.15.662.

Citation: Boyd CM, Chilukuri S (2024) Radiofrequency *vs.* Synchronized Radiofrequency and Targeted Ultrasound Technology for Enhanced Skin Hydration. J Clin Exp Dermatol Res. 15:662.

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INTRODUCTION

The complex process of skin aging results in significant changes within the skin, including the loss of collagen, elastin, and Hyaluronic Acid (HA) [1]. HA is a naturally occurring glycosaminoglycan found in the human body, particularly in the skin, connective tissues, and eyes [2]. In the skin, hyaluronic acid plays a important role in maintaining moisture, elasticity, and overall skin health, as it is responsible for skin hydration and increasing moisture content due to its water-binding capacity [3,4]. HA has been also implicated as a regulator of cell proliferation and motility, thereby promoting wound healing [5-7]. The enzymatic processes that are needed for normal skin desquamation are impaired when moisture levels in the skin are reduced, leading to the appearance of dry, flaky skin [8]. Therefore, maintaining optimal levels of HA over time is essential for preserving a healthy, youthful, and plump appearance of the skin. As we age, our skin undergoes various changes, including a decrease in the amount of HA in the skin. This leads to reduced hydration levels and gradual development of fine lines and wrinkles, skin dryness, dullness, and tired appearance [9-11]. Hydration of the skin diminishes due to various external factors with one of the most significant contributors being daily exposure to sun leading to prominent changes on the facial skin [12]. Safer non-invasive methods for treating facial wrinkles and improving skin quality, such as Radiofrequency (RF) and ultrasound, are preferred as all skin types can be treated with few complications. However, despite efforts to non-invasively stimulate natural HA production studies have been inconclusive or have shown only minimal effects when treated with single modality technology. Despite the widespread use of both RF and ultrasound, research investigating the synergistic effect is lacking. Recent histologic evaluation has already shown that RF treatment can increase the collagen and elastin in the skin [13-18], the primary structural proteins in the skin, responsible for skin elasticity, firmness, resilience, and structure [19-23]. Hence, it seems that the key to enhancing the production of HA, collagen, and elastin, lies in applying both of these energies simultaneously.

This study aimed to investigate the effectiveness of the novel device simultaneously delivering RF and Targeted Ultrasound (TUS), developed to enhance the body's innate capacity to produce HA. To quantitatively measure the increase in hyaluronic acid levels in the skin in this study, a skin hydration assessment was performed after the final treatment.

MATERIALS AND METHODS

Study population and treatment protocol

This is a prospective multi-center, two-arm study. Forty-two subjects (3 males, 39 females, 26-77 years) were recruited and forty-one (N=41, one subject was withdrawn) were randomly allocated into two study groups-group A (N=21) and group B (N=20). The patients' baseline characteristics are shown in Table 1.

Table 1: Patients' baseline characteristics.

Variables	Group A	Group B
Patients	21	20
	Sex	
Male	2	1
Female	20	19
	Age (years)	
Mean	57.5 ± 2.3	56.3 ± 2.0
Range	26-77*	43-73
Median	56	55.5
	Skin types	
I	3	2
II	12	10
III	3	3
IV	2	2
V	1	2
VI	0	1

* Only one subject was 26-year-old in group A, without this patient the range is 50-77 years

Group A was treated with a novel EXION (BTL Industries Inc., Boston, MA) device using the Exion Face applicator delivering monopolar RF and TUS energies simultaneously (Group A). Group B was treated with single-modality monopolar RF. By comparing the two treatments, a better understanding of their mechanisms of action may be understood. In each group, subjects received four full-face treatments delivered once per week. A conductive gel was applied to the treatment area to ensure optimal energy flow. During therapies, RF intensity parameters of the therapy were adjusted according to patient feedback (on a scale of 0% to 100%, where TUS was set to 100% by default). The study participants were continuously monitored and assessed for any potential adverse events that might occur during the study.

Data and evaluation

Skin hydration was measured by MoistureMeterSC (Delfin Technologies Ltd.) and assessed at baseline and immediately after the last treatment visit. The MoistureMeterSC measures the combination of the skin's dielectric constant and the changing thickness of the stratum corneum's dry layer. These values are represented on a scale of 0 to 300 points, indicating a relative dimensionless quantity that corresponds to the hydration

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level of the skin surface. As the moisture content of the skin surface increases, the measured values also increase.

Digital photographs of the treated areas were taken at baseline, after the last (4th) treatment, at 1-month, 3-month, and 6-month (optional) follow-up visits. These photographs were scored by three blinded independent evaluators using the Global Aesthetic Improvement Scale (GAIS) in order to evaluate the changes in skin quality.

A Three-Dimensional (3D) photographic imaging system LifeViz® Mini (QuantifiCare S.A., France) was used to capture facial 2D photographs from the left, right, and front views of the face at multiple angles, and compiled them into a 3D model by using the Quantificare software suite. 3D models were evaluated for skin quality (e.g. skin creases and evenness). Every analysis was assigned a score ranging from -10 to +10. A negative score means the appearance of an individual is worse than the average and positive scores above 0 (i.e. average) indicate how much better the patient's result is than in the case of an average individual of similar age, gender, and skin type as a concerned subject.

Therapy Comfort Questionnaire (TCQ) using the 5-point Likert scale ("I found the treatment comfortable") and Visual Analog Scale (VAS, 0-no pain, 10-maximum bearable pain) was administered after the final treatment session. The 5-point Likert scale (1-strongly disagree, 5-strongly agree) Subject Satisfaction Questionnaire (SSQ) was administered after the final treatment and at all follow-up visits to assess patients' satisfaction with the therapy results.

Statistical methods

All data was analyzed for statistical significance and the descriptive statistic was calculated (mean, standard error of the mean, and median value). Paired variables measured at multiple time points were tested by non-parametric Friedman's test followed by Nemenyi's test used to analyze the significance of observed changes. Wilcoxon signed-rank test for a single sample was used to determine whether a mean GAIS difference showed a significant improvement compared to "no change" (zero score) and for analyzing significance in hydration assessment. The significance level was set to α=0.05 (5%).

RESULTS

Forty-one (56.9±1.5 years old, skin types I-VI) received the RF +TUS treatment (A group, N=21) or RF-only treatment (B group, N=20).

GAIS evaluation

The majority of patients (94.4%) from Group A achieved a significant (P<0.05) improvement according to the GAIS scale (Table 2). The most prominent difference was observed at 3 months (Figure 1) in Group A by +1.3 ± 0.1 points and was maintained with individual slight decrease at 6 months. In Group B, the GAIS scale difference showed only +0.8 ± 0.2 points at a 3-month follow-up visit.

Table 2: GAIS difference average ± Standard Error of the Mean (SEM) values after the treatment, 1-month, 3-month, and 6-month (optional) follow-up visits.

Global Aesthetic Improvement Scale (GAIS)				
	After Tx	**1 month**	**3 months**	**6 months**
Group A	0.6 ± 0.1 (N=19)	0.8 ± 0.1 (N=19)	1.3 ± 0.1 (N=18)	1.1 ± 0.2 (N=9)
Group B	0.5 ± 0.1 (N=19)	0.7 ± 0.1 (N=19)	0.8 ± 0.2 (N=18)	0.7 ± 0.1 (N=6)



Figure 1: A 73-year-old female subject at baseline (left) and at the 3-month follow-up visit after the RF+TUS treatment. Visible improvement of facial appearance by jawline definition, lift of nasolabial and cheeks, and more even skin.

Skin hydration

Up to 71.4% of subjects improved after the RF+TUS treatment. Skin hydration was assessed after the last treatment and increased by +15.4 points (22.8%) in Group A (N=21). Compared to subjects treated with RF only (N=20), a lesser effect was observed (+4.2 points, 7%), pointing out a higher improvement level in group A and healthier-looking skin.

3D analysis of skin texture

Twenty-one (21) patients were included in the 3D analysis, eleven (11) from Group A and ten (10) from Group B. Based on the 3D photo model evaluation with QuantifiCare® software, the more profound skin quality improvement was documented at 1 month and 3 months (Figure 2) in group A against a baseline score of -0.9 ± 1.0 points by +3.5 points (19.3%, P<0.0.5) and +7.3 points (41.6%, P<0.05). This improvement was maintained up to 6 months (+35.1%, P<0.05). The most prominent improvement in Group B (baseline score of 0.1 ± 1.0 points) was documented at 3 months by +5.3 points (28.5%, P<0.05).

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 59

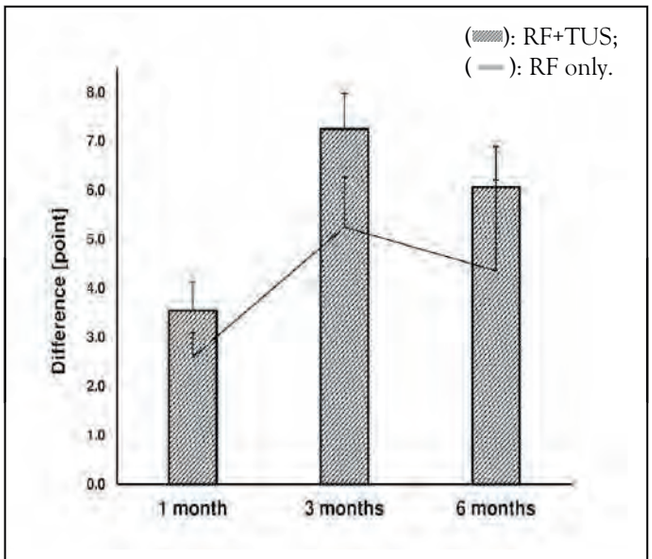


Figure 2: Skin quality by 3D analysis (average±SEM) for Group A (RF+TUS) and Group B (RF only) at 1-month and 3-month follow-up and 6-month optional follow-up visit.

Subject satisfaction and therapy comfort

While almost all subjects found the treatment comfortable, the treatment satisfaction outcomes were higher in Group A with simultaneous delivery of RF+TUS. At 3 months, up to 95% of patients from Group A were satisfied with wrinkle reduction and improvement of skin laxity and overall skin appearance after the treatment. From group B, 90% were satisfied with the RF effects. In addition, all patients from both groups agreed the treatment was comfortable showing 4.6 ± 0.1 points in Group A and 4.5 ± 0.1 points in Group B. During the treatment, only low to mild discomfort was documented by a 10-point visual analog scale showing 1.8 ± 0.4 points for Group A and 1.7 ± 0.5 for Group B. No adverse events were observed.

DISCUSSION

This study aimed to investigate the effectiveness of a treatment utilizing RF and TUS compared to single modality RF by examining the overall change in facial appearance through skin hydration levels and overall skin quality. Based on the results from the 3D analysis, GAIS, and skin hydration assessment, a significant improvement in the RF+TUS group was documented, supporting the hypothesis that the synergy of both technologies is essential for an increase in HA production.

Previous histologic studies have consistently shown the potential of RF+TUS treatment to increase skin hydration *via* hyaluronic acid production. Based on the Matrix Assisted Laser Desorption Ionization-Time of Flight mass spectrometry (MALDI-TOF) evaluation Duncan DI. [24], presented that the amount of HA in the sample showed a gradual increase by 79% at the 1-month follow-up and by 224% at the 2-month follow-up (p-value=0.022) after the RF+TUS treatment. Compared to RF treatment alone, the synchronized application of RF+TUS resulted in more pronounced enhancement, and no clear trend in the HA changes was observed in the RF group only (14% at the 1-month follow-up, and 11% at the 3-month follow-up visit). These results were accompanied by confocal microscopy pictures visualizing the increased amount of HA in the dermis where HA is produced by fibroblasts. Similar results were documented in Fritz K, et al. [25], study which showed an increase in HA production evaluated by ELISA and light microscopy.

Our study aligns with these findings and further contributes to the existing body of knowledge in this field. The findings of our study highlight the benefits of improved skin hydration. Adequate skin hydration is important for maintaining skin health and function. By enhancing skin hydration levels, our findings suggest potential benefits such as improved barrier function, and a more youthful appearance. These results were quantitatively supported by a detailed 3D analysis of skin quality, which revealed a notable decline in natural skin aging indicators following the treatment. Importantly, increased skin hydration has been linked to the enhancement of collagen and elastin production, both of which are important for maintaining skin structure and elasticity. Furthermore, the mechanical effects of TUS, such as acoustic microstreaming, also contribute to stimulating fibroblast repair and consecutive HA production, collagen synthesis, and tissue regeneration, ultimately resulting in improved skin quality and a more youthful appearance [26]. Our study suggests that the observed increase in skin hydration may potentially lead to enhanced collagen and elastin synthesis, thereby contributing to overall skin quality improvement. Treatment with RF+TUS primarily boosts HA production and secondarily increases skin hydration thereby making the whole tissue more viable while the collagen and elastin structural remodeling propagates within 3 months [27,28].

The biggest limitation of the study was identifying suitable subjects. Patients' skin properties differ due to individual hydration levels, age, or the specific conditions in which the subject lives. The uniformity in subjects would provide a more comprehensive understanding of the treatment's effectiveness. It is also worth noting that the 3D analysis of skin quality was not conducted at one site due to technical issues, which limits the generalizability of the findings and a more robust assessment of the treatment's impact on skin quality. Further, the moisture meter measurement proved challenging.

MoistureMeterSC measurements mainly focus on evaluating the epidermal layer (up to 2 mm) while only partly providing information about the subcutaneous area. Due to this limitation, skin hydration was only evaluated immediately after the final treatment. Skin hydration levels can fluctuate over time and are influenced by various factors including environmental conditions (low humidity, surfactants, wind, and sun) and individual differences. Although such variations may potentially influence the study findings in long-term observations, there is current evidence that skin hydration increases with HA production in the dermal layer [24,25]. The real-life effects that the increase of HA levels has on the skin were observed in this study. The sustained effects of the treatment on long-term skin hydration need to be further investigated. Despite the aforementioned limitations, the observed outcomes provide valuable quantifiable findings through GAIS evaluation and 3D analysis.

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 60

CONCLUSION

Overall, no study-related adverse events or side effects were observed in the subjects. Our study demonstrates the efficacy of a novel RF+TUS device in significantly improving skin hydration levels and enhancing overall skin quality. By employing synchronized treatment involving RF+TUS, our findings suggest an even greater potential for skin improvement than RF standalone only. However, future studies addressing the above-mentioned limitations are warranted to validate and expand upon our findings, ultimately advancing the field of skin rejuvenation and hydration.

ETHICAL STATEMENTS

This study was approved by the Advarra Institutional Review Board (ClinicalTrials.gov Identifier: NCT05929625), and its conduct adhered to the ethical principles of the 1975 Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Conceptualization, C.B.; Methodology, C.B. and S.C.; Formal analysis, C.B. and S.C.; Investigation, C.B. and S.C.; Resources, C.B. and S.C.; Writing–Original Draft, C.B.; Writing – Review & Editing, C.B. and S.C.; Supervision, C.B. and S.C.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The study was sponsored by BTL Industries. The investigators may be contracted to speak or present this work on behalf of BTL Industries.

FUNDING STATEMENT

This IRB-approved study (ClinicalTrials.gov Identifier: NCT05929625) was sponsored by BTL Industries.

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BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 61

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Simultaneous Delivery of Radiofrequency and Targeted Ultrasound for Enhanced Hyaluronic Acid Production in the Skin.

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Abstract

The development of a new non-invasive technology combining monopolar radiofrequency and targeted ultrasound represents a significant advancement in skin rejuvenation. Unlike other devices that focus solely on stimulating collagen and elastin production, this technology has been specifically designed to enhance the skin's natural production of hyaluronic acid while also promoting collagen and elastin synthesis. As a key structural component of the skin, hyaluronic acid provides essential support, volume, and hydration. By enhancing hyaluronic acid production, this non-invasive treatment approach offers a comprehensive solution for visible improvements in skin texture and overall appearance.

Keywords: Simultaneous, Radiofrequency, Targeted Ultrasound, Hyaluronic Acid

Introduction

Despite being a natural process and an inevitable part of life, aging is still a topic of much mystery and intrigue. Many don't know that the first signs of aging are often caused by decreasing hyaluronic acid rather than collagen or elastin changes. [1,2] When there is not enough hyaluronic acid to support individual collagen and elastin fibers, the overall skin structure becomes compromised; resulting in the disorganization of collagen and elastin fibers and the appearance of fine lines and wrinkles. [1,2]

Hyaluronic acid is a crucial part of the extracellular matrix (ECM) mainly because of its anionic properties; it can attract water (up to 1000 times its weight in water) to swell and create volume, provide structural support, intense hydration, and naturally plump the skin [3–5] Unfortunately, hyaluronic acid undergoes a significant decline in concentration as we age, particularly after the age of 47. This decline is quite dramatic, with a decline of 50% in the skin's hyaluronic acid concentration observed by the age of 60 and a staggering decrease of more than 75% by the age of 70.

Decreasing hyaluronic acid levels, which lead to the appearance of fine lines and wrinkles as we age, is attributed to a reduction in enzymatic synthesis of hyaluronic acid coupled with an increase in enzymatic degradation. [6–10]

The positive impact and great benefit of hyaluronic acid in the skin have become common knowledge among Aestheticians. Despite efforts to non-invasively stimulate natural hyaluronic acid production using radiofrequency or ultrasound heating technologies, oftentimes, the results have been found to be inconclusive or have shown only minimal effects. Since there has been no way to boost natural hyaluronic acid production, countless companies have offered many different forms of delivering manufactured hyaluronic acid, most frequently obtained by microbial fermentation and hyaluronic acid bacterial production, into the skin.[11] Most common are topical solutions, injectable hyaluronic acid dermal fillers, and oral remedies, which all try substituting the natural function of the skin cells;

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yet, their effect on skin appearance is short-term and limited. [4,12]

Hyaluronic Acid Synthesis

To develop a method that could facilitate the natural production of hyaluronic acid, it is essential first to gain an understanding of the physiology and biochemical processes involved in the synthesis of hyaluronic acid. Typically, fibroblasts (specialized skin cells) continuously produce hyaluronic acid along with other extracellular matrix components through a complex process influenced by various factors such as cell-matrix interactions, growth factors, and external stress.[13,14] When the skin is exposed to external stress, fibroblasts may respond by giving out an order to increase collagen production to help maintain the skin´s strength and integrity. Secondly, fibroblasts may also initiate additional elastin production, but only when enough transforming growth factor beta (TGF-β) and fibroblast growth factor are present. [13,15,16] Under certain external conditions, fibroblasts may also respond with hyaluronic acid production, which is the result of a complex biosynthetic cascade that involves several enzymes and cofactors such as TGF-β, epidermal growth factor, and platelet-derived growth factor, which is ultimately finished by three transmembrane glycosyltransferase isoenzymes named hyaluronan synthases HAS: HAS1, HAS2, and HAS3, whose catalytic sites are located on the inner face of the fibroblast plasma membrane.[17]

Fibroblasts Stimulation

When examining the factors that affect fibroblast activity and the potential for alternation, it becomes evident that external stress may be the most significant factor that can be artificially induced, for example, through exposure to heat or mechanical stimulation. Several studies have investigated the impact of external stress on fibroblasts using techniques such as tissue heating or mechanical stimulation. The results indicate that fibroblasts respond to external stress by increasing collagen and elastin synthesis, with no significant effect on the production of hyaluronic acid.[18–22]

It has been discovered that fibroblasts respond differently to heat stress than to mechanical stress.[23,24] As a result, attempts have been made to apply both stress factors simultaneously to investigate what effects they may have. The results showed that the tissue response was significant, as fibroblast activity increased significantly more than when a single stimulus was applied. This led to the production of collagen, elastin, and hyaluronic acid. [25–29]

The RF+TUS Technology

A novel technology has been developed to enhance the body's innate capacity to produce hyaluronic acid. This pioneering technique involves the synchronized delivery of monopolar radiofrequency and targeted ultrasound. While neither component alone exhibited any measurable effect on hyaluronic acid synthesis, investigations showed that the combination of both monopolar radiofrequency and targeted ultrasound dramatically enhanced hyaluronic acid synthesis. Hence, it seems that the key to enhancing the production of hyaluronic acid, in addition to collagen and elastin, lies in applying both of these energies simultaneously. [25–28]

The first component of the technology utilizes monopolar radiofrequency, which uniformly heats the dermis to a temperature range of 40-42°C. This is a critical step in inducing heat stress to the fibroblasts, explicitly targeting the aged and rigid collagen and elastin fibers throughout the dermis.[18–20,30,31] The heat induces collagen coagulation and rapid skin shrinkage, triggering the restorative process and promoting the production of new collagen and elastin to improve the dermal structure, resulting in skin improvement through neocollagenesis and neoelastinogenesis. [18–22]

The second component of this technology is Targeted Ultrasound, which directs its mechanical waves to the reticular dermis, the area in the skin that houses the most active fibroblasts. The high-frequency sound waves deliver mechanical stimulation to the tissue, effectively vibrating the elements within the reticular dermis, including the fibroblasts residing there. The energy accumulated in a single layer creates an additional heating component that ensures the reticular dermis is heated to 42°C.

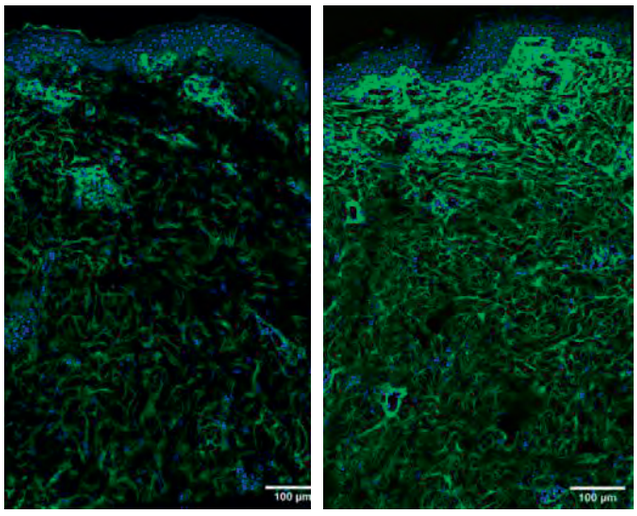
Using mechanical energy to activate receptors on the surface of cells triggers a signaling process that leads to changes in gene expression and protein synthesis within fibroblasts; which can make them more receptive to radiofrequency waves. These waves heat the tissue and cause a controlled cellular environment disruption, significantly increasing the natural production of hyaluronic acid, collagen, and elastin fibers. [21,23,30,32]

Scientific Validation of RF+TUS technology

The impact of simultaneous monopolar radiofrequency (RF) and targeted ultrasound (TUS) on increased hyaluronic acid production has been tested and proven by five different evaluation methods: Polymerase chain reaction (PCR), MALDI-TOF, Confocal microscopy, Enzyme-linked immunosorbent assay (ELISA) and Semi-Automatic Segmentation Analysis.[25–28]

Based on the clinical findings, it is crucial to emphasize the significance of directing the ultrasound energy to the reticular dermis. A study conducted by Duncan et al. aimed to investigate whether non-targeted ultrasound could achieve the same effects on hyaluronic acid as specifically targeted ultrasound. The study involved 12 swine subjects, half of which were treated with a combination of generic ultrasound and radiofrequency (RF+US), while the other half were treated with targeted ultrasound and radiofrequency (RF+TUS). [25]

Three different types of evaluations, including PCR, molecular analysis by MALDI-TOF, and confocal microscopy, consistently showed a significant increase in the concentration of hyaluronic acid in the skin by up to 224% only when using targeted ultrasound and RF. The group treated with generic ultrasound and RF exhibited no significant changes. This finding strongly indicates the importance of fibroblasts located in the reticular dermis and highlights the necessity of targeting these cells to induce changes in the natural process of synthesizing hyaluronic acid.[25]



Confocal microscopy images show that at the 2-month follow-up, the network in the dermis of the RF+TUS group appears denser with more green fibers compared to the baseline on the left

Similarly, Fritz et al. conducted a study to confirm the importance of targeted ultrasound by comparing the use of radiofrequency alone to a combination of radiofrequency with targeted ultrasound. The study involved testing the effects of the treatments on porcine skin samples using the ELISA test and HABP histological staining. The study results showed that the group treated with a combination of radiofrequency and targeted ultrasound (RF+TUS) exhibited a gradual yet significant increase in hyaluronic acid levels about two months after the therapy.

In contrast, the group treated with radiofrequency alone showed no significant changes in hyaluronic acid levels. These findings suggest that the use of targeted ultrasound in combination with radiofrequency can effectively alter tissue composition and increase hyaluronic acid levels, highlighting the importance of targeted ultrasound in such treatments.[27]

In addition to animal studies, the effectiveness of this technology has also been tested on human subjects who volunteered for a study conducted by Goldberg et al. Seven individuals participated in the study, with three receiving RF+TUS treatment, three receiving radiofrequency treatment alone, and one serving as a control subject. The results of this study, involved human histology; confirming that the treatment's impact on human skin is similar to that observed in the animal model. This similarity can be attributed to the fact that human and animal skin share many similarities. Biopsy samples with semi-automatic segmentation have proven a significant increase in the concentration of hyaluronic acid in the RF+TUS treated group, while no effect on the hyaluronic acid levels was seen in any of the other two groups.[28]

Furthermore, as expected based on the proposed mechanism, the dual stimulation of fibroblast not only leads to enhanced hyaluronic acid levels but also promotes the production of collagen and elastin. This was demonstrated in a porcine histology study by Kent et al. which showed a 47% increase in collagen and a 50 % increase in elastin. [29]

The changes observed in the skin structures in the histological studies were also found to translate into an overall improvement in skin appearance. A study by Chilukuri&Boyd investigated 41 participants and looked into the skin hydration linked with hyaluronic acid levels and overall skin texture improvement. This study yielded significant findings, indicating the effectiveness of the technology. Specifically, a 23% increase in skin hydration and a 41 % improvement in skin texture were observed. The technology was also found to improve skin laxity by 85% when used across the body, as seen in the study by Kent&Mueller. [26,33]

Conclusion

The new technology that delivers radiofrequency and targeted ultrasound simultaneously brings totally new approach to skin treatments, as it is the first time we are able to enhance the body's ability to increase hyaluronic acid production. The efficacy of the technology has been proven by 5 different evaluation methods on the cellular level, together with promising results in skin rejuvenation. As such, the technology offers an entirely new alternative to fight hyaluronic acid depletion, which only increases with age and is one of the main contributors to skin aging. Together with its effect on collagen and elastin, it appears to be a complex tool for skin remodeling while targeting all skin structures.

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BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 17

Journal of Women's Health Care

ISSN: 2167-0420

OPEN ACCESS Freely available online

Research Article

360° Radiofrequency Technology for Treatment of Dyspareunia in Women with Genitourinary Syndrome of Menopause

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ABSTRACT

Background and Purpose: This study aims to evaluate the safety and efficacy of a focused, monopolar, 360° energy distribution radiofrequency (RF) device for non-invasive treatment of dyspareunia in menopausal women with genitourinary syndrome of menopause (GSM).

Methods: Thirty-five postmenopausal women with severe dyspareunia and GSM, underwent three sessions of monopolar radiofrequency therapy delivered once a month. Participants were evaluated at baseline and 2 months after their last treatment. The primary outcome was determined by assessing the patient's satisfaction with sexual intercourse at the 2-month follow-up visit. Secondary outcomes included the Vaginal Maturation Index (VMI), Maturation Value (MV), Bachmann´s Vaginal Health Index (VHI), and vaginal pH measurement. Safety outcomes included monitoring any possible complications and adverse events, and patient discomfort was evaluated by the Visual Analogue Scale (VAS).

Results: A total of 83.3% of women initially incapable of sexual intercourse due to severe dyspareunia, were able to fully engage in sexual intercourse without pain 2 months post-treatment. VMI and VHI increased significantly in all parameters for all subjects (P<0.01). The Bachmann´s Vaginal Health Index Score (VHI) improved significantly (P<0.01) by 11.2 points. The analysis of vaginal cells demonstrated complete vaginal restoration with the presence of vaginal Lactobacillus flora, a normal acidic vaginal pH, the absence of inflammatory cells, and even the presence of superficial vaginal epithelial cells in initially severely atrophic tissue. Ninety-eight percent of subjects reported mild to no discomfort during their last treatment. No serious side effects throughout the course of the study were reported.

Conclusion: The present study demonstrates a positive effect of a focused monopolar RF device for non-invasive and non-hormonal vulvovaginal tissue restoration affected by severe GSM. The results indicate clinical improvement in severe dyspareunia as a bothersome symptom of GSM. The treatment is effective and safe with high patient satisfaction.

Keywords: Dyspareunia, GSM, Genitourinary, Menopause

INTRODUCTION

Genitourinary syndrome of menopause (GSM), formerly referred to as vulvovaginal atrophy (VVA), is a widespread condition, affecting 27%-84% of post-menopausal women [1]. The new term, GSM, was introduced in 2013 to describe various non-genital signs and sexual symptoms since VVA (and atrophic vaginitis) but did not cover the full spectrum of symptoms and causes of the condition [2]. GSM is caused by a decrease in circulating estrogen levels at the onset of menopause. Genital symptoms include vaginal dryness, itching, tenderness, and burning. Sexual symptoms are lack of lubrication, dyspareunia, and impaired performance. Urinary symptoms such as

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Received: 19-May-2022, Manuscript No. JWH-22-17569; **Editor assigned:** 21-May-2022, PreQC No. JWH-22-17569(PQ); **Reviewed:** 04-Jun-2022, QC No. JWH-22-17569; **Revised:** 08-Jun-2022, Manuscript No. JWH-22-17569(R); **Published:** 15-Jun-2022, DOI: 10.35248/2167-0420.22.11.585

Citation: Aznar F, (2022) 360° Radiofrequency Technology for Treatment of Dyspareunia in Women with Genitourinary Syndrome of Menopause. J Women's Health Care 11(6):585

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BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 18

urgency, dysuria, and recurrent urinary tract infections (UTIs) may occur [3]. All these symptoms negatively affect sexuality and quality of life. GSM features may appear in premenopausal hypoestrogenic women as well, manifesting in approximately 15% [4].

Primarily, the goal of GSM treatment is symptom relief. Conventional approaches for vulvovaginal symptoms include nonhormonal lubricants and moisturizers [5]. Hormonal and topical therapies mostly affect only the surface of the vaginal epithelium, while these therapies are being actively used [6]. An alternative solution is the use of non-invasive energy-based devices which affect vascularization and all levels of connective tissue in the vaginal canal. Besides laser energy (which lacks substantial safety and efficacy data) [7], non-ablative low-dose radiofrequency (RF) energy is widely used for the treatments [8,9]. The effect of RF devices is based on generating an electrical field that results in an oscillating electrical current that heats up intra-vaginal tissues to 40-45°C. These temperatures lead to increased local circulation and remodeling of collagen and elastin fibers located beneath the vaginal epithelium, in lamina propria. Increased blood flow provides nutrition to atrophic tissue and promotes its regeneration which results in the thickening of the vaginal epithelium. Lastly, collagen remodeling leads to tightening and strengthening of the vaginal wall [10,11].

Multiple studies reported reduced laxity of vaginal tissue [12-14], improvement in symptoms of GSM [8,15,16], better sexual function, and satisfaction [8,13,14,17] following the use of RF devices. Ablation laser energy treatment is superficial and can only treat certain symptoms, whereas non-ablative monopolar radiofrequency (RF) penetrates and affects deeper tissues. The limitation of current RF devices is the design of the applicators which allows treating only one quadrant of the vaginal canal at a time. Such techniques may lead to undertreated or overtreated areas (so-called "hot-spots") because of the non-homogeneous heating. In this study, 360° homogeneous heating has been improved upon by devising temperature tracking via dynamic impedance technology (DIT), which reduces the risk of under or overheating and significantly speeds up the time needed for treating the entire vaginal area, compared to quadrant heating procedure. Such a device has been successfully used for labial tissue rejuvenation and for the improvement of sexual function [18]. We hypothesize that the treatment could be beneficial also for women with GSM.

This study aims to investigate a 360° monopolar RF device with temperature tracking technology for the non-invasive treatment of dyspareunia in menopausal women with GSM.

METHODS

A total of 35 postmenopausal women (6.3 ± 3.2 years post-menopause) aged 56.6 ± 3.4 years were enrolled in the study. Inclusion criteria were defined as follows: females with at least 3 years of severe dyspareunia as a bothersome symptom of GSM, incapable of sexual intercourse with penile penetration (coitus) for at least 12 months. Exclusion criteria included: sexually transmitted infection, sensitivity disorders or burns in the treatment area, metal implants, and conditions contraindicated by the device manual. No anesthesia was required.

The patients underwent treatment with Emfemme 360 device (BTL Industries Inc., Boston, MA). The treatment regimen consisted of three monopolar RF treatment sessions, each lasting for 8 minutes, delivered once a month. Before beginning treatment, the patient received verbal instructions about what to expect during the treatment procedure. The patient was seated in a gynecological chair and the device's applicator utilizing heating at 360° was placed in the vaginal canal. The initial treatment setting was 65% and increased gradually during the procedure according to patient feedback and tolerance. During the treatment session, the operator steadily moved the applicator inward and outwards to ensure homogenous heating of the vaginal canal. The therapeutic temperature was continuously monitored during treatment via a temperature indicator screen. The operator communicated with the patient throughout the treatment to monitor safety. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from the patients.

Participants were evaluated at baseline and 2 months after the last treatment. Gynecological examination using a speculum and penetration with a transvaginal device applicator was done. The clinical improvement in dyspareunia was determined using a dichotomous questionnaire about satisfaction with sexual intercourse. Vaginal wall samples were collected using a swab and evaluated at the baseline and follow-up visits. The Vaginal Maturation Index (VMI) analysis was done under a light microscope (Carl Zeiss Axioskop microscope and Carl Zeiss Axiocam Color camera) by a blinded cytopathologist. Maturation Value (MV) was calculated from the VMI and the vaginal lining samples were further examined for the presence of lactobacillus flora, inflammatory cells, and superficial vaginal epithelial cells. In addition, evaluation included vaginal pH measurement and Bachmann´s Vaginal Health Index (VHI). The occurrence of any adverse events was monitored. Patients rated the comfortability of treatment based on a 10-point Visual Analogue Scale (VAS), no pain (zero) to unbearable pain (ten). Patient discomfort and a 5-point Likert scale. Patients expressed their satisfaction with treatment outcome percentage-wise (0% = dissatisfied; 100% = satisfied). The obtained before and after scores were compared and analyzed using the paired Student t-test, α=0.05.

RESULTS

All 35 patients completed the treatment regimen and underwent the examination at baseline and at 2 months post-treatment. At baseline, all patients reported severe dyspareunia. Two months post-treatment, dyspareunia was completely absent in 29 out of the 35 patients (83%).

Vaginal Health Index

The baseline measurement of the Bachman's VHI score (scale 5-25) comprising the evaluation of 'elasticity', 'fluid secretion type and consistency', 'pH', 'epithelial mucosa', and 'vaginal moisture' was found to be 7.7 ± 1.2 on average, which corresponds to severe GSM. Two months post-treatment the average score significantly ($p<0.01$) increased to 18.7 ± 1.9 corresponding to a normal menopausal healthy vagina. Change in each section of the VHI was highly significant ($p<0.01$) with the highest improvement in pH and epithelial integrity. Figure 1 shows a detailed summary of VHI results (Figure 1).

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 19

The increase in pH score from 1.5 ± 0.5 to 4.2 ± 0.6 corresponds to the restoration of the pH acidity from a nearly neutral pH of 6.6 ± 0.8 at baseline to acidic pH of 4.6 ± 0.61 two months post-treatment.

Vaginal Maturation Index and Maturation Value

The proportion of para basal, intermediate, and superficial cells in samples, categorized by the vaginal maturation index (VMI) showed significant improvement ($p<0.01$) as the average baseline VMI improved from 65.1/34.9/00 (parabasal/intermediate/superficial) to 26.9/66.6/6.6. The corresponding maturation value (MV) calculated from the VMI significantly ($p<0.01$) improved from 17.4±8.7to 39.9 ± 10.0 (0-100 scale).

Vaginal Flora, Leukocytes, and Inflammatory Cells

At baseline, normal vaginal flora consisting of lactobacilli (Döderlein flora) was present in only 10 out of the 30 patients (28%). Two months post-treatment, healthy vaginal flora quantity with Lactobacilli was present in 30 patients (86%). The improvement corresponded with the decrease of inflammatory cells. At baseline, the samples of 12 patients (34%) showed high levels of leukocytes, and 23 patients (66%) showed low levels of leukocytes. At 2 months follow-up, 15 patient samples (43%) had low leukocyte levels, while the remaining 20 (57%) did not contain any leukocytes. Inflammatory cells that were observed during pretreatment were absent in all samples post-treatment. An example of vaginal wall sample analysis results can be seen in figure 2.

Comfort and Satisfaction

At baseline, all patients reported painful gynecological examination using the speculum, and the transvaginal device applicator caused great discomfort, bleeding, and posterior vulvovaginal irritation. The average baseline VAS score was 6.6±1.3 (moderate to severe pain). At the 2-month follow-up visit, most of the patients indicated no to mild discomfort during gynecological examination with the speculum. The average VAS score decreased significantly ($p<0.001$) to 1.4±1.1 (mild to no pain) at the follow-up visit. Figure 3 demonstrates the exceptional difference between the first and last treatment.

The overall patient satisfaction with the treatment results was high (92.9±6.7%). There were no dissatisfied patients. Moreover, at baseline 11 patients suffered from mild stress or mixed urinary incontinence, and 5 patients suffered from overactive bladder. All of these patients reported improvement and nearly 100% control of urination.

Side Effects and Complications

Immediate treatment effects were mild and transient, most of which occurred only during the first session and resolved within 1–2 days. The vaginal discharge occurred in 70% of patients, vaginal bleeding in 50%, introitus itching (45%), burning sensation (30%), and painful urination (20%). No complications or serious side effects were reported. No anesthesia, medications, or downtime was necessary.

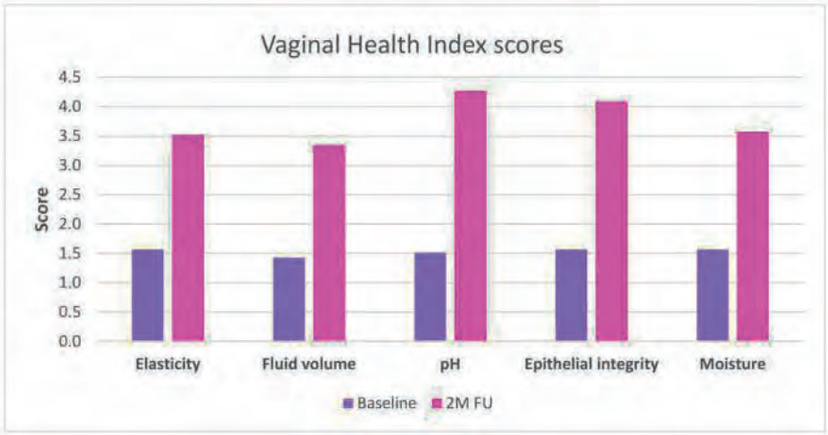


Figure 1: The average scores of individual criteria of the VHI. The total score is calculated as a sum of individual criterion scores. There was an overall improvement in all vaginal health index criteria.

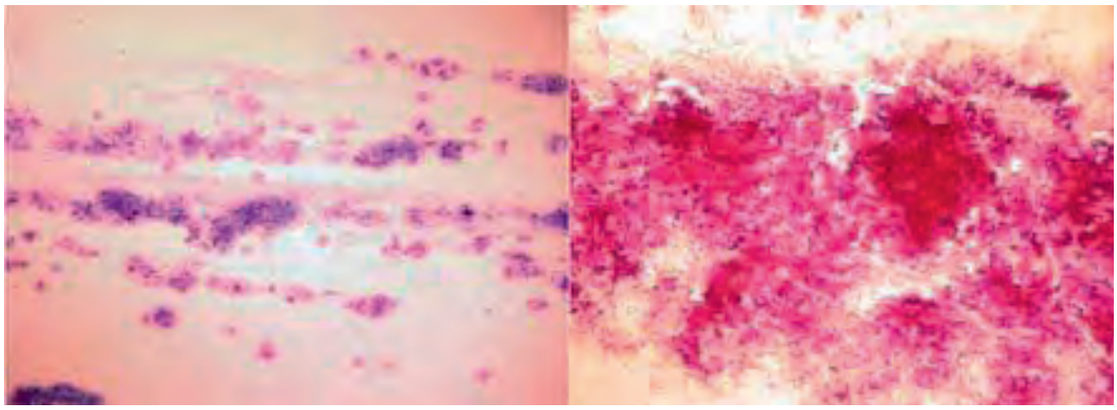


Figure 2: Vaginal lining samples of 57-year old woman (7 years post-menopause) with initially severe GSM. At baseline (left) the VMI score was 70/30/00, inflammatory cells were present, absent Döderlein flora, vaginal pH=7.5 and VHI=7. Two months post-treatment (right) the VMI score improved to 20/70/10 with absent inflammatory cells and presence of Döderlein flora observed, pH=4.4 and VHI=19.

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 20



Figure 3: During the first treatment (left) the probe caused bleeding and vaginal irritation in the initially severely atrophic vagina. During the last treatment (right), no bleeding, irritation or discomfort were observed nor reported.



Figure 4: The figure shows severely atrophic vulva introitus pre-treatment (left) and "rejuvenated" vulva introitus post–treatment (right). Enhanced vascularity can be seen on the inner labial walls and on the introitus.

DISCUSSION

This is the first study examining the efficacy of 360° monopolar RF technology for the treatment of GSM. The results presented herein show that the application of 360° radiofrequency in postmenopausal women with severe GSM leads to restoration of sexual life and vaginal wall quality, including the restoration of acidic vaginal pH and vaginal flora. The procedure effectively treated dyspareunia. VHI and VMI improved, reaching levels corresponding to those of menopausal women with normal vaginal health.

The novel Emfemme 360 device utilizes state-of-the-art temperature tracking technology in real-time, enabling the operator to monitor temperature throughout the therapy, thus, does not have to rely on patient feedback alone. The uniform heating is achieved through dynamic impedance technology, which continuously regulates RF energy flow. The impedance continuously changes; however, the results are constant since there is no fluctuation. The use of a temperature tracker gives the operator complete control over the treatment, which leads to consistent results as the risks of undertreating or over-treating are reduced. The DIT is a smart algorithm-like technology that measures vaginal tissue bioimpedance [19] 1000 times per second and, based on the measurements, adjusts the power in order to constantly deliver the desired energy. This feature avoids energy fluctuations during the treatment as the impedance changes with changes in temperature. Volumetric RF-generated heat is homogeneously distributed through the applicator tip in the treatment area. The highly advantageous uniform heat distribution ensures there are no hot-and-cold spots in the vaginal canal, resulting in short, and uncomplicated treatment administration. The vaginal probe has an ergonomic fit with various tips to suit different patients' needs.

A single treatment session lasts for only 8 minutes, which is sufficient for heating the vaginal tissues up to desired temperature range of 40-45°C, and presumably triggers regenerative processes of neocollagenesis, neovascularization, and growth factor infiltration [20-22]. Increased levels of growth factor ultimately revitalize and restore the elasticity and moisture of the vaginal mucosa and induce epithelial thickening and structural changes [10]. The change in epithelial structure has been observed in vaginal lining cytologic analysis through an increase in VMI/MV in this study. The observed improvements correspond with previous studies using RF for restoring vaginal health in postmenopausal women such as Leibaschoff et al. [20] who reported improvement in VHI from 11.5 ± 0.67 to 19.3±2.01. However, the majority of RF studies does not include quantitative assessment and rely mainly on questionnaire evaluation [14,16,17,23] (Figure 4).

Besides the measured parameters, the patients reported improvement in the vulva appearance even though the treatment was intravaginal and did not include a labial procedure. The improvement in the vulva appearance is demonstrated in figure 4. Additionally, most of the patients reported improved sensitivity in the entire genital area, which was also documented by Alinsod et al [23]. This observation corresponds with the results of Lalji et al., [12]. who reported significantly reduced urine leakage after treatment procedure with the 360° RF technology. In a patient group that was composed only of women with severe GSM unable to engage in sexual intercourse (coitus) for three or more years, the results showed complete restoration of the vaginal health. Based on these outcomes it may, therefore, be assumed that the treatment could reverse certain symptoms of GSM.

Nevertheless, the patient group (35 post-menopausal women) was rather limited. Although such samples cannot be used for

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 21

generalized conclusions, the results give a good overview of the expected treatment outcomes. Patients were evaluated 2 months post-treatment, and certainly, this time period is insufficient to provide information about the sustainability of results. Thus, future studies should include longer follow-ups to address the longevity of the outcomes and whether additional treatments to maintain the achieved results are necessary. A comparative arm group and evaluation of tissue biopsies may be incorporated in upcoming studies. The major strength of this study is that multiple methods for evaluating treatment effects were used to avoid inferring biased conclusions, which could occur when using a single evaluation method, as well as to provide deeper insight into the patient's condition. The statistically significant changes and participants' recovered sexual function (despite prior severe dyspareunia that prevented penetrative sexual intercourse) demonstrated in this study provides strong evidence for the treatment efficacy.

CONCLUSION

Vulvovaginal monopolar radiofrequency resulted in highly significant clinical improvements in all measured parameters in postmenopausal women with severe dyspareunia GSM. Most of the patients recovered the ability to have satisfying sexual intercourse, after years of no sexual life. The monopolar 360° technology is an effective, safe, easy, and time-saving treatment for severe GSM symptoms and dyspareunia without any serious adverse events.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 30

SHORTEST RADIOFREQUENCY TREATMENT FOR WOMEN'S INTIMATE HEALTH

ASSESSING THE EFFICACY OF RADIOFREQUENCY TREATMENT FOR IMPROVING GENITOURINARY SYNDROME OF MENOPAUSE SYMPTOMS, SEXUAL FUNCTION, AND VAGINAL HEALTH

Dr H. W. V. Cheng[1]

1. Vitalage, Central, Hong Kong

Highlights

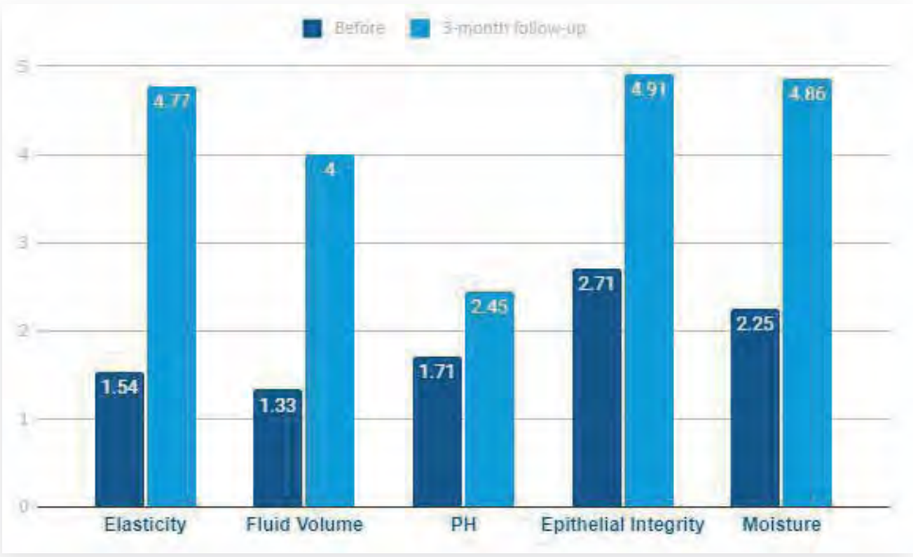
- 24 postmenopausal subjects (av. 56 years)
- 4 EMFEMME 360 treatments with 1 and 3-month follow-up
- Evaluation methods:
  - Female Sexual Function Index **(FSFI)**
  - Vaginal Health Index Score **(VHIS)**
  - GSM Symptoms - Visual Analogue Scale **(VAS)**

123%

Vaginal Health Improvement

68%

Sexual Function Improvement



The Vaginal Health Index scores show an overall improvement in all five criteria

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 33

360° VOLUMETRIC HEATING VAGINAL HEALTH STUDY

360° RADIOFREQUENCY TECHNOLOGY FOR TREATMENT OF DYSPAREUNIA IN WOMEN WITH GENITOURINARY SYNDROME OF MENOPAUSE

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Published in the Journal of Women's Health Care DOI: 10.35248/2167-0420.22.11.585

Highlights

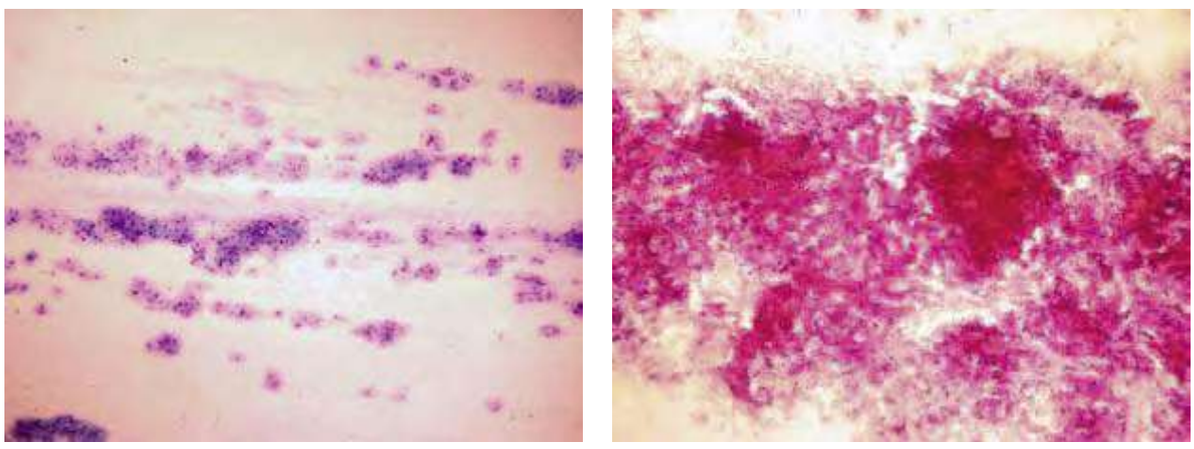
- **35** postmenopausal subjects (av. 56.6 years) received three 8-minute treatments once a month due to severe cases of dyspareunia.
- **Vaginal Maturation Index increased significantly** in all subjects and represents restoration of vaginal premenopausal cells.
- **A high count of inflammatory cells** (leucocytes) observed pre-treatment was significantly reduced and **absent in the follow-up samples**.
- All patients initially suffering from severe dyspareunia were capable of sexual intercourse without pain after the treatments.

93%

Patients were satisfied with the results

83%

Women have pain-free sex post-treatment



An atrophic parabasal cells and absence of superficial cells from vaginal-smear correlate to a menopause patient with a severe vulvovaginal atrophy (left); "estrogenized-like" intermediate cells correlate to a menopause woman without any symptom of the menopause genitourinary syndrome (right).

BLT_Studienbuch_Exion_DRUCK_Layout 1 26.03.24 11:55 Seite 42

Check for updates

Received: 20 October 2023 | Revised: 24 January 2024 | Accepted: 15 February 2024

DOI: 10.1111/jocd.16251

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

The effects of a real-time temperature monitoring non-ablative monopolar radiofrequency technology on vulvovaginal atrophy symptoms in postmenopausal Chinese women

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Abstract

Background: Vulvovaginal atrophy (VVA) includes a wide range of conditions affecting the reproductive and urinary systems, often requiring careful evaluation and management for optimal health.

Aims: This study aims to evaluate the symptom management effects of a real time temperature-monitored non-ablative RF device for the treatment of postmenopausal Chinese women with VVA symptoms.

Methods: This pilot study involved 24 postmenopausal Chinese women with one or more VVA symptoms, who wished to remain sexually active. VHIS, VAS, and FSFI were used to track and evaluate various aspects of the patient's condition. Analyses were conducted at the end of the study to verify the statistical significance of the treatment's results.

Results: All patients reported substantial, statistically significant, improvements on every VVA symptom tracked. Approximately 80% of the patients reported total symptom reversal at 12-week post-treatment follow-up.

Conclusion: This pilot study demonstrated that non-ablative, monopolar RF technology equipped with real time temperature monitoring is feasible and safe in the treatment of postmenopausal women with VVA symptoms, and efficacious at up to 12 weeks post-treatment.

KEYWORDS
energy-based vaginal rejuvenation, GSM, menopause, radiofrequency, vulvovaginal atrophy

1 | INTRODUCTION

Natural menopause occurs at the average age of 51 amongst Hong Kong women.[1,2] Boasting the world's highest life expectancy at 88 years,[3] these women spend more than half their adult lives in a postmenopausal state.[4] With a rapidly aging population, Hong Kong is the home to approximately 1.7 million post-menopausal women, constituting 23% of the city's total population.[5] This segment is projected to comprise more than one-quarter (27%) of the city's total population by 2030, representing almost half (49%) of the entire female population in Hong Kong.[5]

In contrast to the more commonly discussed vasomotor symptoms such as hot flushes and night sweats, vulvovaginal atrophy (VVA) is the most long-lasting symptom of menopause,[6–8] yet is

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given little attention and the topic is rarely discussed in the relatively conservative Chinese society. While this prevalent condition is non- life threatening, it seriously impacts the physical and mental health, well- being, couple's intimacy, and the overall quality of life of postmenopausal women.

VVA is an involution of the mucous membranes and tissues of the vulva and vagina caused by the drop in estrogen that occurs in women during menopause.[9–12] Recent reviews[12–14] on the prevalence of VVA symptoms indicate that about 50% of postmenopausal women report at least one symptom associated with the condition. Patients with VVA complain of vaginal burning, discharges, itching, dryness, irritation, dysuria and dyspareunia.[12,15–18] Moreover, the weakened tissues are more prone to develop trauma, tears, bleeding, and infections.[12,19,20]

Atrophy of the vulva, introitus, and vagina can be especially problematic for women who want to stay sexually active, but experience dyspareunia during sexual intercourse due to vaginal dryness and atrophic changes.[7,19,21–25] According to community studies, the prevalence of sexual dysfunction amongst postmenopausal women is 91.2%.[26] Some vulvovaginal symptoms can be alleviated by the use of vaginal lubricants or moisturizers; however, such solutions offer limited and temporary relief only.[27] In addition, emerging data suggest that lubricants may adversely affect the vaginal epithelium, lamina propria, and the vaginal microbiota.[27–31]

Hormonal replacement therapy (HRT) may be considered for climacteric symptoms in the absence of contraindications, whereas local estrogens are primarily indicated to alleviate symptoms and reverse atrophic changes in cases where VVA represents the sole menopausal complaint.[12,32,33] Although local estrogen therapies are effective and safe at very low doses,[32,34,35] medication adherence is quite variable (52%–74%),[36] mainly due to safety concerns, inconvenience, and inadequate symptom relief from treatment.[12,37,38]

More recently, energy-based vaginal rejuvenation modalities such as lasers, fractional CO_2,[39] fractional Er: YAG, and radiofrequency (RF) devices,[40–42] have brought new hope to patients suffering from VVA symptoms. RF has gained significant popularity in recent years due to its non-invasiveness and rapid results. The mechanism of action is based on elevating the temperature of the treated tissue to initiate biological changes.[43] RF energy heats the connective tissue of the vaginal wall to 40–45°C, triggering microinflammatory stimulation of fibroblasts to stimulate collagen contraction, neocollagenesis, and neoelastogenesis to revitalize and restore the strength, elasticity, and moisture of the vaginal mucosa.[27,44] However, a long-standing disadvantage of some RF devices has been their constrained application due to limitations in application area where the whole vaginal canal is unable to be treated at once. Nowadays, there are solutions employing 360 degrees of RF energy emission, simplifying the procedure.

A number of qualitative studies exist to demonstrate the therapeutic efficacy of RF-based devices in improving VVA symptoms, stress urinary incontinence (SUI), and sexual functions. Treatment effects on postmenopausal Chinese women are, however, lacking. This study aims to evaluate the symptoms management effects of a real-time temperature-monitored non-ablative RF device in the treatment of postmenopausal Chinese women with VVA.

1.1 | Terminology

The term Genitourinary Syndrome of Menopause (GSM)[34,45] emerged following a consensus conference by the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) held in 2013. GSM is a chronic, progressive vulvovaginal, sexual, and lower urinary tract condition.[46] In the absence of medical intervention, this condition does not improve.

While GSM is a more descriptive term than VVA, the term does not necessarily imply pathology. There are some concerns that the term GSM may be overly all-encompassing, as it refers not only to the symptoms resulting from estrogen deficiency but also those arising from the effects of aging and other processes on the bladder and pelvic floor.[47] As the focus of this pilot study is centered specifically on the effect of non-ablative monopolar RF technology on VVA symptoms, precluding other urogynecological symptoms except dysuria, the term VVA will be used throughout this paper.

2 | METHODS

2.1 | Study design

This pilot study was conducted over a period of 18 months between October 2021 and April 2023, involving 24 postmenopausal women of Chinese origin living in Hong Kong. All subjects suffered one or more VVA symptoms of various severity and harbored the wish to remain sexually active. The subject selection for this study was designed to be monoethnic in nature to evaluate the therapeutic efficacy of RF-based devices on Chinese women with VVA symptoms—an area that has not been sufficiently addressed in previous studies. Given the strong association between vaginal microbiota species composition and VVA,[27] and that the former is known to be influenced by the host's race, internal and external factors, and to some extent, diet, medication, and lifestyle habits,[44,48] this study with its monoethnic subject group serves to assess the treatment efficacy on VVA patients and to provide treatment expectations that are more relevant and meaningful to the vast population of postmenopausal women in Hong Kong.

2.2 | Subject selection

Postmenopausal Chinese women seeking the treatment of VVA were recruited for the study from the existing Investigator's

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pool. All subjects were required to be in a postmenopausal state, as defined as the absence of menstruation for a continual 12 months or more,[49] at the time of the subject recruitment process, and have to suffer at least one symptom of VVA, such as dryness, burning, itching, dyspareunia, and/or dysuria, and wished to remain sexually active. Exclusion criteria included: the use of any HRT (either systemic or local, within the 6 months prior to inclusion in the study), antibiotics, probiotics, or prebiotics (either systemic or local, within the 3 months prior to inclusion in the study), vaginal moisturizers, lubricants or any other local preparation (within the 30 days prior to inclusion in the study); the use of any immunosuppressants, steroids or NSAIDs (within the 3 months prior to inclusion in the study); acute or recurrent urinary tract infections, active genital infections; pelvic organ prolapses, previous pelvic reconstructive surgery, serious diseases or chronic conditions, psychiatric disorders; pacemakers, defibrillators, or any metal implants; and/or other contraindications listed on the device manual (Appendix S1).

Prior to commencement, the study protocol was reviewed and approved by the University Institutional Review Board. The study's conduct adhered to the ethical principles of the 1975 Declaration of Helsinki. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been followed. Each patient was assigned a unique subject identification number for anonymization. The patient's medical, obstetric, and gynecological history was thoroughly reviewed during the initial consultation with a clinician. An informed written consent was obtained before the patient was entered into the study.

Each participant underwent a standardized gynecological examination. The clinician also performed a speculum-assisted examination as well as pH testing with pH test strips.

A summary of the demographic and clinical profile of the subjects is presented in Table 1.

When the gyneco-obstetric features of women in the study group were examined, 66.7% had given birth, and one-third of the subjects had no child-bearing experience. 16.7% of the patients had one pregnancy, 41.7% had two, and 9.3% had three or more pregnancies. 41.7% of the subjects had vaginal deliveries, 20.8% had cesarian deliveries, and 4.2% had both. Of those who had given birth, 87.5% had the first delivery at or before the age of 35.

At the time of the study, 33.3% of the patients had been in the menopausal state for 1–4 years, half of the women had been in menopause for 5–9 years and 17% for 10 years or more.

TABLE 1 Demographic & clinical profile of the study cohort ($n = 24$).

Personal history	*N*	Mean ± SD or %
Age (years)	24	55.9 ± 4.1
Age at menopause (years)	24	50.4 ± 3.2
Time-lapse since menopause (years)	24	6.5 ± 3.4
Sexually active[a] in the last 6 months	19	79%
Sexually inactive	5	21%
Nulliparous	8	33%
Childbirth	16	67%
Childbirth history		
Caesarean section only	5	31%
Vaginal delivery only	10	63%
Vaginal & caesarean	1	6%
Smokers	0	0
BMI	24	22.8 ± 4.9
Previous treatment		
No treatment	12	50%
Lubricant/moisturizer	9	38%
HRT	0	0
Other (topical medication, pre−/probiotics)	3	12%

[a]"Sexually active" is defined as having engaged in sexual activities at least once every month.

2.3 | Treatment protocol

The machine used in this pilot study was the Exion BTL-785F, with an EMFEMME 360 applicator (BTL Industries Ltd). The device emits RF energy in 360 degrees, thus treating the entire vaginal canal at once. It also uses a built-in temperature sensor for real-time temperature tracking.

Each patient underwent four weekly treatment sessions, carried out as an outpatient procedure by a clinician with the assistance of a designated clinic personnel. The procedure involved 8 min of intra-vaginal RF treatment and 12 min of extra-vaginal RF treatment. The patients were treated in a lithotomy position on a gynecology bed. No anesthesia was required for this non-ablative monopolar RF procedure. A grounding pad was firmly attached to the subject's musculus gluteus maximus area during the entire treatment.

Real-time temperature was monitored through the infrared thermal sensor on the handpiece. All applicator tips used were for single use only and were properly disposed of after each treatment.

During the treatment, RF energy was emitted through a 360-degree metal ring located at the upper part of the intra-vaginal applicator, while the plastic cap covering the top of the applicator prevented the RF energy from reaching the cervix. Within 90 s into the intra-vaginal treatment, the vaginal tissue was gradually heated to the therapeutic level of 40–45°C. As for the extra-vaginal session, the treatment areas including the labia majora, labia minora, introitus, and perineum,[50] reached the therapeutic temperature of 40°C within 60 s. Patients could return to their normal activities immediately afterwards and did not need to avoid coital sexual activity after the procedure.

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Follow-up appointments were arranged 4 weeks (R1) and 12 weeks (R2) after the last treatment session. Treatment safety and experience, with special attention to heat, pain, and discomfort, were assessed at each visit.

2.4 | Data collection & analysis

Three evaluation systems, namely the Vaginal Health Index Score (VHIS), the 10-cm Visual Analog Scale (VAS), and the Female Sexual Function Index (FSFI), were used concurrently in this pilot study. The patients' conditions were evaluated with VHIS and VAS at the initial visit (baseline), at each of the weekly treatment visits, and during the two follow-up appointments. As the FSFI measures sexual function in six domains over the previous 30 days,[51] the patients were asked to complete the FSFI questionnaire during their initial visit (baseline), at the 4th treatment visit, and at the two follow-up appointments.

2.4.1 | VHIS

At each point of time during the study, the patients were evaluated using the VHIS. The system consists of five parameters: Elasticity, Fluid volume, pH, Epithelial Integrity, and Moisture. Each parameter is graded from 1 to 5, with 1 being the least desirable and 5 being the most satisfactory; if the total score is <15 out of a total score of 25, the vagina is considered atrophic.[52] Assessment of clinical changes related to vaginal atrophy was evaluated through clinical examination and the VHIS system developed by Gloria Bachman et al.[53]

2.4.2 | 10-cm VAS

Using VAS, the intensity of VVA symptoms (vaginal burning, vaginal itching, vaginal dryness, dyspareunia, and dysuria) were evaluated by patients themselves, with the left extreme of the scale (0) indicating *"absence of symptom"* and the right (10) indicating *"symptom as bad as it could be"*.[54] The VVA symptoms evaluations were conducted before the first RF application (baseline), at every subsequent treatment visit, and again at the 4- week and 12- week follow- up.

2.4.3 | FSFI

FSFI is a broadly used and highly reliable instrument for assessing female sexual functions; the system was recently validated for use amongst Chinese women,[55,56] and was used in this study. The FSFI questionnaire consists of 19 items across six domains, namely, Sexual desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain.[57] This self- report system uses a 5- point Likert scale ranging from 0 to 5 or 1–5 with higher scores indicating greater levels of sexual functioning on the respective item.[58,59] The scores are then summed up within each domain and multiplied by a domain factor ratio to yield the individual domain scores.[56] The total FSFI score is the sum of the six domain scores, which ranges from 2 to 36; a higher FSFI score is associated with a lesser degree of sexual dysfunction.[60] A total score below 26.55 indicates sexual dysfunction.[61] Use of FSFI in postmenopausal women suggests that a lower threshold of 20 may be appropriate for identifying women with sexual dysfunction.[62]

Statistical analyses were conducted using the Minitab® Statistical Software to evaluate: the statistical significance of the differences (improvements) between the scores at baseline and at 12-week follow-up. In view of the relatively small sample size and the data type, we have opted for a combination of One-Way ANOVA tests and Two- Sample *t*- Tests in our statistical analysis.

3 | RESULTS

Twenty-four postmenopausal Chinese women (47–64 years, BMI $22.8 \pm 1.0\,kg/m^2$) were recruited for the study from the existing Investigator's pool.

3.1 | VHIS

At baseline, 100% of the patients scored 1 or 2 on the Fluid Volume and Elasticity. 75% and 46% of the patients scored 1 or 2 on the parameters of pH and Epithelial Integrity respectively, and 71% on Moisture. The distribution is shown in Figure 1A.

At the 3-month post-treatment follow-up, vaginal conditions of Moisture and Elasticity were reversed in all 24 patients. On the Fluid Volume measure, 18 out of 24 subjects (75%) showed moderate or normal amounts of fluid volume in vagina (scored 4 or 5). While 71% of the patients still scored 1–3 on the pH, which is equivalent to a pH value of 5.1 or above—an elevated level that increases the patients' susceptibility to vaginal infections. The distribution is shown in Figure 1B.

Both the VHIS total score as well as the scores on individual parameters recorded marked improvements after the completion of four treatment sessions. The improvement in pH, however, was quite unremarkable. It is interesting to note that while all five parameters improved steadily over the six measurement points, the improvement in pH did not follow the same pattern. After a relatively dramatic initial improvement recorded following the first treatment, further improvement as measured by pH at subsequent visits was notably lacking.

The charts showing the improvement trends of the VHIS average score and the VHIS improvements by measure are shown in Figure 2A,B. Trend charts showing the improvement trends on the five measures are shown in Appendix S1.

The average VHIS score increased from 9.42 ± 2.36 (baseline) to 21.00 ± 2.43 (3-month follow-up), representing a 123% improvement. When the two sets of data were compared, the difference

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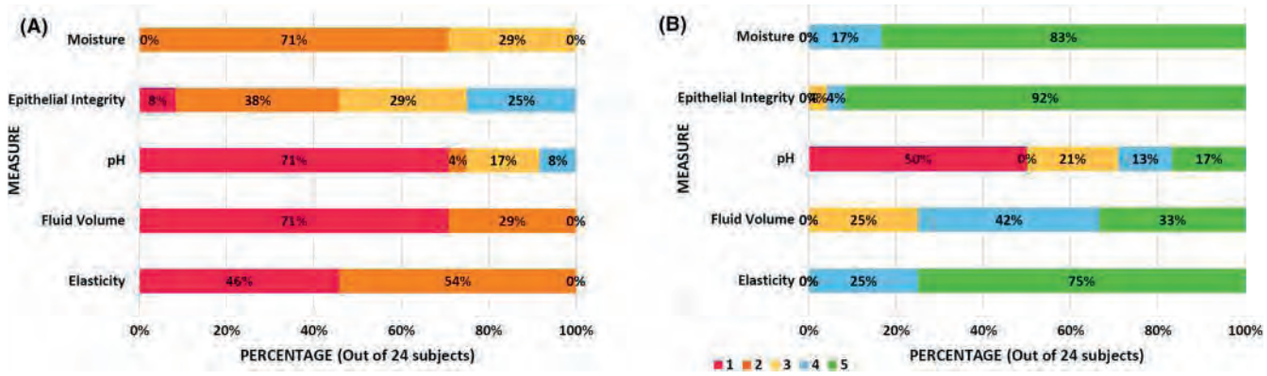


FIGURE 1 VHIS baseline score by measure (left) and VHIS Score at 3-Month f/u by measure (right).

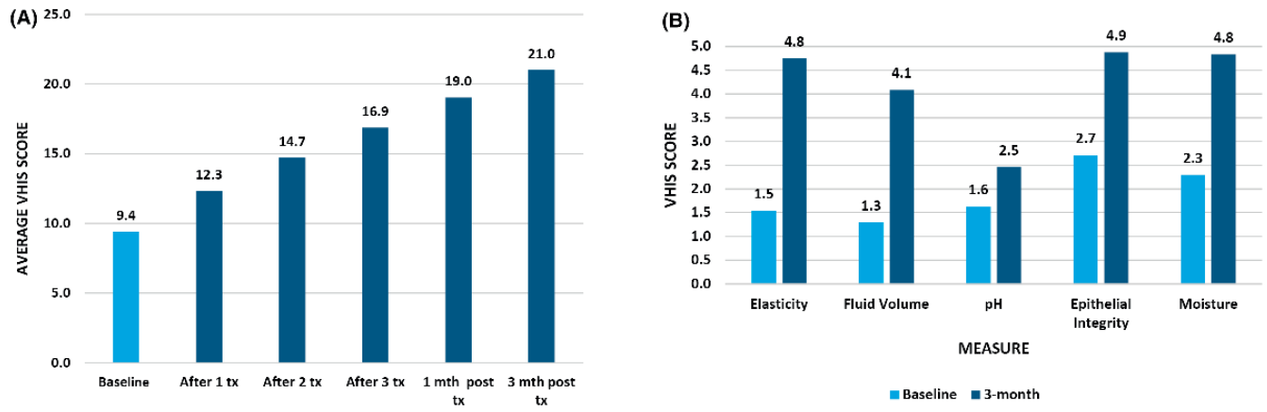


FIGURE 2 Average VHIS at each f/u (left) and comparison of VHIS score by measure (24 subjects) at baseline versus 3 months post-treatment (right).

TABLE 2 Summary of VHIS scores.

VHIS	Baseline	3-Mth f/u	% Increase	*p*-Value
Average	9.42 ± 2.36	21.00 ± 2.43	123%	0.000
Elasticity	1.54 ± 0.54	4.75 ± 0.44	208%	0.000
Fluid volume	1.29 ± 0.46	4.08 ± 0.78	216%	0.000
pH	1.63 ± 1.06	2.46 ± 1.61	51%	0.041
Epithelial integrity	2.71 ± 0.96	4.88 ± 0.49	80%	0.000
Moisture	2.25 ± 0.44	4.83 ± 0.38	115%	0.000

(improvement) was shown to be statistically significant (p-value <0.05), with a p-value of 0.000. All five parameters also logged drastic, statistically significant improvements. The results are summarized in Table 2. The Two-sample t-Test boxplot and the corresponding statistical analysis of the VHIS Total Score are shown below in Figure 3; the analyses on the five measures are presented in Appendix S1.

It is interesting to note that while the analyses on VHIS Total Score and the parameters of elasticity, fluid volume, epithelial integrity, and moisture all showed very strong evidence (p-value = 0.000) that the post-treatment improvements were statistically significant, the pH parameter was borderline with a p-Value of 0.041. This is consistent with our previous observation that pH improved after the first treatment but subsequently plateaued.

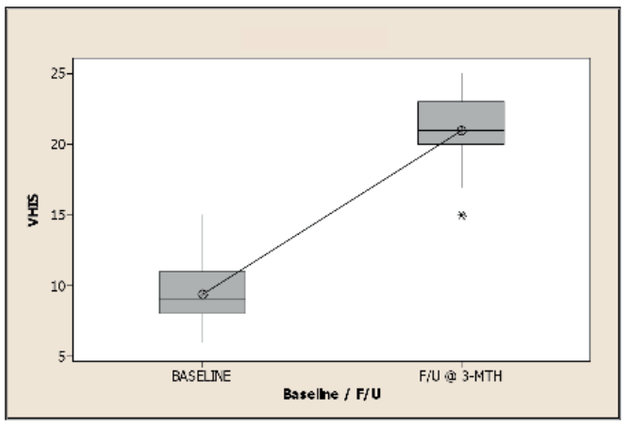
3.1.1 | 10-cm VAS

Based on the average scores at baseline, dyspareunia, and dryness were the top two highest-scoring VVA symptoms, with average scores of 7.0 and 5.5 respectively. At the 12-week follow-up visit, the average scores of dyspareunia and Dryness were 1.5 and 0.6 respectively, representing a decrease of 78.6% and 89.1%. The average scores of all 5 VVA symptoms also recorded improvements. Comparisons of the scores at baseline (Before) and the score at 12-week follow-up (After) are summarized in Figure 4.

Prior to treatment at baseline, 83% of the patients had a dyspareunia score of >5.0, more than 67% of the patients had a Dryness score >5.0, and 46% had an Itchiness score >5.0. The distribution

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Two-Sample T-Test and CI: VHIS, Baseline / F/U

Two-sample T for VHIS

Baseline / F/U	N	Mean	StDev	SE Mean
BASELINE	24	9.42	2.36	0.48
F/U @ 3-MTH	24	21.00	2.43	0.50

Difference = mu (BASELINE) - mu (F/U @ 3-MTH)
Estimate for difference: -11.583
95% CI for difference: (-12.976, -10.191)
T-Test of difference = 0 (vs not =): T-Value = -16.75 P-Value = 0.000 DF = 45

FIGURE 3 Boxplot of VHIS score at baseline and 3-month f/u and its statistical description.

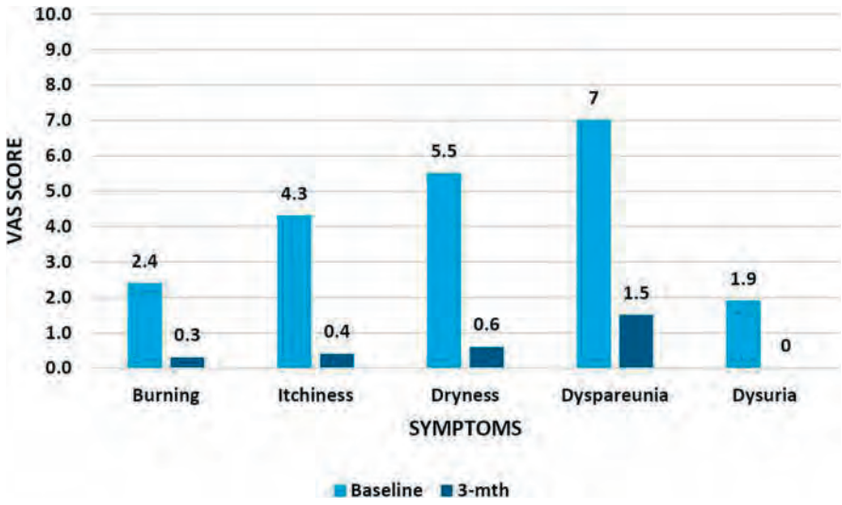


FIGURE 4 VVA Symptoms average score before & after (baseline vs. 3-Month f/u).

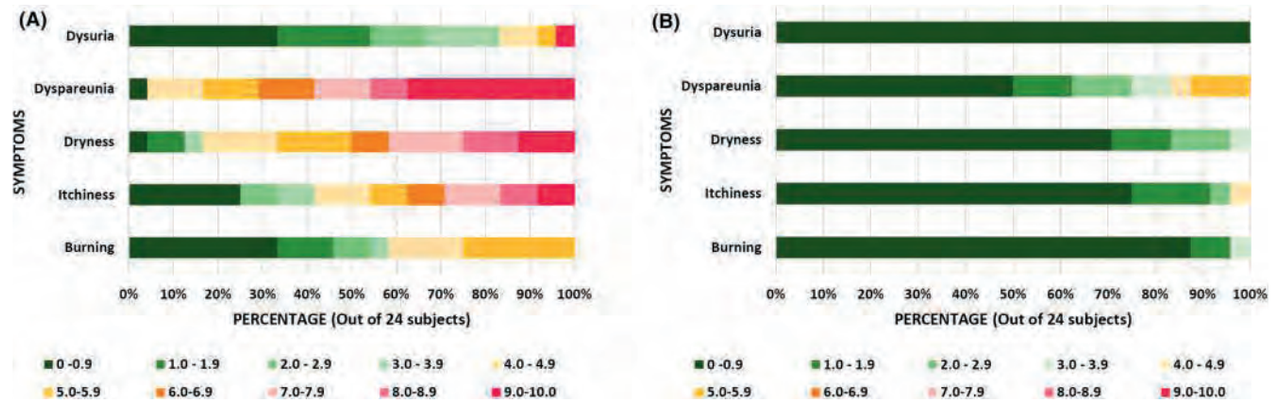


FIGURE 5 VVA Symptoms at baseline (left) and at 12-week f/u (right)—24 subjects.

is shown in Figure 5A. At the 12- week post- treatment follow- up, all 5 VVA symptoms recorded marked improvements. Issues of Burning, Dryness, and Dysuria were resolved; only one patient still suffered Itchiness (scored 4), and four subjects still suffered Dyspareunia scores of 4.0–5.9 after treatment. The distribution of VVA Symptoms Severity at 12- week post-treatment follow- up is shown in Figure 5B.

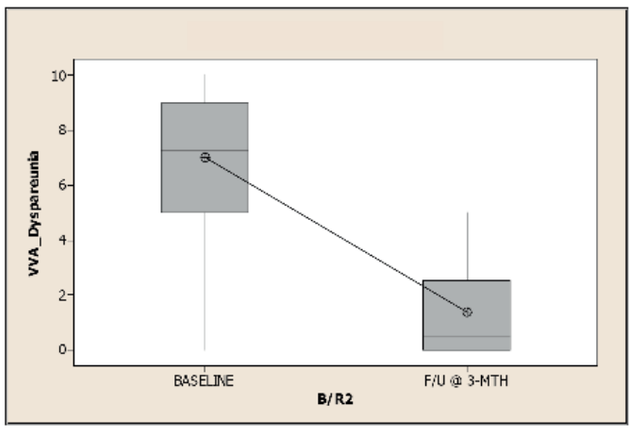
Using the data on the patient's VAS scores at baseline (BASELINE) and the corresponding VAS scores after treatment at 12- week follow-up (F/U@ 3-MTH), analysis showed that the differences were

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TABLE 3 Summary of VAS scores.

VVA Symptom	Baseline	3-Mth f/u	% decrease	*p*-Value
Burning	2.35 ± 2.12	0.26 ± 0.66	88.9%	0.000
Itchiness	4.25 ± 3.23	0.44 ± 0.924	89.6%	0.000
Dryness	5.54 ± 2.57	0.58 ± 0.86	89.5%	0.000
Dyspareunia	7.00 ± 2.57	1.38 ± 1.74	80.7%	0.000
Dysuria	1.94 ± 2.29	0.00 ± 0.00	100%	0.000



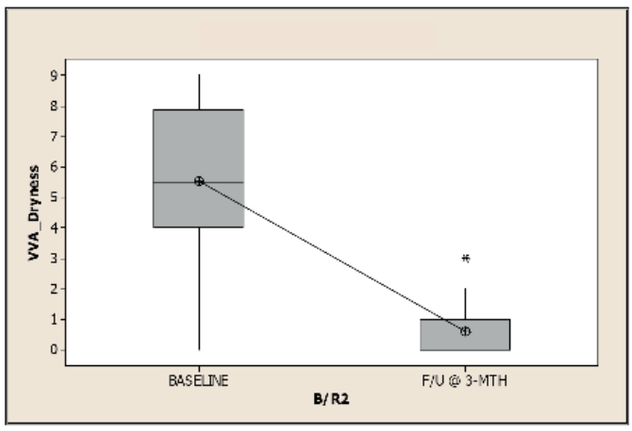
Two-Sample T-Test and CI: VVA_Dyspareunia, B/R2

Two-sample T for VVA_Dyspareunia

B/R2	N	Mean	StDev	SE Mean
BASELINE	24	7.00	2.57	0.52
F/U @ 3-MTH	23	1.38	1.74	0.36

Difference = mu (BASELINE) - mu (F/U @ 3-MTH)
Estimate for difference: 5.617
95% CI for difference: (4.329, 6.906)
T-Test of difference = 0 (vs not =): T-Value = 8.81 P-Value = 0.000 DF = 40

FIGURE 6 Boxplot of symptom "dyspareunia" at baseline and 3-month f/u and its statistical description.



Two-Sample T-Test and CI: VVA_Dryness, B/R2

Two-sample T for VVA_Dryness

B/R2	N	Mean	StDev	SE Mean
BASELINE	24	5.54	2.57	0.53
F/U @ 3-MTH	24	0.583	0.856	0.17

Difference = mu (BASELINE) - mu (F/U @ 3-MTH)
Estimate for difference: 4.958
95% CI for difference: (3.824, 6.093)
T-Test of difference = 0 (vs not =): T-Value = 8.95 P-Value = 0.000 DF = 28

FIGURE 7 Boxplot of symptom "dryness" at baseline and 3-Month f/u and its statistical description.

statistically significant across all 5 symptoms, with *p*-value = 0.000. A summary of the VAS scores is shown in Table 3.

The Two-sample *t*-Test boxplot and statistical outputs of Dyspareunia and Dryness—the top two scoring concerns—are shown below as Figures 6 and 7 respectively; the Minitab® outputs on Burning, Itchiness, and Dysuria are shown in Appendix S1.

3.1.2 | FSFI

Scoring may not be accurate in circumstances where the patient did not engage in sexual intercourse attempting vaginal penetration in the 4 weeks prior completing the FSFI questionnaire,[52] since the absence of sexual activity is not necessarily attributable to sexual dysfunction, although the assigned FSFI score is identical (zero) for either.[52,62] In view of this, we have excluded five patients from our FSFI analysis. These patients did not engage in sexual intercourse during the course of this pilot study and thus, could not provide fair evaluations. Nevertheless, they entertained the wish to remain sexually active in the future. Information on the five patients is shown in Appendix S1.

Prior to treatment at baseline, the average FSFI score of the 19 patients was 15.05 ± 6.07. The score improved after three weekly treatments by 53.9% to 23.16. At 3 months post-treatment, the

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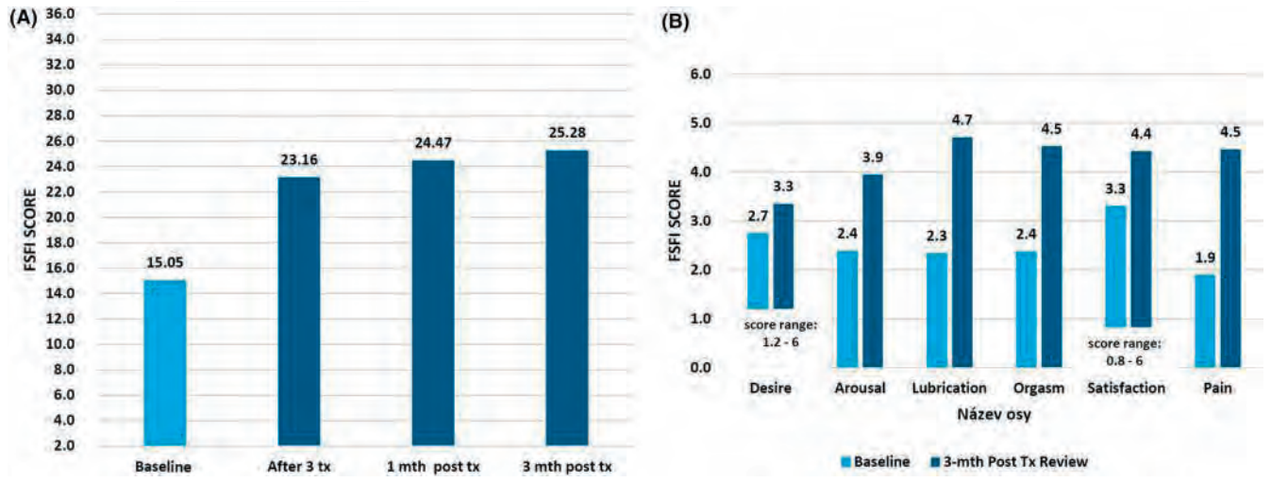


FIGURE 8 Average FSFI score (19 subjects) at each f/u (left) and FSFI average score by domain (19 subjects) before & after (baseline vs. 3-month f/u) (right).

average FSFI score was 25.28, representing a 68.0% increase (Figure 8A) from baseline.

At 12 weeks post-treatment, all six domains recorded drastic improvements. Pain—the lowest scoring domain at baseline—recorded the most significant improvement; the average score logged a 136% increase from 1.89 to 4.46. Only 16% (3) of subjects still experienced some pain (score 0–3). Other domains, namely Arousal, Lubrication, and Orgasm also logged improvements, at 66.0%, 101.3%, and 90.3% respectively. It is interesting to note that at 21.8% and 33.5% respectively, the improvements on Desire and Satisfaction were relatively modest. Psychological factors may play a more significant role in these two domains.

The FSFI average score by domain is shown in Figure 8B.

Despite the substantial improvements and symptom relief recorded, the average FSFI score did not reach the FSFI cutoff score of 26.55. Only 8 out of 19 patients, representing 42.1%, reported FSFI scores above the optimal cutoff score of 26.55 at the 12-week post-treatment follow-up, and are qualified as being without sexual dysfunctions.[52,61] However, at the lower threshold suggested for peri- and post-menopausal women, 18 out of 19 patients, representing 94.7%, met the cutoff score of 20.0 and were qualified as being sexually functional. The distribution of the patients' FSFI scores at baseline (Before) and at 12-week follow-up (After) is shown in Figure 9.

The Average FSFI score increased from 15.05 ± 6.07 at baseline to 25.28 ± 4.69 at the 3-month follow-up, representing a 68.0% improvement. When the two sets of data were compared, the difference (improvement) was shown to be statistically significant, with a *p*-value of 0.000. The Two-sample *t*-Test boxplot and the corresponding statistical analysis are shown in Figure 10. All domains logged strong, statistically significant, improvements; the domain Desire exhibited a borderline *p*-value of 0.05. The results are summarized in Table 4. The Minitab® outputs on the six domains are shown in Appendix S1.

4 | DISCUSSION

In contrast to the more commonly discussed vasomotor symptoms, VVA is the longest-lasting symptom of menopause.[6,7] Large cohort studies have depicted a 27%–55% prevalence of vaginal atrophy in menopausal women.[56,63,64] Contrary to the vasomotor symptoms, which tend to be milder over time, VVA symptoms rarely resolve spontaneously and, in most cases, deteriorate if left untreated, thereby negatively affecting patients' confidence and intimacy with their partners.[21,32,46,65] Despite the prevalence of VVA symptoms and their long-term effects affecting both the patients' quality of life and couples' intimacy, it is estimated that only 1 in 4 women experiencing VVA symptoms seek medical attention.[32,56]

With the loss of follicular activity, ovarian estrogens reduce dramatically, leading to significant changes in the structure of the vaginal mucosa, and consequently, the impairment of numerous physiological functions.[66] After menopause, a woman's estrogen level in plasma decreases from 129 ng/L during her reproductive period to 18 ng/L.[67] This drastic drop in the level of estrogen—a vasoactive hormone—decreases blood flow to vagina and vulva, leading to reduced vaginal lubrication and loss of libido.[68]

Estrogen deficiency also impacts mucosal elasticity through matrix glycosaminoglycan depletion and the hyalinization, fragmentation, and fusion of collagen and elastin fibres.[17,32] Such changes are represented by the progressive loss of elasticity and the rugal folds of the vaginal lining becoming thinner with potential petechiae.[12] Rugae aids in expandability, distensibility, and lubrication of the vagina during sexual stimulation. These pro-lubricative and pro-elastic functions are lost due to diminished collagen, elastin, and hyaluronic acid content, leading to thinned epithelium, impaired smooth muscle proliferation, denser connective tissue arrangement, and loss of vascularity.[14] In more persistent cases, the vagina becomes narrower and shorter and the introitus can constrict.[12,32,69]

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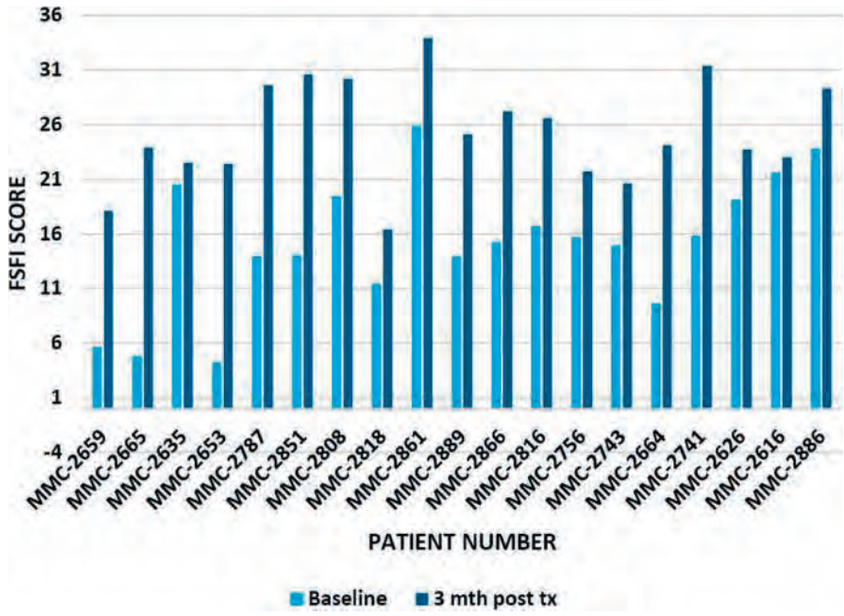
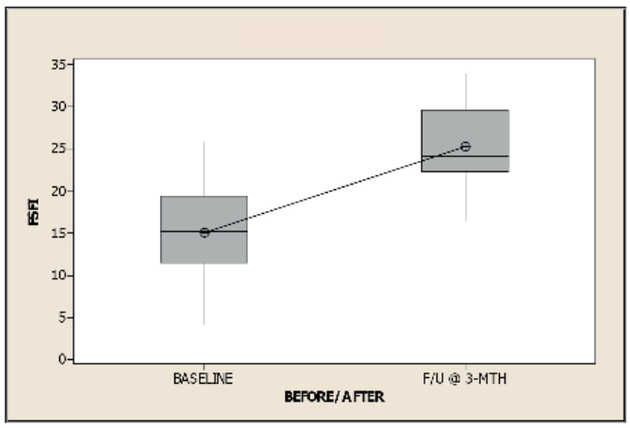


FIGURE 9 FSFI total score before & after (19 subjects).



Two-Sample T-Test and CI: FSFI, BEFORE/AFTER

Two-sample T for FSFI

BEFORE/AFTER	N	Mean	StDev	SE Mean
BASELINE	19	15.05	6.07	1.4
F/U @ 3-MTH	19	25.28	4.69	1.1

Difference = mu (BASELINE) - mu (F/U @ 3-MTH)
Estimate for difference: -10.23
95% CI for difference: (-13.81, -6.65)
T-Test of difference = 0 (vs not =): T-Value = -5.81 P-Value = 0.000 DF = 33

FIGURE 10 Boxplot of symptom FSFI at baseline and 3-month f/u and its statistical description.

Increased sexual activity is advised for maintaining robust vaginal muscle condition. Sexual activity, with or without a partner, improves blood circulation to the vagina.[70] A positive link between sexual activity and the maintenance of vaginal elasticity, pliability, and lubricative response to sexual arousal has been demonstrated.[71] With heterosexual intercourse, the seminal fluid contains sexual steroids, prostaglandins, and essential fatty acids, which serve to maintain the vaginal tissues.[72] Deficiency of estrogen and androgen in postmenopausal women is often associated with a loss of libido.[73] Decreased frequency or sexual abstinence exacerbates vaginal atrophy,[74,75] leading to unpleasant sexual experiences due to vaginal dryness and dyspareunia, which further disrupt the intimacy- based sexual response cycle.[76]

4.1 | Vaginal dryness and dyspareunia

The most predominant complaints of sexually active, postmenopausal women are vaginal dryness and dyspareunia.[46] Defined by genital pain that can be experienced before, during, or after intercourse, dyspareunia can have a significant effect on physical and emotional health. Since the condition affects the patient's partner and couples' intimacy, this condition is the primary reason VVA patients seek medical attention.

Vaginal lubrication is caused by fluid transudation from blood vessels, and from endocervical and Bartholin glands. With the drastic reduction in estrogen after menopause, sebaceous glands reduce the production of secretions and therefore, during sexual activity, lubrication is decreased and delayed.[12,19,35,71] Postmenopausal women have a total estimated volume of vaginal fluid of 0.0825 g per 15-min collection, compared to 0.214 g in fertile women. The majority of vaginal fluid in postmenopausal women appears to be secreted from the vaginal epithelium.[12,77]

The prevalence of vaginal dryness and dyspareunia has been reported to be 90% and 80% respectively.[46] Data from this pilot study validated the trend, although dyspareunia seemed to be more prevalent amongst the study subjects. Based on our records, 96% of

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TABLE 4 Summary of FSFI scores.

FSFI	Baseline	3-Mth f/u	% Increase	*p*-Value
Total	15.05 ± 6.07	25.28 ± 4.69	68%	0.000
Desire	2.75 ± 0.92	3.35 ± 0.90	22%	0.050
Arousal	2.38 ± 1.41	3.95 ± 1.09	66%	0.001
Lubrication	2.34 ± 1.33	4.71 ± 0.85	101%	0.000
Orgasm	2.38 ± 1.41	4.53 ± 1.16	90%	0.000
Satisfaction	3.31 ± 1.13	4.42 ± 0.76	34%	0.001
Pain	1.89 ± 1.35	4.46 ± 1.39	136%	0.000

the 24 subjects recruited for this pilot study suffered dyspareunia of various severities prior to treatment. The FSFI data also showed "Pain" as the domain with the lowest score at baseline. With regard to reduced lubrication, the data obtained from this pilot study indicated that 84% of the patients suffered vaginal dryness of various severities. RF was shown to be an effective approach for the treatment of these symptoms of VVA.

The minimal clinically important difference (MCID) was introduced to determine the least threshold of beneficial outcomes. Previous research identified that the MCID for the FSFI questionnaire may lie in the range of 2.1–4.0[78] points which was notably overstepped by the results documented in this study (+9.3 points) and therefore can be considered clinically significant. For the VAS scores used as the primary mode of assessing response to treatment in this study, there has not been a well-established MCID yet. For VHI, the cutoff value (<15) is used instead of MCID. This threshold was surpassed on average since the 4th treatment and gradually reached the 3- month follow- up value of 21.1 points.

4.2 | Increased pH in menopause

Besides subject symptoms, low estrogen levels are associated with unfavorable changes in the bacterial flora colonizing the vagina, which leads to elevated vaginal pH and a heightened risk of infection with pathogenic bacteria in postmenopausal women.[79,80]

The vaginal flora composes of a variety of aerobic and anaerobic, gram- positive, and gram- negative bacteria.[72] In fertile women, *Lactobacilli* metabolize glucose into lactic acid and acetic acid, thus lowering the vaginal pH. The normal acidity of an estrogenized vagina is usually moderately acidic, favoring *Lactobacilli*. A lactobacillus-dominant flora protects its host against vaginitis and urogenital tract infections through the maintenance of an acidic vaginal pH in the range of 3.6–4.5.[56,81] Elevated vaginal pH higher than 4.5 is associated with vaginitis, which causes various vaginal symptoms.[56,82]

In post- menopausal women, low estrogen levels and a decrease in the epithelium glycogen concentrations hinder the production of lactic acid by *Lactobacilli*.[56,75] The more alkaline pH leads to a shift in the vaginal flora toward more coliforms and, together with other atrophic changes, is responsible for increased susceptibility to and frequency of infections, malodors, and exacerbation of vaginal symptoms associated with VVA.[12,62,83,84]

4.3 | RF for VVA

The present pilot study demonstrated that RF technology with real-time temperature control monitoring is an effective treatment option for postmenopausal women with VVA symptoms. Data from the study showed that all patients reported substantial symptom alleviation after 4 weekly treatment sessions. Patients' VVA symptoms on all dimensions recorded statistically significant improvements. More than 90% of the patients experienced total symptom relief from dyspareunia and vaginal dryness—the most prevalent and concerning VVA symptoms both globally and amongst our subjects.

Study procedures were conducted without incident. No thermal burns or injuries occurred, and according to treated patients, procedures were painless and the temperature emitted by the device was acceptable. No adverse effects were reported during or after treatments.

RF has been established as an excellent modality for tissue tightening via stimulation of neocollagenesis, denaturation of collagen, contraction, and activation of the healing cascade.[47] Numerous studies in dermatology[47,82] have demonstrated tissue contraction and have determined a therapeutically ideal temperature range of 40–45°C. Neocollagenesis is stimulated without causing unnecessary damage to the skin or integral tissue structures.[85,86] The same treatment concept applies in the application of RF for vulvovaginal rejuvenation.

The RF device used in this pilot study is equipped with real-time temperature monitoring and regulation, ensuring the therapeutic temperature is reached, but more importantly, that the temperature is maintained throughout the treatment timeframe. The goal of treatment is to heat vaginal and vulvar epithelium to approximately 40–45°C, for 20 min (8-min intra-vaginal, 12-min extra- vaginal). This temperature has been shown to be necessary to stimulate fibroblast activity, which contributes to the production of new connective tissue matrix molecular components.[87] The biostimulative effect of RF restores most vaginal functions such as secretion, absorption, elasticity, lubrication, and vaginal epithelium thickness.[88]

Several studies have investigated different modalities for VVA, including hormonal and nonhormonal approaches. Hormonal treatments like estrogen creams or tablets have been widely studied and shown effectiveness in alleviating VVA symptoms by replenishing

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estrogen levels.[89] They've demonstrated improvements in vaginal health, moisture, and pH balance.[89] However, some patients are cautious about hormonal treatments due to concerns about potential side effects, especially for those with a history of hormone-sensitive cancers or conditions.[89] Nonhormonal options, including lubricants, moisturizers, and medical devices like vaginal dilators or lasers, offer alternatives for those who prefer to avoid hormonal interventions.

The study conducted by Pacik and Geletta[90] focused on the use of vaginal dilators in postmenopausal women with VVA have suggested that regular use of dilators helped alleviate pain during intercourse. Further, laser therapy, similar to the RF technology used, has reported similar improvements in VVA symptoms such as dryness, elasticity, and pain (fractional CO2 lasers have shown positive outcomes in vaginal health, aligning with the RF study's focus on VHIS).[91]

However, the use of both, dilators or lasers, can be discomforting, and time- consuming, raising safety concerns, while also lacking comprehensive long- term data on its efficacy and accessibility, posing adherence challenges, potentially leading to limited effectiveness and psychological barriers for some individuals.[91,92]

The provided study on RF technology for treating VVA shows promising results, especially in safety and improving symptoms like dryness, dyspareunia, and VHISs. The novel device delivers RF energy at 360° simultaneously which increases the comfort of the patients and minimizes the therapy time. However, more research is needed to solidify the long- term effects, optimal treatment protocols, and comparisons with other therapies are areas requiring further exploration.

Results from this pilot study validated the effectiveness of RF in the reversal of vaginal symptoms. At the 12- week follow- up, the majority of women were satisfied with the treatment, and no related adverse events were recorded.

The potential systematic biases could occur during the selection of the patients from the Investigator's pool and could affect the results. To prevent potential systematic biases, a set of objective selection criterion and exclusion criterion were devised prior to the selection process. Patient selection for the study was conducted with strict adherence to these criteria. In addition, a unique 4- digit patient number was assigned to each patient upon her arrival for the initial visit. The patient number was used in place of the patient's given names on all patient records for this study. This served to protect the patient's data privacy, as well as a mean to "blind" the selector during the selection process.

The generalizability of the finding is partly limited by the study's focus on postmenopausal Chinese women only. Different ethnic groups can exhibit variations in genetic makeup, hormonal profiles, lifestyle, and environmental factors, all of which can influence the manifestation and progression of VVA.[93–95] Further, variations in menopausal symptoms, hormonal profiles, cultural attitudes toward menopause and sexual health, as well as lifestyle factors such as diet, physical activity, healthcare access, and, in the end, responses to treatment alone can occur. Therefore, results derived from a monoethnic cohort might not apply to women from other ethnic backgrounds.

Similar findings were observed in Spanish postmenopausal women with GSM in Aznar et al study[96] evaluating the safety and efficacy of a 360° energy distribution RF device for non-invasive treatment of dyspareunia and demonstrating positive effects on the nonhormonal restoration of the vulvovaginal tissue.

The absence of a control group might lead to an overestimation of the treatment's effectiveness. Participants knowing they are receiving some form of treatment (and not a placebo) might report improvements due to psychological factors rather than actual physiological changes. Further, a control group could help with an objective comparison within ethnicity. Despite these factors, the study can still be compared to other studies with different ethnicities using the same validated questionnaires and although the sample size is small, it is still sufficient for the statistical analysis. On the other hand, this study can help to understand the outcomes of underrepresented Asian ethnicities in the population, a cohort that presents considerable recruitment challenges for VVA- related studies. When considering the questionnaire, the incorporation of subjective patient assessment could help the patient to participate more in the treatment and could increase the probability of active treatment participation.

The missing nonfunctional measurements could also have helped us analyze tissue composition and have a more exact description of the patient's condition at baseline, after therapy, and at follow-up visits. Obtaining the patient's consent to participate could, however, be extremely challenging. The length of follow- up period is always disputable according to the patient's comfort and the importance of long- term observation of the changes induced by the treatment.

This pilot study demonstrated that non-ablative, monopolar RF technology equipped with a real-time temperature monitoring system is feasible, and safe for the treatment of postmenopausal Chinese women with VVA symptoms, and efficacious up to 12-week post- treatment.

Given the limitations, the study's conclusions regarding the efficacy and safety of RF treatment for VVA in postmenopausal women may not fully represent the broader population. The findings are, however, valid for the specific group of Hong Kong postmenopausal women, caution should be exercised when extrapolating these results to other ethnic groups or a more diverse population. Future studies with unbiased patient selectors, long-term data, and more diverse ethnic representation with a larger sample size and a robust control group are needed to validate these findings universally. Additionally, nonfunctional measurements including histological analysis, CHIP cytometry, or VMI analysis should be included as well as the patient experience and treatment perception monitoring.

4.4 | Study limitations

Small sample size, no nonfunctional measurement (e.g. histological analysis, CHIP cytometry, etc) no patient experience and treatment perception questionnaire, long- term follow-up, monoethnic focus,

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and the absence of a comparator (sham procedure, placebo, or other active treatment) are some of the known limitations of this pilot study.

AUTHOR CONTRIBUTIONS

Vivian Cheng contributed to the study design and performed all the treatments together with a designated Clinic Assistant, Ms. Rita Lee. Dr. William Tai provided advice on the scientific part of the whole research. Ms. Athena Lee was responsible for statistical analyses of the data.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

The instrument EXION, model BTL-785F, and all EMFEMME 360 consumable treatment tips, used in this study were provided by BTL Industries.

CONFLICT OF INTEREST STATEMENT

The authors did not report any potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the PolyU Institutional Review Board (The Hong Kong Polytechnic University) for ethical review for research involving human subjects for a period from 01-Aug- 2021 to 01-Aug- 2023, reference number HSEARS20210625001.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cheng V, Chi-Shing WT, Lee A, Lee R. The effects of a real-time temperature monitoring non- ablative monopolar radiofrequency technology on vulvovaginal atrophy symptoms in postmenopausal Chinese women. *J Cosmet Dermatol*. 2024;00:1-14. doi:10.1111/jocd.16251

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LOCALIZED FAT REDUCTION

THE EFFICACY AND SAFETY EVALUATION OF A TECHNOLOGY USING RADIOFREQUENCY HEATING WITH SUPERFICIAL ACTIVE COOLING FOR LOCALIZED FAT REDUCTION

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Highlights

- 25 enrolled patients (29-60 years; skin types II-IV)
- Four treatments of various body areas delivered 7-14 days apart
- **Ultrasound fat thickness** measurements were taken at 1-month and 3-month follow-ups
- **83%** of patients who attended 3-month follow-up (23) reported a **reduction of fat deposits in the treated area**

22%

Localized fat reduction

87%

Improvement in overall appearance



Reduction in fat was observed in a 60-year-old patient at the 6-month follow-up visit (right) compared to baseline (left)

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SKIN LAXITY IMPROVEMENT ON THE BODY

A NOVEL TECHNOLOGY COMBINING RADIOFREQUENCY AND TARGETED ULTRASOUND FOR IMPROVEMENT IN SKIN LAXITY: THE EFFICACY AND SAFETY EVALUATION

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Presented at the American Society for Laser Medicine and Surgery (ASLMS), Phoenix, Arizona, April 13-16, 2023

Highlights

- 30 subjects (33-73 years) received 4 treatments 7-14 days apart
  - Treatment of **Abdomen or Upper Arms**
- **Evaluation of skin laxity** improvement at 1 month and 3 months post-treatment
- The treatment's efficacy was assessed using the **GAIS evaluation**, and the overall score of 2 indicated a **significant improvement**

85%

Improvement in skin laxity

96%

Satisfaction rate



Improvement in skin laxity on the upper arm of a 60-year-old patient at 3-month follow-up (right) compared to the baseline (left)



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American Journal of
Biomedical Science & Research

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ISSN: 2642-1747

Mini review

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A Novel Technology Combining RF and Magnetic Fields: Technical Elaboration on Novel RF Electrode Design

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To Cite This Article: *Diane Duncan, A Novel Technology Combining RF and Magnetic Fields: Technical Elaboration on Novel RF Electrode Design. 2020 - 11(1). AJBSR.MS.ID.001608.* DOI: 10.34297/AJBSR.2020.11.001608.

Received: November 28, 2020; **Published:** December 08, 2020

Abstract

The article provides an insight into the technological aspects of a novel technology in body shaping allowing simultaneous delivery of HIFEM magnetic fields and radiofrequency energy. The device utilizes circular coil for magnetic field induction and radiofrequency electrodes in a single applicator which poses a technological challenge to the construction. To overcome the challenges a novel electrode design has been introduced for avoiding interferences between the two types of energy. As such the device presents a shift in the body contouring segment of aesthetic medicine, because it allows a simultaneous treatment of muscle laxity through supramaximal muscle stimulation and reduction of excessive adipose tissue through radiofrequency heating.

Keywords: HIFEM, Radiofrequency, Synchrode RF Electrode, Body Contouring

Abbreviations: HIFEM: High Intensity Focused Electromagnetic Field; RF: Radio Frequency

Introduction

In aesthetic medicine, various technologies are used for non-invasive body shaping. Two of the most widely used modalities are radiofrequency heating of tissues and high-intensity electromagnetic muscle activation. These two principles represent energy application arising from two different frequency bands of the electromagnetic spectrum within humans. Radio frequency (RF) are waves in the frequency range of roughly 20 kHz to 300 GHz. These are the frequencies with the ability to create heat through the oscillation of molecules while propagating within the tissue. In the aesthetic medicine, the RF energy is usually emitted by a solid metal electrode, which is normally in direct contact with the patient. The heating effects of the RF technology can be used for wide range of applications such as fat cell disruption, skin tightening or cellulite reduction [1-3]. For muscle activation, a high-intensity electromagnetic field (HIFEM) is used. The HIFEM field represents a very-low frequency range (<10kHz).

During the application, rapid alternations in the magnetic field induce a secondary electric current in the tissue. These currents do not create any heat but are able to both polarize and depolarize the motor neurons that innervate the muscle, thus eliciting muscle contractions of supramaximal nature that cannot be achieved voluntarily. Such stimulation was found to result in muscle hypertrophy [4-6]. To emit HIFEM energy for muscle activation, an applicator with an embedded round metal coil is used without direct contact with the patient. Until recently, these two energies have been used solely as standalone modalities, and their combination in close-space engineering would be restricted by physical laws, due to frequency incompatibility and technical interference. However, the latest breakthrough in the field presented a technological solution overcoming these issues. The main goal of this article is thus to describe and explain the technical aspects of this innovation. Technical issues associated with simultaneous HIFEM and RF application In order to apply both RF and HIFEM at the same time within the same location, the metal RF electrode and the magnetic coil generating HIFEM field would need to be incorporated in a single applicator that is in contact with the patient.

However, while the magnetic fields easily pass through most common materials such as wood, plastic or even human tissue,

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they cannot pass through metal without mutual interactions. Any metals, when exposed to rapidly changing HIFEM fields quickly heat up (see Picture 1) and also tend to be physically repulsed. For this same reason, HIFEM is strictly contraindicated in patients with metal and electronic implants. With this known contraindication, HIFEM and ordinary RF can't be emitted simultaneously within the same field without overheating the metal electrode generating RF as the electrodes are made of a solid metal. Although the RF electrodes are used to generate heat, their overheating could result in malfunctions in the RF delivery but most importantly would expose the patient to risk of burns. An evidence of the heating effect can be seen in the Figure 1 where metal plates are placed over the magnetic coil applicator (Figure 1).

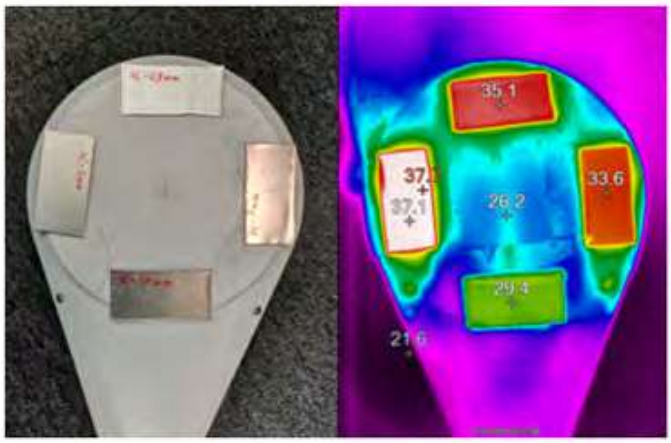


Figure 1: Digital photographs of running applicator containing the circular coil and metal plates placed over. The right image shows the metal plates' temperature elevation as captured by the thermal camera.

Technical solution allowing simultaneous application

To enable HIFEM to pass through the electrode without this heating phenomenon an entirely new electrode technology has been developed and patented by a leading company in the aesthetic market (BTL Industries Inc., Boston MA). While solid electrodes represent an issue for the magnetic field, the patented Synchrode RF electrode uses a special design concept which makes it transparent to the HIFEM energy. Instead of using a single coherent metal structure, the Synchrode RF electrode is comprised of 56 smaller segment pairs, with each segment pair laid out close to each other, creating individual positive and negative (+/-) RF poles (112 segments per applicator). The main purpose for using this segmented design and for having multiple interspacings is to achieve selective tissue heating effects as with large-sized solid electrode but without the technical limitations associated with a solid electrode (see Figure 2). The device utilizing this technology offers two treatment applicators, allowing a total of 224 interspaced electrode segments to work in synchrony during the treatment (Figure 2).

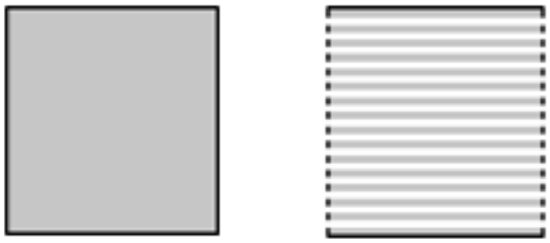


Figure 2: Illustration of the difference between standard and segmented electrode. Standard electrodes are made of compact material as a single piece (left), while the segmented electrode is composed of multiple interspaced segments (right).

The key to this breakthrough technology is the interspacing. This interspaced design allows the HIFEM to pass through the electrode easily without any unfavorable interaction with its metal parts. Instead, the electrode is transparent to the magnetic fields, allowing them to continue in their intended direction (See Figure 3). Through years of development and testing, the Synchrode RF electrode's overall size and shape is specifically tailored to work in synchrony with the HIFEM magnetic fields. The electrode design takes into consideration the exact shape, the depth of penetration, as well as the intensity of HIFEM fields. The magnetic coil and the Sychrode RF electrode are thus truly synchronized with each other from an engineering standpoint (Figure 3).

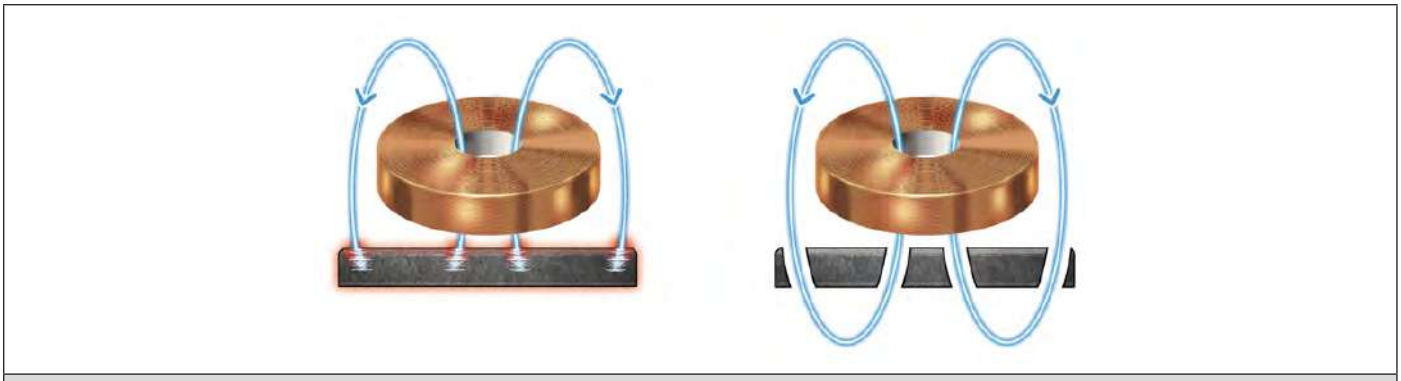


Figure 3: Illustration of the mutual interaction between magnetic coil and underlying electrode. The interspaced electrode is transparent to the HIFEM's magnetic field and the magnetic waves can pass without interaction, while standard electrode absorbs the HIFEM energy, resulting in heat.

Conclusion

For the very first time in the aesthetic field, this patented concept allows practitioners to simultaneously apply RF heating and high-intensity electromagnetic muscle (HIFEM) activation in the same treatment area, at the same time. This represents an engineering breakthrough that now allows leveraging both the clinical, as well as commercial synergies of combining two gold standard technologies from a single device applicator. The company holding the patent rights (BTL Industries Inc., Boston MA) has already implemented this solution in a novel body shaping device introduced in October 2020 (EMSCULPT NEO) and presented the results of several clinical studies showing synergistic effects on muscle and fat tissues [7-10]. Although this electrode design solution has been first used for body shaping where it shows superior results, its' use may not be limited only to aesthetic medicine but could found a variety of other applications in another medical areas such as physiotherapy or rehabilitation.

Conflict of Interest

Dr. Diane Duncan is medical advisor for BTL, no funding was received for this article.

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Simultaneous Application of High-Intensity Focused Electromagnetic and Synchronized Radiofrequency for Fat Disruption: Histological and Electron Microscopy Porcine Model Study

Robert A. Weiss, MD, FAAD,* Jan Bernardy, PhD,† and Frantisek Tichy, CSc‡

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BACKGROUND Radiofrequency (RF) and high-intensity focused electromagnetic (HIFEM) technologies are used for noninvasive body shaping as standalone modalities.

OBJECTIVE To examine the effects of novel synchronized RF and HIFEM on subcutaneous adipose tissue in a porcine animal model.

MATERIALS AND METHODS Seven large white pigs aged 6 months received 3 abdominal treatments of simultaneous application of synchronized RF and HIFEM (30 minutes, once per week). Punch biopsies of treated and control subcutaneous tissue were collected at the baseline, 4 days, 2 weeks, 1 month, and 2 months. Specimens were examined by light and scanning electron microscopy. Adipocyte volume was analyzed. Fat tissue temperature was measured in situ (fiber optic probes) and superficially (thermal imager).

RESULTS Fat layer was heated to temperatures of 42 to 45°C. Signs of fat apoptosis (shape alternations and pyknotic nuclei) appeared at day 4 and peaked between 2 weeks and 1 month. Adipocyte volume decreased significantly ($p < .001$) by 31.1% at 2 weeks, 1 month (−23.6%), and 2 months (−22.0%). Control samples showed healthy adipocytes. Scanning electron microscopy micrographs corroborated histology findings, showing flattened, volume-depleted and disrupted adipocytes.

CONCLUSION Synchronized RF with HIFEM procedure resulted in a significant and sustained fat reduction with no adverse events.

Noninvasive techniques for body shaping as an alternative to the invasive methods are generally sought and well accepted by the public because they pose less risk with minimum side effects and no downtime.[1] Novel synchronized radiofrequency (RF) and high-intensity focused electromagnetic (HIFEM) technologies were recently developed to provide noninvasive body shaping using heat and intensive muscle contractions, respectively.

The effect of RF technology is based on generating heat in different tissues through the transformation of RF energy into heat.[2] Certain frequencies of the RF spectrum allow for selective heating of skin or subcutaneous adipose tissue because of the different dielectric properties of biological tissues. Hence, RF is often used for fat removal, skin tightening, or cellulite reduction.[3–8]

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R.A. Weiss receives research grants from BTL. The other authors have indicated no significant interest with commercial supporters.

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http://dx.doi.org/10.1097/DSS.0000000000003091

High-intensity focused electromagnetic technology induces muscle contractions through stimulation of the nerve pathways. The magnetic field induces electric currents, depolarizing the cell membranes of nerve cells to propagate an action potential and contract muscle fibers.[9] Intense muscle contractions (referred to as supramaximal) result in an increase in the muscle mass through hypertrophy/hyperplasia.[10]

Noninvasive fat reduction requires lipolysis, which is the breakdown of triglycerides stored in the fat cells into glycerol and free fatty acids (FFAs). Radiofrequency-targeted heating of subcutaneous tissue results in increased fat cell metabolism, which facilitates this breakdown.[11,12] In addition, a simultaneous intensive muscle workload, such as during HIFEM treatment, is accompanied by an elevated level of lipolysis due to the increased local energy consumption.[13]

For long-term reduction of subcutaneous fat tissue, necrosis or apoptosis must be achieved and seen on histological studies.[11] Necrosis is immediate cell death that can follow various external factors, such as excessive heat, cold, and toxins, and can lead to untoward side effects.[14,15] It is usually linked with intensive inflammation and possible panniculitis (e.g., significant lymphohistiocytic infiltrate).[16,17] By contrast, apoptosis, a process by which the body replaces old/damaged cells, manifests itself with very mild immune response[18,19] and is therefore known as the

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"silent cell death." Importantly, it has been shown that apoptosis is usually a temperature-dependent event. With a minimal 15-minute exposure time, apoptosis can be initiated with temperatures of 42°, and exposure time to trigger apoptosis decreases as the temperature rises. Apoptosis is achieved with temperatures of up to 45°C, whereas higher temperatures may result in immediate cell death or necrosis.[11,20–22] Regarding necrosis versus apoptosis, necrosis is immediate death of tissue that can cause a whole host of problems including panniculitis and should be avoided. Apoptosis is a slow programmed death that is associated with less side effects and is preferable.

When applying RF and HIFEM simultaneously, a primary effect on fat tissue is attributed to the RF-heating–induced apoptosis. Hypothetically, the use of a dual-modality approach might boost the metabolic activity for more effective fat reduction. High-intensity focused electromagnetic contractions might also aid with heat distribution and reduce risk of hot spots.[23,24]

Technical limitations have previously prevented the concurrent use of HIFEM and RF technology because of the interference between 2 competing electromagnetic fields. This study describes a novel synchronized RF that allows simultaneous combination of both technologies. In this porcine study, the use of HIFEM and synchronized RF determines effects on adipose tissue using both H&E histology and scanning electron microscopy (SEM).

Materials and Methods

An institutional review board approved this prospective animal study of 7 large white pigs (females) aged approximately 6 months. The number of animals was chosen to respect the 3Rs principle for animal experimentation as much as possible, and the study was performed in accordance with the EU Directive for animal experiments. A certified veterinarian supervised all the procedures.

All animals received active treatment 1 week after the acclimatization period. Three 30-minute abdominal therapies once a week for 3 weeks per pig were performed using Emsculpt Neo device (BLT Industries Inc., Boston, MA), which simultaneously combines novel synchronized RF and HIFEM technologies in a single applicator. The applicator was placed on the abdominal area, affixed by a fixation belt, and therapy power was set to maximum allowed intensity for both modalities. Animals were under general anesthesia. Before each therapy, anesthetic premedication was performed by the mixture of tiletamine 2 mg/kg, zolazepam 2 mg/kg, ketamine 2 mg/kg, and xylazine 2 mg/kg. During the therapy, anesthesia was maintained because of the continual influx of 2% propofol solution (1–2 mg/kg) by a cannula inserted into the auricular vein. The vital functions of animals were monitored during the therapy.

Using ultrasound guidance (Mindray M5Vet, probe 10L4s), a flexible fiber optic temperature probe (LumaSense Technologies Inc., Raunheim, Hessen, Germany) was inserted into the subcutaneous fat tissue just below the applicator (the middepth of the fat layer) to monitor in situ the temperatures of the adipose tissue during the therapy (Figure 1). The superficial skin temperature was monitored immediately after removing the applicator at the end of the procedure by a thermal imaging camera (Fluke Ti300, Fluke Corporation).

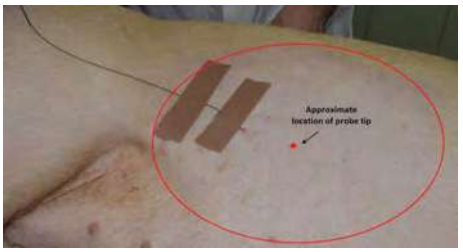


Figure 1. Fiber optic temperature probe inserted into the mid-depth of subcutaneous tissue. The probe tip (red dot) was located in the center of the shaved treated area (circled). The fiber was fixed by an adhesive tape to prevent its displacement during the therapy.

Biopsy specimens of the fat tissue for histological and SEM examination were collected at baseline, 4 days (D4), 2 weeks (W2), 1 month (M1), and 2 months (M2) posttreatment for each animal by biopsy punch (6 mm in diameter). Two specimens per time point (one for histology and one for SEM) were collected from the treatment site. Control specimens of abdominal fat tissue were collected from the opposite side of each subject animal.

For histological examination, hematoxylin and eosin (H&E) staining was used. In total, 252 tissue slices were analyzed. The samples for SEM were fixed with 3% paraformaldehyde and 2% glutaraldehyde and then gold stained. Micrographs were taken using a JSM-6380LV microscope (Jeol Ltd, Akishima, Japan). Expert evaluation of all slices and micrographs in a random order was performed by an experienced histopathologist.

Adipocyte cross-sectional area measurements were made using ImageJ v1.52p software. The area of fat cells was calculated for each analyzed image. Descriptive statistics (mean and SD) were used to identify the change in adipocyte size. Significance of this change was analyzed by one-way analysis of variance, followed by the Tukey–Kramer post hoc test. A p value less than 0.05 was accepted as the level of statistical significance.

Results

Clinical examination during all phases showed normal health of all animals, and no complications regarding animal care occurred. Animals always recovered well from the anesthesia procedure without any treatment-related complications or side effects.

Temperature Measurements

Subcutaneous fat temperature measured in situ reached 42°C in the first 4 minutes (Figure 2). Then 44°C was reached soon after, and for the rest of the procedure (23 minutes), temperature was maintained in a 44 to 45°C range. The skin temperature measured immediately after the treatment showed safe values between 42°C and 43°C in all animals.

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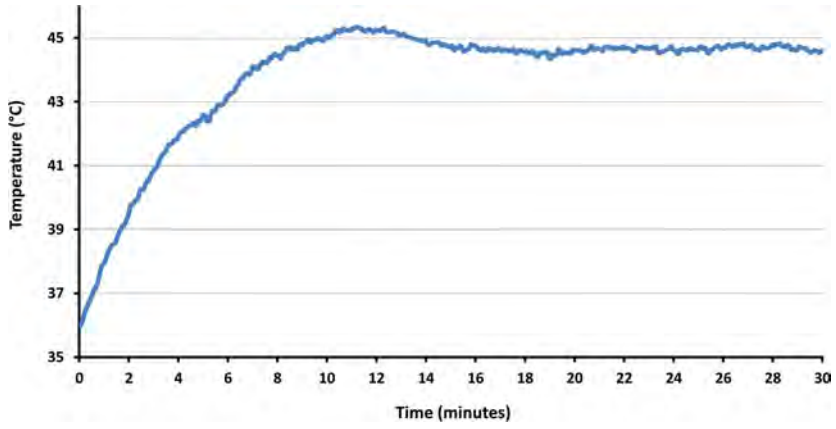


Figure 2. Continuous temperature measurement by the fiber optic probe located in the middle of fat tissue layer depth (Pig No. 3; first therapy, RF, and HIFEM set to maximum allowed intensity). The therapeutic temperature was achieved in the first 4 minutes, and it was maintained at a stable level of 44 to 45°C, during most of the procedure. HIFEM, high-intensity focused electromagnetic; RF, radiofrequency.

Histology Evaluation

Baseline and control samples showed predominantly normal round/polygonal-shaped healthy adipocytes without any damage to fat tissue (Figure 3). Four days after the last treatment, alternations of the cell shape were present. Adipocytes were noticeably flattened and of a smaller size ($p < .001$; Figure 3) with multiple adipose cells showing membrane rupture. Connective tissue (collagen fibers) shows conformational changes. Initiation of a mild inflammatory response was also observed with some neutrophils, lymphocytes, and macrophages seen perivascularly and surrounding adipocytes. The presence of subtle infiltration by these cells indicated that the elimination of damaged fat cells had already been initiated.

Two weeks after the final treatment, adipocytes were flattened and of significantly ($p < .001$) smaller size because of the release of their lipid content caused by the lipolytic effect of the simultaneous application of RF and HIFEM therapy (Figures 3 and 5). Multiple adipocyte nuclei demonstrated pyknotic appearance (a sign of apoptotic changes), as evidenced by their small and shrunk nuclei with dark, highly condensed nuclear chromatin. Furthermore, some membranes manifested rupture with unusual shape alternations, whereas immune cells were observed perivascularly. Macrophages (foamy histiocytes) and lipophages could be seen in areas where the damaged fat cells were being cleared.

One month after the last treatment, unstructured spaces of various sizes were present, caused by the elimination of fat cells (Figure 4). Ruptures in some adipocyte membranes were still visible. The inflammatory infiltrate receded, indicating that the removal of damaged tissue peaked in between 14 and 30 days. The diameter of the intact adipocytes was below the baseline values because they seemed to contain less lipids than pretreatment ($p < .001$; Figure 5).

At 2 months, the inflammatory infiltrate was occasionally present as a part of late tissue healing response along with a few ruptured membranes of adipocytes (Figure 4). Adipocytes showed no major alterations in shape but still remained smaller compared with the baseline ($p < .001$). In addition, as a result of the collagen remodeling induced by the RF,[25] the interlobular septa seemed well-developed. Notably, no damage to the blood vessels or necrosis of the fat tissue was observed.

Area of Adipocytes

Treated adipocytes showed a smaller diameter than at baseline (Figure 5). Overall, the fat tissue showed a

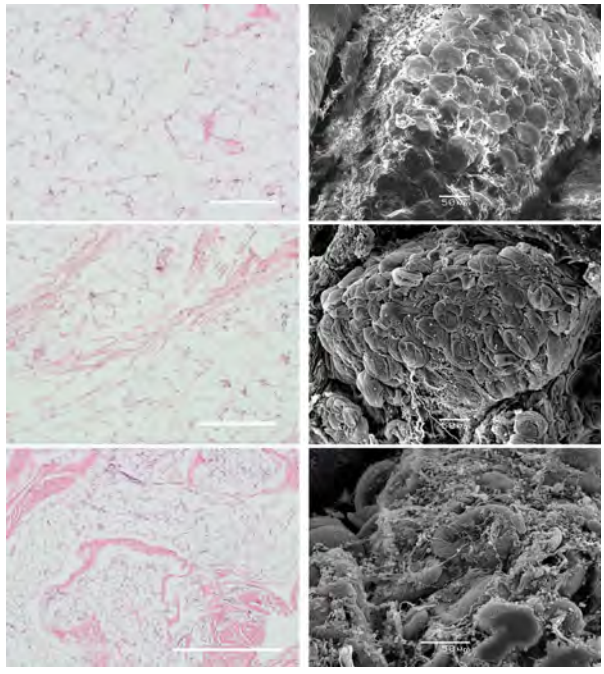


Figure 3. Light microscopy and SEM findings side by side: control/baseline (up, bar = 100 μm), 4 days (mid, bar = 200 μm), and 2 weeks (down, bar = 500 μm). Changes of fat tissue include delaminated membranes of adipocytes, alternations of their shape, presence of pyknotic nuclei, and subtle immune response, which started by day 4 and further propagated at 2 weeks. Conformational changes of collagen fibers were seen by day 4. SEM, scanning electron microscopy.

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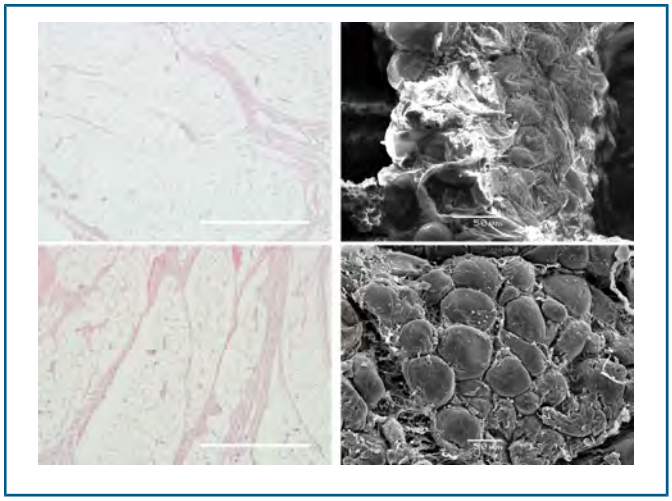


Figure 4. Light microscopy and SEM findings side by side at 1 month (up) and 2 months (down). At 1 month, the adipocytes still show membrane ruptures and alternations of their shape; however, the immune infiltrate is receding. At 2 months, the adipose tissue regenerates and is consisted of healthy-looking fat cells of smaller diameter. The architecture of interlobular septa was noticeably improved. SEM, scanning electron microscopy.

considerable decrease of adipocytes' area with the greatest reduction observed at 4 days (−25.9%; −337.8 μm^2) and 2 weeks (−31.1%; −405.5 μm^2) after the last procedure, when the most prominent changes in fat tissue were observed. Notably, the size of the adipocytes remained smaller at 1-month and 2-month follow-up compared with the baseline.

Scanning Electron Microscopy

Scanning electron microscopy micrographs corroborate the histology findings (Figures 3 and 4). At baseline, once again, healthy fat cells with well-defined shapes were observed. At the same time, 4 days after the last treatment, the adipocytes shrunk by 30% because of lipolysis with noticeable signs of membrane rupture. Fat cell elimination was more pronounced at 2 weeks with clearly visible lipolysis and the apoptotic events (Figure 3). A large number of disrupted adipocytes with extrusion of lipid droplets outside the ruptured and damaged cells were observed. A mild inflammatory infiltrate was present, indicating a local response to remove adipocyte cell remains.[20,21]

At 1 month, SEM micrographs showed that the adipose tissue still contained some damaged adipocytes, which had not yet been cleared (Figure 4). Surviving adipocytes were smaller because of lipolysis but showed signs of recovery and restoration of cell shape. Finally, 2 months after treatments, volume-depleted surviving adipocytes were almost back to baseline, although they still occasionally showed shape alternations (Figure 4).

Discussion

The histological and SEM evaluation of fat tissue after the dual RF/HIFEM treatment showed a corresponding pattern. Both H&E and SEM demonstrated lipolysis and a decrease in fat cells predicted to be long-term. Treatment effects in fat tissue peaked between 2 weeks and 1-month posttreatment when the most significant changes were seen. At 2 months, fat tissue still showed a significant and sustained fat reduction.

To accomplish a therapeutic effect in adipose tissue, it is necessary to achieve heating in a narrow range of 42 to 45°C, which triggers alternations in the structural integrity of the fat cells.[2,15] As shown in Figure 2, the lower limit of this temperature range was already achieved during the first 4 minutes. Temperature was then maintained within this range for the rest of the treatment. Such a rapid increase followed by a steady temperature profile allows for high efficiency because the therapeutic effect is delivered for 26 minutes of 30. This temperature profile is believed to be attributed to more uniform distribution of RF-generated heat, which is augmented by concomitant muscle activity and augmented blood circulation.[24] This hypothetically eliminates hot spots and contributes to treatment efficacy.

Previous studies have shown that controlled RF heating used as a standalone modality induces apoptosis.[20,21] Because only a mild inflammation response was observed, we believe

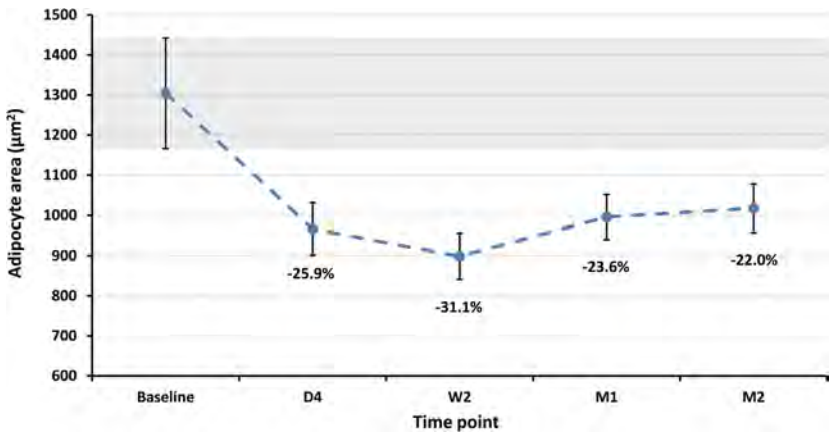


Figure 5. Average adipocyte area (mean ± standard error; μm^2) during the study. The decrease was highly statistically significant ($p < .001$) at all time points. The range for control and baseline samples is highlighted in gray.

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that heat-induced necrosis was not the primary effect. This study shows that apoptosis is the more predominant mechanism than necrosis, with treated adipocytes showing pyknotic nuclei, delaminated membranes, shape alternations, and only a mild inflammatory response. Adipocytes also suffer apoptosis when their size significantly fluctuates while becoming too large or too small[11,26] and are stressed by the excessive efflux of FFAs.[13,27] Although RF is assumed to play a major role in the effect on fat tissue, HIFEM-induced lipolysis may augment the overall fat cell shrinkage and thus enhance the apoptotic effect of the RF treatment.

We believe that the very significant lipolysis observed in this study reflects simultaneous use of both modalities. First, RF heats the tissue and activates the sympathetic branch of the autonomic nervous system. This leads to the release of catecholamines (adrenaline and noradrenaline), which triggers lipolysis.[5] The magnetic field simultaneously applied leads to intense muscle contractions that requires considerable amount of energy. This additional energy demand is believed to stress adipocytes to deliver more by increasing metabolic pathways such as breakdown of triglycerides. More triglycerides are broken to FFAs, which are delivered through the circulation to the muscle tissue for β-oxidation and ATP production.[28]

Although RF heating alone induces lipolysis, some of the released FFAs may be a subject to lipogenesis if not consumed for energy, which may occur in all noninvasive fat reduction modalities.[26] The results from our study showed a sustained reduction of fat cells' size after 2 months, indicating that lipolysis was predominant. A major role in long-term fat reduction is extensive apoptosis. Our study shows extensive fat cell disruption by apoptosis in histological and SEM images.

In safety, neither RF (when used within safe parameters) nor HIFEM injures the skin, blood vessels, or other adjacent structures when used as a standalone modality for noninvasive body shaping.[3,5,8,11,13,20,23,27,29] This porcine study corroborates this finding with additional effects of better organization of interlobular septa with RF-induced activation of fibroblasts and subsequent collagen remodeling.[25,30] This study objectively shows effects of novel simultaneous synchronized RF and HIFEM technologies for porcine subcutaneous fat reduction. Limitations include whether this animal study will reflect results in human, although previous studies have shown that results in porcine models often reflect the results in human fat tissue.[31,32]

Conclusion

Simultaneous delivery of synchronized RF and high-intensity focused electromagnetic procedure demonstrated an excellent safety profile with no adverse events documented after 3 weekly treatments in a porcine model. Histology and SEM examination of adipose tissue revealed strong evidence of elimination of adipocytes through an apoptotic mechanism accompanied by a lipolytic effect, resulting in an overall fat tissue reduction. Induced changes were observed to peak during the first month, whereas at 2 months, a significant reduction of fat tissue was observed.

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Check for updates

Received: 4 November 2020 | Revised: 22 January 2021 | Accepted: 26 January 2021

DOI: 10.1111/jocd.13970

ORIGINAL CONTRIBUTION

JCD Journal of Cosmetic Dermatology WILEY

Deletion of adipocytes induced by a novel device simultaneously delivering synchronized radiofrequency and hifem: Human histological study

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Funding information
BTL Industries Inc., Grant/Award Number: This study was funded by a research grant

Abstract

Background: Radiofrequency (RF) is commonly recognized treatment option for fat reduction, utilizing heat-induced adipocyte deletion. HIFEM treatment has been proven to be an effective tool for body shaping.

Objectives: To document the structural changes in human subcutaneous tissue induced by the combination of RF treatment with the HIFEM procedure.

Methods: Four subjects (51.50 ± 6.35 years, 22.59 ± 3.21 kg/m^2) received three 30-minute abdominal treatments consisting of RF therapy and HIFEM. One subject (57 years, 23.60 kg/m^2) served as a control. Punch biopsies were collected at baseline, 1-week, and 1-month post-treatment. Samples were sliced and stained with H&E. Waist circumference, digital photographs, satisfaction, and therapy comfort were assessed. Subjects were monitored for any adverse event, and fat temperatures were measured.

Results: Baseline samples showed a healthy appearance of adipocytes, composed of round-shaped unilocular cells of uniform size. At follow-up, treated adipocytes demonstrated nuclear and shape changes with consequent fat reduction. Adipocytes were found to be flattened/shrunken and of smaller size (−33.5% at 1 week; −31.7% at 1-month) along with occasional ruptures of the cytoplasmic membrane. In contrast to baseline, pyknotic nuclei with condensed nuclear chromatin were seen at 1-week and 1-month post-treatment. The control samples showed no treatment-related changes. Waist circumference decreased by an average of 2.20 cm in the treated patients. No adverse events were observed. The fat temperature reached 42-45°C, during treatment; the therapy was comfortable with high patient satisfaction.

Conclusions: Results suggest the efficacy and safety of the therapy combining RF and HIFEM. The adipocyte deletion and shrinkage resulted in overall reduction of fat tissue.

KEYWORDS

apoptosis, HIFEM, histology, radiofrequency

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1 | INTRODUCTION

Human subcutaneous fat tissue has a layered structure primarily consisting of fine collagen fibrous septa meshed with clusters of round-shape cells termed adipocytes.[1] Their cytoplasm is occupied by a large single lipid droplet, which serves as an energy reservoir, and is responsible for adipocytes spherical shape. Based on the amount of stored lipids, the adipocyte volume fluctuates throughout their lifetime.[2,3]

The continuous imbalance of caloric intake leads to the gradual accumulation of the adipose tissue since the excessive energy, which is not utilized by the body, is being stored in the lipid droplet in the form of triglyceride content.[2,3] A sedentary lifestyle and an unbalanced diet are considered the main contributors to increased fat storages in healthy human.[4] Besides the health risks and a need of considerable medical attention that often arise in the case of an overweight body,[5] the social aspects of a patient's well-being should not be underestimated as well. Aesthetically displeasing localized fat deposits are distressful for many and may result in the loss of self-esteem or trauma from embarrassment. Therefore, noninvasive body contouring has received increased attention in the recent years as a convenient solution for improving body image.

Noninvasive fat tissue reduction is energy-dependent and may be achieved either by reducing the fat stores or permanently removing adipocytes.[2] The first effect occurs when adipocytes are appropriately stimulated with energies of lower intensities, such as during low-level laser therapy (LLLT).[6] The catabolic process referred to as lipolysis is initiated, leading to a breakdown of the triglycerides stored in fat vacuoles into glycerol and free fatty acids (FFA) released into the vasculature.[7,8] However, although the decrease in adipocytes volume may be achieved by lipolysis, the cells are still viable and present in the same amount as before the therapy.

In addition to lipolysis, the adipose tissue can be eliminated permanently via various regulated cell death programs such as pyroptosis, necroptosis, and apoptosis.[9] Apoptosis is a complex intracellular pathway that allows the organism to control cell number and tissue size.[3,10] Morphologically, the most distinctive signs of apoptotic processes are cell shrinkage accompanied by nuclear changes in the form of chromatin condensation (pyknosis) and nuclear fragmentation (karyorrhexis).[2,11] Also, late plasma membrane disintegration may occur in case of extrinsic pathway of apoptosis.[9] Consequently, the cell remnants are digested by the immune cells during a phagocytic clearance.[12]

A specific amount of energy transformed into heat is required to induce fat apoptosis, elevating fat temperatures to 42-45°C. At the same time, it is necessary not to exceed the upper limit of 45°C in the long-term to avoid a risk of necrosis.[1,13-15] To safely heat the adipose tissue, various devices and technologies utilizing radiofrequency (RF) energy for fat apoptosis have been developed.[13,14,16,17] Due to the extensive research in the recent past, there exists a clear association between RF heating and adipocyte apoptosis documented in vivo in humans,[17] and correspondingly in porcine animal model.[14]

Nonetheless, body contouring may also be achieved via a nonthermal manner due to the muscle toning delivered by a high-intensity focused electromagnetic field (HIFEM) procedure.[18-20] HIFEM utilizes strong alternating magnetic fields, and based on the law of electromagnetic induction, it induces electric currents that depolarize neuromuscular tissue causing supramaximal muscle contractions. Such contractions demand a considerable amount of energy that is supplied in the form of FFA from adipose tissue via lipolysis.

The different modus operandi of the thermal (RF) and nonthermal (HIFEM) body contouring technologies allows for its combined use. An assumption arises that RF-induced fat loss may even be further promoted by the metabolic effect of HIFEM on fat when used simultaneously. Therefore, this study aims to document structural changes in human subcutaneous tissue induced by a novel device utilizing the simultaneous delivery of synchronized radiofrequency and HIFEM energy.

2 | MATERIALS AND METHODS

This was a prospective single-center study. Inclusion criteria were specified as BMI < 35.0 kg/m^2, no pregnancy or breastfeeding, injury in the treated area, active participation in any other concurrent therapy, and general contraindications for HIFEM and RF application to the human body. Five subjects were enrolled while four subjects (51.50 ± 6.35 years; BMI of 22.59 ± 3.21 kg/m^2) were assigned for active treatments, and one subject served as a control (57 years; BMI of 23.60 kg/m^2). At the time of enrollment, all study subjects were instructed about the study and associated procedures in detail. Written informed consent was obtained from all participants, and the study adhered to the ethical principles for medical research involving human subjects (1975 Declaration of Helsinki).

In total, the participants received three 30-minute abdominal treatments with a frequency of 1 treatment per week. No anesthesia or pretreatment, preparation was needed for the procedure. A device (Emsculpt NEO, BTL Industries INC., Boston MA) simultaneously delivering synchronized RF and HIFEM energies were used in this study. It utilizes a novel interspaced design of RF electrode that allows emitting radiofrequency and HIFEM fields in a synchronized manner, meaning that the apparatus for delivering both energies is embedded in one single applicator. Based on the patient's physical constitution, one or two applicators were placed over the treated area and affixed by an elastic fixation belt. The output power of RF was set to 100% in the active treatments and 5% for sham treatments. The intensity of HIFEM (0%-100%) in active group was cautiously adjusted according to the patient's feedback, ending up at a maximum tolerable level. HIFEM intensity in sham treatments was again set to 5%.

Punch biopsies (4 mm in diameter) of adipose tissue, after 1% lidocaine local anesthesia, were obtained from each subject at baseline, 1 week after the last treatment, and at 1-month follow-up. The baseline samples were collected at least 5 cm away from the

treatment site to avoid bleeding in the treated area and minimize patient discomfort during the therapy. Three tissue samples were collected from each subject (15 samples total). All specimens were preserved in a fixation solution (phosphate-buffered formalin), dehydrated, cleared, embedded in paraffin wax, and sectioned into thin (6 μm) slices using a microtome (120 micrographs in total). The slices were stained by the hematoxylin and eosin to finalize the processing for examination under the light microscope (Leica DM1000; Leica Microsystems, Germany). To evaluate structural changes of fat tissue, slices were subjected to detailed analysis by a certified histopathologist. The area of adipocytes (μm^2) in the examined slices was measured using Leica Application Suite Core Software and statistically analyzed by a two-tailed paired t test with $\alpha = 5\%$.

To verify the temperature distribution in the subcutaneous layer, the direct temperature measurements were taken using a flexible optic probe (LumaSense Technologies Inc, Germany) in one subject from the active group. Ultrasound-guided insertion of the probe into mid-depth of subcutaneous tissue was performed, and the temperature changes were monitored during the whole 30-minute treatment period.

Aside from histology, the secondary outcomes included documentation of treatment area by digital photographs, waist circumference, weight measurements, 5-point Likert scale satisfaction questionnaire, and 10-point visual analog scale (VAS) therapy comfort questionnaire assessed at baseline, 1-week, and 1-month follow-up. Any occurrence of adverse events was monitored throughout the study.

3 | RESULTS

All subjects successfully finished their treatments and follow-up visits. There were no adverse events reported. The only documented side effects were transient muscle soreness the day after the therapy and erythema that resolved within a few hours. Subjects rated their therapy comfort very high with average scores of 0.83 (active) and 0 (sham) at 10-point VAS (0 = no discomfort, 10 = unbearable discomfort).

Histological examination of baseline and control samples revealed healthy unilocular cells of round/polygonal shape. There were no deviations from the usual structure of adipose tissue (see Figure 1). On the contrary, the samples of treated tissue taken at 1 week showed visible shape alternations of fat cells and occasional fat ruptures. The evidence of ongoing programmed cell death processed was documented by the presence of pyknotic nuclei manifested by hypercondensation of chromatin and destructive fragmentation of the nucleus (Figure 2). Those findings persisted up to 1 month since the fat tissue still demonstrated an elevated level of adipocyte deletion and structural changes manifested as the flattening and plasma membrane disintegration (Figure 3). No such changes were found after the administration of sham treatment. Furthermore, no signs of necrosis were present after the active or sham treatments.

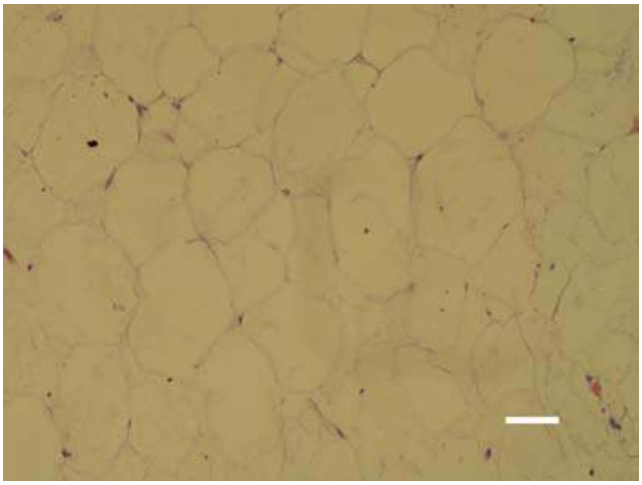


FIGURE 1 Subcutaneous tissue at baseline is consisted of healthy unilocular cells of round/polygonal shape (bar = 40 μm)

The outcomes of adipocyte size measurements can be seen in Figure 4. The fat cells in control samples were of a uniform size (approximately 1750 μm^2) throughout the study. The baseline measurements in the active group showed similar values, as seen in the control subjects. However, post-treatment samples showed a significant reduction in the adipocyte's size. At 1-week follow-up, the reduction in active group was 33.5% (−583 μm^2; $P = .009$), which was sustained at 31.7% (−552 μm^2; $P = .01$) at 1 month post-treatment. The loss of adipocytes content followed by its shrinkage/flattening was also apparent in examined histological samples. See Figures 2 and 3.

Fiber optic probe measurements showed a rapid increase in fat temperature in the first four minutes when the level of 42°C was achieved. The steady temperature range of 43-45°C was maintained for most of the therapy. In summary, the effective temperature needed to induce structural changes in adipose tissue was held most of the treatment time (Figure 5).

Weight fluctuations in the active group were insignificant (−0.2 kg at 1 week and −0.3 kg at 1 month, respectively). The changes in fat tissue observed by the microscopic evaluation were projected into a visible improvement of abdominal body contour (see Figure 6). The average waist circumference reduction in the active group was −2.20 cm with a maximum 5.4 cm reduction. Concurrently, the control subject showed no improvement in waist circumference. Active treatment resulted in a much greater satisfaction rate with therapy outcomes. Patients who received therapy with maximum intensities agreed (4) or strongly agreed (5) with the statement that the appearance of their abdominal area improved while the sham subject disagreed (2).

4 | DISCUSSION

The study investigated the effects of a novel technology utilizing simultaneous delivery of synchronized radiofrequency heating and

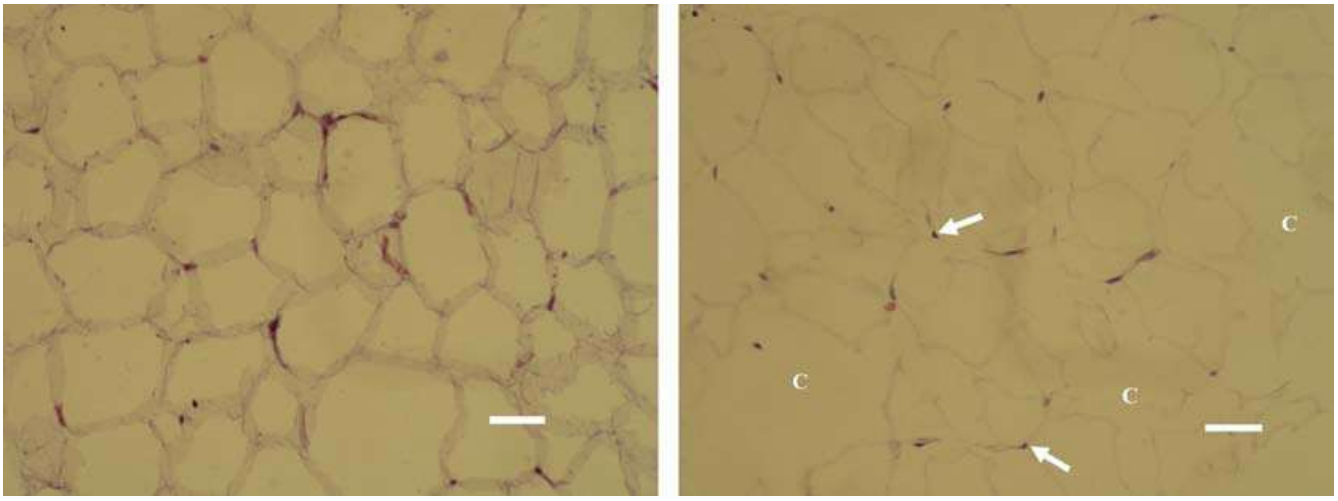


FIGURE 2 Elimination of fat cells (C), noticeable shape alternations, and pyknotic nuclei (depicted by an arrow) found in the treated adipose tissue at 1 wk (right, bar = 30 μm). No changes were found in control/sham subject (left, bar = 30 μm)

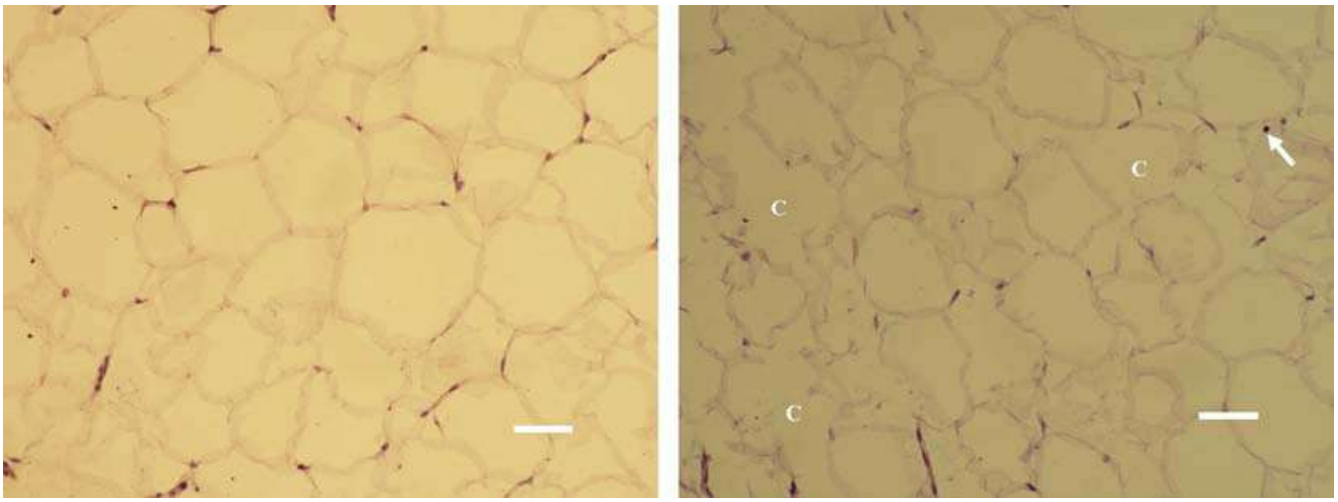


FIGURE 3 Elimination of fat cells (C), pyknotic nuclei (arrow), and shrinkage of adipocytes were found at 1 mo in treated subjects (right, bar = 30 μm). No changes were present after the sham treatment (left, bar = 30 μm)

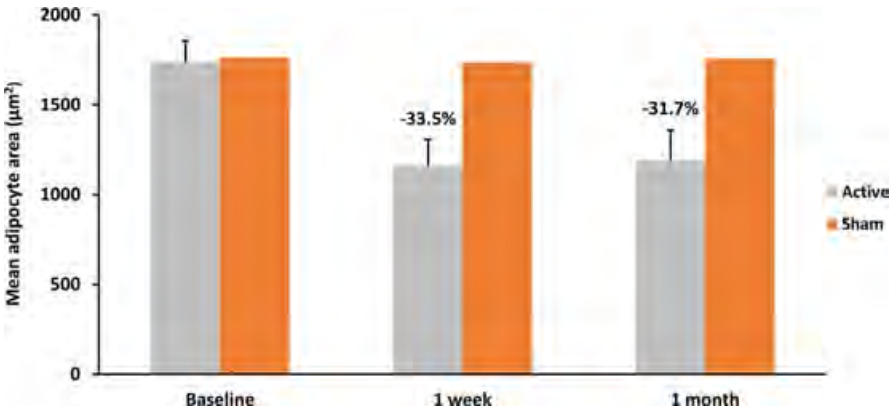


FIGURE 4 Adipocytes showed a significant ($P < .05$) decrease in size after the active treatment compared with sham at 1 wk and 1 mo. The error bars represent the variability of results among the subjects

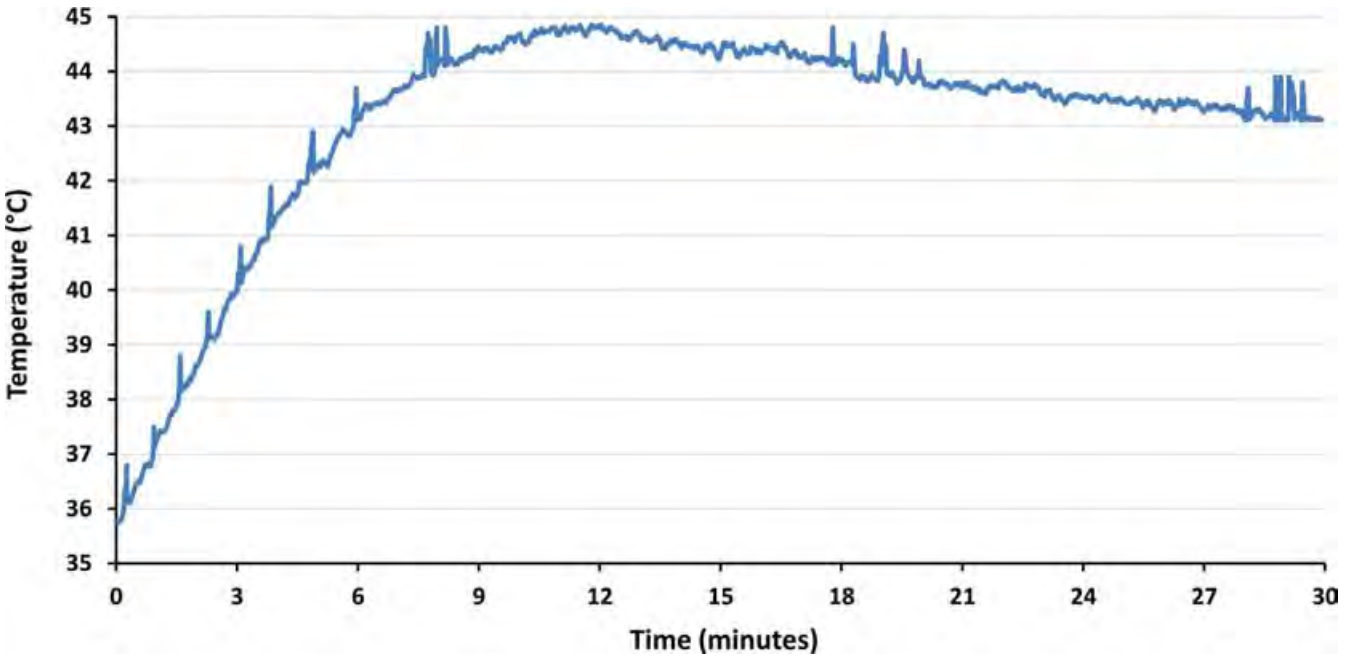


FIGURE 5 Rapid increase in fat temperature was seen, exceeding 42°C after the fourth minute. For most of the therapy time, the temperature was maintained at the level needed to induce structural changes to adipose tissue

FIGURE 6 Illustration of treatment outcomes by digital photographs (57 y, 22.98 kg/m^2). There is a noticeable improvement of the abdominal body contour seen at 1 mo (right) compared with baseline (left)



HIFEM stimulation on subcutaneous adipose tissue. Histological evaluation based on H&E staining showed prominent alterations within the adipose tissue at 1 week and 1 month post-treatment in subjects who received active treatment. No changes in the tissue were seen in the sham patient.

The results indicate that the simultaneous treatment triggers lipolysis along with fat cell elimination. The reduced adipocyte size is strong evidence for lipolysis as the adipocytes lose their intracellular content due to the breakdown of triglycerides into glycerol and FFA, which are subsequently liberated into the blood stream. The intracellular content has been reduced by 33.5% at 1 week and by 31.7% at 1 month compared with baseline. Also, the mean cross-sectional area at both follow-ups shows relatively small variation (see Figure 4), indicating that decrease in adipocytes size was uniform across all cells rather than it was a matter of some extreme values or outliers. Supposedly, the lipolytic effect of the simultaneous treatment may be attributed to both modalities, HIFEM and RF, as radiofrequency heating is known to trigger the lipolysis, and the supramaximal contractions induced by HIFEM were documented to result in increased metabolic activity, also leading to the fat lipolysis.[21]

Regarding adipocyte deletion, the presence of pyknotic nuclei, alternations of adipocytes shape, and absence of the inflammation are strong indicators of apoptotic changes happening in the tissue, since the pyknosis is irreversible and leads to nuclear fragmentation and cell death. Thus, the increased presence of pyknotic nuclei suggests elevated number of cells that entered the apoptotic process. This is also supported by the temperature measurements which

have shown that the temperature in the fat tissue reaches 42°C after 4 minutes and remains between 43 and 45°C during the most of the treatment, effectively triggering the adipocyte apoptosis.[16] On the other hand, although the observed plasma membrane disintegration might be a consequence of apoptotic-related decomposition, it also may indicate the presence of distinct regulated cell death pathways like pyroptosis.[9] However, the examination of the fat tissue at molecular level needs to prove this hypothesis which is beyond the scope of this study.

The efficacy of the simultaneous application of HIFEM and synchronized RF seen herein is in agreement with previous research that has shown a 29.8% reduction in the subcutaneous fat layer, as measured by ultrasound imaging system, and similar histological changes as seen in this study.[22] Future research can be used to look at programmed cell death markers for adipocytes[9,23] as well as to determine the duration of induced changes in a broader patient sample.

Individuals willing to improve their abdominal body contour may benefit from a mutual combination of the synchronized RF and HIFEM energies. This study documents that the simultaneous use of both investigated technologies is safe and results in noticeable body shaping effect, achieved primarily by the reduction in size and numbers of fat cells.

CONFLICT OF INTEREST

This study was funded by a research grant from BTL Industries Inc.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Goldberg DJ. Deletion of adipocytes induced by a novel device simultaneously delivering synchronized radiofrequency and hifem: Human histological study. *J Cosmet Dermatol*. 2021;00:1–6. https://doi.org/10.1111/jocd.13970

Efficacy and Safety of Simultaneous Application of HIFEM and Synchronized Radiofrequency for Abdominal Fat Reduction and Muscle Toning: A Multicenter Magnetic Resonance Imaging Evaluation Study

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BACKGROUND Radiofrequency and high-Intensity Focused Electromagnetic (HIFEM) field procedure are well-known, stand-alone, body-shaping modalities, yet their simultaneous application has not been investigated.

OBJECTIVE The aim is to evaluate the efficacy of a novel device simultaneously delivering HIFEM and radiofrequency for subcutaneous fat reduction and muscle toning.

MATERIALS AND METHODS Forty-one subjects with an average age of 39.7 ± 11.5 years were recruited. The subjects received 3 abdominal treatments (one per week). Magnetic resonance imaging images of the treated area were evaluated at baseline and at 1-, 3-, and 6-month visits for changes in subcutaneous fat, muscle thickness, and abdominal separation (AS). Anthropometric data and digital photographs were collected. Subject satisfaction and therapy comfort were evaluated.

RESULTS The muscle mass increase peaked at 3 months, showing 26.1% thickening. The fat thickness reduction was most prominent at 3 months, showing a 30.8% reduction. The AS decreased by 18.8% at 3 months after treatment. The waist circumference reduced by 5.87 ± 3.64 cm at a 3-month follow-up. Six-month data showed maintenance of these outcomes. The treatment was considered as comfortable with high patient satisfaction.

CONCLUSION The analysis of magnetic resonance imaging images and waist measurements showed that the therapy combining HIFEM and radiofrequency is highly effective in reducing subcutaneous fat and muscle thickening.

The field of noninvasive body shaping is primarily represented by 2 types of devices.[1] The first type is focused on subcutaneous fat reduction through thermal stress, either heating or cooling, which induces damage to fat cells. These devices utilize cryolipolysis, radiofrequency (RF), focused ultrasound, or lasers to induce the thermal stress.[2]

The second approach in noninvasive body shaping is focused on muscular tissue. The first widely used device introduced only in 2018[3] is based on high-Intensity Focused Electromagnetic (HIFEM) technology, which generates an alternating magnetic fields that induce electric current in the tissue, which stimulates motor neurons and triggers muscle contractions. The therapy was found to result in a significant thickening of muscle tissue while having an effect on subcutaneous adipose tissue as well.[4–6]

However, to achieve the total body shaping effect, that is, fat reduction and toned muscles, a combination of these 2 modalities would be optimal. This approach is common, but it is time consuming for the patient and the practice because the devices can only be used consecutively. Therefore, a technology that simultaneously combines the muscle stimulation and fat reduction modalities would be highly beneficial.

The outcomes of recent research suggest that muscle stimulation and tissue heating could work in synergy and promote the effects on the muscles.[7–9] Goto and colleagues[10] showed that the simultaneous application of heat and mechanical stimulation to muscle induces significantly higher expression of heat shock proteins that play a crucial role in muscle hypertrophy by promoting muscle protein synthesis.[11] Similarly, both heat and mechanical stimuli can activate myosatellite cells—muscle-derived stem cells involved in myofiber development and renewal.[12]

Synergistic effects of the simultaneous application of heat and muscle stimulation could also manifest in the adipose tissue. Also, HIFEM-induced localized muscle workload increases the demand for energy and thus the fat metabolism.[4,5] Heat itself increases lipolysis, and when sustained at temperatures of 42 to 45°C, adipocytes lose their cellular integrity and undergo apoptosis.[13] Adipose tissue could thus be affected in 2 different ways, which may translate into boosting the treatment outcomes.

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http://dx.doi.org/10.1097/DSS.0000000000003086

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For such purpose, a novel technology allowing simultaneous application of HIFEM and RF in a synchronized manner has been developed. The technology overcomes the interferences between the 2 modalities by a unique design of synchronized RF electrodes that prevent the creation of eddy currents. It is hypothesized that the technology for the simultaneous application of HIFEM and synchronized RF should result in synergistic effects in both muscle and adipose tissues. Therefore, this study aims to investigate the efficacy and safety of such novel technology for abdominal body shaping.

Materials and Methods

Study Population

Forty-one subjects (17 men and 24 women) interested in the noninvasive aesthetic improvement of abdomen participated in this prospective, multicenter, open-label, single-arm study. The inclusion criteria included adult subjects of any gender with a body mass index (BMI) lower than 35 kg/m^2. The study's exclusion criteria were pregnancy, postpartum period, breastfeeding, injury in the treatment area, or any other medical conditions that contraindicate the application of electromagnetic fields and RF, such as cardiovascular disease, malignant tumor, metal, or electronic implants. Subjects who met the inclusion criteria and were recruited as study participants were, on average, 39.7 ± 11.5 years old and had a BMI of 26.56 ± 3.73 kg/m^2 at the beginning of the study.

Study Design

The study design and the treatment protocol were approved by the Institutional Review Board and followed the ethical guidelines of the 1975 Declaration of Helsinki.

Each subject received three 30-minute treatments on the abdomen with the device simultaneously delivering HIFEM and RF energies through a single applicator (Emsculpt NEO, BTL Industries, Inc., Boston, MA). The treatments were administered once a week. All of the patients were instructed to maintain their daily routine and not to change their lifestyle. Before the treatment, each subject received detailed instructions about the study and signed informed consent.

During the treatments, no anesthesia was required. Patients were positioned in a supine position with the applicators centered over the umbilicus. In case the patients' constitution allowed, 2 applicators were used bilaterally, centered above both lateral sides of the rectus abdominis. Applicators were affixed with a fixation belt to avoid the possibility of movement during the treatment. Each treatment lasted for 30 minutes, starting with the HIFEM intensity set to 0%, increasing it to the maximum tolerable level. The RF intensity was set to 100% since the beginning of the procedure. Patients were regularly asked about the therapy comfort during the whole treatment time, and the energy settings were adjusted accordingly. Digital photographs of the treatment area, waist circumference measurements, weight and height records, and magnetic resonance imaging (MRI) images of the treatment area were collected at baseline and at 1-, 3-, and 6-month follow-up visits.

Data Collection and Evaluation

Magnetic resonance imaging was used as the primary evaluation modality for assessing the treatment effects on muscle and adipose tissue thickness and abdominal separation (AS) width. The scanning area was defined by T12 and S1 vertebrae. The images were acquired by the FIESTA and FSPRG sequences (Matrix: 380 × 380, ST: 5 mm, Spacing: 1 mm) in a transverse plane. The muscle and fat thickness measurements were performed supraumbilically and infraumbilically, approximately 2 inches (5 cm) above and below the umbilicus. The AS was measured at the same MRI slices as a perpendicular distance between the 2 parallel pairs of rectus abdominis muscle. Data collection was done at baseline and at 1-, 3-, and 6-month follow-ups.

The patient's satisfaction with the treatment results was assessed using the Satisfaction Questionnaire with a 5-point Likert scale after the last treatment and each follow-up visit. The therapy comfort was evaluated using 10-point visual analogue scale (VAS) after each treatment session.

All data were statistically analyzed using repeated-measures analysis of variance, paired, and 2-sample *t*-test. Analyses showing *p*-values of $<.05$ were considered as significant.

Results

Forty patients completed the entire treatment procedure and attended the MRI screening at 1-month follow-up. One subject withdrew from the study before completing the whole procedure. Twenty-nine patients attended the 3-month follow-up visit, and 20 patients participated at the 6-month follow-up visit, including the MRI screening. The dropout rate seen at the MRI follow-up visits was considerably affected by the outbreak of COVID-19, which did not allow the patients to attend the visits in person. Therefore, 4 of these patients attended the 3- and 6-month follow-up visits virtually, where they were asked to report any adverse events, satisfaction with results, weight, and waist circumference measurements. These patients did not undergo MRI screening due to the restrictive measures.

Magnetic Resonance Imaging Evaluation

Subcutaneous Adipose Tissue

Evaluation of 1-month scans showed an average fat reduction across the abdomen by 24.4%. The patients lost 23.6% on average (−6.61 ± 2.9 mm) infraumbilically and 25.3% on average (−5.9 ± 2.7 mm) supraumbilically. The results were fairly consistent; although only 2 patients showed a reduction lower than 5%, 37 patients showed a reduction higher than 15%, and 33 patients showed a reduction higher than 20%.

At 3 months, the results further improved significantly ($n = 29$; $p < .05$) in comparison to 1 month as the patients lost, on average, 30.8% of fat since the baseline visit. Supraumbilically, the patients lost 7.3 ± 3.3 mm (31.9%) on average and 7.9 ± 2.5 mm (29.7%) infraumbilically. At 3-month follow-up, there were no nonresponders with

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TABLE 1. Detailed Result Summary of MRI Measurements

Measurement	Location	Baseline ($N = 40$)	1M FU ($N = 40$)	3M FU ($N = 29$)	6 M FU ($N = 20$)
Fat thickness	Infraumbilicus	28.6 ± 11.8 mm	22.0 ± 10.0 (−23.6%)	19.9 ± 8.1 (−29.7%)	21.0 ± 8.9 (29.1%)
	Supraumbilicus	24.2 ± 11.7 mm	18.3 ± 9.8 (−25.3%)	16.4 ± 8.5 (−31.9%)	17.8 ± 8.2 (27.5%)
Muscle thickness	Infraumbilicus	9.2 ± 2.3 mm	11.2 ± 2.5 (+22.0%)	11.6 ± 3.0 (+24.7%)	11.2 ± 2.2 (26.4%)
	Supraumbilicus	8.7 ± 2.3 mm	10.7 ± 2.5 (+24.9%)	11.1 ± 2.7 (+27.4%)	10.6 ± 2.0 (24.1%)
Abd. separation	Infraumbilicus	16.6 ± 6.3 mm	13.7 ± 5.6 (−17.8%)	12.9 ± 4.9 (−19.6%)	12.4 ± 5.3 (20.0%)
	Supraumbilicus	21.4 ± 6.3 mm	18.1 ± 5.5 (−15.8%)	17.4 ± 5.2 (−18.8%)	17.8 ± 5.3 (19.6%)

MRI, magnetic resonance imaging; FU, follow-up; M, month.

reduction lower than 5%. Twenty-eight out of the 29 patients showed a reduction higher than 20%, and in 23 patients, the reduction exceeded 25%. All changes were statistically significant ($p < .05$).

In the group of 20 subjects who underwent the MRI screening at 6-month follow-up showed that the improvement achieved at 3 months (30.8%) was mostly preserved with the average reduction of 28.3% in comparison to baseline, yet showing a statistically insignificant ($p > .05$) decreasing trend. At 6 months, 7 out of the 20 subjects showed a decrease in the improvement of more than 5% when compared with the results at 3-month follow-up.

Table 1 shows a detailed result summary. An example of a patient MRI scan can be seen in Figure 1.

Muscular Tissue

The thickness of the rectus abdominis was increased by 23.5% on average at 1-month posttreatment. At infraumbilical slices, the average increase was equal to 1.9 ± 0.7 mm in absolute values corresponding to an average 22.0% increase in the thickness. Supraumbilical slices showed thickening by 2.0 ± 0.8 mm, corresponding to 24.9% increase on average. There were no nonresponding patients, and in 32 out of 40 patients, the thickness of rectus abdominis increased by more than 18%.

Similar to the fat tissue, the results in muscles continued to improve at 3-month follow-up. The average increase in muscle thickness was 26.1% (+2.3 ± 0.8 mm), whereas 24.8% thickening was seen infraumbilically and 27.4% supraumbilically. All changes were statistically significant ($p < .05$).

At 6 months, the MRI scans of 20 subjects showed that the results of these patients were maintained. Data of this group showed a 25.8% thickening at 3 months, which was then maintained at 25.3% at 6-month follow-up visit.

Table 1 shows a detailed result summary.

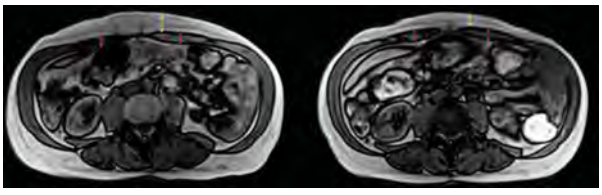


Figure 1. Magnetic resonance images illustrating the changes in the treated area. Supraumbilical slices taken at baseline (left) and at 3-month follow-up (right) of a 62-year-old woman. Individual patient's improvement reached −45.6% in fat reduction and +14.6% in muscle thickness, respectively. Fat tissue is marked with yellow arrows, rectus abdominis muscle by red color.

Abdominal Separation

The width of AS reduced significantly ($p < .05$) at both the supraumbilical and infraumbilical slices in all of the examined subjects. Supraumbilically, the average width of AS was reduced by 16.0% at 1-month follow-up and by 17.6% at 3-month follow-up. Infraumbilically, the AS reduced by 16.4% at 1 month and by 19.2% reduction at 3-month follow-up (detailed results are given in Table 1).

According to the supraumbilical slices, 8 out of the 40 patients experienced diastasis recti at baseline. It is a condition when the gap between the 2 sides of rectus abdominis muscles exceeds 27 mm.[14] In this group, the AS was reduced by 4.8 ± 1.7 from 30.1 ± 2.1 mm at baseline to 25.4 ± 2.0 mm at 1-month follow-up. In 6 patients, the condition was fully corrected at 1-month follow-up.

At 6 months, the overall reduction in AS was 19.8%. Of the 20 subjects examined at 6 months, 5 experienced diastasis recti at baseline. At 6 months, 4 subjects were fully without diastasis recti, and only a single subject exceeded the 27-mm range, yet this subject showed a prominent reduction as at baseline: the AS was 33.4 mm, whereas the 6-month measurements showed an AS of 27.5 mm.

Patient Satisfaction and Treatment Comfort

The patients found the treatments comfortable with a score of 2.3 ± 1.8 on a 10 point VAS (0 = no discomfort; 10 = unbearable pain). By the end of the first treatment, most patients reached 100% intensity of the HIFEM field. The intensity of RF was adjusted in most patients based on their individual perception of the heat.

The satisfaction questionnaire's analysis revealed high patient satisfaction as 91% of patients reported satisfaction

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with the treatment results at 3-month posttreatment. Ninety-four percent of patients reported improved appearance of the abdomen, and 91% reported improvement in both muscle and fat.

No severe adverse events or side effects of the treatment were reported. In all patients, the treatment was associated with mild erythema following treatment and dissipated rapidly, and some patients experienced mild muscle soreness on the day after treatment.

Waist Circumference and Weight Measurements

The waist circumference was reduced by 3.3 ± 3.1 cm on average at 1-month follow-up visit. At 3 months, the average circumferential reduction was 5.9 ± 3.6 cm. The patients attending 6-month visit showed a 6.7 ± 3.5 cm reduction in waist circumference. The weight did not show any major fluctuations between any of the time points. Digital photographs showed notable improvement. Figure 2 provides an example of patients' result.

Discussion

The treatments with a novel device that delivers HIFEM and synchronized RF energies simultaneously resulted in a statistically significant increase in muscle mass, reduction in the fat layer thickness, and reduction in AS. The results in all 3 measured parameters showed improvement up to 3 months at which time the results peaked. The MRI observations were accompanied by reduced waist circumference and improved body image in digital photographs. At 6 months, no further improvements were observed, but the results seen at a 3-month follow-up were maintained in the majority of the patients. Although the results at 6 months are still highly above baseline values, the patients may benefit from additional maintenance treatments to reverse the declining tendency and to prolong the longevity of achieved outcomes.

The study did not include control groups that would receive HIFEM-only and RF-only treatments. However, several studies were published in the past solely for these modalities, allowing for comparison with the outcomes of this study. Studies on the abdominal application of HIFEM did show an average subcutaneous fat reduction[6,15,16] of 19.6% (17.5%–23.3%), average muscle thickening[6,15] of 15.1% (14.8%–15.4%), and an average reduction in AS[6,15] by 9.95%. When compared with our results with the simultaneous application of HIFEM and RF, it appears that the synergy of the 2 energies has a truly high impact on the final outcome because it yields more than 50% higher improvement in all 3 measured parameters.

Studies[13,17–21] investigating the application of RF systems for subcutaneous fat reduction report a fat thickness reduction ranging from 4.9% to 29.0% with a weighted average of 14.58%. Nevertheless, the comparison with other RF studies may not be as precise because the studies investigate various systems of different frequencies and other properties. However, they do provide an overview of the expected patient results of treatment with this modality.

Our results are in agreement with the fact that combination treatments in general are considered more effective than stand-alone treatments. Study by Kilmer and colleagues[22] found that consecutive treatments of cryolipolysis and electromagnetic technology result in better subjective perception of the treatment outcomes than stand-alone treatments as seen in patient satisfaction or photographic evaluation. The study also reported higher waist circumference reduction after the combined treatments of 1.5 cm. Considering this result, it can be seen that simultaneous application of HIFEM and RF is more effective in waist reduction (−5.9 cm) than consecutive application of cryolipolysis and electromagnetic technology (−1.5 cm).

Although this is a first MRI study investigating the effects of simultaneous application and further research is necessary to validate these findings, the results seem to exceed the outcomes of individual HIFEM and RF treatment. Regarding muscle tissue, it is assumed that the synergistic effect could be attributed to the physiologic nature of muscle synthesis regulating molecules, such as heat shock proteins[10] and satellite cells,[12] which concentrations and state can be altered by both mechanical stimulation and heat.

One of the study limitations is the high dropout rate at the 3- and 6-month follow-ups, mainly attributed to the outbreak of COVID-19, as attending follow-up visits would pose risks of infection to the patients. However, 29 patients out of 40 at a 3-month visit represent 72.5% of the initial population and still provide valuable data about the treatment outcomes. The lack of a control group can also be considered as a limitation and should be implemented in future studies.



Figure 2. Digital photographs taken at (left to right) baseline and at 1-month posttreatment. At 6 months, the 50-year–old woman showed 24.8% fat reduction, 23.7% muscle thickening, and 8-cm waist circumference reduction.

Conclusion

Simultaneous application of HIFEM and RF is safe and effective for muscle toning and fat reduction. The results suggest this application as more effective for fat reduction and muscle increase than using these energies stand-alone or

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consecutively. Further studies are required to support these outcomes.

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Aesthetic Surgery Journal
2021, 1–9
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DOI: 10.1093/asj/sjab002
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Activation of Skeletal Muscle Satellite Cells by a Device Simultaneously Applying High-Intensity Focused Electromagnetic Technology and Novel RF Technology: Fluorescent Microscopy Facilitated Detection of NCAM/CD56

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Abstract

Background: Myosatellite cells are myogenic stem cells that can transform to provide nuclei for existing muscles or generate new muscle fibers as documented after extended exercise programs.

Objectives: The authors investigated whether the simultaneous application of High-Intensity Focused Electromagnetic (HIFEM) and Synchrode radiofrequency (RF) affects the levels of satellite cells similarly as the prolonged exercise does to achieve muscle growth.

Methods: Three 30-minute simultaneous HIFEM and Synchrode RF treatments (once a week) were administered over the abdominal area of 5 Large White swine aged approximately 6 months. All animals were anesthetized during the treatments and biopsy acquisition. Biopsies of muscle tissue were collected at baseline, 4 days, 2 weeks, and 1 month post-treatment. After binding the specific antibodies, the NCAM/CD56 levels, a marker of activated satellite cells, were quantified employing the immunofluorescence microscopy technique with a UV lamp.

Results: Examined slices showed a continuous increase in satellite cell levels throughout the study. Four days after the treatment, we observed a 26.1% increase in satellite cells, which increased to 30.2% at 2-week follow-up. Additional histological analysis revealed an increase in the cross-sectional area of muscle fibers and the signs of newly formed fibers of small diameters at 2 weeks after the treatment. No damage to muscle tissue and no adverse effects related to the treatment were observed.

Conclusions: The findings indicate that the simultaneous application of HIFEM and novel Synchrode RF treatment can initiate differentiation of satellite cells to support the growth of existing muscles and, presumably, even the formation of new myofibers.

Editorial Decision date: December 18, 2020; online publish-ahead-of-print January 12, 2021.

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It was reported that 60.7% of men and 71.6% of women are dissatisfied with their body shape.[1] As a result, aesthetic medicine is often sought to correct body imperfections. Patients seek surgical as well as non-invasive procedures to improve their body contours.[2] For a long time, physicians' non-surgical treatment options were limited to excessive fat reduction and skin rejuvenation. In 2018, an electromagnetic High-Intensity Focused Electromagnetic (HIFEM) technology opened up an entirely new segment in body contouring due to its unique effects on muscles. Until then, physicians did not have a tool to alter the body musculature non-invasively, which significantly contributes to a toned, firm, and aesthetically pleasing appearance.

The technology is based on the induction of supramaximal muscle contractions not achievable voluntarily. Such intense mechanical stress in the muscle tissue triggers processes to adapt to a higher load. Clinical studies investigating the efficacy of HIFEM showed 15% to 18% muscle thickening of abdominal muscles[3-5] and a 10.3% increase in the volume of gluteal muscles.[6]

Because the HIFEM technology was the first of its kind, further innovations were inevitable and led to the development of a novel technology simultaneously combining HIFEM's muscle conditioning with radiofrequency (RF) heating intended for fat elimination. Under normal circumstances, it is impossible to simultaneously utilize the HIFEM and RF energies due to the interference between the HIFEM alternating magnetic field and the solid RF electrode. This interference induces Eddy currents, which results in the heating of the metallic electrodes. This may cause damage to the device and harm the patient. The device thus employs a novel and patented Synchrode RF electrode that eradicates this interference. The unique interspaced design combines hundreds of microelectrodes that make the electrode transparent to the HIFEM-emitted magnetic fields. The technology (EMSCULPT NEO, BTL Industries Inc, Boston, MA) has been cleared by the US FDA for non-invasive lipolysis (breakdown of fat). Based on the FDA's public database, the clinical trials reviewed by the agency during the registration process[7] showed an average 29.8% reduction in abdominal fat thickness and provided histological evidence of fat cell membrane disintegration. However, this innovation is twofold. Firstly, it ranks the technology among the top tier of non-invasive technologies affecting fat. Secondly, it has been evidenced that muscle tissue heating during muscle work positively affects the muscle response to the workload.[8-11] The synergistic effect of simultaneous delivery of HIFEM and Synchrode RF enhances the muscle hypertrophy. HIFEM-induced mechanical stress and RF-induced heat stress to the muscle leads to the release of heat shock proteins (HSP), signaling molecules that promote muscle protein synthesis and thus enhance the muscle hypertrophy.[12,13] A study by Goto et al[14] documented that the HSP expression is highest when heat and mechanical stress are applied simultaneously, proving the synergy between the 2 energies.

Satellite cells, muscle-derived stem cells, which on activation regenerate and strengthen the existing muscle fibers through differentiation,[15] are also essential for muscle hypertrophy. They are usually activated in response to an intense muscle exercise,[16,17] but it has been found that heating may also lead to their activation.[18] Simultaneous application of Synchrode RF and HIFEM should thus result in high activation of satellite cells and consequent magnification of muscle hypertrophy.

We sought in this study to investigate the effect of the simultaneous application of HIFEM and Synchrode RF energies on the levels of satellite cells through immunofluorescence and to assess any structural changes in the muscle tissue through conventional histology.

METHODS

The study was designed as a prospective single-arm trial and was approved by the IRB of the respective authorized body for veterinary trials (The Ministry of Agriculture of the Czech Republic). A representative of the institution supervised the study execution. The animal care complied with the convention to protect vertebrate animals utilized for experimental and other scientific purposes. The study experiment was carried out in between May 2019 and July 2019.

Study Animals

The study included 5 Large White swine (weight ranging between 78 and 83 kg of live weight) with an average age of 6 months. The animals were stabled at the veterinary institute 1 week before the experiment to acclimate them to the new environment and monitor their condition under the supervision of a veterinarian. The condition and health of the animals were assessed through blood analysis 2 days before the experiment.

Study Experiment

All animals received an active treatment procedure with the investigated device combining the HIFEM procedure and Synchrode RF heating (EMSCULPT NEO, BTL Industries Inc., Stevenage, United Kingdom). The treatment procedure included three 30-minute treatments (one per week) applied over the abdomen. Only the left side was treated, and right side of the animal served as a control area. For the execution of the treatment and biopsy collection, the animals were under general anesthesia to

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minimize the stress. Anesthesia (2% propofol) was administered by a veterinarian who determined the dosage. The treated area was shaved with an electric clipper beforehand, and a single applicator, secured by a fixation belt, was applied over the treated area. The intensity was set to 100% for both HIFEM and Synchrode RF. The animals were monitored during the entire treatment procedure.

In Vivo Temperature Measurements

The muscle temperature was monitored during the entire treatment for safety reasons and to rule out any possibility of muscle tissue overheating. A thermal probe (FOT Lab Kit Fluoroptic Thermometer, LUXTRON, Advanced Energy, Denver, CO) was inserted into the muscle tissue utilizing ultrasound guiding (Mindray M5Vet, probe 10L4s) to ensure correct probe placement. Temperature recording was active during the whole procedure, after which the probes were removed.

Tissue Collection

The biopsy samples of muscle tissue were collected at baseline, 4 days, and 2 weeks for the immunofluorescence analysis and conventional histology. At 1 month, additional samples were collected for conventional histology. At baseline, the biopsies were collected only from the control site, opposite to the treated area, to avoid bleeding in the treatment area during the muscle contractions and tissue heating. The post-treatment biopsies were always collected from both the treatment site and the control site, resulting in 60 biopsy samples. Self-contained samples were taken for immunofluorescence analysis and conventional histology. The biopsy collection was performed utilizing a disposable biopsy punch with a diameter of 6 mm.

Tissue Sampling and Processing

On collection, the tissue samples intended for histological analysis were preserved utilizing 10% buffered formalin and fixed in paraffin blocks. The blocks were cut into five 5- to 10-µm-thick slices (175 slices in total) and were stained with hematoxylin and eosin staining. The slices were examined by a certified histopathologist employing light microscopy for any structural changes.

The samples for immunofluorescence were embedded in OCT-cryoprotective embedding medium Tissue Tek (O.C.T. Compound, Sakura-Finetek, Tokyo, Japan) and frozen by supercooled n-heptane placed on dry ice. Then, each tissue sample was cut into four 5- to 10-µm-thick slices (100 slices in total) on the cryostat (Leica Microsystems, CM 1900, GmbH, Wetzlar, Germany) at a temperature of −20°C. Slices were placed on slides and fixed in pre-cooled acetone for 5 minutes and stored at −80°C.

Immunofluorescence aimed to target the NCAM/CD56 marker, which is known for the successful labeling of both quiescent and activated satellite cells and has been utilized by most studies investigating the satellite cells.[19-22] Protein Block (DAKO, Glostrup, Denmark) was applied on the slides to prepare the slides for the analysis, and the slides were then incubated at 37°C in a humid chamber for 30 minutes. Then, anti-Hu CD56, clone MEM-188 (Exbio Praha a.s., Vestec u Prahy, Czech Republic), and anti-Laminin, clone A5 (OriGene Technologies GmbH, Herford, Germany) primary antibodies were applied, and the slides were incubated for 60 minutes at 37°C in a humid chamber. The slides were washed, and goat anti-mouse IgG2a Alexa Fluor 594 (ThermoFisher Scientific, Waltham, MA) and goat anti-rat IgG Alexa Fluor 488 (ThermoFisher Scientific, Waltham, MA) secondary antibodies were added and incubated for 60 minutes at 37°C in a humid chamber. Then, the slides were washed, and Vectashield mounting medium with 4′,6-diamidino-2-phenylindole (Vector Laboratories, Burlingame, CA) was applied.

Evaluation of Satellite Cell Levels

The pre-processed slides were examined at magnifications of 40× and 200× utilizing a fluorescent microscope (Olympus IX51, Tokyo, Japan) with UV-lamp (Olympus u-RFL-T, Tokyo, Japan). A Canon EOS 1100D camera (Tokyo, Japan) and software CellSens Standard software (Den Haag, the Netherlands) were used to capture the slides as images.

The pre-processing procedure ensured that satellite cells were labeled in red, myonuclei as blue, and cell membranes of individual muscle fibers as green. Obtained images were evaluated by utilizing Cell Profiler software that calculates color clusters. The level of satellite cells in each slide was determined as a ratio of labeled satellite cells to the total number of myonuclei. The differences between baseline, post-treatment, and control slides were statistically tested employing a 2-way ANOVA test with a level of significance $\alpha = 0.05$.

Muscle Fiber Size Evaluation

Processed slides were further utilized for evaluation of muscle fiber size. In each slide, the cross-sectional area of individual muscle fibers was measured with ImageJ software, version Fiji.[23] The area of up to 800 muscle fibers was measured for each time point. Obtained values for each time point were clustered into groups according

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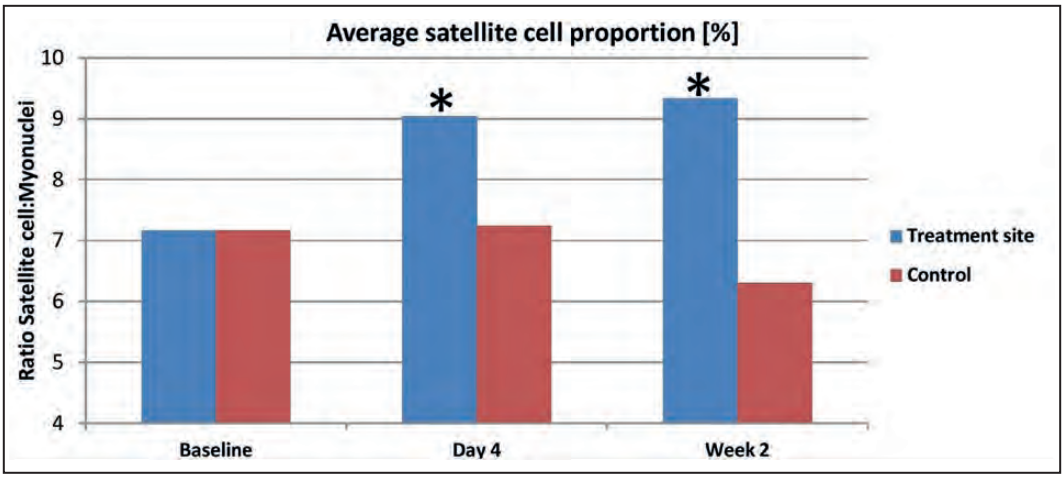


Figure 1. Measured satellite cell proportion at baseline, 4 days, and 2 weeks post-treatment. Statistically significant changes are labeled by asterisk.*

to the size to monitor the fiber size frequency distribution over time.

RESULTS

Pretreatment blood analysis confirmed the good health condition of all pigs. The animals withstood the anesthesia without any complications, and the treatments were well tolerated without any observable side effects. Throughout the experiment, the animals were stabled at the veterinary institute to monitor their health conditions and potential treatment-related complications and side effects. The follow-up sample collection from all animals was administered at exactly 4 days, 14 days, and 30 days after the last treatment. On completion of the experiment and collection of the final biopsies, the animals were euthanized by a certified veterinarian.

Immunofluorescence

The assessment of satellite cell proportion within the stained slides showed a statistically significant ($P < 0.05$) increase by 26.1% on the fourth day after the last treatment. At 2 weeks post-treatment, the level of satellite cells further increased by 30.2% compared with baseline. In absolute values, the satellite cell proportion ($N_{satelite}/N_{myonucleus}$) increased from 0.071 ± 0.012 at baseline to 0.09 ± 0.016 on the fourth day post-treatment and 0.093 ± 0.038 at 2 weeks post-treatment. The same increasing pattern was observed in all of the treated animals. The control samples collected from the opposite site after 4 days (0.072 ± 0.011) and 2 weeks (0.063 ± 0.012) did not show any statistically significant changes from baseline. A detailed comparison of the results is shown in Figure 1, and an example of stained slides captured by a fluorescent microscope is shown in Figure 2.

Histological Examination

A histopathologist examined the histological slides for any structural changes in the muscle tissue. The post-treatment slices obtained after 4 days did not show visually noticeable structural changes. However, at 2 weeks, the muscle tissue showed enlarged hypertrophic fibers, with the most prominent enlargement seen at 1 month post-treatment. At 1 month, the muscle tissue showed apparent hypertrophic changes compared with baseline, accompanied by a decreased intramuscular sheaf space, as shown in Figure 3.

The histological slides did not show any deviations from normal healthy muscle structure, and no signs of muscle tissue damage or adverse events were observed. A few samples did contain blood hemorrhage, which is something that cannot be entirely avoided during the invasive nature of biopsy sample collection. Lastly, several slices of the muscle tissue collected 1 month post-treatment showed structures that were not present at baseline slices and appeared to be newly formed muscle fibers (see Figure 4).

Muscle Fiber Size Measurements

The baseline measurements showed that the majority (69%) of all fibers ranged between 2000 and 6000 μm^2, whereas only 17% were smaller and only 14% exceeded 6000 μm^2. After the treatments, a significant shift in the distribution has been seen: the ratio of small muscle fibers increased from 17% to 21% at 2 weeks post-treatment and to 22% at 1 month post-treatment. Similarly, the ratio of large

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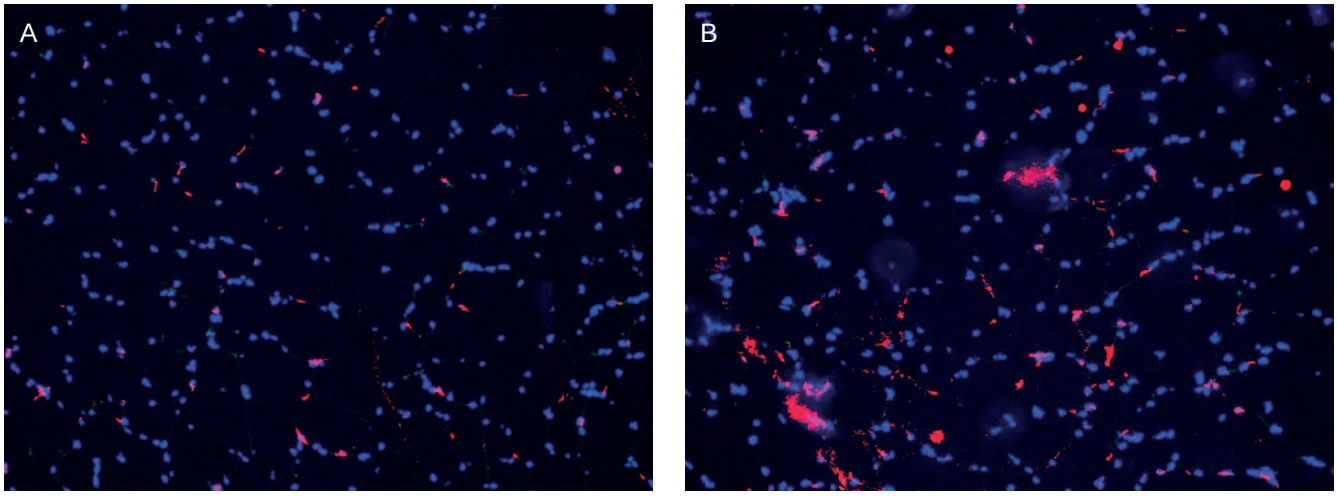


Figure 2. (A) An Example of the stained slides of baseline (B) and 2-week muscle tissue viewed under a fluorescent microscope. The satellite cells are colored by red and myonuclei by blue.

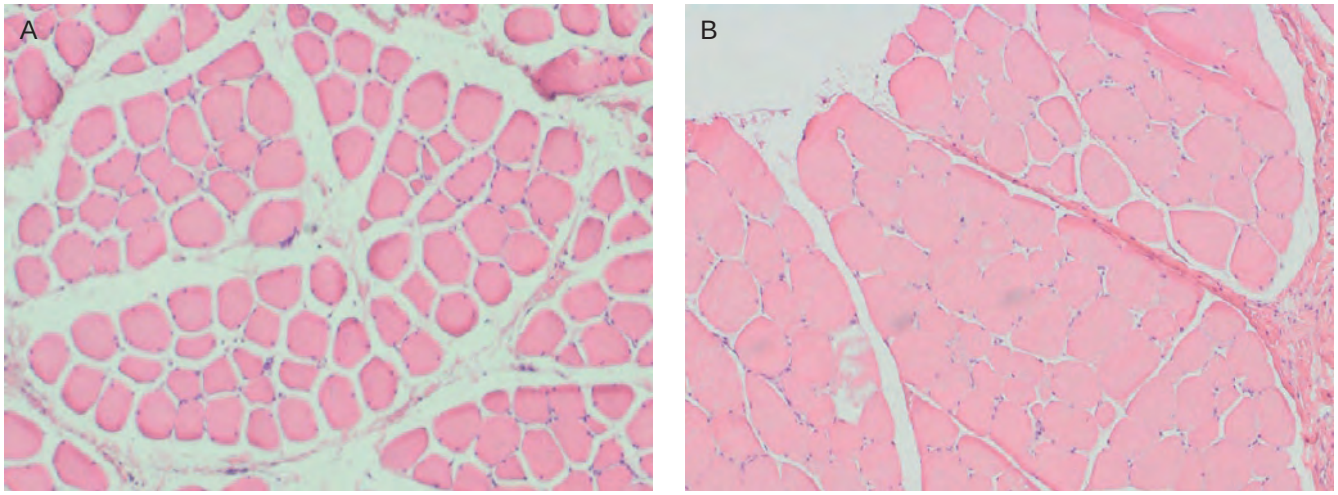


Figure 3. (A) An example of the histology images of muscle tissue collected at baseline (B) 1 month post-treatment. The post-treatment tissue shows hypertrophic fibers and a noticeable increase in the muscle tissue with decreased intramuscular sheaf space.

hypertrophic cells increased from 14% at baseline to 29% at 2 weeks and even up to 33% at 1 month. Control measurements at 1 month did not show any significant fluctuation in the distribution compared with baseline. The detailed results can be seen in Figure 5, where the frequency ratio of each size group is displayed.

Temperature Monitoring

On initiation of the treatment, the muscle temperature quickly increased from 38°C to 40°C in only 2 minutes. The temperature was then maintained between 40° and 41°C for the entire treatment. Throughout the treatment, the temperature did not exceed 41°C and was constant without any large fluctuations, ensuring therapy safety (Figure 6). for the muscle temperature graph during the treatment.

DISCUSSION

The study investigated the effect of the simultaneous application of HIFEM and Synchrode RF energies on muscle tissue. The results showed a significant increase in satellite cell levels, which play a vital role in the tissue adaptive response to the muscle work. These observations were coupled with hypertrophic changes seen in the histological slides.

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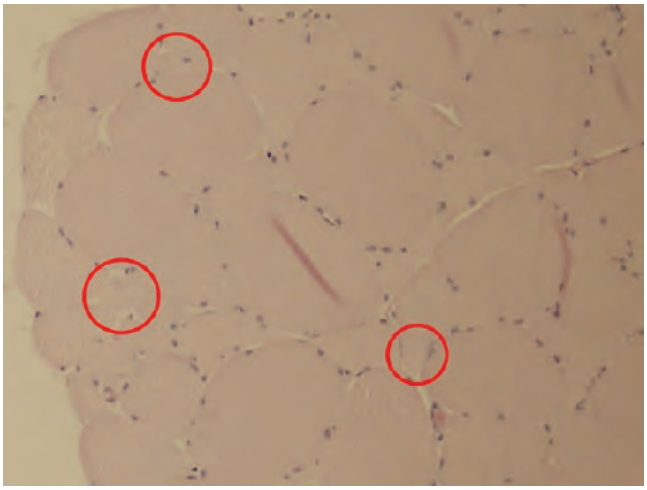


Figure 4. The red circles mark the area with muscle fibers of small diameter that may indicate newly formed muscle fibers at histology slice collected 1 month post-treatment.

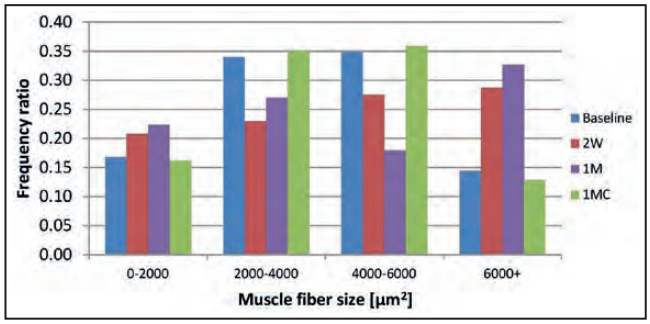


Figure 5. Frequency distribution of muscle fiber size at baseline, 2 weeks (2W), 1 month (1M), and 1 month control (1MC).

Satellite cells are usually activated by intense muscle exercise to regenerate and strengthen the existing muscle fibers. However, it has been found that heating also activates satellite cells.[18] It is unknown whether the application of both types of stimuli leads to differentiation of the satellite cells, but higher levels of active satellite cells increase the chances of differentiation. Comparing our findings with previous studies[24-26] investigating the satellite cell levels post-exercise showed that the 30.2% increase after 3 sessions of HIFEM + RF treatment was comparable and even exceeded the activation levels seen after 12 to 16 weeks of intense exercise programs. The detailed comparison is shown in Table 1. Although a portion of the investigational treatment results may be associated with the supramaximal nature of HIFEM contractions, this comparison strongly indicates the importance of controlled heating during the contractions. The role of heating on muscle tissue has already been documented in studies investigating HSPs, signaling molecules promoting muscle protein synthesis.[12,13,27,28] Studies found that HSPs can be activated by mechanical stress (intense muscle contraction) as well as by heat stress of 40°C to 41°C. A study comparing the effect of such heat stress, mechanical stress, and simultaneously applied heat and mechanical stress showed the highest muscle protein synthesis when the heat and mechanical stress were applied simultaneously.[14]

An equivalent temperature within the 40°C to 41°C range was also measured throughout the whole procedure in our study. Thus, the conditions were very similar to those in the studies mentioned above and may explain the high activation of satellite cells. The temperature did not exceed 41°C. It was stable for the entire treatment time, which is important for safety reasons because a temperature of 42°C may be potentially harmful to the muscle.[29]

Unfortunately, to date, there is no established way of measuring the level of differentiation of satellite cells. It is not possible to determine whether the differentiation would result in the formation of new muscle fibers or new myonuclei to support the existing muscle fibers. This is the reason why the histological assessment was also included. The slide observations were in agreement with the satellite cell results as notable hypertrophic changes were seen, most prominent at 1 month post-treatment. No damage or harmful reaction of tissue was present in the slides, further confirming the treatment safety. Aside from hypertrophic changes, the post-treatment slides showed structural formations that appeared to be newly formed muscle fibers, which would suggest that some of the satellite cells differentiated into new fibers. Although not statistically significant, signs of hyperplasia post HIFEM treatments have already been documented in a study by Duncan at al.[30] Our histological and immunofluorescence observations strongly support the premise put forth in the previous paper that HIFEM directly causes both muscle hyperplasia and hypertrophy.

The results of muscle fiber size measurements showed an increased number of large hypertrophic fibers on post-treatment slides, indicating that the treatment triggered hypertrophic changes in the tissue as the fibers grew in time and the frequency ratio of large fibers increased by 135.7% from 0.14 at baseline to 0.33 at 1 month. Aside from fiber growth, the number of small-diameter fibers was increased on post-treatment slides compared with baseline or control. The frequency ratio of small fibers increased by 29.4% from 0.17 at baseline to 0.22 at 1 month. This finding strongly suggests muscle fiber hyperplasia as an answerable phenomenon explaining this increase. Hyperplasia hypothesis corresponds to the observation of increased levels of activated myosatellite cells, which may in fact differentiate to form new muscle fibers. Yet, the number of small fibers did not further increase at 1 month compared with the 2-week measurements. A possible explanation could be a continuous growth of these fibers, which are thus allocated into

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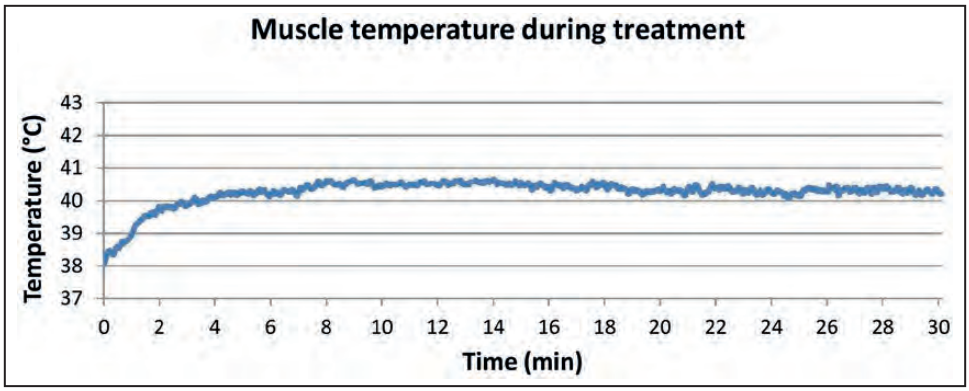


Figure 6. The graph shows the measured rapid temperature elevation in the first 2 minutes from 38°C to 40°C and a stable temperature within the 40°C to 41°C range for the rest of the treatment.

Table 1. Comparison of Results With Studies Investigating the Effect of Exercise on Satellite Cell Levels

Study	Program	Satellite cell content
Current study	3 sessions HIFEM+RF	+30.2%
Mackey et al[24]	12 weeks exercise (females)	+18%
Mackey et al[24]	12 weeks exercise (males)	+36%
Olsen et al[25]	16 weeks exercise	+27%
Olsen et al[25]	4 weeks exercise	+22%
Kadi et al[26]	30 days exercise	+19%
Kadi et al[26]	90 days exercise	+31%

HIFEM+RF, procedure delivering high-intensity focused electromagnetic and radiofrequency simultaneously.

different size group at 1 month. Newly formed fibers between 2 weeks and 1 month thus represent the same ratio.

Limitations of this study include a relatively low sample size of 5 animals utilized due to ethical reasons to minimize the number of experimental animals. To compensate for the smaller sample size, each tissue sample was cut into 5 to 10 slices (depending on the evaluation method), which increased the statistical power. Another limitation of this study is the short-term follow-up limited to 1 month. However, the goal of this study was to investigate immediate tissue response to supramaximal contractions in adjunction with heating. Monitoring longevity of these outcomes should be a subject of further research. The utilization of a single marker for satellite cells could also be considered as a limitation. However, the collected samples' preparation process did not allow the application of more markers; therefore, the most commonly employed marker NCAM/CD56 was chosen. Furthermore, the utilization of an animal model itself is a limitation because a human tissue response may show some discrepancies. It is known that the relative distribution of skeletal muscle fiber types differs between humans and pigs: human muscle tissue contains 50% to 65% of type I fibers, whereas pig muscle tissue contains only 9% to 11%.[31] It could thus be argued that the results observed in this study may not be transferable to humans, and in fact the applicability of these results should be evaluated in humans as well. However, the properties of the magnetic stimuli such as frequency, pulse duration, or pulse shape delivered during the HIFEM treatments were designed to be able contract both types of fibers. Moreover, the results of pilot studies[32,33] investigating the simultaneous delivery of HIFEM and RF document greater muscle thickening effect (24.2%-26.1%) than that of HIFEM only treatments[3,34] (14.8%-15.4%), which suggests our results may be applicable to humans. Further research including human patients should be conducted to verify the outcomes.

This was the first trial, to our knowledge, to investigate the effects of the simultaneous application of HIFEM and Synchrode RF heating on muscle tissue. Future studies should include comparison with consequent or individual treatments. To fully understand the synergy between heat and HIFEM-induced mechanical stress, it would be beneficial to investigate the HSP phenomenon with HIFEM and Synchrode RF and its correlation with existing research. Further research is also necessary to examine the longevity of the results, and longer follow-ups should thus be included. Lastly, we believe that the signs of hyperplasia should be further investigated.

CONCLUSIONS

The simultaneous application of HIFEM and Synchrode RF energies significantly enhances the levels of satellite pool

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and results in muscle hypertrophy and likely in muscle hyperplasia. The results of 3 treatments are comparable with programs involving 12 to 16 weeks of intense exercise, making the technology a convenient tool for enhancing muscle mass that could be highly attractive for body contouring purposes.

Disclosures

Dr Duncan and Dr Halaas are medical advisors for BTL Industries Inc. (Stevenage, United Kingdom). The other authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding

The authors received no financial support for the research, authorship, and publication of this article.

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SYNCHRONIZED RF & HIFEM: ULTRASOUND EVALUATION OF FAT TISSUE

ULTRASOUND EVALUATION OF THE SIMULTANEOUS RF AND HIFEM TREATMENTS ON HUMAN FAT TISSUE

Radina Denkova MD[1]

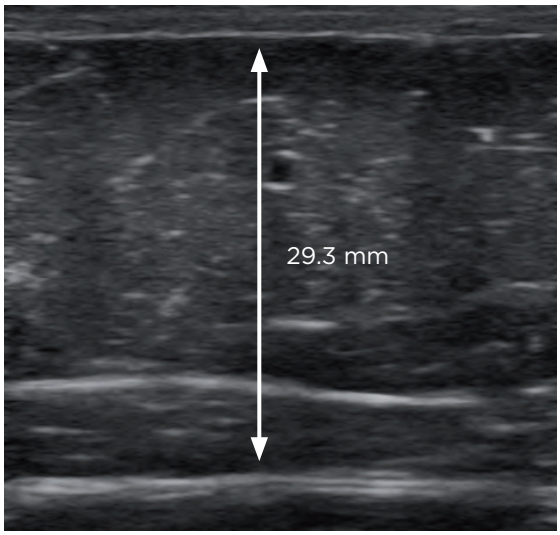
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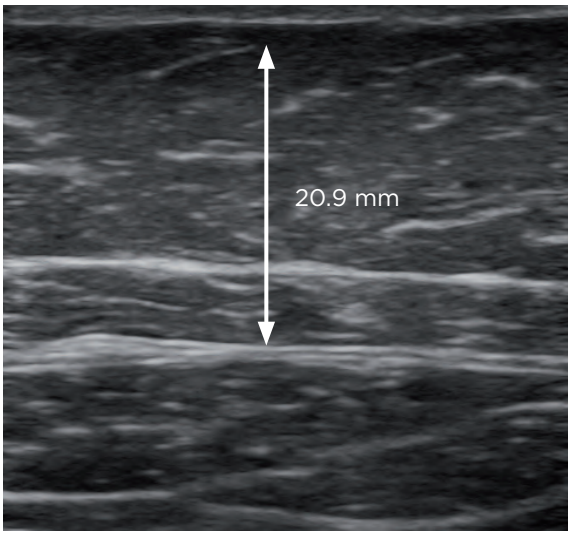
HIGHLIGHTS

- **Reduction** in **subcutaneous fat thickness** at 3 months was **29.8%**.
- A total of **88.1%** of patients **were satisfied** with treatment outcomes.
- **92.9%** of patients found the treatments **comfortable**.
- Waist **circumference** was **reduced** on average **by 3.2 cm**.

BASELINE



3 MONTHS AFTER



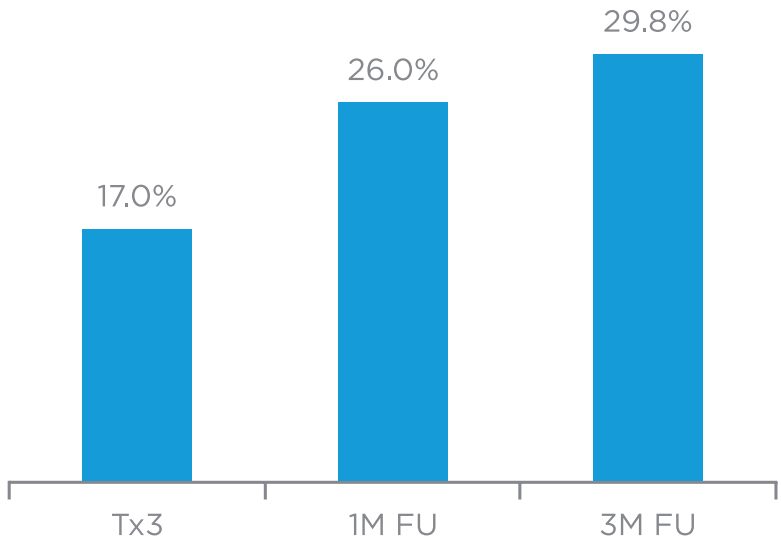
Ultrasound images of a 42-year old female, who also showed a 4-cm reduction in waist circumference.

STUDY DESIGN

- 42 subjects (29 females, 13 males).
- Three 30-minute treatments on abdomen.
- Evaluation by ultrasound imaging.

RESULTS

- Results showed continuous improvement over time.



The chart showing continuous improvement in the fat reduction over time.

BASELINE



3 MONTHS AFTER



A 49-year old female at baseline and 3 months post-treatment showing 4.5 cm waist circumference reduction and 29.2% reduction in abdominal fat layer.

SYNCHRONIZED RF & HIFEM: MULTI-CENTER ABDOMINAL ULTRASOUND STUDY

RADIOFREQUENCY HEATING AND HIFEM DELIVERED SIMULTANEOUSLY - THE FIRST SHAM-CONTROLLED RANDOMIZED TRIAL

Bruce Katz MD[1], Robert Weiss MD[2], Julene B. Samuels MD[3] F.A.C.S

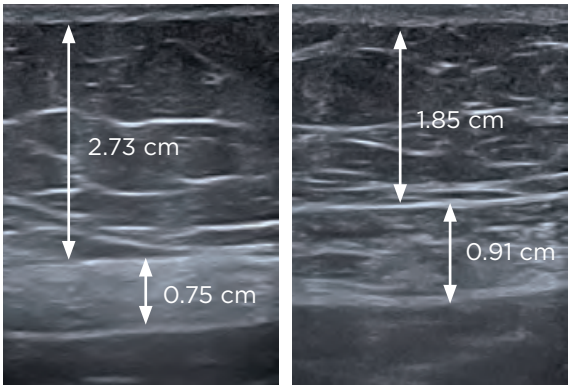
1. Juva Skin and Laser Center, Manhattan, NY, USA; 2. Maryland Laser Skin & Vein Institute, Hunt Valley, MD, USA; 3. Julene B Samuels MD. F.A.C.S, Louisville, KY, USA

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

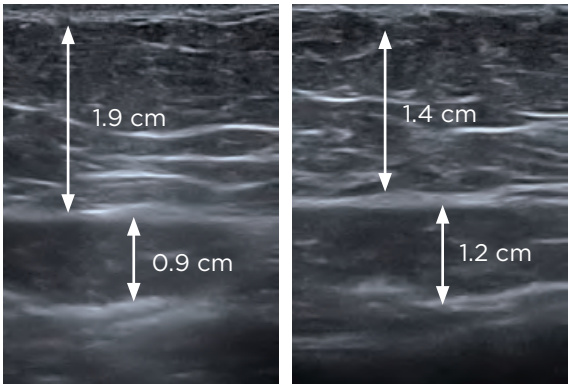
HIGHLIGHTS

- A total of 72 subjects allocated into two groups (Active: N=48, **BMI of 25.8 kg/m2)**; Sham: N=24, **BMI of 25.6 kg/m2)**.
- Active group showed **28.3% reduction in subcutaneous fat** at **3-month** follow-up visit.
- **Muscle thickness** increased by **24.2%** at **3-months** post-treatment in **active group**.
- At 3 months **38/40 patients** showed fat reduction **higher than 20%**.

A 64-YEAR OLD FEMALE



A 51-YEAR OLD FEMALE



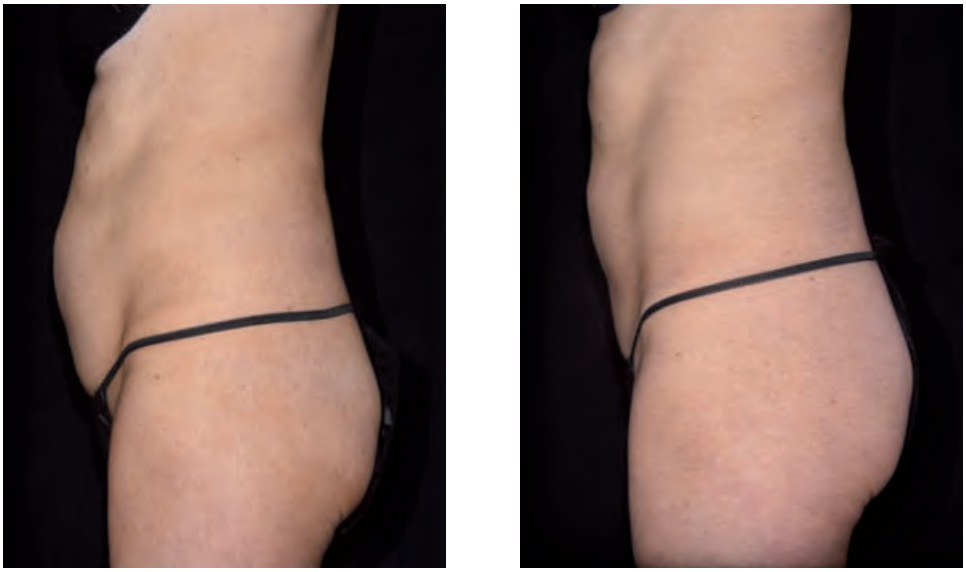
Ultrasound images of patients in active group taken before (left) and 1 month after (right) the treatments.

STUDY DESIGN

- Both groups received three 30-minute treatments on abdomen (active: maximum tolerable intensities, sham: intensities of 5%).
- Ultrasound images were taken at baseline, 1M and 3M after the last treatment.
- Evaluation included measurements of subcutaneous fat and muscle mass thickness.

CONCLUSION

- **Dual field technology** showed **high efficacy** for subcutaneous **fat reduction** and thickening of **rectus abdominis muscle**.
- **93.9%** of patients reported satisfaction with the results.
- **Sham treatments did not induce** any **significant changes**.
- **The procedure** combining HIFEM and RF energy **was safe** and did not cause any adverse events.



Digital photographs of a 55-year old female, taken before (left) and 3 months after (right) the treatments.

SYNCHRONIZED RF & HIFEM: HISTOLOGICAL EVALUATION OF THE EFFECT ON FAT IN HUMANS

HISTOLOGICAL EVALUATION OF THE SIMULTANEOUS RF AND HIFEM TREATMENTS ON HUMAN FAT TISSUE

Radina Denkova MD.

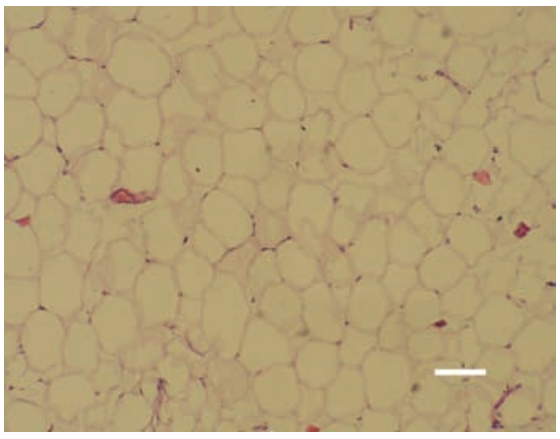
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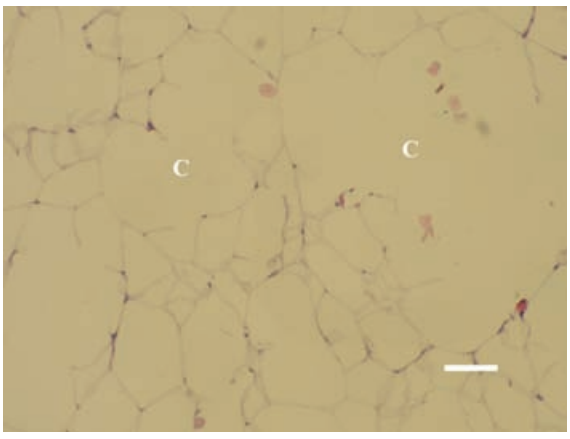
HIGHLIGHTS

- **Intensive fat cell disruption peaking at 20 days post-treatment**.
- **Non-invasive lipolysis** seen in the **first 10 days** post-treatment.
- Investigated device was found to be effective for **elimination of fat cells**.
- **No damage** to skin, sweat glands and sebaceous glands was observed, ensuring procedural safety.
- **Deformed nucleus** and pyknotic nucleus indicating **cell death**.

BASELINE



20 DAYS AFTER



Normal subcutaneous tissue morphology with typical uniform size of adipocytes at the left; bar = 40 micrometers. Intensive fat cell disruption (C) and alternation of adipocytes shape 20 days post-treatment at the right; bar = 30 micrometers.

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