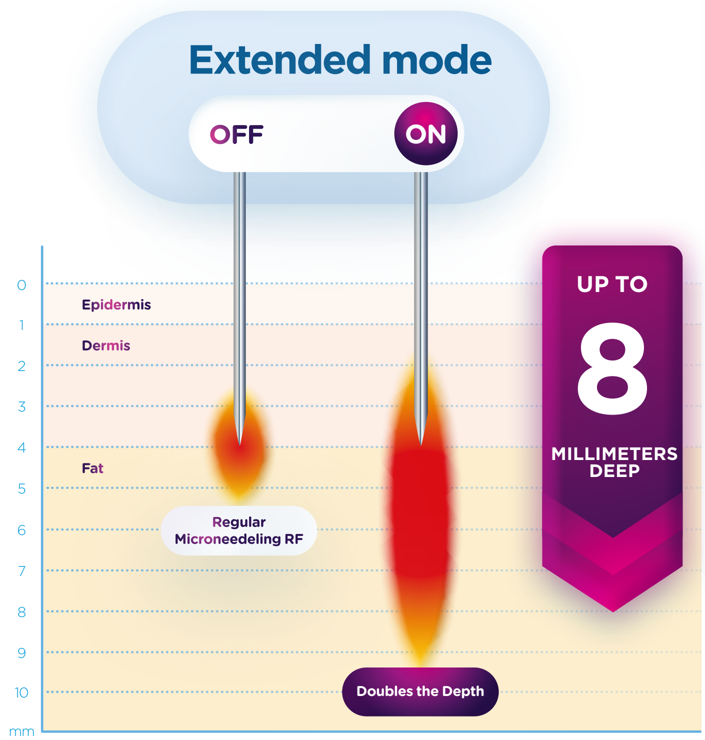
EXION™ Fractional RF Applicator

MECHANISM OF ACTION PAPER

RF microneedling is a minimally invasive cosmetic treatment that improves the skin's appearance by inducing controlled thermal damage in the deeper layers of the dermis. This is achieved through the use of micro needles that deliver radiofrequency energy. Throughout the treatment, the targeted tissue is heated to temperatures ranging from 60 to 80°C, resulting in the coagulation and denaturation of old collagen and elastin fibers.[1–4]

Mechanical and thermal injuries trigger a wound healing cascade that leads to remodeling of the affected tissue, resulting in increased dermal thickness, density, firmness and elasticity. However, existing technologies have a drawback in high treatment discomfort. This discomfort often deters patients from seeking further treatment sessions due to the pain experienced from needle penetration and RF heating, particularly in subdermal treatments that require deep needle penetrations. The pain sensation increases with the depth of needle penetration, which is associated with the activation of several types of mechanoreceptors in the dermis, including nerve pain receptors [5,6].

EXION Fractional RF technology offers a more comfortable experience by using a unique combination of monopolar radiofrequency and AI-controlled energy delivery that allows deep tissue penetration without full needle insertion. The EXION Fractional RF technology overcomes intense pain sensation by inserting the needle to only 4 mm and creating an additional 4 mm thermal gradient below the needle. This way the deep mechanical pain receptors are bypassed and the subdermal tissue can be affected up to 8 mm depth.



illustrative depiction

EXION Fractional RF is equipped with an AI pulse control system that eliminates the need for multiple passes during treatment. The AI retrieves impedance measurement from every single needle and adapts the major pulse parameters to optimize energy delivery for highest efficacy, automatically setting the RF power, pulse length, and delivery rate for each pulse. The technology ensures that the necessary energy is effectively delivered during each shot from each needle, resulting in a single-pass procedure that minimizes discomfort.

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., as well as Clark-Loeser & Halaas, conducted studies on single-pass therapy on the face and thermal gradient treatment on the body, respectively. Both studies involved three therapy sessions and showed impressive results with high patient satisfaction rates. Clark-Loeser 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 second study showed that 90% of subjects self-reported significantly improved appearance with only mild discomfort, and 98% expressed satisfaction with the results [7,8].

3 MONTHS AFTER THE LAST TREATMENT, COURTESY OF: DIANE DUNCAN, M.D.

EXION Fractional RF is a breakthrough technology that changes the perception of microneedling RF as a painful procedure. It improves the patient's perception of the treatment while yielding great results in treating stretch marks, acne scars, and overall skin rejuvenation along with subdermal remodeling.

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Revolutionary Fractional RF Microneedling Enables Deep Tissue Penetration Without Full Needle Insertion for Skin Rejuvenation and Fat Reduction.

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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].

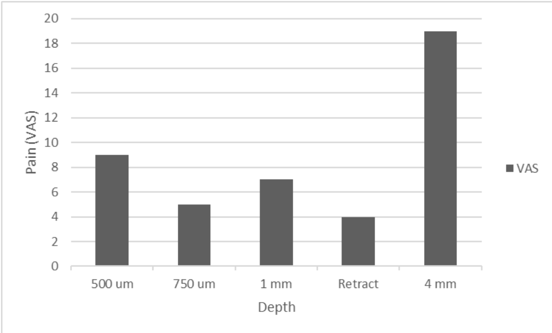
Exion Fractional RF

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].

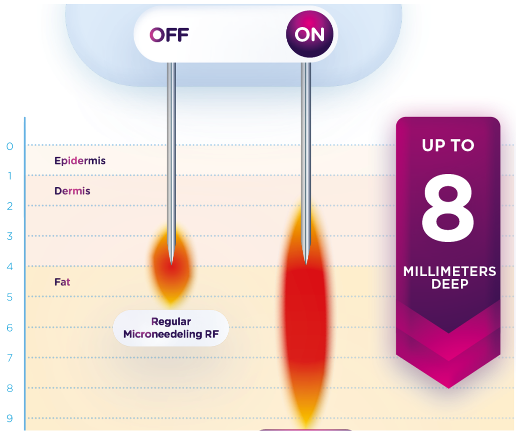
Although the pain sensation generally increases with needle penetration depth, there is a significant escalation in perceived pain intensity when needles are inserted to depths of 4 mm or greater.. The induction of heightened pain sensation is primarily attributed to the nerve pain receptors rather than 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 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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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)

SKIN LAXITY IMPROVEMENT ON THE BODY

A NOVEL TECHNOLOGY COMBINING RADIOFREQUENCY AND TARGETED ULTRASOUND FOR IMPROVEMENT IN SKIN LAXITY: THE EFFICACY AND SAFETY EVALUATION

David E. Kent, M.D.[1], Gregory Muller, M.D.[2]

1. Skin Care Physicians of Georgia, Macon, GA, USA, 2. Gregory Mueller, MD, FACS, CA, USA

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)

STUBBORN FAT REDUCTION IN HARD TO REACH AREAS

THE EFFICACY AND SAFETY EVALUATION OF A TECHNOLOGY USING RADIOFREQUENCY HEATING WITH SUPERFICIAL ACTIVE COOLING FOR LOCALIZED FAT REDUCTION

Nicole Hayre[1]

1. Cosmetic Dermatology Center, McLean, VA, USA

Highlights

- 25 enrolled patients (29-60 years; skin types II-IV)
- Four treatments of various hard to reach 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%

Fat reduction in hard to reach areas

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)

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

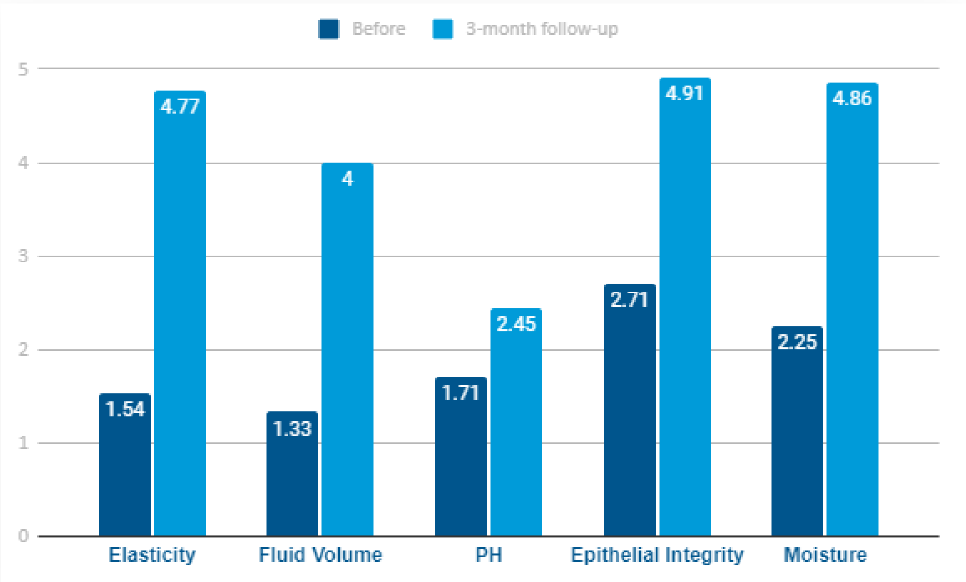
- 24 postmenopausal subjects (av. 56 years)
- 4 EMFEMME 360 treatments with 1 and 3-month follow-up
- Evaluation methods:
  - Female Sexual Function Index **(FSFI)**
  - Vaginal Health Index Score **(VHIS)**
  - GSM Symptoms - Visual Analogue Scale **(VAS)**

130%

Vaginal Health Improvement

67%

Sexual Function Improvement



The Vaginal Health Index scores show an overall improvement in all five criteria

THE STIMULATION OF COLLAGEN & ELASTIN PRODUCTION VIA RF+TUS

MONOPOLAR RADIOFREQUENCY AND TARGETED ULTRASOUND INDUCES REMODELLING OF FIBRILLAR COLLAGEN AND ELASTIN FIBERS: HISTOLOGICAL PORCINE MODEL STUDY

David E. Kent, M.D.[1]

1. Skin Care Physicians of Georgia, Macon, GA, USA

Presented at the American Society for Laser Medicine and Surgery (ASLMS). San Diego, California, 27 April 2022

Highlights

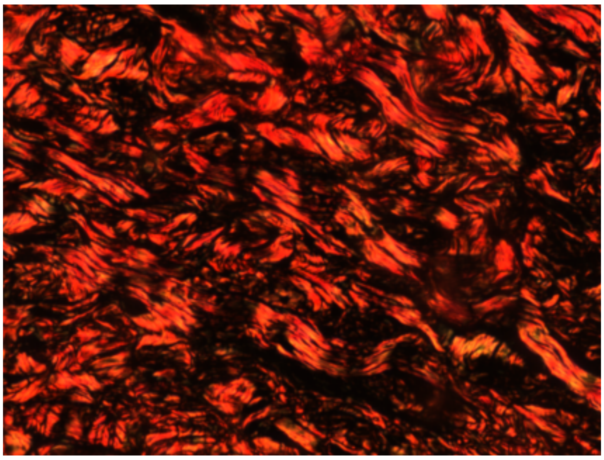
- 5 swines were used in the study
  - One side of the abdomen was treated with **RF+TUS technology**, while the other side served as a control
  - Four treatments were administered, one week apart
- Porcine samples were stained with **Picrosirius red (for collagen) and Orcein (for elastin)**, and analyzed under a polarized microscope

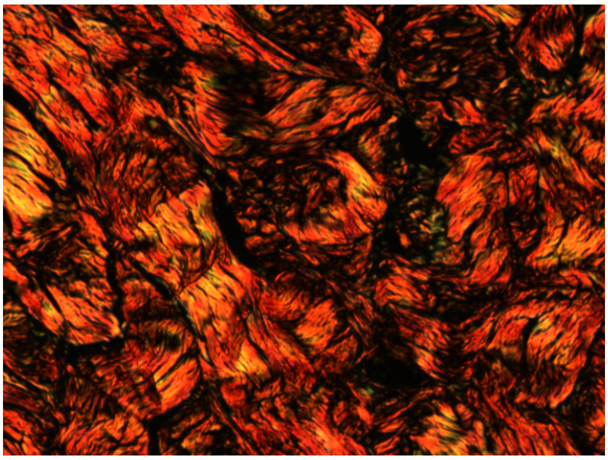
47%

More collagen

50%

More elastin





Overall collagen content increase was significantly higher at 3-month follow-up (right) compared to baseline (left)

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

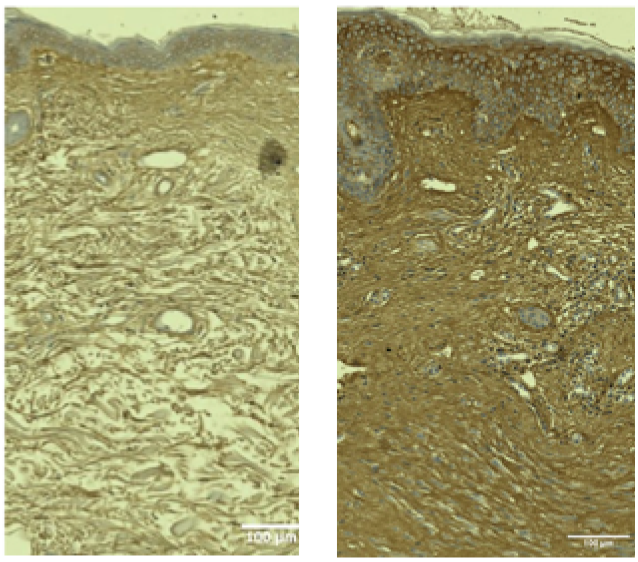
- 7 patients divided into 3 groups received four treatments one week apart
  - Three subjects **(RF alone)**
  - Three subjects **(RF+Targeted Ultrasound)**
  - One control subject
- Biopsy samples were taken for analysis of HA levels by semi-automatic segmentation

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)

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)

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

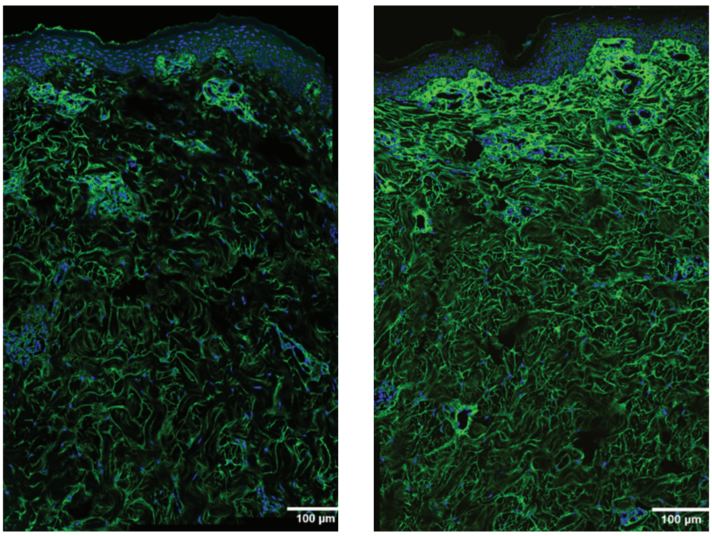
- 12 swines had four treatments of 30 minutes on each side of the abdomen
    - 6 treated by **RF + Targeted Ultrasound (TUS)**
    - 6 treated by **RF + Non-Targeted Ultrasound**
- 252 samples collected and analyzed using three different evaluation methods **(PCR, MALDI-TOF, and Confocal Microscopy)**
- 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.

PRODUCTION OF HYALURONIC ACID INCREASED BY RF+TARGETED ULTRASOUND

RADIOFREQUENCY AND TARGETED ULTRASOUND HAVE SHOWN TO ENHANCE NATURAL HYALURONIC ACID PRODUCTION: PORCINE ANIMAL STUDY

Klaus Fritz, M.D.[1], MvDr. Jan Bernardy, PhD[1]
MSc. Rea Jarosova[2], MA. Natalie Kralova[2]

1. Dermatology and Laser Center, Landau in der Pfalz, Germany, 2.Veterinary Research Institute, Brno, CZ

Presented at the American Society for Laser Medicine and Surgery (ASLMS). San Diego, California, 27 April 2022

Highlights

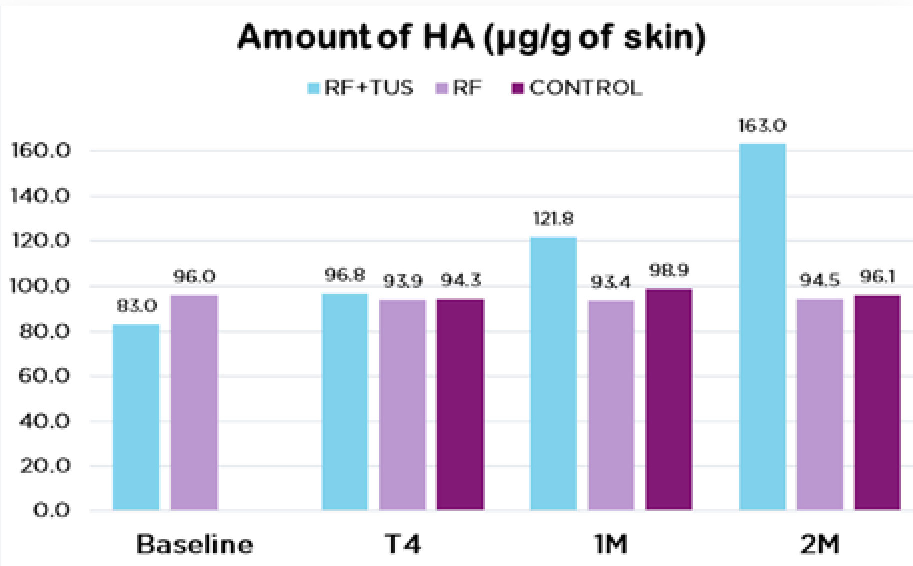
- 12 swines divided into 2 groups were treated on the side of the abdomen
  - 9 received **RF+Targeted Ultrasound**
  - 3 received **RF only**
- Both groups received four 30-minute treatments, once a week
- **168 samples** were collected and evaluated by ELISA test

+80 µg/g INCREASE OF HA

RF+TUS group

NO SIGNIFICANT CHANGE IN HA

In RF only group



The concentration of Hyaluronic Acid was assessed using ELISA kit in samples from three different groups at baseline, after the final treatment, and during the 1-month and 2-month follow-ups

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)

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

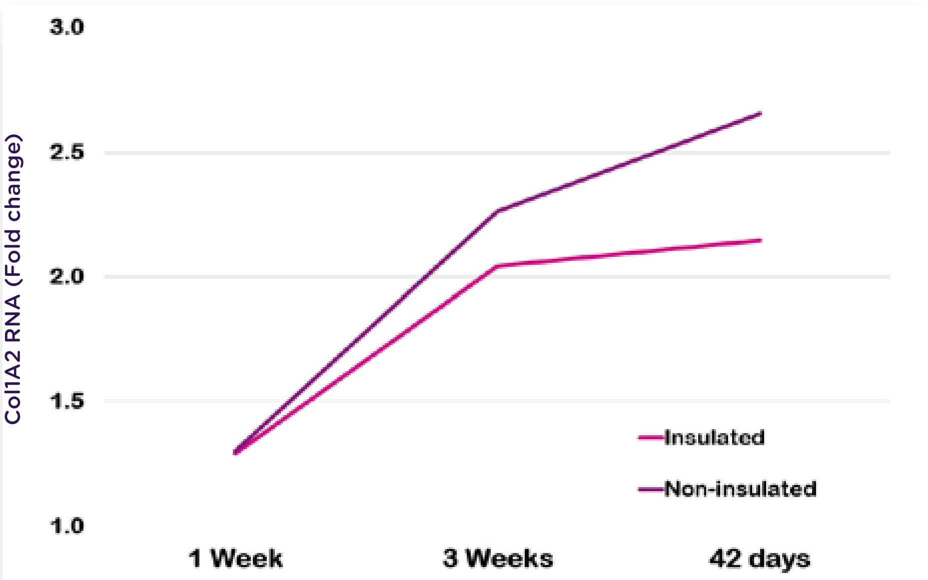
- Three swines were treated (on average 5 years old)
- The goal of this study was to evaluate **effects of insulated** and **non-insulated needles on skin texture**
- Samples were collected 1 week, 3 weeks, and 42 days post-treatment and evaluated by **PCR assessment of collagenases**
- **Both needle 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

Simultaneous Delivery of Radiofrequency and Targeted Ultrasound for Enhanced Hyaluronic Acid Production in the Skin.

Diane Duncan, M.D., FACS[1]

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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;

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.

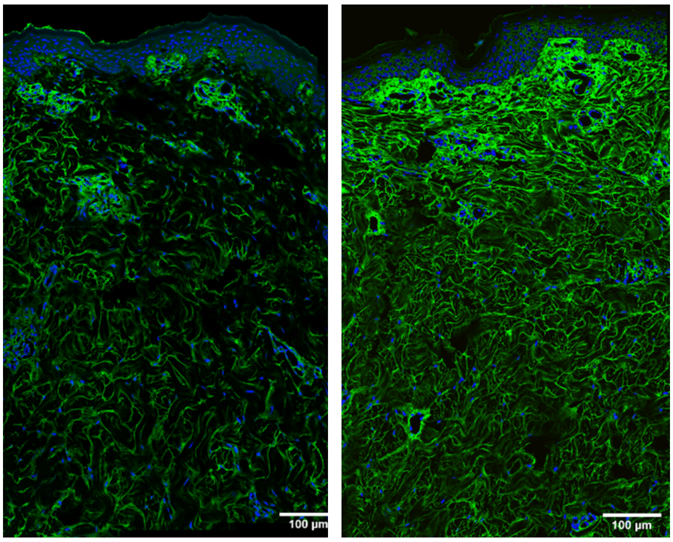
Using mechanical energy to activate receptors on the surface of cells triggers a signaling process that leads to changes in gene expression and protein synthesis within fibroblasts; which can make them more receptive to radiofrequency waves. These waves heat the tissue and cause a controlled cellular 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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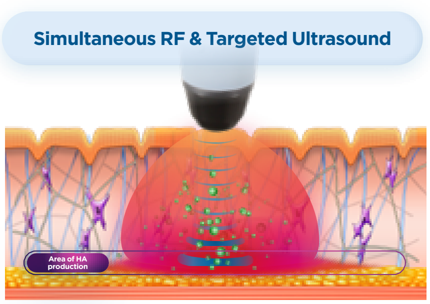
MECHANISM OF ACTION PAPER

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]

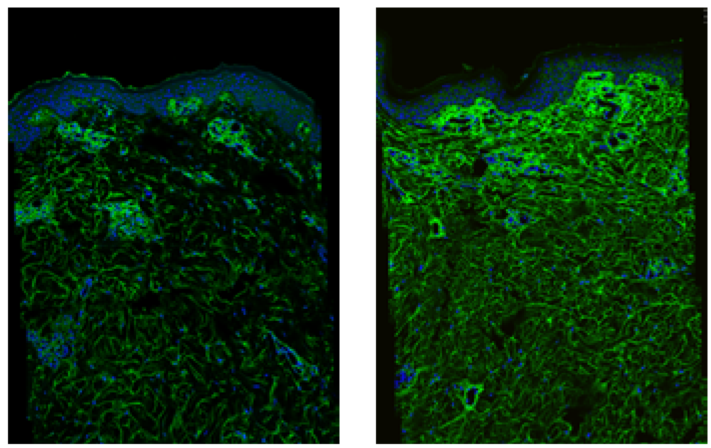
The monopolar radiofrequency homogeneously heats the entire dermis to 40-42°C which induces therma stress on fibroblasts and targets aged and rigid collagen and elastin fibers in the dermis.[10] The thermal energy triggers collagen coagulation and rapid skin tightening, evoking the restorative process, 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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