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;

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.

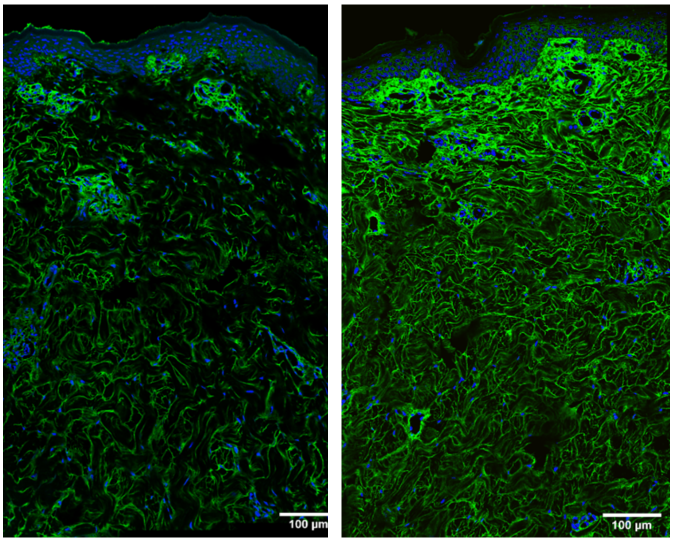
Using mechanical energy to activate receptors on the surface of cells triggers a signaling process that leads to changes in gene expression and protein synthesis within fibroblasts; which can make them more receptive to radiofrequency waves. These waves heat the tissue and cause a controlled cellular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