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Collagen biostimulation in skin aesthetics with micro-focused ultrasound in the presence or absence of calcium hydroxyapatite and poly-L-latic acid: a concise systematic review

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Abstract

Introduction: In the context of skin aesthetics, the spotlight is focused on non-invasive cosmetic procedures. Studies have shown that micro-focused transcutaneous ultrasound (MFU). A commercially available device combines MFU with high-resolution ultrasound imaging. Some clinical studies have shown clinical synergy of MFU-high resolution with poly-L-lactic acid and a fractional or diluted CO2 laser with calcium hydroxyapatite. **Objective:** A systematic review was carried out on the main clinical findings of the use of micro-focused ultrasound and collagen biostimulation, with or without combination with calcium hydroxyapatite and poly-L-lactic acid, in the aesthetics of human skin, to highlight the safety, efficacy, and risk of bias. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 20 years were selected. The quality of the studies was based on the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results:** A total of 112 articles were found, and 12 articles were included in the systematic review. It has been shown that MFU-high resolution enables non-invasive tightening and lifting of sagging skin, and when combined dilute calcium hydroxyapatite, polycaprolactone, and/or poly-L-lactic acid is effective in improving sagging skin. **Conclusion:** It was concluded that MFU-high resolution targets the facial superficial musculoaponeurotic system, achieving non-invasive tightening and lifting of sagging skin, and when combined with dilute calcium hydroxyapatite, polycaprolactone, and/or poly-acid L-lactic is effective in improving sagging skin and cellulite.

Keywords: Aesthetics. Skin. Collagen. Biostimulation. Micro-focused ultrasound. Noninvasive procedure.

Introduction

In the context of skin aesthetics, the spotlight is focused on non-invasive cosmetic procedures [1,2]. In this sense, the literature presents several types of treatments. For example, botulinum toxin can reduce forehead and glabellar wrinkles [3-6], and hyaluronic acid dermal fillers can improve hollow folds and redefine jaw lines [5]. Calcium hydroxyapatite (CaHA) [6,7], polycaprolactone, and poly-L-lactic acid stimulate dermal collagen production [8,9], and fractional CO2 and Herbium lasers improve skin thickness and texture [10,11], and superficial and deep heating can be used for noninvasive skin hardening [12,13].

Also, the aesthetic literature has presented several studies using platelet-rich plasma that show an increase in dermal matrix elements, improving skin texture and treating acne scars and burns [14-17]. Treatments presented above have disadvantages and information gaps, sometimes requiring dermal fillers [18] or retreatments (hydroxyapatite, polycaprolactone, and poly-L-lactic acid). They may also experience prolonged downtime with fractional CO2 laser and adverse events with radiofrequency Thermage CPT System [19].

As an effective safe alternative to overcome these challenges, studies have shown that micro-focused transcutaneous ultrasound (MFU), a device approved by the Food and Drug Administration (FDA) [20,21], can be beneficial for skin tightening and works in a non-invasive way [22,23]. MFU can be focused on

subcutaneous tissue where the temperature briefly reaches over 60°C, producing small points of thermal coagulation (<1 mm3) to a depth of up to 5 mm within the middle reticular layer. The dermal and epidermal papillary layers of the skin remain unchanged. The application of heat causes the collagen fibers of the skin to be denatured, such as the superficial musculoaponeurotic system and platysma, as well as the deep reticular dermis, contracting and stimulating collagen.

Besides, a commercially available device combines MFU with high-resolution ultrasound imaging (MFU-high resolution), enabling visualization of tissue planes to a depth of 8 mm and allowing the user to see where MFU energy will be delivered (Ultherapy @; Ulthera Inc., Mesa, AZ, USA). Using different transducers, the MFU-high resolution treatment can be customized to meet the unique physical characteristics of each patient by adjusting the energy and focal depth of the emitted ultrasound to achieve noninvasive contraction and lifting of sagging skin as well improvements in the appearance of wrinkles [21].

Despite this evidence, treatment protocols for the use of high-resolution MFU continue to be optimized, even with adjuvant treatments. The brief discomfort that often occurs during treatment can be minimized with oral non-steroidal anti-inflammatory drugs. Other treatment-related adverse events include transient erythema, edema, and occasional bruising. MFU-High Resolution is best suited for patients with mild to moderate skin and soft tissue sagging. For elderly patients with severe skin flaccidity and marked platysmal bandage, surgical treatment should be considered [24]. Furthermore, some clinical studies have shown clinical synergy of high-resolution MFU with poly-Llactic acid [25] and a fractional CO2 laser [26] or with diluted calcium hydroxyapatite [27].

Therefore, the present study aimed to carry out a systematic review of the main clinical findings of the use of micro-focused ultrasound and collagen biostimulation, with or without combination with calcium hydroxyapatite and poly-L-lactic acid, in the aesthetics of human skin, to demonstrate safety, efficacy, and risk of bias.

Methods

Study design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Aesthetics. Skin. Collagen. Biostimulation. Micro-focused ultrasound. Non-invasive procedure*". The research was carried out from May to June 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 20 years were selected. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study quality and risk of bias

The quality of the studies was based on the GRADE instrument. The highest ratings were for controlled clinical studies with a sample size with statistical significance. The risk of bias was analyzed using the Cochrane instrument, based on the effect size of each study versus the sample size.

Results and Discussion

Major findings

A total of 112 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 60 articles. A total of 42 articles were fully evaluated and 12 articles were included and developed in this systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 32 studies that did not meet the GRADE that was removed.

Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the base of the graph and in studies with a large sample size that are presented in the upper region of Figure 2.

Major clinical findings

Based on the literature findings, the clinical efficacy and patient satisfaction of MFU-high resolution were demonstrated in several clinical studies in Caucasian and Asian patients, and its safety profile was evaluated [28-30]. According to author Fabi, in his publications in the

Figure 1. Flowchart showing the article selection process.

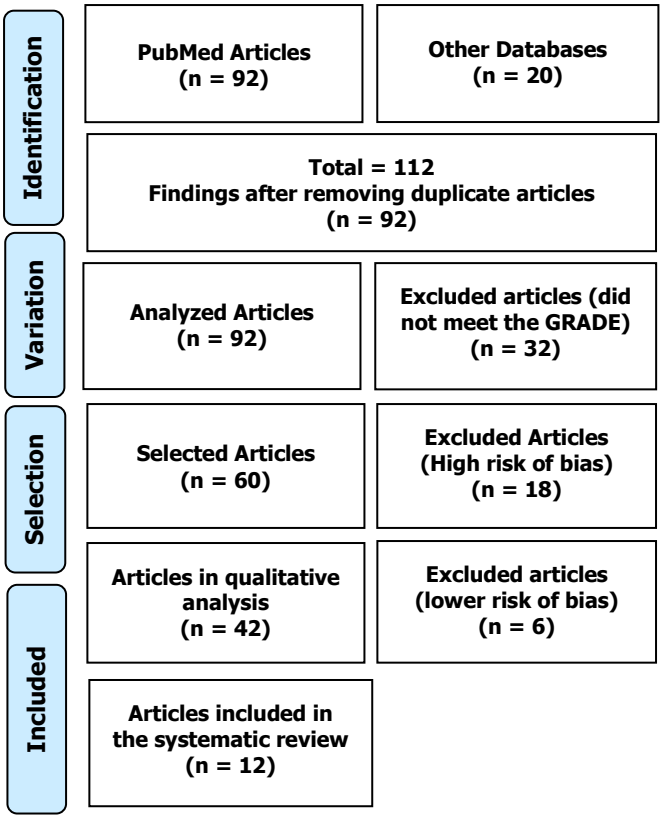
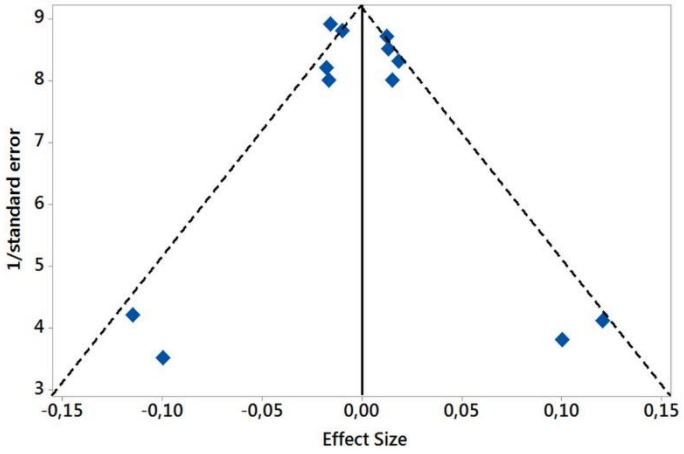


Figure 2. The symmetrical Funnel Plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph.



years 2014, 2015 and 2020, MFU-high resolution showed significant esthetic improvement for up to 180 days after a single treatment in women with moderate to severe lines of wrinkles [31-33]. Furthermore, this author showed that high-resolution MFU targets the superficial facial muscle-aponeurotic system, achieving non-invasive tightening and lifting of sagging skin.

In this context, authors Montes and Santos in 2019 [34] interviewed 52 patients undergoing treatment on the lower face and submentum. A total of 41% of them reported that their treatment results met or exceeded their expectations, but 52% of them needed a follow-up appointment. Furthermore, the MFU-high resolution needs to be applied to the superficial muscular aponeurotic system, subcutaneous tissue and deep dermis using the 3 available transducers. To obtain an ideal lifting effect, the collagen in all these layers must be stimulated.

In this regard, there is an Araco 2020 study protocol [35], published in the Aesthetic Surgery Journal, which was performed in a single treatment session, as the heat released in a targeted layer spreads up and down the levels, increasing collagen stimulation. Thus, high-resolution MFU delivered in a single session with 3 modalities appears to be better than a standard isolated therapy with 3 separate modalities, as the hemoglobin level was also shown to increase, suggesting that high-resolution MFU improves target tissue vascularization. In addition, no complications were observed after the treatments, not damaging the skin surface.

Also in this study by Araco 2020, the primary outcome of the study was the improvement of sagging and ptosis of the facial skin, the secondary outcome was the improvement of wrinkles, texture and hemoglobin content, and the third outcome was the patient's responses to a patient satisfaction questionnaire. From November 2017 to November 2018, 47 women and 3 men with a mean age of 52.8 ± 7.43 years and Araco's Ptosis Scale System 2.7 ± 0.46, who met the inclusion criteria, were included. in the study. No major side effects were reported during the study and all patients completed followup after 6 months. Wrinkles, texture, Surgeon Assessment Scoring System scores, and patient satisfaction questionnaire scores improved significantly. Patients found the treatment tolerable according to the patient's pain scale rating. Therefore, this study showed that microfocused ultrasound with visualization in a single treatment session in monotherapy is safe and effective for the treatment of sagging and ptosis of the face [35].

Furthermore, a retrospective clinical study developed by Casabona and Pereira, 2017, evaluated the effects of MFU-high resolution (Ultherapy@) in combination with diluted calcium hydroxyapatite (CaHA; Radiesse@) on cellulite appearance and neocollagenesis. A total of twenty women (18-55 years) with sagging skin and moderate to severe cellulite on the buttocks and thighs were included. MFU-high resolution was applied with 4 and 7 MHz transducers (25 lines/transducer/site) and immediately followed by subdermal injection of CaHA (1 mL/buttock or thigh). Baseline and 90-day photographs were evaluated by 2

independent, blinded raters using a 5-item cellulite severity scale. Both raters reported statistically significant improvements compared to baseline for each item on the cellulite severity scale ($p<0.001$) with a 4.5-point improvement in the mean overall score ($p<0.001$) after a single treatment with MFU-high resolution and CaHA. At 90 days, histological analysis showed peak neocollagenesis in samples treated with the 1:1 dilution, either with CaHA alone or in combination with MFU-high resolution. The highest conversion of type III collagen to type I collagen at month 3 occurred in samples injected with 1:1 and 1:0.6 dilutions of CaHA without subsequent MFU-high resolution treatment. Both procedures were well tolerated and participant satisfaction was high. Therefore, combined treatment with high-resolution MFU and diluted CaHA is effective in improving sagging skin and the appearance of cellulite on the buttocks and upper thighs [36].

In addition, a randomized controlled clinical study evaluated the clinical efficacy and tolerability of MFU-high resolution in the injectable filler of calcium hydroxyapatite (CaHA) diluted with normal saline, for the correction of age-related changes and to assess the satisfaction of the patients with this combination therapy. Immunohistochemical analysis was performed on 20 individuals with an indication for lower face, neck, and décolleté lifting. Over five visits, CaHA diluted with normal saline (1:2) was injected subdermally into the lower third of the face, neck and décolleté, and lower abdominal quadrant. The MFU-high resolution was performed on the lower third of the face, neck, and décolleté and the lower right abdominal quadrant. The procedures were well tolerated and participant satisfaction was high. CaHA injections in combination with MFU-high resolution treatment stimulated neoangiogenesis, led to increased synthetic cell activity, marked increase in collagen and elastin fibers, and remodeling of the superficial and deep layers of the dermis. An improvement in the severity of age-related changes was observed in all areas studied [37].

Besides, one study investigated the efficacy and safety of MFU-high resolution in the treatment of sagging lower abdominal skin and soft tissues in postpartum women. The lower abdomen of 20 female patients between 6 and 24 months postpartum was treated with high-resolution MFU using 1.5, 3.0, and 4.5 mm transducers. Data were prospectively collected and analyzed at 3 and 6 months using subject and investigatorreported outcome measures. An additional patient underwent planned abdominoplasty 6 weeks after MFU-high resolution treatment with tissue evaluated intraoperatively and histologically. There was a mean improvement of 1.0 and 1.3 degrees at 6 months using the investigator-reported and patient-reported skin sagging scale, respectively ($p<0.001$). Patient-reported results and satisfaction surveys showed consistent improvement at 6 months. Histological examination of the pre-treated tissue showed an increase in total collagen, an increase in the number and thickness of fibrous septa, and no change in fat cells in the pre-treated tissue compared to the control. No significant adverse events were recorded. Therefore, high-resolution MFU is an effective and safe treatment modality for sagging lower abdominal skin in postpartum patients [38].

Finally, a case series evaluated the effectiveness of MFU-high resolution in improving sagging skin, leading to slimming of the lower third of the face in women who wanted to naturally improve their face shape. A total of four women between 29 and 36 years old underwent a specific protocol with 4 MHz - 4.5 mm and 7 MHz - 3.0 mm transducers (Ulthera®) in the buccinator region in a single session and the patients were evaluated after 180 days. The GAIS (Global Aesthetic Improvement Scale) was assessed using standardized photographs (Day 0 versus Day 180). All subjects noticed a slimming of the face after 180 days, as well as an improvement in sagging and skin contour. The degree of satisfaction with the patients' results was significant. The GAIS assessment (day 0 vs. day 180) resulted in a score of 3 (much improved) for three participants and a score of 2 (improved) for one woman. All patients rated pain during the procedure as mild to moderate [39].

Conclusion

Based on the objective of this study, it was concluded that MFU-high resolution targets the facial superficial musculoaponeurotic system, achieving non-invasive tightening and lifting of sagging skin, and when combined with dilute calcium hydroxyapatite, polycaprolactone, and /or poly-L-lactic acid is effective in improving sagging skin and the appearance of cellulite.

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Ethics approval

Not applicable.

Informed consent

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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