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Effectiveness of growth factor-induced therapy for skin rejuvenation: A case series

Souphiyeh Samizadeh BDS, BSc, MJDF, RCS, (Eng), PGCert, (Clin, Edu), MSc, (Aesth, Med), FHEA[1,2,3] | **Lakhdar Belhaouari MD**[4]

[1]Great British Academy of Aesthetic Medicine, London, UK

[2]University College London, London, UK

[3]Visiting Clinical Teacher, King's College London, London, UK

[4]Centre de Chirurgie Esthétique, Toulouse, France

Correspondence
Souphiyeh Samizadeh, Great British Academy of Aesthetic Medicine, London, UK
Email: info@baamed.co.uk

Abstract

Background: Microneedling in combination with the use of growth factors can help with a range of indications, including skin rejuvenation. There is an increase in request for safe minimally invasive procedures with no-to-minimal downtime. This procedure offers regeneration and is becoming popular as part of the regenerative, minimally invasive era.

Aims: To examine the efficacy of a course of two sessions of growth factor-induced therapy using propriety preparation of AQ recovery serum.

Methods: Thirty women with various ethnic backgrounds (Chinese, Caucasian and Latino) with an average age of 38 years old participated and mild-moderate visual facial aging signs Two sessions with 2-week intervals were completed using a derma stamp (transdermal drug delivery method) and 2 mL of growth factor serum (AQ Skin Solution recovery serum-contain a mixture of contains a mix of transforming growth factor beta (TGF-β), granulocyte monocyte-colony-stimulating factor, and platelets-derived growth factor with patented technology for extraction and composition at each session. The procedures were carried out for anti-aging and skin rejuvenation. Clinical assessment, VISIA photography, independent assessment of before and after photographs baseline and six weeks by two clinicians and two laypersons were carried out. The participants used FACE-Q questionnaire (outcome satisfaction) and scored changes in terms of their skin texture, radiance, pore size, wrinkles, pigmentation, tightness and overall skin appearance.

Results: Physician's global assessment revealed growth factor-induced therapy resulted in skin rejuvenation in all races with 95% confidence, and this increased to 98% confidence for Latinos and Caucasians within the six weeks. Participants' subjective rating revealed improvement of overall skin appearance with 95% confidence. Most noted improvements were in brightness, skin texture, and tightness.

Conclusion: This study revealed improvement in overall skin appearance, brightness, skin texture, and tightness. The treatment is non-invasive, safe, with no or minimal downtime and resulted in high participant satisfaction.

KEYWORDS

facial rejuvenation, growth factor-induced therapy, growth factors, microneedling, skin aging

1 | INTRODUCTION

Regenerative approaches are developing as the front runners in the field of esthetic medicine and for rejuvenation purposes. Regenerative medicine focuses on making changes at a molecular level.

Microneedling (also known as percutaneous collagen induction, collagen induction therapy) uses needles of 0.5-3 mm in length, to cause the formation of microchannels.[1,2] This process produces controlled trauma to the skin and hence stimulates the release of growth factors, collagen production, neovascularization, and new elastin in the papillary dermis, hence resulting in skin rejuvenation (skin laxity, rhytids, firmness, photoaging, and hydration) and reduction of scars (acne, surgical, and stretch marks).[3-10] Aust et al reported a considerable increase in deposition of collagen and elastin six months after treatment with epidermis showing 40% thickening of stratus spinosum and normal rete ridges one year after treatment.[3] Literature reviews confirmed microneedling as a safe and effective treatment for several dermatologic conditions with significant clinical results and fast recovery. [11-14] Microneedling systems or devices can be used as a transdermal drug delivery method. This enables temporary disruption of the skin to allow delivery of the therapeutic molecules that would induce a therapeutic response.[15,16] The use of microneedling to deliver active ingredients (eg, ascorbic acid, eflornithine, peptides, retinyl retinoate) is gaining importance in cosmetics. [16-21]

Growth factors play a key role in wound healing and initiate skin repair (Figure 1). [22-24] Synergic interaction and communication between many growth factors determine the outcome of skin repair.[25] Examples include transforming growth factors that are involved in wound healing including inflammation, stimulation of the following processes; angiogenesis, fibroblast proliferation, collagen production and deposition, and also the new extracellular matrix remodeling. [3,24-26] TGF-β plays a critical role in various phases of wound healing, and granulocyte-macrophage colony-stimulating factor is a multipotent growth factor and can accelerate wound healing, and platelets-derived growth factor stimulates cell types considered essential for tissue repair and plays key role at each phase of repair. [27-30]

The combination of microneedling and simultaneous use of growth factors would allow the ani-aging benefits of microneedling itself, in addition to enhancing the transdermal penetration, and hence the availability of growth factors at the time of injury. Lee et al reported significant improvement of wrinkles and pigmentation after five microneedling treatments (2-week intervals) using secretory factors of endothelial precursor cells differentiated from human embryonic stem cells in Asian skin.[31] Furthermore, Seo et al reported significant improvement of skin roughness and rejuvenation when stem cell-conditioned medium (a large number of growth factors and cytokines) was used in combination with microneedle radiofrequency.[32]

Although growth factors are macromolecules and their topical application and penetration through the dermis are unlikely, various studies have reported significant clinical benefits. [25,33,34]

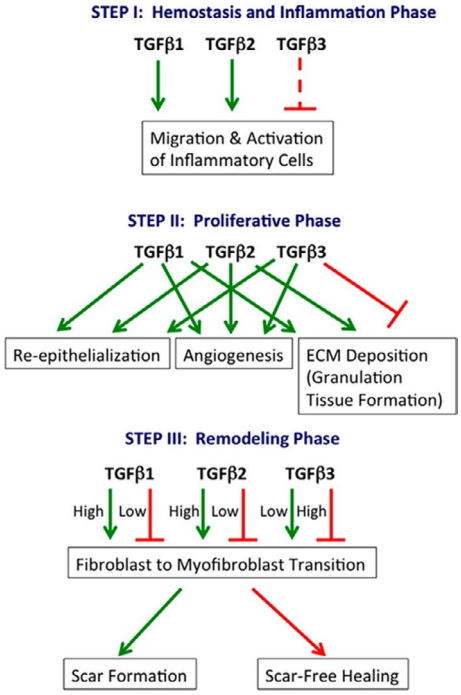

FIGURE 1 Transforming growth factors plays a key role in wound healing and hence skin rejuvenation. "TGFβ isoforms in cutaneous wound healing. TGFβ1, TGFβ2, and TGFβ3 play central roles in all three phases of wound healing. Generally, TGFβ1 and TGFβ2 are stimulatory, while TGFβ3 is inhibitory. However, TGFβ3 can also stimulate specific processes (eg, re-epithelialization). Green arrow: stimulatory; continuous red line: inhibitory; dashed red line: potentially inhibitory, inferred from relative levels at the beginning (low) and end (high) of the hemostasis and inflammation phase."[19]

Post-treatment, use of clinically proven skincare and growth factors are recommended to help skin repair and rejuvenation. Also, pre-preparation of the skin for one month before and post-treatment with vitamin A and C may be beneficial (Figure 2). [3,10,35,36]

In this study, the efficacy of a course of two sessions of the growth factor-induced therapy (GFIT) was examined. This method uses microneedling as method of transdermal drug delivery and the mentioned combination of growth factors for skin rejuvenation.

2 | METHOD

This study followed AQ Skin Solution's protocol for GFIT,[37] where a deeper penetration of growth factors into the dermis is facilitated using microneedling. Two sessions with 2-week intervals were performed. Clinical assessment and VISIA photography were performed at the baseline and two weeks after the second treatment.

In this pilot study, thirty participants participated, twenty Chinese, five Caucasian, and five Latino ladies. All female, with an average age of 38 years old and twenty-seven, completed. The

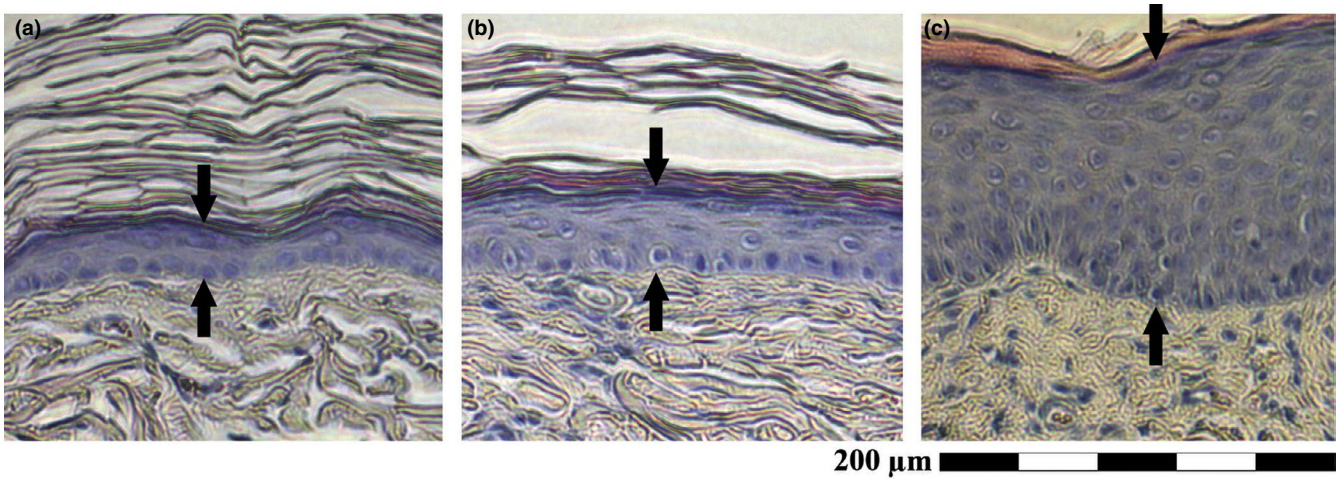

FIGURE 2 Zeitter et al evaluated singular and repetitive skin needling with and without skincare in an animal model. "Microphotographs taken of representative skin samples stained with hematoxylin-eosin (examplary shown) presenting the epidermal thickness. (a) Once needled animal without skin-care—represents group C. (b) Four-times needled animal without skincare—represents group D. (c) Four-times needled animal with topical retinyl-palmitate and ascorbyl tetra-isopalmitate—represents group E. All microphotographs share the same scale of 200 µm. (c) The increase in thickness of the epidermis with repetitive treatments in addition to the topical retinyl-palmitate and ascorbyl tetra-isopalmitate shows how effective these combined techniques are. Furthermore, it can be seen that the stratum corneum is much more compacted in the repetitive needled animals (b) and (c)."[25]

participants had mild-moderate signs of skin aging including fine lines and wrinkles and their primary desire was to rejuvenate and improve their overall skin appearance. The participants were informed of the benefits, risks, and possible complications of the treatment during the consultation session and provided written informed consent before participation. The tenants of the Declaration of Helsinki were followed. Selection criteria included no non-surgical, minimally invasive, or surgical cosmetic procedures for six months prior to the study and for the duration of the study, no history of systemic disease.

A 0.8mm microneedling stamp (140 Micro-needles with a planar surface-punctures made at a 90-degree angle to the skin to enable effective transdermal delivery of growth factors) was used with application of 2ml of growth factor serum (AQ recovery serum produced by AQ Skin Solutions, containing human Fibroblast Conditioned Media, Water (Aqua), SD Alcohol 40, Propylene Glycol, Cellulose Gum, Polysorbate 20, Tetrahexyldecyl Ascorbate, Tocopheryl Acetate, Menthyl Lactate, Lactic Acid, Sodium Hyaluronate, Phenoxyethanol, 1,2-Hexanediol, Caprylyl Glycol) at each session. Two treatments were carried out with two-week intervals. This interval was chosen following a consensus from a group of senior Chinese dermatologist who use this technique with minimal interval of two weeks with no adverse effects. The focus of the protocol is on the transdermal drug delivery of the growth factors with additional benefit of initiation of repair process of the skin and predictable rapid healing post procedure.

All participants were advised to avoid touching their face, use of any products, heat, sun exposure, massage, exercise, and intense activity for 8 hours after the treatment. All participants were given a hydrating face mask to apply the day after the procedure after washing their face with water only and a serum containing stabilized growth factors (AQ Active Serum produced by AQ Skin Solutions containing human Fibroblast Conditioned Media, Water (Aqua), Glycerin, Polysorbate 20, Cellulose Gum, Tetrahexyldecyl Ascorbate, Tocopheryl Acetate, Lactic Acid, Citrus Aurantium Bergamia (Bergamot) Fruit Oil, Phenoxyethanol, 1,2-Hexanediol, Caprylyl Glycol) to apply topically twice a day for the duration of the study. They were advised to stop all other topical skincare apart from daily sunscreen. The use of other topical agents and the administration of any medication/products were not permitted during the study period. Exclusion criteria included any surgical or non-surgical cosmetic procedures (eg, chemical peels, lasers, dermal fillers, and botulinum toxin) within six months prior to the treatment, pregnancy or breastfeeding, any uncontrolled systemic diseases (eg, uncontrolled diabetes), immunosuppression, presence of skin cancers, warts or any skin infection, history of keloid scarring, use of other active products such as Retin-A 2 days prior to the treatment.

Two clinicians and two laypersons assessed the photographs taken at the baseline and at six weeks after first treatments independently. The 7-point global assessment scale was used, significant deterioration, −3 points; moderate deterioration, −2 points; slight deterioration, −1 point; no change, 0 points; slight improvement, +1 point; moderate improvement, +2 points; and significant improvement, +3 points. A comments box was included for any additional observations. This scale enabled us to review the overall outcome.

The participants used FACE-Q questionnaire to evaluate the outcome of their treatment and a 5-point scoring system, 0- no change, and 5-significant improvement. FACE-Q™ satisfaction is a scoring system, where higher scores reflect a better outcome. The raw scale summed score was then converted into a score from 0-worst to 100-best equivalent RASCH transformed score.[38-40] They were also

FIGURE 3 (1) Photographs at baseline, left-hand side, and after two treatments, right-hand side. Improvement of the periorbital lines, skin brightness and texture. (2) Photographs at baseline, left hand side, and after two treatments, right hand side. Clinical photographs showed significant improvement of fine rhytids, dilated pores, skin tightness, and skin tone. Reflection of light is improved in the after picture. (3). Photographs at baseline, left-hand side, and after two treatments, right-hand side. Clinical photographs showed significant improvement of fine rhytids in the periorbital area, skin tightness, and skin tone. Reflection of light is improved in the after picture. (4). Photographs at baseline, left-hand side, and after two treatments, right-hand side. Clinical photographs showed significant improvement of fine rhytids in the periorbital area, skin tightness, and skin tone. Reflection of light is improved in the after picture. (5). Photographs at baseline, left-hand side, and after two treatments, right-hand side. Clinical photographs showed significant improvement of fine rhytids around the periorbital and perioral areas, skin tightness, and skin tone. Reflection of light is improved in the after picture. (6). Photographs at baseline, left hand side, and after two treatments, right hand side. Significant improvement of the periorbital area can be observed

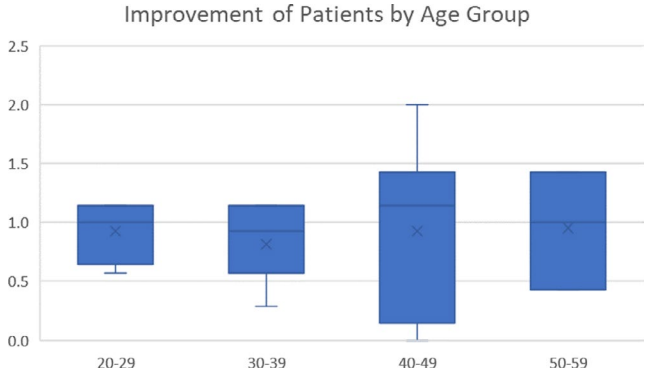

FIGURE 4 Skin improvement in participants in global assessment by age group has revealed improvement and rejuvenation of the skin in all age groups, and no deteriorations were noted for any participants. Improvements increased with age

asked to score changes in terms of their skin texture, radiance, pore size, wrinkles, pigmentation, tightness, and overall skin appearance.

3 | RESULTS

The global assessment revealed the treatment improves skin and helps rejuvenation in all races (95% confidence) with an average of +1.40 standard deviation of 0.72. The assessment increased to an average of +1.64 with a standard deviation of 0.71 for Caucasian and Latinos (98% confidence) within the 6 weeks (Figure 3 (1 to 6)). This could be due to Asians aging differently to the Caucasians and Latinos of the same age.[41]

The global assessment revealed the treatment improves skin and helps rejuvenation in all age groups with 95% confidence (Figure 4).

The evaluators recorded 38 comments. The most common improvements observed by the evaluators in the comments are,

"reduction of pigmentation or brightening of the skin or radiance"—24 comments, and "lifting or tightening of the skin"—23 comments, "wrinkle reduction"—6 comments.

FACE-Q questionnaire completed by the participants revealed reported extremely high satisfaction with their treatment outcome (average of 72 with a standard deviation of 18). Participants rated their skin improvement (skin texture, radiance, pore size, wrinkles, pigmentation, tightness, and overall skin appearance) six weeks after the first treatment using an analogue scale (0—no improvement and 5—100% improvement). With 95% confidence, participants have seen improvement overall skin appearance. Most noted improvements were in brightness, skin texture (how smooth the skin felt to the participants), and tightness (Figure 5). 17 of the 27 participants reported improvement in pore size, and 13 of the 27 participants reported improvement in pigmentation. The results on pore size and pigmentation were not statistically significant as several participants reported no improvement in these two factors.

All age groups noted improvement of their skin following the treatments.

No adverse effects were reported.

Physicians perceived better improvements than the layman. Noteworthy, the physicians seem to have a slight bias toward the skin type and race they are most familiar with; however, the study's sample size was not large enough to arrive at this conclusion with a high degree of confidence and could be an area for further research.

4 | DISCUSSION

The differences between skin and aging in different ethnicities have been published previously. [41-43] Nouveau et al reported that the onset of wrinkles in Chinese women in comparison to French women age is delayed by approximately ten years and non-linear (fast aging between 40-50 years old). However, pigmentation in Chinese women was reported as a more prominent sign of aging

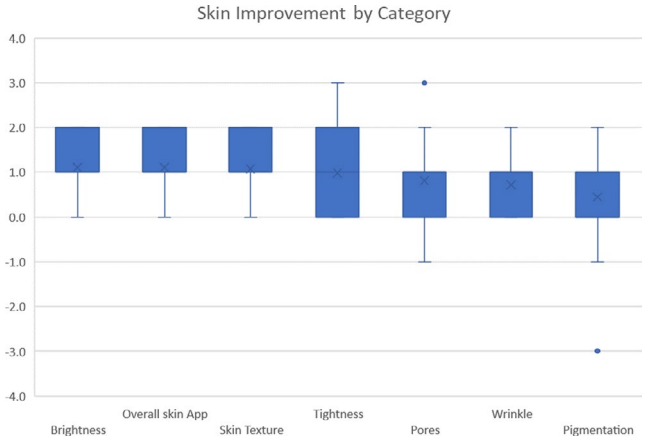

FIGURE 5 Skin improvement by category (skin brightness, overall skin appearance, skin texture, tightness, pores, wrinkles, and pigmentation) as rated by the participants. The participants' skin improved in all cases in most categories

than wrinkles. [41] This could explain the better improvement noticed for Latinos and Caucasian participants in this study in comparison to the Chinese participants.

More noticeable changes in 40+ age group could be explained by more noticeable visual aging signs such as lines and wrinkles and hence changes better visually appreciated by the participants and the evaluators. Topical application of growth factors can help skin rejuvenation. Mehta et al reported reduction of fine lines and wrinkles three months post daily use of "proprietary mixture of over 110 growth factors, cytokines, and soluble matrix proteins secreted by human dermal fibroblasts".[33] In a pilot study, Fitzpatrick and Rostan reported clinical improvement of photodamaged facial skin, reduction of fine rhytids and textural irregularities, and increased epidermis thickening after 60 days of application of a "combination of multiple growth factors" twice per day.[34] Gold et al examined the use of "a mixture of human growth factors and cytokines" and reported a significant reduction of perioral and periorbital rhytids, and improved skin texture after 30 days of use and further improvement after 60 days and twice-daily application.[44] They further published a reduction in skin roughness.[45] Post-treatment use of clinically proven skincare and growth factors are essential in reversing signs of aging, also, to help supplement the ability of the skin to heal itself.[25]

The rejuvenation effects can be enhanced, and healing time reduced when a physiologically balanced mixture of growth factors is used in addition to microneedling procedure. The crucial role of growth factors in wound healing is well established.[22-24,46] Seo et al reported improved outcome when microneedle fractional radiofrequency was used in combination with stem cell-conditioned medium.[32] Lee et al used a 0.25-mm microneedle roller and secretory factors of endothelial precursor cells differentiated from human embryonic stem cell in twenty-five Asian women in a split-face study. They reported statistically significant effects of the combination treatment on pigmentation and wrinkles in comparison to microneedling alone.[31] Similar to the current study, they used microneedling to enhance transdermal penetration.

Lifting effect has been reported with the fractional radiofrequency factor-induced system in addition to significant wrinkle reduction. [32] Reduction in skin laxity as reported by other studies also could result in a visual presentation of mild lifting effect.

During the early stages of wound healing, there is an increased level of TGF-β and platelets-derived growth factor (mainly from macrophages). Fibroblasts are stimulated to produce collagen and extracellular matrix. In response to upregulation of vascular endothelial growth factor, angiogenesis is then initiated.[22] The mixture of growth factors in this study mimics the naturally produced cytokines by the body and enforces the early stage of wound healing.

Zhang et al in their systematic review and meta-analysis assessing randomized controlled trials reported that addition of growth factors (fibroblast growth factor, epidermal growth factor and granulocyte macrophage-colony-stimulating factor) significantly improved wound healing in burn scars (partial thickness burn) including scar tightening and significantly improved scarring (pigmentation, pliability, height, and vascularity). In comparison to standard treatment

with no topical application of growth factors, the average healing time was reduced by 5 days.[47] Akita et al reported improvement of pediatric burn scars in term of pigmentation, pliability, height, and vascularity by early administration of basic fibroblast growth factor.[48] Weshay et al used the same combination of growth factors as the current study in combination with fractional CO2 laser for treatment of mature facial burn scars. They reported improved results with significant collagen production and shorter downtime (range and mean ± SD: 5-7 and 4 ± 1) for the growth-factor-treated side.[49]

Microneedle technology as transdermal drug delivery systems is gaining importance in healthcare and cosmetics and reported to be used successfully in delivery of a variety of compounds (eg, macromolecules and hydrophilic drugs) into the skin.[16-20] Advantages of this treatment include no open wounds, short duration of treatment, quick healing and recovery time, and none-to-minimal downtime. The short interval of two weeks between treatments with no reported side effects, short duration of post procedure sequelae such as redness with no downtime resulted in high patient satisfaction. However, given the immediacy of the results, there is a danger that the practitioners may overtreat patients. It is important to be mindful of this. In terms of regular microneedling, the interval of 4-6 weeks should be respected.

This study used AQ growth factors; the reported efficacy of this treatment modality cannot extrapolate to all other growth factors available commercially. Challenges that need to be overcome for effective growth factor mixtures and serums include stability, expression yield, purification, storage, and delivery system. An advantage of using a specific combination of stabilized growth factors is the focus on anti-inflammation and repair with predictable result.

Source of the growth factors is important, and manufacturing should be done in a pharmaceutical facility. A variety of sources are used to obtain growth factors. These include recombinant bacteria, yeast, plants, animals, and human or produced synthetically.[50] Human-derived growth factors can be from epidermal or placental cells, foreskin, and colostrum.[51]

Growth factors are morphogenetic proteins; therefore, factors affecting the stability of these proteins should be understood and taken into consideration. For example, fibroblast growth factor-1 has low stability with a functional half-life of one hour in serum at 37°C.[52]

Other challenges include manufacturing, recombinant expression yield, purification process and its difficulties, storage and stability during storage, and suitable delivery methods.[52]

More and more studies are being published on the use of growth factors for regenerative medicine and rejuvenation. Large, multicenter, double-blind studies are the gold standard and will help toward evidence-based practice.

Study limitations include a small number of participants, relatively few ethnicities, and a short follow-up duration. Other methods such as silicone impressions like the study carried out by Sundaram el al. could have been complementary to the current data.[25] Pretreatment priming of the skin would be beneficial in enhancing the outcome and regenerative properties of the skin.

5 | CONCLUSION

More and more participants are requesting and opting for non-surgical, less aggressive treatments with no to minimal downtime. Microneedling is a non-invasive method for skin rejuvenation and can be used for skin rejuvenation for all skin types, face and body. Use of a physiologically balanced mixture of growth factors can help reduce skin repair time and enhance treatment outcome. In this study, use of microneedling and growth factors over six weeks and provision of 2 treatments at 2-week intervals revealed improvement in overall skin appearance, brightness, skin texture, and tightness. The procedure is non-invasive, safe, with no or minimal downtime and resulted in high participant satisfaction. These results may not be replicable using other growth factor serums.

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CONFLICT OF INTEREST

The author has no financial interest to declare in relation to the content of this article. No commercial interest. Dr Samizadeh - international consultant and/or training activities for various pharmaceutical companies including Allergan Plc, Galderma, Merz, and AQ Skin Solutions.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Souphiyeh Samizadeh https://orcid.org/0000-0003-4626-3896

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