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# A Comprehensive Review of Microneedling and Facial Skincare Strategies in Anti-Aging Dermatology

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**Abstract**

These days, there are different techniques for skin rejuvenation. One of them is microneedling, which can improve skin health with minimal side effects and good results. Microneedling is an effective skincare method for facial rejuvenation. It is a good source of growth factors, cytokines, and other biologically active substances that can enhance rejuvenation and wound healing processes. During the microneedling method, all these substances are obtained from the patient's blood without any pain and have the advantage of reducing the immune response, making the procedure safer and better tolerated, with minimal side effects and lower cost. Therefore, it is a useful approach for skin anti-aging. It is currently being used extensively for facial rejuvenation. In this process, using a combination of microneedling, mesotherapy techniques, and facial skincare for treating acne scars, melasma, and facial scars is more powerful. So, in this article, the microneedling method and its remarkable effects on skin anti-aging and reducing skin problems will be studied.

## 1. Introduction

Skin aging includes some skin problems like pigment changes, wrinkles, thinning, and loss of elasticity due to both genetic and environmental factors. A variety of medical procedures and topical cosmetics are used to treat different signs of aging. Microneedling is a relatively new, minimally invasive procedure that can create tiny holes in the surface of the skin in a controlled manner and depth, by rolling and penetrating different layers of skin with its tiny needles. It quickly became widely popular and accepted because it requires minimal training and is a simple, inexpensive, safe, and effective technique for all types of skin and most skin issues. These days, microneedling is being used as a collagen induction therapy for facial scars and skin rejuvenation more than before. It is now also commonly used as a transdermal delivery system for therapeutics and vaccines instead of some injections that have a lot of side effects for the skin in the near future. The emergence of the concept of microneedling dates back to 1995, when Orentreich described dermal needling in a subcision format for scar treatment, and then, when a plastic surgeon used a tattoo gun in 1997 and independently described it by Kamiland (Buzalaf and Levy, 2022; Orentreich and Orentreich, 1995; Camirand and Doucet, 1997). In 2006, Fernandez, as a surgeon, designed his drum-shaped device with several thin protruding needles and used it for transcutaneous collagen induction for skin (Amit, 2013; Fernandes, 2005).

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## 2. Skin Aging

Skin aging is a visible sign of physical aging (Yaar *et al.*, 2002). As collagen and elastic fibers decrease in the skin, wrinkles appear gradually over time (Gilchrest, 1989), and with the loss of fat and skin moisture, the process of skin aging accelerates (Yaar and Gilchrest, 2001). Therefore, there is a growing demand for surgical treatments and skin rejuvenation. So, it is better to have some useful non-surgical treatments to reduce the percentage of unnecessary surgeries and their side effects. Its usefulness is determined by minimal invasiveness and downtime. Currently, different types of non-invasive cosmetics are available on the market. However, limited efficacy is often due to low skin penetration of active compounds, as the stratum corneum acts as an external barrier. This protocol is within the principles of good clinical practice and applicable regulatory requirements. The Institutional Review Board of the Human Research Ethics Committee of Thammasat University (Medicine) approved all study protocols (number: MTU-EC-OO-0-078/64, November).

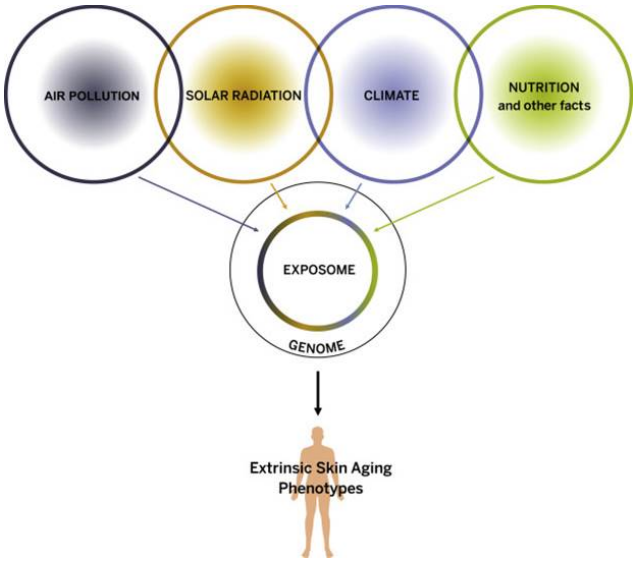


**Fig. 1.** Different external factors can affect skin cells and cause skin aging, and in some conditions, can increase the speed of skin aging (Krutmann *et al.*, 2021).

According to one of the references that showed good results, the microneedle patch and HA were applied to the right side of the patients, and the microneedle patch only was applied to the left side. Each treatment was applied to the nasolabial folds for 8 weeks. The density of the microneedle array in this study was 265 needles/cm, and the shape of the microneedle patch was designed to cover the nasolabial fold area. Based on these specifications, the total area of the microneedle array within the patch was 7.5 cm. The fins of each four-pronged star-shaped microneedle formed a gap or channel between the groove of the microneedle and the tissue when penetrated into the skin. The reservoir was applied only to the contralateral side every 2 weeks for a total of 8 weeks. All applications were performed after washing the face, and no local anesthetic was administered during the clinical trial. Participants were instructed to massage both sides of the patch for 5 minutes before removing it. Moisturizer was provided to each participant. The drug or solution delivery mechanism of the four-pronged star microneedle array was fabricated on a tissue substrate. In this method, the image shows hyaluronic acid solution being forced through a syringe connected to a microneedle patch. According to the patient characteristics, the participants in this study had a mean age of $50.78 \pm 6.41$ years. Of the total respondents, 9 were 40 years old and below, constituting 39.13%; 12 were 50 years old and below, constituting 52.17%; and 2 were 60 years old and below, constituting 8.69%. All participants were female.

## 3. Intrinsic and Extrinsic Skin Aging Processes

The aging of the skin involves gradual deterioration. This is because of both intrinsic and extrinsic skin aging processes. Intrinsic aging is a natural function, a progressive physiological process, and can cause the formation of fine lines, thinning, and dryness in the skin structure. In addition to all these, gradual skin atrophy can be seen. Extrinsic aging is caused by the influence of external environmental factors such as ultraviolet (UV) light, infrared radiation, environmental pollution, smoking, malnutrition, and psychological stress. These items can lead the skin to a loss of skin elasticity, which increases sagging and the formation of coarse wrinkles (Wadstein *et al.*, 2022; Zhang and Duan, 2018). External factors also appear to reduce the levels of antioxidants in the skin texture and can increase the levels of reactive oxygen species (ROS) in the skin. A middle-aged woman whose skin shows signs of aging most of the time may present with hyperpigmentation, erythema, telangiectasia, wrinkles, and localized dryness (Kammeyer and Luiten, 2015).

## 4. Skin Microenvironment

Currently, the evidence suggests that changes in the skin microenvironment can significantly improve wrinkles, pores, and elasticity in the combination group compared to MN alone. A recent study concluded that skin structural remodeling in skin biopsy pathology can be observed primarily at the junctional side (El-Domyati *et al.*, 2020). Additionally, epidermal histology shows a significant increase in epidermal thickness on both the skin needling side and the combined side (i.e., skin needling and mesenchymal stem cell-derived amniotic fluid). It became clear that this is consis-

tent with current results, showing that improvement in skin rejuvenation was greater on the combined side than on the MN-alone side. This difference may be due to differences in microneedle length (0.25 mm in the Korean study and 0.5 mm in another target study) (Cassiano *et al.*, 2019). According to references and previous studies, MN single treatment of melasma with a needle length of 0.5 mm significantly reduced melanin density, pendulous melanocytes, and pathological basement membrane (Cassiano *et al.*, 2019). These studies provide strong evidence for effective treatments. Therefore, this method will be used successfully for facial anti-aging. Data from papers show that combination therapy with MN and MSC derivatives can have significant improvement over MN alone. In summary, the combination of MN and hUC-MSCs-CM is a safe and effective treatment for facial rejuvenation and may be used as a new method for anti-aging therapy in recent years (Cassiano *et al.*, 2019).

## 5. Physiological Parameters of Skin Water Content and TEWL

Maybe it raises a question: What are the water content and TEWL in the skin? They are indicators of skin barrier function. After treatment, there were no significant changes in hydration content between the MN with hUC-MSCs-CM side (P=0.06) and the MN-alone side (P = 0.12). There was no comparison with the baseline, and skin elasticity was significantly improved in both groups (P=0.00). There were no side effects during the study period. Cell therapy is a kind of skin rejuvenation method using extracellular vesicles and stem cells such as MSCs and BMMSCs due to their ability to repair and regenerate tissues and organs in cosmetic and reconstructive surgery (Zarei and Abbaszadeh, 2019; Suh *et al.*, 2019). Effects of conditioned media derived from BMMSCs or adipose tissue and the impacts of derived stem cells on skin rejuvenation have been demonstrated (Kim *et al.*, 2021; Li *et al.*, 2019). Skin brightness and texture are more closely related to skin rejuvenation (the less pigment in the skin and the lighter the color). Therefore, vascular permeability is needed to improve tissue nutrition.

## 6. Skin Moisture and Elasticity

Skin moisture and elasticity were assessed using a Cutometer (Ahn *et al.*, 2007), which represents the overall elasticity of the skin, including viscous deformation. It showed no statistically significant improvement (p=0.098). Furthermore, the water content of the skin, called skin viscoelasticity, did not show statistically significant improvement throughout the main study (p=0.205).

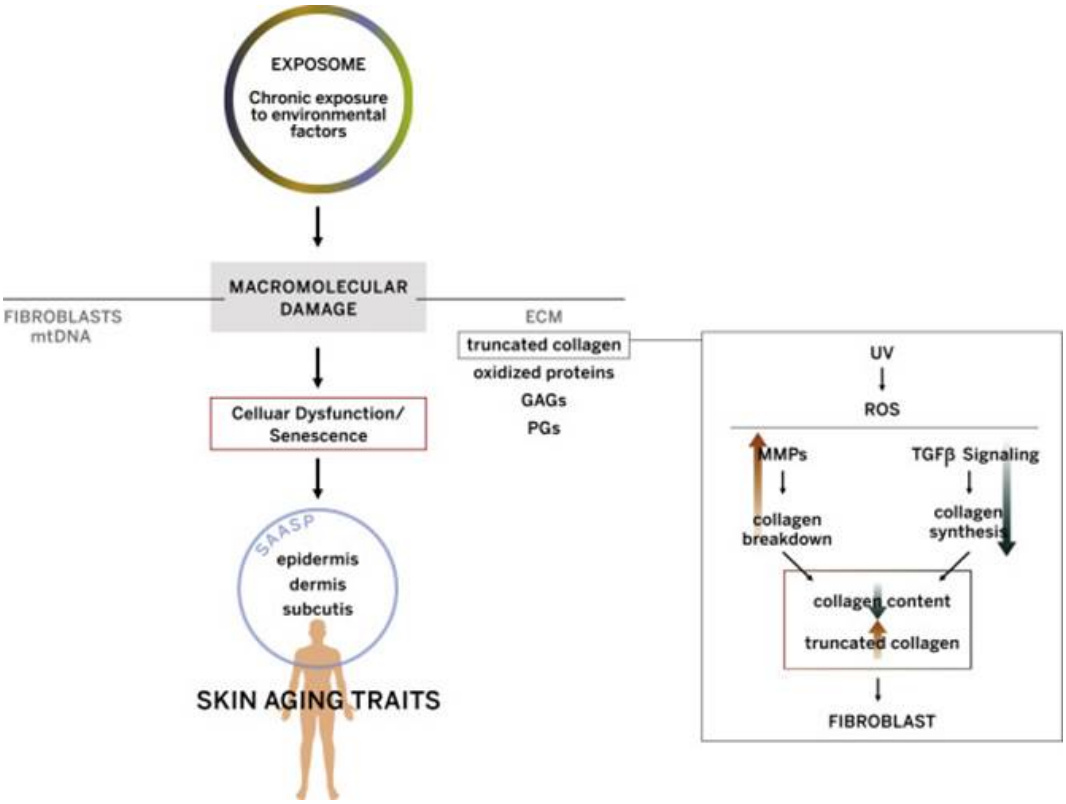


**Fig. 2.** According to all skin aging conditions, external factors can penetrate into the skin layers and cells (like UV) and affect the core and its DNA. These factors can cause changes in cells like fibroblasts, and subsequently, problems can be seen in the levels of ROS, MMPs, and TGFB (Krutmann *et al.*, 2021).

According to references, some skin features like wrinkles, roughness, and pore volume improved after the first treatment session. Wrinkles improved by 9.12% positive changes, according to data measured with the Antera 3D Image Capture System. The degree of improvement in wrinkles was clearly significant after the first and second treatments and continued with positive changes without additional treatment sessions. Overall, wrinkles improved by 11.72% positive changes. Wrinkle improvement was statistically significant ($p < 0.001$) throughout the study (Akhtar *et al.*, 2011).

## 7. Factors for Improving Skin Rejuvenation

### *7.1. Endothelial Progenitor Cells and Cytokines*

Endothelial progenitor cells (EPCs) differentiated from human embryonic stem cells (hESCs) showed improved blood perfusion of injured tissues and secreted high levels of growth factors and cytokines to the main sections (Cho *et al.*, 2007; Lee *et al.*, 2011b). Conditioned medium (CM) of hESC-derived EPCs (hESC-EPCs), containing multiple growth factors and cytokines, significantly enhanced the proliferation and migration of Mal-fibroblasts and epidermal keratinocytes, as well as increased collagen synthesis in fibroblasts (Lee *et al.*, 2011b). In this regard, growth factors help reduce the signs of aging (Fitzpatrick and Rostan, 2003). Some growth factors exhibit skin whitening effects by inhibiting melanin production (Kim *et al.*, 2008). However, recently, the beneficial roles of growth factors in skin rejuvenation have only been investigated (Velugotla *et al.*, 2017; Kim *et al.*, 2009a; Park *et al.*, 2008), and no controlled clinical trials have been conducted. Hydrophilic molecules larger than 500 Da have poor penetration into the stratum corneum (Bos and Meinardi, 2000; Jakasa *et al.*, 2007). Most growth factors are large hydrophilic molecules larger than 20 kDa. Therefore, they are unlikely to penetrate the epidermis in measurable amounts and cause pharmacological effects. Microneedling was used to improve skin penetration of hESC-EPC CM, and it was successful. Triplex cytokine analysis is a useful method for analyzing CM, and it showed that hESC-EPCs highly expressed several growth factors including fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), fractalkine, and granulocyte-macrophage colony-stimulating factor. It has become clear that this is truly occurring. Of course, it stimulates factors like interleukin-6 (IL-6), GM-CSF, vascular endothelial growth factor (VEGF), platelet-derived growth factor AA (PDGF-AA), and PDGF-BB, which is involved in fibroblast proliferation and regulates cell growth. VEGF promotes skin angiogenesis and can increase vascular permeability and improve tissue nutrition (Fabi and Sundaram, 2014).

## 8. Recent Treatments for Rejuvenation

Combating signs of aging such as wrinkles, enlarged pores, decreased resistance, and irregular pigmentation, and rejuvenating the skin is one of the biggest challenges of the 21st century (Boismal *et al.*, 2020). Recently, mesenchymal stem cells (MSCs) and microneedling (MNs) have been widely used for anti-aging treatments. The purpose of this study is to evaluate the efficacy of the combination of MN and conditioned medium (hUC-MSCs-CM) and human umbilical cord-derived mesenchymal stem cells in skin brightening and rejuvenation, which are the most important factors in the anti-aging process. Skin aging can be influenced by both intrinsic (chronological) and extrinsic (environmental) factors, leading to deterioration in appearance and loss of function (Choy and Prausnitz, 2011). Skin aging not only affects the physiological functions of the skin but also impacts people's psychology and social life. As a result, several non-surgical treatments have been developed in recent years to combat skin aging, including oral treatments, ointments, dermabrasion, chemical peels, and laser treatments. However, these may be associated with prolonged recovery, hyperpigmentation, and scarring. Microneedling (MN) is widely used Microneedling (MN) is widely used as a treatment for skin diseases and skin rejuvenation because of its safety and effectiveness. There are two main reasons for its medicinal use: (a) MN can promote the skin's natural healing process more than alone, and it is exciting and hopeful. It can penetrate the epidermis and papillary dermis layer (Yang *et al.*, 2021) and form pores, so it can start the skin's repair mechanisms better than other processes (Soliman *et al.*, 2018). Also, this can lead to short-term aggregation of inflammatory cells, fibroblast proliferation, long-term remodeling, and collagen and elastin synthesis (Yang *et al.*, 2021). (b) MN can improve drug penetration; this is due to penetrating the stratum corneum barrier (Choy and Prausnitz, 2011). Therefore, it is difficult for drugs to be absorbed through the skin layers. MNs create small temporary holes that penetrate the stratum corneum barrier over a short period of time (Gupta *et al.*, 2011). According to the reference, before the treatment in the MN method, all participants' faces had to be cleaned with facial cleanser. MN treatment was performed in eight rows using a total of 192 needles with a length of 0.5 mm (Gupta *et al.*, 2011).

## 9. Microneedling Devices

- Dermaroller
- Dermapen

### *9.1. Dermaroller*

A standard medical dermaroller has a 12 cm long handle with a 2 × 2 cm wide drum-shaped cylinder at one end, which consists of 192 thin microneedles (usually 0.5 to 3 mm) arranged in 8 rows and 24 circular arrays. The length and diameter are 0.1 to 0.25 mm, and it is not an automatic device (Amit, 2013).

### *9.2. Dermapen*

Dermapen is an automatic microneedling device that looks like a pen. This ergonomic device uses disposable and sterile needles and guides to adjust the length of partial mechanical resurfacing needles. Nine to twelve needles are arranged in a row at the tip. It uses a rechargeable battery and operates in two modes: fast mode (700 cycles/minute) and slow mode (412 cycles/minute), which vibrates like a stamp on the skin in each mode (Arora and Gupta, 2012). The needle tip is hidden in a guide, making this process safe and comfortable in tight areas such as the nose. In this method, eyes and lips can be treated without damaging adjacent skin, and this is a really positive point for this method. This makes the procedure less painful and more economical, as there is no need to purchase new instruments each time. This technique was developed to overcome the problems of pressure application and resulting penetration depth. So, all the pressure and depth depend on the part of the skin that is selected for treatment and repair.

## 10. Microneedling

Microneedling, also known as percutaneous collagen induction (PCI), is a minimally invasive technique that was first described in principle by Orentreich (Orentreich and Orentreich, 1995). It is a subcutaneous excisional procedure that removes the skin beneath recessed scars and wrinkles and stimulates collagen in the body. Fernandes used a similar technique of inserting a 15-gauge needle into the skin beneath the wrinkle (Fernandes and Signorini, 2008; Fernandes, 2005). Fernandez's technique was developed at that time and then followed by the dermal roller (Fernandes and Signorini, 2008). The dermal roller is a sterile plastic cylinder with stainless steel needles protruding 1 to 3 mm from the surface of the cylinder. The skin roller is forcefully rolled over the skin, creating numerous needle pricks and resulting in the formation of thousands of microscopic wounds in the dermis, which triggers the natural inflammatory response after trauma (i.e., growth factor release). As a result, formation of collagen and elastin occurs (Fernandes and Signorini, 2008; Fernandes, 2005). The latest automated microneedling devices are replacing dermal rollers. The needle barrel is typically replaced with a sterile disposable needle cartridge with a variety of different needle configurations for different parts of the skin with different conditions. The automated device allows the operator to define the puncture depth and frequency of needle punctures and control the treatment area and coverage, rather than relying on the operator physically rolling the device over the skin. Currently, needles of automated microneedling devices consist of several thin sterile needles, typically 0.5 to 1.5 mm in length. In addition to age-related skin conditions (wrinkles, laxity, etc.), there is a growing list of skin conditions that respond to PCI therapy. This list includes skin issues like acne scarring, hyperpigmentation, alopecia, hyperhidrosis, and PCI. It has also been reported that it is being used in transdermal drug delivery systems. However, most studies on microneedling are case series or small randomized controlled trials (Hou *et al.*, 2017). In this paper, the research objective was to assess the effectiveness and outcome of best practices such as microneedling for repairing or treating various skin afflictions and diseases and to establish safety precautions for facial skin renewal and rejuvenation with percutaneous collagen injection. Volunteers who were on anticoagulant therapy or taking aspirin or high-dose non-steroidal anti-inflammatory drugs (NSAIDs) in the previous 14 days were excluded. Further exclusion criteria were: hepatitis, active acne vulgaris on the face, inflammatory skin disease, uncontrolled diabetes, keloid scars, human papilloma virus (HPV), birthmarks, eczema, known malignancy, chemotherapy, radiation therapy or high-dose corticosteroid treatment, known allergy to local anesthetics, and past treatment with filler injections or neuromodulators within 3 months (Hou *et al.*, 2017).

## 11. Microneedling Delivery Systems

Microneedle delivery systems provide a minimally invasive and painless transdermal drug delivery method that is particularly useful for vaccines. An insulated needle is used to penetrate the skin and emit high-frequency current from the tip of the needle, without damaging the overlying epidermis (Cohen and Elbuluk, 2016). The needle depth can be adjusted from 0.5 mm to 3.5 mm, allowing careful targeting of different layers of the dermis (Chandrashekar *et al.*, 2014). Microneedling Radio Frequency Technology (MNRF) is safe for all skin types because it does not damage the epidermis. So, it is a good method for treating scars, hyperhidrosis, skin tightening, and rejuvenation.

## 12. Effects of Microneedling on Skin

When a dermaroller is applied to the skin with its 192 needles, 2 mm long and 0.07 mm in diameter, and applied 15 times to that section of the skin, various pro-

teins, potassium, and growth factors are released from the cells. As a result, fibroblasts migrate to the injury site and collagen is induced. Keratinocyte hyperproliferation is downregulated by microneedle treatment in acne patients to balance overall cellular activity (Liebl and Kloth, 2012). Microneedling improves the delivery of various drugs across the skin barrier by bypassing the stratum corneum and delivering drugs directly to the vascularized dermis.

It was also shown that the follicular infundibulum was significantly dilated by 47%, which may partially explain the increased drug penetration. Additionally, it removes scale and sebum residue around the infundibulum area (Serrano *et al.*, 2015). Micropuncture is performed using microneedling, and depending on the applied pressure, holes per square centimeter reach the papillary dermis layer (Serrano *et al.*, 2015). Each pass creates 16 micropunctures per square centimeter in the stratum corneum without major damage to the epidermis (Nair and Arora, 2014). These microinjuries result in minimal superficial bleeding and trigger a wound healing cascade, releasing various growth factors including connective tissue activation protein, connective tissue growth factor, and fibroblast growth factor (FGF) (Freinkel and Woodley, 2001). Additionally, needles dissolve old and hardened scar strands and allow the texture to undergo revascularization, angiogenesis, and collagenogenesis. These are initiated by fibroblast migration, proliferation, and intercellular matrix deposition (Fabbrocini *et al.*, 2009). A fibronectin matrix is formed after 5 days of injury, which determines collagen deposition and results in skin formation. The tightening effect lasts for 5 days, and collagen III forms for 7 years. The depth of neocollagen with a 1.5 mm needle was found to be 5–600 $\mu$m. Histological examination of skin treated with 4 microneedling sessions, spaced 1 month apart, showed up to a 400% increase in collagen and elastin deposition at 6 months postoperatively and an increase in the stratum spinosum at 1 year postoperatively. A thick, normal rete-canthus was observed (Aust *et al.*, 2008a). The collagen fiber bundles appear to have a regular lattice pattern rather than parallel bundles like in scar tissue (Nair and Arora, 2014). Libre *et al.* proposed an alternative hypothesis to explain how microneedling works (Liebl and Kloth, 2012). The resting potential of the cell is approximately -70 mV, but as the needle approaches the membrane, the internal potential increases rapidly to -100 mV. This function increases cellular activity and releases various proteins, growth factors, and potassium from the cells, leading to fibroblast migration and collagen induction (Majid *et al.*, 2014; Liebl and Kloth, 2012; Kloth, 2005). Keratinocyte hyperproliferation is downregulated by microneedle treatment in acne patients to balance the overall cellular activity (Liebl and Kloth, 2012). As a result of using microneedling, it improves the delivery of various drugs across the skin layers by bypassing the stratum corneum and delivering drugs directly to the vascularized dermis. Additionally, it also removes scale and sebum residue around the infundibulum (Serrano *et al.*, 2015). Microneedling is a simple in-office procedure that takes 10 to 20 minutes, and the process depends on the area being treated. Before the procedure, patients must receive counseling that explains the expected results, delayed response, and the need for multiple sessions for optimal outcomes. At this time, for maximizing collagen formation in the skin, it is advisable to prepare the skin preoperatively with vitamin A and vitamin C preparations twice a day for at least one month. According to references, it is important to know that vitamin A affects 400–1000 genes that control the proliferation and differentiation of all major cells in the epidermis and dermis, and vitamin C is essential for normal collagen production (Aust *et al.*, 2008a).

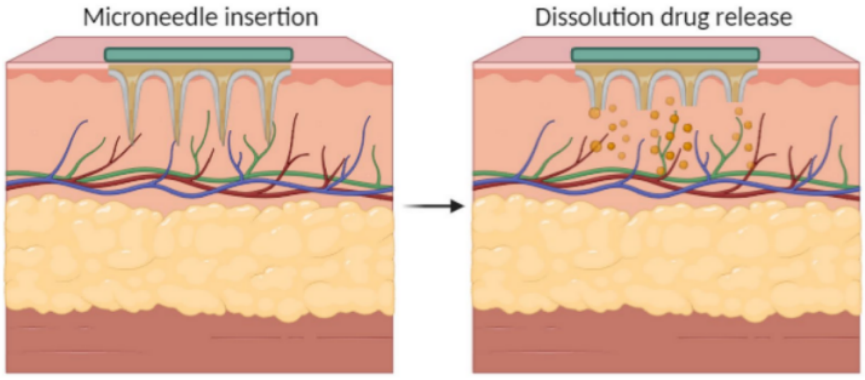


**Fig. 3.** After performing microneedling on skin tissue, the needles create pores in the skin, allowing drugs to be released more easily into deeper layers. Blood vessels can absorb the drug effectively. So, it is a good method for drug delivery systems (Dave *et al.*, 2024).

## 13. Microneedling Function

During the procedure, by driving microneedling into the skin, microscopic wounds are formed within the papillary dermis, causing the normal chemical cascade that follows trauma. This includes an inflammatory phase with the release of cell growth factors, followed by a proliferative phase, and finally a remodeling phase with stimulation of collagenogenesis and the formation of a stronger collagen matrix for repairing the skin texture. References showed improvement in facial wrinkles and skin texture at the end of its 90-day treatment with microneedling, but the largest (statistically significant) effect was observed on day 150. This improvement in facial wrinkles demonstrates the cumulative effects of transdermal collagen induction and ongoing dermal collagen remodeling (Fernandes and Signorini, 2008; Fernandes, 2005). Improved skin laxity is primarily a result of collagen III and collagen I quantity. One of the most important changes in this process is skin tightening. This process takes up to 12 months, so it is not surprising that statistically significant results were not obtained until day 150 of the study. Future studies would benefit from a preliminary follow-up of 120 days and an extended follow-up of 6 to 12 months to fully exploit the potential of this technology. On the other hand, statistically significant improvements in skin texture were observed at the end of treatment on day 90, due to the conversion of collagen III to collagen I and subsequent skin tightening. Additionally, epidermal remodeling is expected to be more measurable in the early stages of PCI treatment than in the later stages. Wrinkle evaluation results and skin texture improvement were confirmed by 3D shape measurement in the reference. As expected, the observed improvement in the common roughness index appeared to be greater than the observer rating measurements (Fernandes and Signorini, 2008; Fernandes, 2005). This is consistent with data previously reported by Friedman and Fujiwara. However, the results provide evidence of the feasibility and usefulness of 3D profilometry in obtaining a skin topography with higher resolution than clinical examination alone, supporting the use of 3D profilometry in clinical evaluation. It is argued that this measurement indicates adaptive improvements that may not be detected by expert evaluators. According to the reference, the epidermis was structurally relatively healthy and the basement membrane was not damaged during PCI treatment with the study device (Aust *et al.*, 2008b). Side effects associated with the use of this technique were well managed. As a result, the treatment effect was adequate and well tolerated by patients. No serious adverse events were reported. No abnormal skin observations were recorded by physicians after treatment or during the treatment session, and the subjects themselves did not report any such issues. Of these, no cases of hyperpigmentation, transient or otherwise, were reported. That is, only in some references, the number of melanocytes remained constant in subjects who received microneedle treatment. Studies on skin condition after microneedling treatment were conducted by Aust (Aust *et al.*, 2008b) and Bonati (Bonati *et al.*, 2017).

## 14. Microneedling and Growth Factors

The use of growth factors in microneedling, according to skin texture functions, has shown certain results regarding collagen remodeling. In a case series, the use of topical growth factors on photodamaged skin was reported in 8 patients who received a total of 3 treatments with microneedling, spaced 10 days apart. The growth factor gel contained epidermal growth factor, fibroblast growth factor, hepatocyte growth factor, and insulin-like growth factor. An independent physician clinical evaluation using the Fitzpatrick Wrinkle Scale showed significant improvement in skin texture, fine lines, and wrinkles (Pamela, 2018). Another study examined 25 patients in a split-face randomized controlled trial and concluded that dermaroller microneedling was associated with growth factors (Lee *et al.*, 2014). In a split-face study involving 10 patients, El-Domyati *et al.* (El-Domyati *et al.*, 2020) investigated the use of their manual dermaroller using amniotic fluid-derived stem cells on acne scars. Although serum itself does not contain growth factors, stem cell therapy stimulates paracrine secretion of growth factors, extracellular matrix molecules, and interleukins. After performing five sessions spaced one month apart, the authors observed improvement in the histological structure of collagen and elastin, as well as statistically significant histological and clinical improvement. Another study using 12 human embryonic stem cells with flat microneedling (0.25 mm roller) showed improved pigmentation and wrinkles by physician and software analysis after five sessions at 2-week intervals. This study showed statistically significant improvement in 13 dermatological evaluation parameters, including uniformity of skin tone, melanin index, texture, and firmness. After that, clarity evaluation by subjects was observed in control subjects. Some studies have shown that microneedling and growth factors significantly improve skin texture, fine lines, wrinkles, pigmentation, and acne scarring, as well as histological changes in epidermal thickness and scar appearance. Clinical improvement has been shown in the results. Further studies are needed to characterize the effects of topical growth factors as adjuvants in dermatological procedures.

## 15. Microneedling and Skin Aging

Topical application of growth factors via microneedling has the potential to ameliorate signs of aging. Clinical symptoms of intrinsic and extrinsic skin aging include changes in pigment, thinning of the skin, formation of wrinkles and fine lines, loss of moisture and elasticity. Growth factors act as chemical messengers that mediate cell proliferation, repair processes, and ECM formation. Microneedling creates controlled micropunctures in the skin that induce collagen formation, angiogenesis, and wound healing. Thus, anti-skin aging functions of microneedling can help the skin texture increase its ability to remain healthy and youthful (Schaefer and Lademann, 2001).

## 16. Microneedling and Collagen

Microneedling, also known as collagen induction therapy, is a common skin therapy that uses a device to penetrate the dermis to an even depth and create controlled skin damage (Sun *et al.*, 2024). This injury induces rapid healing, which then stimulates the production of collagen and elastin fibers, resulting in skin remodeling and rejuvenation (Iriarte *et al.*, 2017; Wu *et al.*, 2020). However, in recent years, the microneedling device has been combined with the delivery of radiofrequency energy to heat the underlying skin layers, improving skin remodeling and clinical outcomes (Kim *et al.*, 2013). Microneedling is generally considered a safe and inexpensive alternative to other forms of skin rejuvenation. Local anesthetic is usually used before the procedure to minimize discomfort. In a recent review, the most common side effects associated with this treatment include temporary pain or discomfort, erythema, and edema (Juhasz and Cohen, 2020). These effects are mild and self-limiting but can cause concern about the patient's appearance. Therefore, this method can increase healthy collagen levels, and due to its minimal side effects, it is a highly effective way to help the skin maintain optimal collagen levels and remain in a healthy state.

## 17. Combination of Microneedling and Chemical Peels

In recent years, a combination of chemical peels and antioxidants has become an option to rejuvenate the skin without any damage. Microneedle mesotherapy can increase the penetration of active ingredients. According to the reference (Wadstein *et al.*, 2022), the entire face was first treated with azelaic acid, and next, a 40% vitamin C solution was administered to the right side and 10% vitamin C to the left side using microneedling. Some skin characteristics like skin hydration and elasticity were significantly improved, and better results were observed with microneedling. Melanin and erythema index decreased with treatment. No serious side effects were observed. The combination of active ingredients and delivery technologies has great potential to enhance the efficacy of cosmetic formulations, possibly through multidirectional mechanisms of action. In that study, both 20% azelaic acid + 40% vitamin C treatment and 20% azelaic acid + 10% vitamin C + microneedle mesotherapy treatment were effective in improving skin aging parameter evaluation. They have proven that the use of microneedling and mesotherapy techniques serves as a means of delivering active ingredients directly to the dermis and improves the efficacy of the studied formulations. Skin aging is a complex and multifactorial process that appears gradually from the third decade of life and accelerates with age (Wadstein *et al.*, 2022). As aging occurs earlier than in other tissues, likely due to environmental stressors and exposure to hazards, the main characteristics of skin aging commonly include loss of elasticity, appearance of wrinkles, and a rough texture (Zhang and Duan, 2018). These changes are associated with phenotypic changes in skin cells and structural and functional changes in extracellular matrix components such as elastin, collagen, and proteoglycans. These components are necessary for skin elasticity, tensile strength, and hydration (Huertas *et al.*, 2016). Skin aging is reflected by a decrease in collagen I content, fragmentation of collagen fibrils, and accumulation of amorphous elastin material (elastosis) (Aldag *et al.*, 2016). Age-related changes in skin appearance can negatively impact self-esteem and lead to significant psychosocial stress (Wadstein *et al.*, 2022). Therefore, products that help slow down this ongoing process are very important in daily life. A wide range of cosmetic and medical anti-aging products have been developed and introduced into the market. However, their efficiency varies. Despite manufacturers' guarantees, only a few topical anti-aging ingredients can effectively penetrate the dermis. Thus, various resurfacing techniques such as chemical peels, mesotherapy, filler injections, and laser/radio-frequency tightening are used to improve the delivery of active substances. The results show that all skin parameters evaluated were significantly improved after both treatment types. Both 20% azelaic acid + 40% vitamin C treatment and 20% azelaic acid + 10% vitamin C + microneedling mesotherapy effectively improved skin hyperpigmentation and erythema. Other related studies have also shown that azelaic acid has a positive impact on hyperpigmentation by inhibiting tyrosinase and exerting antiproliferative effects on the melanin production pathway (Bergman and Luke, 2017; Nautiyal and Wairkar, 2021). So, a combination of 5–20% azelaic acid and phytic acid, ferulic acid, 4N-butylresorcinol, or mandelic acid is most effective in reducing hyperpigmentation. Additionally, the use of vitamin C has been found to successfully reduce pig-

mentation (Mazurek and Pierzchała, 2016). A clinical trial evaluating the efficacy of a formulation containing 25% L-ascorbic acid and a chemical penetration enhancer demonstrated a significant reduction in pigmentation severity in patients with melasma (Hwang *et al.*, 2009). Vitamin C has been shown to affect blood microcirculation and reduce skin redness. Furthermore, the addition of ferulic acid not only increases the stability of vitamin C supplements but also improves whitening properties, as ferulic acid inhibits tyrosinase activity. Kameyama *et al.* (Oresajo *et al.*, 2008; Murray *et al.*, 2008) noticed that when MAP was used as a topical application to the skin, it actually bleached the skin in patients with hyperpigmentation diseases such as melasma and solar lentigines (Kameyama *et al.*, 1996). In this study, formal treatment provided patients with significant benefits in enhancing skin hydration, as well as in self-administered treatment (Algiert-Zielińska *et al.*, 2019). However, according to recent suggestions, this procedure may make the skin more moisturized (Matthews-Brzozowska *et al.*, 2017). In another study, azelaic acid was shown to balance sebum excretion and minimize aging effects, particularly dryness. Most conditions promote the skin to synthesize more collagen and elastin (Jung *et al.*, 2018; Tedeschi *et al.*, 2015). Fibroblasts synthesize various substances that help retain youthful skin condition (Jung *et al.*, 2018). The reason for this result is the use of active ingredient microinjection, which has been shown to stimulate the production of elastic/tendon and collagen fibers, promoting skin regeneration and repair during the healing process (Matthews-Brzozowska *et al.*, 2017). So, it seems that the enhanced skin elasticity achieved by the treatments—especially mesotherapy with microneedling—is not only due to vitamins but also the method of administration (Wójcik *et al.*, 2013).

## 18. Microneedling and Scar Treatment

The benefits of needles in scar treatment were first described over 20 years ago. Microneedling (MN), or percutaneous collagen induction therapy (PCI), has recently gained popularity due to its effectiveness in skin rejuvenation, retardation reduction, acne vulgaris, alopecia, scar remodeling, melasma, and other pigmentary diseases. Minimally invasive procedures use instruments with up to 540 needles that penetrate the epidermis and/or dermis to create microscopic channels (Yadav and Dogra, 2016). These needles have a diameter of 0.1 to 0.25 mm and a length of 0.5 to 3 mm. The small size of the needle allows drugs to penetrate into the dermis, and this controlled skin damage allows for the release of growth factors such as transforming growth factors alpha and beta (TGF$\alpha$, TGF$\beta$) and fibroblast growth factor (FGF) (Yadav and Dogra, 2016). Ultimately, the microtrauma promotes the formation of new components like collagen, elastin, capillaries, and other skin substances. MN is a highly effective method that is usually used with various topical agents or other techniques to enhance the therapeutic efficacy of the topical agent or procedure itself. Generally, MN is a safe procedure, but sometimes unexpected side effects and reactions may occur. The literature used for this study was selected through a PubMed database search and matched with other topical reviews. The search terms included combinations of the following words: "Microneedling", "transdermal collagen induction", "collagen induction", "dermal roller", "dermal needling", "ring", "dermal rolling", "skin needling", "side effects", and "reaction". Adverse events were categorized based on the modality of MN studied: roller MN device (RMN), derma-stamp, pen MN device (PNM), and fractional radio-frequency MN device (RFMN). All reactions that occurred after combined treatment with MN were divided into appropriate sessions (Garg and Baveja, 2014; Majid, 2009; Sharad, 2011b; Leheta *et al.*, 2011; Khater *et al.*, 2016; Pahwa *et al.*, 2012). However, in one case with RMN, ecchymosis developed and resolved spontaneously within a few days (Park *et al.*, 2012). Ecchymosis may also be seen in RMN in patients without a history of bleeding disorders (Fabbrocini *et al.*, 2014; Dogra *et al.*, 2014). In referenced studies, 3 of 60 patients with subsequent 3 monthly RMN sessions—who did not have bleeding or collagen disease or were not receiving anticoagulant therapy—developed bony prominences. A mild ecchymotic lesion developed with no residual pigmentation. Other side effects have also been reported. Although rare, RMN use has been associated with these side effects (Fabbrocini *et al.*, 2014). It also caused scars (Dogra *et al.*, 2014; Pahwa *et al.*, 2012), milia (Sharad, 2011a; Asif *et al.*, 2016), Pruritus and eschar formations were recognized by RMN (Majid, 2009; Asif *et al.*, 2016; Cachafeiro *et al.*, 2016). In the case of acne scars in patients treated with RMN, there is a possibility of recurrence of acne scars (Leheta *et al.*, 2011; Asif *et al.*, 2016).

## 19. Effects of Microneedling on Acne and Melasma

In treating acne and melasma, due to its strong antibacterial and anti-inflammatory properties, microneedling has been successfully used in anti-acne treatments, melasma, and rosacea (Wójcik *et al.*, 2013). Before the treatment, the entire face was generally cleansed, and the skin was carefully cleaned with a pre-peel product containing 2% salicylic acid. Next, 20% azelaic acid (pH 2.7) was applied to the entire face for 10 minutes, and then the first steps of the main treatment were completed.

**Fig. 4.** This figure presents a representative case with multiple skin scars before treatment by the author using the microneedling method as part of a personalized skin rejuvenation protocol.

## 20. Microneedling Results

Microneedling results in the reorganization of old collagen fibers and the formation of new collagen, elastin, and capillaries, resulting in skin tightening. In this process, El-Domyati *et al.* showed that after six microneedling sessions every two weeks, levels of collagen types I, III, VII, newly synthesized collagen, and tropoelastin were significantly increased from baseline. According to references, this transdermal collagen induction reduces fine lines and wrinkles, decreases pore size, and makes the skin more elastic and supple. As a result, it makes the skin more youthful and is a powerful function for skin rejuvenation. Combining this procedure with topical anti-aging vitamin C serum and tretinoin will further increase its effectiveness. Microneedling also demonstrated a significant reduction in wrinkles and pigmentation when combined with endothelial progenitor cells derived from human embryonic stem cells (Lee *et al.*, 2014; Seo *et al.*, 2013). In addition, radio-frequency fractionated microneedling was evaluated in a large multi-center study and found to be effective in reducing wrinkles (Calderhead *et al.*, 2013).

**Fig. 5.** This figure presents a representative case treated by the author after one session of microneedling as part of a personalized skin rejuvenation protocol. The intervention was conducted under clinical supervision, and the image demonstrates the observed therapeutic response.

**Fig. 6.** In pictures (A, B), on day 3, excess melanin pigments migrate toward the superficial part of the skin tissue. Damaged cells with excess pigments separate from the skin by day 4. On days 30, 60, and 90, the skin appears brighter, and rejuvenation is visible.


**Fig. 7.** Compared to before, the picture of the case on day 0 and after microneedling on day 120 shows visible effects on scars and melasma, skin lifting, stratum corneum debris removal, and overall skin rejuvenation.

## 21. After Facial Microneedling

A skin care protocol was developed for use after facial radio-frequency microneedling procedures. When used immediately after the procedure, it improves normal activity, comfort, perceived age, overall treatment satisfaction, and the need for re-treatment, while providing essential mineral sun protection factor, HEV protection, and defense against environmental pollution. This skin care protocol is also suitable for use after other minimally invasive facial treatments (Juhasz and Cohen, 2020). Most subjects (90%) were very likely to undergo another microneedling procedure after receiving the skin care protocol, and all subjects (100%) said their protocol was radio-frequency based and reported that microneedling influenced their perception of improvement. After this experience, 86% of participants felt very comfortable scheduling their next microneedling treatment on any day or time. Overall, 96% of subjects were very satisfied with their experience, making it a positive report (Iriarte *et al.*, 2017; Wu *et al.*, 2020). After the procedure, self-confidence and social life may be negatively affected. After applying post-procedure skin care products, subjects were shown before-and-after photos and asked to answer several questions. 50% of subjects felt very uncomfortable immediately after the procedure, whereas 94% would have otherwise felt very or extremely self-conscious in public. Additionally, 88% said their skin felt more comfortable after using skincare products, 95% felt less self-conscious in public, and 94% felt better about their appearance after using the products. 97% said they intended to continue treatment and were more likely to recommend it to others. 87% felt their overall impression of the treatment process had improved. After 4 weeks, most participants felt their skin looked younger and healthier (94%). They were confident in repeating the treatment (94%) and continued using skin care products as part of their daily routine (94%). In these studies, the average age of subjects was 42.7 years (range: 23–63 years). Subjects were Caucasian, Fitzpatrick skin types I, II, III, and IV. Before applying the skin care protocol on day 1 post-treatment, a third group used a non-drug barrier ointment without any injection. Before treatment, more than half (59%) of participants reported being very concerned about their appearance. After all processes, 52% of subjects seemed unsure of their appearance following radio-frequency microneedling treatment (Iriarte *et al.*, 2017; Wu *et al.*, 2020; Kim *et al.*, 2013).

## 22. Lifestyle and Rejuvenation

In recent years, life expectancy and demand for youthful skin have increased, creating a demand for effective cosmetic facial treatments—especially non-invasive, non-surgical, and low-risk skin rejuvenation methods. Aging is associated with morphological changes in the skin, caused by a decrease in the number of fibroblasts and levels of collagen, elastin, and glycosaminoglycan (GAG) biosynthesis.

**Fig. 8.** A comparative evaluation of the patient's skin condition between the first session on day 3 and the fourth session on day 120 after microneedling revealed substantial improvements in dermal texture, pigmentation uniformity, and overall skin vitality. The observed changes suggest that microneedling induces not only superficial enhancement but also deep-level rejuvenation through stimulation of neocollagenesis and dermal remodeling. The degree of transformation—evident in both clinical photographs and tactile assessment—highlights microneedling as a highly effective and non-invasive modality for skin rejuvenation. The progressive reduction in hyperpigmentation, smoothing of fine lines, and restoration of epidermal tone collectively support its role as a superior therapeutic approach in aesthetic dermatology.

These changes can cause skin laxity, structural alterations, and wrinkles (Uitto, 2008). According to the aim of treatments, insulated or non-insulated microneedles are used to penetrate the skin, resulting in partial destruction of the epidermis and subsequent regeneration. The RF energy produced by the microneedle heats the superficial and deep dermis, creating zones of clinically imperceptible thermal micro-wounds between areas of normal, healthy skin, which trigger a wound healing cascade (Arnoczky and Aksan, 2000; Dierickx, 2006). Zones of normal and untreated skin improve skin texture, reduce wrinkles, and tighten the skin due to the formation of new collagen, elastin, and GAGs in response to treatment (Hantash *et al.*, 2009b; Hantash *et al.*, 2009a; Hruza *et al.*, 2009; Seo *et al.*, 2012; Lee *et al.*, 2011a; Gold *et al.*, 2016; Tanaka, 2015; Alexiades-Armenakas *et al.*, 2010; Shapiro, 2015). According to the results, the primary endpoint was met, and improvements in skin texture and wrinkles were clearly detected. The researchers assessed and showed statistically significant improvements one month after the sixth treatment session and three months after the third session ($p<0.005$ at both time points).

## 23. Clinical Study

According to references, in one clinical study, twenty-five participants were recruited for a prospective, randomized, controlled, observer-blinded, split-face study. Most participants were between 41 and 64 years old (mean: 51.6 years) and had Fitzpatrick skin type III or IV. Extrinsic senescence affects cellular and extracellular components. As an alternative treatment strategy for repairing damaged tissues, cell-based treatments using the body's own stem cells and growth factors have recently been applied to skin rejuvenation. In addition to their direct cellular effects, stem cells exert beneficial effects on tissue regeneration through complex paracrine mechanisms (Cha and Falanga, 2007). Previous studies found that hESC-EPC conditioned media (CMs) promoted wound healing and increased wound tensile strength after topical treatment and subcutaneous injection. In vitro, hESC-EPC CM significantly improved mechanisms such as proliferation and migra-

tion of dermal fibroblasts, epidermal keratinocytes, and collagen synthesis (Lee *et al.*, 2011b). Additionally, conditioned medium from adipose tissue-derived stem cells (ADSC CM) inhibited melanogenesis by down-regulating the expression of tyrosinase and tyrosinase-related protein 1 in B16 melanoma cells and ADSCs (Kim *et al.*, 2009b). It was hypothesized that hESC-EPC CM can improve signs of skin aging such as wrinkles and pigmentation. This result highlights the importance of transdermal penetration and epidermal-dermal communication for the application of growth factors in skin rejuvenation. In another study, 48 subjects were selected and all completed treatment. No subjects discontinued due to protocol-related problems or adverse events. The mean age was 55.1 years (range: 39–67 years), and the subjects were primarily female. Fitzpatrick phototype ranged from I to V, with an average of 2.2. Baseline scores for wrinkles, skin laxity, and skin texture were 3.2 (range: 2.2–4), 2.8 (2–3.5), and 2.7 (1.5–3.5), respectively. Changes were summarized at days 90 and 150. At day 90, four facial areas improved at least one level: glabellar wrinkles, periorbital wrinkles, cheek wrinkles, and lip wrinkles. The mean improvement in total score was 0.93 (99%). By day 150, six of nine facial areas improved at least one level: horizontal forehead lines, glabellar lines, periorbital lines, cheek lines, upper lip lines, and lip lines. The mean global score improvement was 1.23 (99%) with $p = 2.5 \times 106$ (i.e., highly significant). Average improvements were observed in all roughness parameters in the periorbital and mid-labial regions at both 90 and 150 days. Overall, microneedling or PCI appears to be effective and successful in treating facial wrinkles, sagging skin, and skin texture issues. Previous studies lacked sufficient sample sizes. In the present study, a microneedle system was evaluated for treating facial aging in a moderately sized patient sample (Cha and Falanga, 2007; Lee *et al.*, 2011b; Kim *et al.*, 2009b).

## 24. Discussion

The recent microneedling method is one of the most effective treatments for achieving healthy and youthful skin texture and rejuvenation. This method is especially beneficial for patients with Fitzpatrick skin types IV and V. It is a powerful technique that can resolve scar problems and hyperpigmentation successfully. Unlike other methods that may have side effects, microneedling is safer and has numerous applications with a growing number of modifications. This method is considered a valuable technology. We do not recommend self-use of dermapen or microneedling devices. It is best to receive treatment from a specialized doctor. The results of endogenous aging include clinical symptoms such as genetic mutations, hormonal changes, and metabolic shifts, while extrinsic factors include pollutants, ultraviolet radiation, and ionizing radiation (Makrantonaki and Zouboulis, 2007). Over time, aging and photoaging due to environmental factors lead to changes in pigmentation, loss of elasticity, fine lines and wrinkles, moisture loss, and telangiectasia—thus increasing the risk of skin cancer (Mukherjee *et al.*, 2011). Additionally, aged skin undergoes extracellular matrix atrophy and destruction of collagen and elastic fibers, manifesting as epidermal thinning and flattening of the dermal-epidermal junction (Makrantonaki and Zouboulis, 2007). Microneedling is one of the best ways to prevent these negative changes in skin texture. Photoaged skin is characterized by the accumulation of abnormal elastic tissue called solar elastosis. This abnormal tissue can replace the normal matrix, which is primarily composed of collagen. Glycosaminoglycans are usually distributed between collagen bundles and have the ability to bind water, increasing skin hydration. Although they increase in photoaged skin, their function is altered due to association with abnormal elastic fibers (Makrantonaki and Zouboulis, 2007). Collagen is the most important component of human skin, synthesized from procollagen derived from dermal fibroblasts. Transforming growth factor $\beta$ (TGF-$\beta$) is a cytokine that regulates dermal fibroblasts and may promote collagen degradation via upregulation of matrix metalloproteinases (MMPs). Extrinsic factors can promote reactive oxygen species (ROS), increasing MMP-mediated collagen degradation and inflammation through the NF-$\kappa$B pathway. Ultraviolet (UV) light can directly cause DNA cross-linking and modification of structural proteins (Mukherjee *et al.*, 2011; Aldag *et al.*, 2016).

Therefore, the effects of the topical application of growth factors have been studied for skin remodeling and wound healing. In this process, there are other proteins in the skin which are considered of great importance—these are growth factors. These are proteins produced by cells such as keratinocytes, fibrocytes, and melanocytes, and they affect collagen synthesis. These cytokines include platelet-derived growth factor, epidermal growth factor (EGF), granulocyte colony-stimulating factor, vascular endothelial growth factor (VEGF), keratinocyte growth factor, and hepatocyte growth factor. Since growth factors cannot pass through skin layers, their molecular weights restrict them—most are greater than 15,000 kDa. In fact, molecules greater than 500 kDa cannot penetrate the stratum corneum. However, when microneedles are used to pierce the skin at different layers, large molecules may penetrate more easily. These molecules include cytokines, platelet-derived growth factor, EGF, granulocyte colony-stimulating factor, VEGF, keratinocyte growth factor, and hepatocyte growth factor (Aldag *et al.*, 2016; Sproul and Argraves, 2013; Uitto and Kouba, 2000; Verrecchia and Mauviel, 2007). Due to their molecular size, growth

factors cannot enter the stratum corneum unless an entry route such as microneedling is provided. Stem cell biology and its applications in tissue engineering and regeneration involve three primary properties, including cell migration. Migration produces intercellular matrix, and fibroblast proliferation leads to collagen fiber deposition (Aldag *et al.*, 2016). The effect of skin tightening and collagen augmentation remains for 5 to 7 years after the procedure (Schaefer and Lademann, 2001). In the current research, the outcomes of microneedling in combination were compared with a recently introduced topically applied growth factor. These variables are believed to reduce inflammation recovery time and progressively enhance textural character by stimulating collagen synthesis induced by microneedling.

As the Future Perspective, in a split-face clinical study, the effectiveness of the microneedle patch in improving nasolabial folds was investigated. As evaluated by dermatologists, both the microneedle patch with HA solution and the microneedle patch alone significantly improved the Mertz aesthetic score of the nasolabial folds. Both patient groups showed significant improvement from week 4 to the end of the study, but no significant difference was observed between the two groups. Possibly, the low concentration (1.8%) of the HA solution was the reason for this result. In theory, both the microneedle patch and the 1.8% HA solution can improve wrinkles. However, the effect of the microneedle patch may be greater than applying 1.8% HA. According to data, there was no significant difference between the two groups in wrinkle improvement. Nonetheless, the satisfaction score for the microneedle patch with HA solution group was higher than the microneedle patch alone group, based on self-ratings by participants (Yaar *et al.*, 2002). This improvement may be due to the percutaneous microtrauma caused by the microneedle patch and increased permeability of the drug across the channels created by microneedles (Gilchrest, 1989). Many previous studies have suggested the utility of microneedle devices for delivering substances through the skin (Tammi *et al.*, 2005). Tammi *et al.* showed that skin microtrauma itself can stimulate epidermal HA synthesis via upregulation of hyaluronan synthase expression. In dermatology, medical needling causes skin color normalization and healthy skin adaptation after repeated treatments of hypertrophic burn scars (Kay-Hendrik *et al.*, 2018). Kim *et al.* showed that in cosmetics, due to their patient-friendliness, safety, and effectiveness in improving wrinkles, microneedle patches can be efficiently and confidently used in various conditions (Kim *et al.*, 2014). Microtrauma with small needles and subsequent tissue regeneration can induce collagen synthesis and deposition, resulting in skin rejuvenation and improvement. Furthermore, the needle-stick device itself has been shown to influence angiogenesis by stimulating it in the post-needle wound healing cascade. Specifically, epidermal penetration causes microtrauma and intradermal hemorrhage through parenchymal channels without affecting the basal layer's regenerative ability of stem cells. In this way, transdermal collagen induction enhances the endogenous potential for regeneration, and a modified wound healing cascade increases the expression of growth factors such as VEGF (Bao *et al.*, 2009) and TGF-$\beta$ (Faler *et al.*, 2006), both of which are important in angiogenesis and cell differentiation. Medical needles stimulate both gene expression and skin cell proliferation, which are essential for skin remodeling. Transdermal collagen induction can alter the TGF-$\beta$ signaling pathway, as TGF-$\beta$3 reaches high expression levels during early wound healing stages. This factor allows scar-free collagen synthesis and wound healing (Bandyopadhyay *et al.*, 2006; Ferguson and O'Kane, 2004). Moreover, the post-needling cascade leads to the formation of a physiological lattice-like collagen matrix of type I rather than type III collagen, which is parallel-oriented and less strong and stable (Aust *et al.*, 2008a). Over the past decade, radio-frequency microneedling (MRF) has been widely used to combat skin aging and is a useful method for treating various skin problems (Tan *et al.*, 2021; Dayan *et al.*, 2019; Alessa and Bloom, 2020).

## 25. Conclusion

Microneedle patch alone has the same effect as adding 1.8% HA solution to the microneedle patch for improving nasolabial folds. Using the microneedle patch alone is expected to improve wrinkles due to its favorable safety profile. Because the current study focused only on female participants and a low concentration of non-cross-linked HA solution, it is possible to apply this to a larger population, a wider range of skin types, and higher concentrations—or perhaps a cross-linked HA solution. A clinical trial is scheduled to be conducted. Linked HA solutions are beneficial in extending these results. Additionally, long-term follow-up is needed to examine the persistence of the observed effects. Future clinical evaluation of the technology may support previous authors' suggestions that microneedling is the most reliable alternative to more ablative therapies, particularly in skin phototypes IV to V. Such studies would benefit from research groups that include more ethnically diverse populations. This technique does not cause thermal or excessive epidermal damage. Microneedling is a simple procedure that can be performed in-office. The device is cost-effective, and the only recurring cost is the disposable microneedle cartridge. The treatment appears to be well tolerated, with minimal pain, discomfort, and downtime. Compared to other invasive techniques such as laser ablation and radio-frequency, side effects appear to be mi-

nor and easily managed. Therefore, we suggest choosing this method to guarantee skin health and restore youthful skin.

## Author Contributions

All processes for preparing the draft, writing, and editing were done by Arash Younesi as the first author. Under the supervision of Professor Hassan Morovvati and Hossein Najafzadeh Varzi, they have read, reviewed, and agreed to the published version of the manuscript.

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