Section A-Research paper

Brief overview about treatment of Post-Acne Scars and Possible Role of Nanofat injection

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Abstract

Acne is a very common inflammatory disorder of the pilosebaceous unit that consists of comedones, inflammatory papules, pustules, and nodules involving the face, chest, and back. The pathogenesis of acne is complex and involves inflammation and release of cytokines around the pilosebaceous unit, abnormal keratinization, increased sebum production, and Propionibacterium acnes. An unfortunate sequela of acne is residual scarring and disfigurement. Acne and acne scarring can have a detrimental impact on the quality of life and lead to feelings of embarrassment and low selfesteem. Therapies for acne scarring included surgical modalities, such as subcision, and punch excision and elevation, injectable fillers, chemical peels, dermabrasion, microneedling, and energy-based devices. In the past decade, there has been a trend toward using cosmetic fillers and energy-based devices to improve acne scarring. Fat grafting has the advantages of wide source, convenient acquisition, good biocompatibility, and less surgical trauma, and was first applied in soft tissue filling, such as defect repair and deformity correction. In recent years, with the deepening of research, it has been found that stromal vascular fraction (SVF) cells and adipose-derived stem cells (ADSCs) in transplanted fat have multilineage differentiation ability, can differentiate into adipocytes, osteocytes, chondrocytes, and nerve cells in different environments, and can secrete cytokines such as vascular endothelial growth factor (VEGF), hematopoietic growth factor, and basic fibroblast growth factor (bFGF), which can effectively improve the survival rate of transplanted fat. Although nanofat does not contain mature adipocytes, it is rich in a large number of SVF, which contains different types of cells such as endothelial cells, granulocytes, monocytes, and macrophages, and also includes a large number of MSCs. ADSCs are MSCs found within the SVF of subcutaneous adipose tissue. ADSCs self-renew display a multilineage developmental plasticity used in various tissue repair and regeneration clinical studies, nanofat injection could be effective in improving the scar characteristics as well as symptoms and aiding in scar rejuvenation.

Keywords: Nanofat injection, Post Acne Scars

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Acne is a very common inflammatory disorder of the pilosebaceous unit that consists of comedones, inflammatory papules, pustules, and nodules involving the face, chest, and back. The pathogenesis of acne is complex and involves inflammation and release of cytokines around the pilosebaceous unit, abnormal keratinization, increased sebum production, and Propionibacterium acnes. An unfortunate sequelae of acne is residual scarring and disfigurement. Acne and acne scarring can have a detrimental impact on the quality of life and lead to feelings of embarrassment and low selfesteem **(1)**.

Acne scarring may be either atrophic or hypertrophic. Atrophic acne scars are further subdivided morphologically into boxcar, icepick, or rolling, with the choice of treatment modality often based on scar type **(2)**.

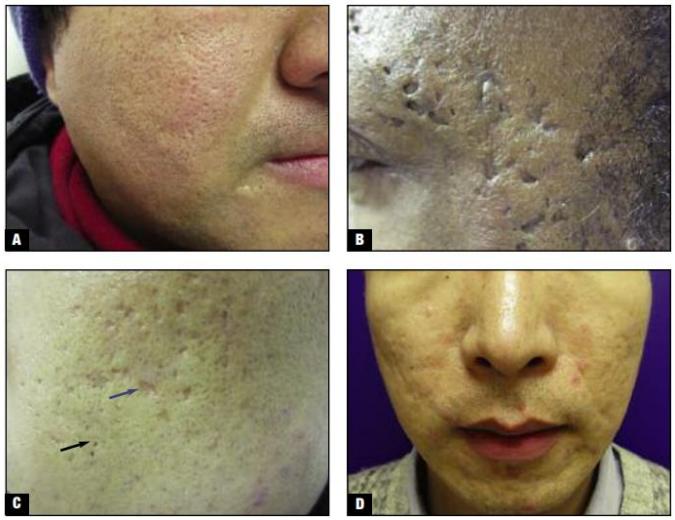

Figure (1): Atrophic acne scar types **(2)**.
(A) Icepick.
(B) Boxcar.
(C) Icepick (*black arrow*) and boxcar (*blue arrow*).
(D) Rolling.

Therapies for acne scarring included surgical modalities, such as subcision, and punch excision and elevation, injectable fillers, chemical peels, dermabrasion, microneedling, and energy-based devices. In the past decade, there has been a trend toward using cosmetic fillers and energy-based devices to improve acne scarring **(3)**.

Cosmetic fillers:

In the past decade, there has been a rapid influx of cosmetic injectable fillers, from temporary hyaluronic acid (HA) fillers to semipermanent and permanent fillers. Several of these cosmetic fillers have been used for atrophic acne scars to increase tissue volume in these lesions and to stimulate collagen production. Superficial rolling and boxcar scars respond best to cosmetic fillers and have been combined with subcision to enhance results **(4)**. **Abdel Hay et al. (5)** found moderate-quality evidence for the efficacy of cosmetic fillers in atrophic acne scars. There are many injectables available internationally that can also be suitable for the treatment of acne scarring.

Punch excision:

Punch excision is an excellent option for the treatment of icepick and deep boxcar scars. In this method, a punch biopsy instrument is used to remove deep atrophic scar tissue to the level of the subcutaneous fat and then closed with sutures. The scars should be at least 4 to 5 mm apart to prevent excess traction in the skin, or at least a 4-week interval between procedures can avoid these adverse cosmetic effects. For scars larger than 3.5 mm, elliptical or punch elevation is recommended for best cosmetic outcome **(6)**.

Although a new scar is formed in this method, it is usually less noticeable than the previous deep atrophic scar. Using a resurfacing procedure 4 to 6 weeks after punch excision can also improve the appearance of the scar. Punch excision can be safely and effectively combined with laser skin resurfacing on the same day for acne scarring **(7)**.

Punch elevation:

Punch elevation is a useful tool for shallow and deep boxcar scars. This technique combines aspects of punch excision and grafting. A punch biopsy tool is used to excise the scar down to the subcutaneous fat, and the tissue is then elevated slightly above the plane of the skin and fixed into place with sutures or steristrips. During the wound healing process, the elevated graft retracts slightly to the surface of the surrounding skin to improve the appearance of the scar **(8)**.

Chemical peels:

A chemical peel is a quick outpatient procedure that can be used to treat acne scarring. Mild acne lesions and shallow atrophic acne scars can respond well to mild and medium depth peels, such as 20% to 35% TCA, alpha hydroxy acids, salicylic acid, and Jessener's solution **(9)**.

However, these chemical peels usually work best for macular scars, have limited use for deeper atrophic scars, and should be used cautiously in darker-skinned patients because of the potential for pigmentary alterations. Deep chemical peels have fallen out of favor for the treatment of acne scars because of their significant side effect profile, such as dyschromia and scarring **(2)**.

Dermabrasion:

Dermabrasion involves the use of manual derma-sanding using sandpaper and hydrogen peroxide for hemostasis, or a rotating motorized hand piece attached to either a serrated wheel, wire brush, or diamond-embedded fraises to remove the epidermis and upper dermis. By removing the superficial layers of the skin, the wound healing process creates a smoother and more regular appearance of the scar, and new collagen is formed **(10)**.

Dermabrasion is useful for superficial atrophic acne scars, such as rolling or shallow boxcar scars, but is less effective for icepick scars. Advantages of dermabrasion include improvement in the appearance of superficial atrophic scars with only one treatment. However, the dermabrasion technique is operator-dependent, and that the procedure is painful and requires local or general anesthesia. There is significant postoperative pain and a lengthy healing time lasting up to several weeks with prolonged erythema and postprocedural dyschromia. There are other resurfacing modalities that offer fewer side effects and have a quicker recovery time, such as fractional ablative lasers **(11)**.

Microneedling:

Microneedling is an inexpensive treatment option for acne scars. It consists of a sterile rolling device with several fine sharp needles applied to acne scars to create multiple small micropunctures in the papillary to mid-dermis. By creating these small wounds in the dermis, a cascade of growth factors is initiated that results in collagen stimulation and production. As microneedling penetrates only to the depth of the upper dermis, it is most useful for shallow boxcar and rolling scars. A usual treatment course with microneedling consists of 3 to 5 sessions spaced 4 weeks apart, and results are seen in 3 months. Patients usually experience a moderate improvement in acne scar appearance **(9)**.

Platelet-rich plasma:

Plasma-rich plasma (PRP) is an emerging therapeutic tool that consists of a preparation of the patient's own concentrated platelets in plasma to promote wound healing through several growth factors and cytokines present in the concentrate. Plasma-rich plasma has been used in several areas of medicine, including for tendon injury, chronic ulcers, and alopecia **(12)**.

Circi et al. (13) have investigated PRP for acne scars, and they have shown that this treatment is safe and mild to moderate clinical improvement after intradermal or laser-assisted PRP delivery. **Lee et al. (14)** treated 14 patients with acne scars with an ablative CO2 laser, and on one side of the face applied PRP. They showed slightly faster healing and clinical improvement on the PRP-treated side.

Radiofrequency:

Radiofrequency (RF) is an evolving tool that was used initially in dermatology for skin rejuvenation. This device uses electromagnetic radiation to generate an electric current that heats the dermis causing neocollagenesis and skin contraction **(15)**.

Radiofrequency has decreased downtime and risk of scarring and infection compared with ablative lasers, and it can be safe to use in all skin types as it is chromophore-independent, unlike other energy-based modalities, such as CO2 laser. The initial RF device was monopolar and has evolved into bipolar and later fractional bipolar RF (FRF). The earliest studies using RF to treat acne scars were with the monopolar and bipolar RF devices **(16)**.

Fat transfer:

Fat transfer (FT) offers the advantage over synthetic fillers because of its autologous nature. Acne scars are often subcised immediately prior to treatment with FT. Some fat does not survive the transfer process, and survival is often practitioner-dependent. Thus, most patients require subsequent transfer procedures **(17)**.

In one study comparing three sessions of fractional CO2 laser to one session of FT in 22 acne scar patients, FT proved more effective. In the fractional CO2 laser group, less than 20 percent of patients had excellent scar improvement and 0 had marked scar improvement. Alternatively, in the FT group, scar improvement was graded as 30 percent excellent and 30 percent marked. Thus, although FT may be effective for acne scarring, results are not permanent and the procedure is highly operator- dependent **(18)**.

Nanofat injection

Fat grafting has the advantages of wide source, convenient acquisition, good biocompatibility, and less surgical trauma, and was first applied in soft tissue filling, such as defect repair and deformity correction. In recent years, with the deepening of research, it has been found that stromal vascular fraction (SVF) cells and adipose-derived stem cells (ADSCs) in transplanted fat have multilineage differentiation ability, can differentiate into adipocytes, osteocytes, chondrocytes, and nerve cells in different environments, and can secrete cytokines such as vascular endothelial growth factor (VEGF), hematopoietic growth factor, and basic fibroblast growth factor (bFGF), which can effectively improve the survival rate of transplanted fat **(19)**.

There are three types of fat used for fat grafting: macrofat, microfat, and nanofat:

1) **Macrofat:** Fat grafts are harvested with volume larger than 2.4 mm, is indicated for filling a wide range of sites such as the breast and buttocks and is generally injected using blunt needles with a diameter of 2 mm and above **(20)**.
2) **Microfat:** Fat grafts are harvested using a cannula with a hole diameter ranging from 1.2 to 2.4 mm, an emulsifier with a hole diameter of 1.2 mm, and a parcel diameter of less than 1.2 mm. Using the mircofat on the forehead, eyelids, brows, as well as the nose and hands, is highly advised, without concern for possible complications when injecting larger fat particles through bigger instruments **(20)**.
3) **Nanofat:** Fat grafts extracted using a 1.2 to 2.4 mm diameter cannula, 400 to 600 μm emulsifier, and 400 to 600 μm parcel diameter. The intradermal use of nanofat for the treatment of superficial rhytids is highly recommended. Macrofat grafting is mainly used to establish large volumes. Keeping as many viable adipocytes as possible is important, especially in cases of breast reconstruction **(21)**.

Due to the inability to establish large fat volumes, nanofats are not suitable for these indications. Microfat and nanofat injections are typically performed concurrently. Microfat offers soft tissue structural support and filling effect, whereas nanofat enhances skin quality and promotes tissue regeneration in applications of scars, chronic wounds, and facial rejuvenation **(21)**.

The concept of nanofat was first proposed by **Tonnard et al. (21)**, where the obtained particulate fat was extracted for mechanical emulsification followed by filtration to obtain SVF-gel rich in ADSCs. By repeating or improving ***Tonnard***'s nanofat preparation method, researchers have successively reported the preparation techniques of nanofat.

Yu et al. (22) indicated that all mature adipocytes in nanofat were destroyed. However, there were still many mesenchymal stem cells (MSCs) with great stem cell proliferation ability, which also had a number of differentiation functions and paracrine abilities and were the main components in nanofat. Nanofat is rich in SVF and ADSCs, which can regulate neovascularization and tissue regeneration through paracrine effects or directly differentiate into adipocytes to improve fat graft survival rates and play an essential role in tissue repair and regeneration.

Harvesting and preparation of nanofat:

Tonnard technique:

To obtain nanofat, a patient's fat tissue is first harvested from a donor area, such as the hips, abdomen, or back. Negative pressure liposuction is performed using a standard liposuction device. The liposuction tube was selected as a 3-mm diameter cannula with multiple orifices, a sharp side hole of 1 mm in diameter. The obtained fat is rinsed with normal saline and filtered through a sterile nylon cloth with a 0.5-mm pore size. The filtered fat is transferred into two 10-mm syringes and connected with Luer-Lok connecting tube. After

pushing back and forth about 30 times, the granular fat is seen to become chylous. Finally, the emulsified fat is filtered once again on the nylon gauze with a diameter of 0.6 mm. The collected nanofat is injected intradermally with a 27-G needle **(21)**.

Other techniques:

Based on the ***Tonnard*** technique, different scholars have modified it accordingly. **Liang et al. (23)** transferred the fat between two 20-cc syringes connected by a medical female-to-female Luer lock connector to achieve mechanical emulsification.

Bi et al. (24) suggested that nanofat prepared by ***Tonnard*** were obtained by physical methods, which severely disrupt the activity of adipocytes during the processing of fat. They reported a new approach to nanofat by chemical digestion with type I collagenase followed by centrifugation. The obtained nanofat includes adipocytes, adipose progenitor cells, and MSCs. The obtained nanofat was named "Vivo nanofat." They determined that the Vivo nanofat contained active components of adipose tissue-derived MSCs by cell colony formation assay, flow cytometry, adipogenesis, and osteogenesis induction. The study also found that Vivo nanofat contained more stem cell active components than nanofat, which expressed intercellular markers and had multilineage differentiation potential.

Liang et al. (23) showed that Vivo nanofat had a higher survival rate and a lower absorption rate. The size of the transplanted Vivo nanofat was 0.81 ± 0.07 cm3, which was more significant than that of nanofat 0.50 ± 0.17 cm3.

Pallua et al. (25) proposed a two-step centrifugation protocol based on the ***Tonnard*** technique and named the obtained concentrated nanofat as lipoconcentrate. They indicated that the lipoconcentrate contained a significantly higher amount of ADSCs and endothelial progenitor cells than nanofat centrifuged one time.

Lo Furno et al. (26) concluded that the ***Tonnard*** technique lost a large number of ADSCs during the preparation of nanofat and proposed the concept of second-generation nanofat (Nanofat 2.0), which have the same preparation process as the ***Tonnard*** technique, except that the last step, that is, the filtration of emulsified fats, is omitted. They suggested a higher ADSCs content and better differentiation ability in Nanofat 2.0.

Mechanism of nanofat:

Nanofat is a natural emulsified suspension derived from adipose tissue. Nanofat can promote skin regeneration because of the presence of stem cells and growth factors. **Xu et al. (27)** have shown that grafted adipocytes in adipose tissue are destroyed after emulsification. Still, the emulsification process does not significantly affect several differentiation abilities such as stem cell yield, viability, or adipogenesis. Hence, stem cells, instead of grafted adipocytes, are more likely to be responsible for the regenerative effect on skin. Although nanofat does not contain mature adipocytes, it is rich in a large number of SVF, which contains different types of cells such as endothelial cells, granulocytes, monocytes, and macrophages, and also includes a large number of MSCs. ADSCs are MSCs found within the SVF of subcutaneous adipose tissue. ADSCs self-renew display a multilineage developmental plasticity used in various tissue repair and regeneration clinical studies. The addition of ADSCs to injectable autologous particulate fat improves the survival of transplanted fat. SVF also has regenerative properties compared with ADSCs, and it is easy to collect **(28)**.

Although microfat contains adipocytes that are intact and alive, as well as their surrounding cell milieus such as SVF, ADSCs, and CD34(+), it requires needles larger than 27 G for smooth fat injection. However, nanofat with the above mentioned benefits can achieve skin regenerative purposes with smaller needles by reducing the number of adipocytes **(21)**.

Yu et al. (22) transplanted nanofat combined with macrofat into the subcutaneous tissue in nude mice. The results at 12 weeks after transplantation showed that the combination group exhibited higher graft weight and volume retention, better tissue structure, and higher capillary density than the macrofat group. They suggested that cotransplantation nanofat can strongly and effectively enhance neovascularization and fat graft survival. Moreover, nanofat contains dead adipocytes, releasing cytokines, and attracting macrophages to release growth factors, thereby stimulating the differentiation of ADSCs and tissue regeneration.

ADSCs have wound repair function and multilineage differentiation ability, differentiated into adipocytes, osteoblasts, chondrocytes, and self-renewal ability under certain conditions. ADSCs have also been found to have paracrine functions and can secrete various growth factors such as VEGF and bFGF. VEGF and bFGF play a key role in fat transplantation **(29)**.

VEGF binds to vascular endothelial growth factor receptor 2 to promote vascular endothelial cell proliferation and cell migration, thereby inducing the regeneration of blood vessels, and increasing the permeability of blood vessels and the reconstruction of the neovascular network, hence improving the fat graft survival and reducing fat graft resorption **(14)**.

BFGF contributes to angiogenesis and regeneration and can also activate various repair cells. BFGF can act on endothelial cell chemokines and promote the division of endothelial cells, so it has a vital role in promoting adipocyte proliferation and differentiation and skin regeneration, and wound repair **(30)**.

ADSCs can secrete various antifibrotic factors, such as interleukin-10 and hematopoietic growth factor, through paracrine effects. These substances can participate in the repair process of mucocutaneous wounds, inhibit scar formation while improving skin texture, and play an excellent therapeutic effect in facial rejuvenation and scars **(31)**.

ADSCs have also been found to inhibit the expression of scar-promoting proliferation genes in hypertrophic scar fibroblasts (HSFs) through paracrine effects, such as type I and III collagen, transforming growth factor β1, interleukin-6, alpha-smooth muscle actin, fibronectin, and connective tissue growth factor, while promoting the expression of antifibrotic genes, such as decorin and matrix metalloproteinase-1 **(31)**.

In addition to inhibiting scar hyperplasia by secreting antifibrotic factors, ADSCs in nanofat may have other mechanisms against fibrosis. **Redd et al. (32)** have shown that the inflammatory environment of the wound healing can stimulate MSCs to initiate immunomodulatory effects, such as upregulating the expression of prostaglandin E2 and cyclooxygenase-2, thereby inhibiting or alleviating local inflammatory response and immune dysfunction. Besides, ADSCs can also inhibit the protein expression levels of transforming growth factor β1 and its intracellular signaling pathway-related molecules such as phospho-mothers against decapentaplegic homolog 2 (p-sma2), p-smad3 in HSF, thereby inhibiting the proliferation, migration, and contraction of HSF, and ultimately achieving the inhibition of scar hyperplasia.

Clinical applications of nanofat:

Application in facial skin rejuvenation:

Since nanofat has no filling ability, nanofat grafting achieves the purpose of facial skin rejuvenation by injecting regenerative cells and extracellular elements **(21)**. According to the study of **Tonnard et al. (21)**, **Tonnard et al. (21)** have demonstrated an improvement in skin quality immediately after nanofat grafting in 67 patients in the treatment of facial wrinkles and photoaged skin, reaching the best 4 to 6 months after surgery. Besides, 6 months after nanofat transfer, the clinical effect of facial skin rejuvenation in the surgical area is significant, without complications or other adverse reactions.

Mesguich Batel et al. (33) performed intradermal injection of nanofat with a small needle into perioral wrinkles in four elderly patients aged 50 to 59 years and found significant improvement in perioral wrinkles and high patient satisfaction after 4 months.

Menkes et al. (34) used nanofat combined with platelet-rich fibrin injection to treat facial skin aging, and the results showed that 103 patients who received nanofat combined with platelet-rich fibrin injection had more significant improvement in facial skin texture and satisfaction than 128 patients who received hyaluronic acid injection, without causing any complications (eg, infection, allergic reactions, or paresthesia).

Kim et al. (35) have shown that ADSCs can whiten the skin by inhibiting melanin synthesis by downregulating the expression of tyrosinase and tyrosinase-associated protein 1. **Oh et al. (36)** applied nanofat to treat 19 cases of lower eyelid skin pigmentation, and follow-up of 2 to 4 months revealed that the dark coloration of all patients was significantly improved, with only mild ecchymosis and swelling after surgery.

Nanofat injection in acne scars:

Because the scar tissue contains fibrotic tissue and has a hard texture, the injection of fat into the scar requires that the injection needle be thin enough. Nanofat particles have a small diameter, smoothly pass through a

27-G needle, and have a relatively large contact area with the scar after injection, so nanofat has unique advantages in treating scars repair **(37)**.

Neuber first described autologous fat grafting (AFG) in 1893 and it was further recognized by Coleman. In addition to its known filling effect, AFG is considered a potential mechanism for treating scars owing to the presence of adipose tissue derived stem cells (ADSCs) which have a high regenerative ability and can repair injured tissues **(38)**.

Fat grafting has emerged as a credible solution for the reconstructive treatment of scars. ADSCs contribute to wound healing by inducing new blood vessels formation and releasing growth factors that help reduce inflammation and fibrosis. ADSCs resemble "seeds" which can recultivate their environment with new cells inducing tissue regeneration **(39)**.

The mechanical procedure of emulsifying and filtration of fat to obtain "nanofat" was firstly recognized by **Tonnard et al. (21)**. Nanofat is considered a substantial source of ADSCs which can promote wound healing and help in tissue reconstruction through release of growth factors.

Uyulmaz et al. (40) injected nanofat intradermally or directly into the scar tissue at the scar, wrinkle, or skin discoloration in 52 patients. The skin quality was assessed according to the scoring system, and patient satisfaction was recorded. Follow-up of 155 ± 49 days revealed that 40 cases of scars, 6 cases of wrinkles, and 6 cases of skin discoloration were effectively treated. The quality of scars was significantly improved after treatment high patient satisfaction. They demonstrated that nanofat transplantation helped to improve scars, wrinkles, and skin discoloration.

Tenna et al. (41) injected nanofat subcutaneously and found that nanofat treatment was effective in atrophic scars. They treated acne scar patients aged 18 to 52 years with platelet-rich plasma plus nanofat for an average of two treatments, some of which were followed by fractional CO2 laser resurfacing treatment. They showed that platelet-rich plasma plus nanofat with or without laser treatment had good clinical effects on acne-induced scars with increased skin thickness.

Jan et al. (42) injected "unfiltered nanofat" into the subcutaneous or intradermal layers of 48 postburn facial scars and found significant improvements in both pigmentation and flexibility in scar tissue after 6 months of follow-up.

The pathological changes could be owed to the presence of ADSCs within nanofat which are able to stimulate hyperplasia of epithelium and induce new blood vessels formation. The heterogeneous multipotent stem cells within the ADSCs can transform into the host cell lineage such as adipogenic, chondrogenic, cardiogenic, and neurogenic **(43)**.

Shalaby et al. (44) showed that nanofat injection has been shown to have beneficial effects in the treatment of atrophic scar, wrinkles, and skin discolorations. It is highly effective in improving the height and pliability of all scars with mild improvement in pigmentation and vascularities.

Rageh et al. (45) evaluated the role of autologous nanofat injection in refining the esthetic appearance of post-traumatic scars, along with pathological correlation of the results. They concluded that nanofat injection for treating post-traumatic scars resulted in a significant improvement from both clinical and pathological perspectives.

Abd Elfatah et al. (46) evaluated the effect of nanofat grafting on postburn and post-traumatic facial scars. They concluded that autologous emulsified nanofat injection is effective in improving the scar characteristics as well as symptoms and aiding in scar rejuvenation.

Applications in other aspects:

Nanofat has been used in joint diseases. **Mahmmood and Shihab (47)** applied nanofat injection on 11 patients (3 males and 8 females) diagnosed with temporomandibular joint disease, aged between 18 and 34 years, of which 3 cases undergo unilateral intra-articular nanofat injection, and 8 cases undergo intra-articular nanofat injection. They showed that the degree of pain was reduced, and the maximum mouth opening was increased in patients, suggesting that the nanofat injection is effective, safe, and simple in the treatment of temporomandibular joint disease, which is acceptable to patients without significant adverse reactions. Nanofat has also been applied to vulva lichen sclerosus with good clinical results.

Tamburino et al. (48) injected nanofat into the subcutaneous layer of the labia majora and clitoris. Although some patients had a recurrence of clitoral phimosis, the skin texture and elasticity were improved, and the postoperative itching and burning sensation were also reduced.

Also, compared with lipofilling grafting, nanofat grafting is easier to apply to scalp areas requiring high-precision injections. This technique can be used as a supplement for hair follicle transplantation or as a regenerative treatment for alopecia **(49)**.

Conclusion

nanofat injection could be effective in improving the scar characteristics as well as symptoms and aiding in post acne scar rejuvenation.

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