Discussion: Effects of Nanofat in Plastic and Reconstructive Surgery: A Systematic Review

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We read with great interest the article entitled "Effects of Nanofat in Plastic and Reconstructive Surgery: A Systematic Review," by Tran et al.[1] The authors performed a systematic review, starting with 611 articles and ending with 12 articles, that showed, although with a low level of evidence, a beneficial effect of nanofat on skin rejuvenation, scars, fat grafting, diabetic wound healing, and hair growth. They conclude that nanofat has a regenerative effect; is practical, safe, and time- and cost-effective; and has no severe complications. In the decade following the introduction of nanofat in 2013,[2] research has shown that nanofat has anti-inflammatory, antifibrotic, antiapoptotic, immunomodulatory, and pigment-regulating properties. It also remodels the extracellular matrix and enhances angiogenesis.[3] So nanofat has obvious regenerative and tissue remodeling potential, and it could be a great application in translational and regenerative medicine, orthopedic and sports medicine, plastic surgery, and dermatology. The main concerns about nanofat are the difficulty in explaining the effects and the mechanisms of action, as well as the multitude of methods that were introduced after we described our original technique of nanofat grafting in 2013.

From time to time, colleagues ask us, "How did you actually invent nanofat?" We have to admit that, in plastic surgery, nothing is really invented. It is more a question of progressive insights. It started with the clinical observation, made by us and many other colleagues, that skin quality improved after a microfat grafting procedure was performed in the subcutaneous layer. So, we tried to find a way to inject the microfat precisely with very small needles into the superficial layer of the skin. This is where we decided to emulsify (or fractionate or dissociate or whatever you want to call it) the microfat by squeezing it from a full to an empty syringe through a small-diameter luer-lock connector, after which we filtered the emulsified microfat through a 500-µm filter. After injecting the "nanofat" in a series of aging skin conditions, we saw obvious clinical improvements in skin texture, pigmentation, and fine rhytids. Microscopic analysis revealed that the emulsification process destroyed the adipocytes, but the smaller cells of the stromal vascular fraction (SVF), including the adipose-derived stem cells (ASCs), were kept intact. These cells also kept their adipogenic capacity. In the years following the introduction of nanofat, a multitude of other mechanical devices were introduced. The developers pretended that they had a better stem cell count and viability, while not showing any difference in clinical activity. In recent years, more and more attention has been paid to the function of the ASCs instead of viability and cell count. Llull's group discovered that, functionally, the SVF obtained by mechanical dissociation performs better than enzymatically isolated SVF, although this technique was long seen as the accepted standard.[4] This proves that cells of the SVF perform better in their native niche and that cellular action without intercellular communication is useless. All the different emulsification devices on the market nowadays have only one thing in common: they produce a mechanical trauma to the adipose tissue. Two things happen during whatever dissociation process is used: mature adipocytes are destroyed and the smaller cells of the SVF are stressed. In their research, Evans' group suggested the term "stress-induced SVF," as they claim that nanofat processing is more than breaking down adipocytes.[5] The mechanical stress leads to upregulation of pluripotent markers that connote a

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Fig. 1. (*Left*) A 73-year-old woman requested facial rejuvenation without incisional surgery. Microfat grafting was performed in the infrabrow region (2 cc/side); malar area (10 cc/side); nasolabial folds (1.5 cc/side); marionette grooves (1.5 cc/side); sharp-needle intradermal fat grafting perioral region (3.8 cc); glabella (1 cc); forehead (3 cc); and white roll of the upper lip, lower lip, and philtrum (3.2 cc each). Microliposcution of the jowls (2 cc/side) was also performed. Full face and neck nanofat mcironeedling was performed (10 cc of nanofat). The surgery was performed with the patient under local anesthesia and took 1.5 hours. Chemical denervation of the corrugator, procerus, and frontalis muscles was performed and maintained every 6 months. (*Right*) The postoperative result is shown 5 years postoperatively. Note the improvement in skin quality more than 5 years after a single nanofat treatment.

Fig. 2. (*Left*) A 41-year-old woman is shown at consultation for a rhinoplasty. An open structural rhinoplasty was proposed, along with microfat grafting to optimize facial volumetric proportions and nanofat microneedling to improve skin quality. Microfat grafting was performed in the infrabrow region (1.5 cc/side), malar area (5 cc), upper lip (12 cc), sharp-needle intradermal fat grafting white rolls (2 cc), and philtrum (2 cc). Full face and neck (10 cc) nanofat microneedling was also performed. (*Right*) Result is shown 3 years postoperatively. Note the change in skin quality, from dull and uneven pigmented skin to shiny, healthy skin.

Fig. 3. (*Left*) A 51-year-old woman with moderate skin laxity, centrofacial deflation, and sun-damaged skin requested full facial rejuvenation. A simple minimal-access cranial suspension lift was performed using 2 pursestring sutures, along with a gliding browpexy and a reduction neck lift with removal of the superficial lobe of the submandibular gland, shaving of the anterior belly of the digastricus, and resection of subplatysmal fat. The procedure was completed with a median platysmaraphy and complete transection of the platysma below theraphy. Centrofacial microfat grafting of the infrabrow region (1.5 cc/side), malar area (8 cc/side), and sharp-needle intradermal fat grafting perioral region (3.4 cc) was also performed, along with nanofat microneedling of the full face and neck (12 cc). (*Right*) The result is shown 10 months postoperatively. Note the improvement in skin quality (radiance and pigmentation).

regenerative capacity. All of this matches with an evolutionary mechanism of how trauma can trigger repair and regeneration. Indeed, after 23 years since the discovery of ASCs in fat tissue in 2001,[6] we are still not able to regenerate organs or even tissues, neither in vitro nor in vivo. Stem cells were considered a kind of magic cell containing the "intelligence" to regenerate tissues. In recent years, more emphasis has been placed on the paracrine functions of stem cells. The research of this so-called secretome of the stem cells, together with their intercellular crosstalk and signaling between cells, revealed the importance of exosomes and other microvesicles. Recent research has revealed that even a cell-free fat extract has similar regenerative capacities as cell-containing nanofat.[7–9] This highlights the matter from a completely different view. If we could find out which signals are responsible for skin regeneration, fat graft enhancement, hair growth, and cartilage regeneration, or for optimizing wound healing, then we could personalize the treatment for any indication. This research is actually ongoing right now,[10,11] and as Tran et al. mention in their article, the purpose of this systematic review is to attract the focus of fellow plastic surgeons to the research possibilities of nanofat. Indeed, many questions remain unanswered. What happens during the destruction of adipocytes and mechanical stress of the SVF with regard to upregulating regenerative parameters? What causes the histological changes in nanofat-injected tissue? How can the improvement in volume retention of nanofat-enriched fat grafting be explained? Should we discard the oil from the nanofat, or does it contain any regenerative potential? Exploring the regenerative capacities of living tissues dives into the fundamental questions of what life and death really are, and we are still far from finding answers to all these questions. In this context, we hope Tran et al.'s article will stimulate researchers to further explore this interesting and intriguing field.

As mentioned in the article, the complications and side effects of nanofat are negligible, whereas the clinical results are obvious, so we routinely incorporate nanofat microneedling as a routine procedure in almost every facial rejuvenation procedure we perform.[12] As the results keep improving up to 3 years after application, we now

Fig. 4. (*Left*) A 55-year-old woman presented with moderate skin laxity, centrofacial deflation, and heavily sun-damaged skin with pigment distortions and deep wrinkling. A simple minimal-access cranial suspension lift was performed using 2 pursestring sutures combined with a gliding browpexy. Centrofacial microfat grafting was performed in the infrabrow region (2 cc/side), malar area (10 cc/side), upper lip (2.7 cc), lower lip (3 cc), sharp-needle intradermal fat grafting upper lip (2.3 cc), glabella (0.5 cc), and forehead (2.3 cc). A lip lift was also performed, along with centrofacial erbium laser resurfacing of the nonundermined skin. Immediate nanofat microneedling (12 cc) of the whole face, including the lasered area, and the neck was performed. Nanofat cream (10 cc of nanofat + 10 cc of Cetomacrogol) was given to the patient as dressing in the first postoperative week. (*Center*) Result is shown at 5 weeks postoperatively. Note the quick healing and negligible redness after a deep resurfacing procedure. (*Right*) Result at 3 years postoperatively. Note the stable result with regard to the improved quality of the skin.

see nanofat treatments as a real antiaging tool in our rejuvenation/regeneration strategy (Figs. 1 through 3). We also use nanofat microneedling immediately after a resurfacing procedure (laser or peel) to promote faster healing of the skin and reduce postresurfacing redness (Fig. 4). The extra challenge in modern facial rejuvenation surgery is not only to make our patients look younger, but also to slow down, stop, or even reverse the skin's aging process. This is where regenerative techniques come into play.

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DISCLOSURE

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PATIENT CONSENT

Patients provided written informed consent for the use of their images.

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