JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2021, VOL. 55, NO. 3, 173–180
https://doi.org/10.1080/2000656X.2020.1856678

ARTICLE

# Immediate fat and nanofat-enriched fat grafting in breast reduction for scar management

Cemal Alper Kemaloğlu[a], İrfan Özyazgan[a] and Zeynep Burçin Gönen[b]

[a]Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey; [b]Genome and Stem Cell Center (GENKOK), Erciyes University, Kayseri, Turkey

**ABSTRACT**

**Background:** Reduction mammoplasty can be successful but surgical scars may continue to be a most undesirable and unavoidable outcome. Various medical and non-invasive methods are available to minimize scar formation but as yet no methods have been discovered to eliminate them. We hypothesize that immediate fat and nanofat-enriched fat graft transfer may improve the scar quality and optimize results.

**Materials and methods:** This prospective study comprised 45 superomedial pedicle wise-pattern breast reduction patients divided into three groups of 15 in a randomized fashion. The control group had no additional injections whereas the other two groups received injections of fat and nanofat-enriched fat grafts immediately under their surgery scars, respectively. Surgical scar formation was evaluated at six months and scars were scored using the Vancouver scar scale and a visual analogue scale.

**Results:** Fat and nanofat-enriched fat graft-injected groups scored significantly better on all items of the Vancouver scar scale, except for scar height, compared to the control group ($p < 0.05$). Visual analogue scores were significantly lower in the fat and nanofat-enriched fat graft-injected groups compared to the control group ($p < 0.05$).

**Conclusions:** In breast reduction patients, simultaneous fat and nanofat-enriched fat grafting appears to be a safe and promising strategy for scar management.

**ARTICLE HISTORY**
Received 15 September 2020
Revised 31 October 2020
Accepted 23 November 2020

**KEYWORDS**
Breast reduction; scar management; fat graft; nanofat graft

## Introduction

Reduction mammoplasty is one of the most frequently performed operations worldwide. Wise-pattern skin reduction, in particular, is the commonly preferred technique for breast reduction as it can be applied to all varieties and sizes of breast [1]. However, a lengthy but poor-quality scar along the inframammary fold (IMF) is a major cause of dissatisfaction with this technique [2,3].

A scar is a sign of tissue repair that develops after surgery, injury, burns and cuts. Although scar formation is crucial for healing, it poses a major problem for patients due to the cellular and mechanical nature of the scar, creating cosmetic, psychological and functional limitations [4]. Thus, numerous measures have been reported, such as laser treatment, silicone sheets, topical creams and intralesional application of medical agents, to improve scar quality and decrease potentially related symptoms [5–9]. In recent decades, fat grafting has gained popularity for scar modulation. Previous studies have shown that fat grafting improves scar quality and provides good cosmetic results in patients with various scars developed due to trauma, surgery and burns [10–12]. This improvement may be attributed to adipose-derived stem cells (ADSCs) releasing several factors beneficial for wound healing and regeneration [13–15].

The purpose of this study is to analyze and compare the effects of an immediate fat graft and a nanofat-enriched fat graft (fat$^n$ graft) in wise-pattern breast reduction patients. In light of previous studies, we have postulated that the introduction of fat and fat$^n$ grafts will improve scar quality and provide patient satisfaction owing to the actions of ADSCs.

## Materials and methods

We performed a single-center prospective study to evaluate the effects of fat graft and fat$^n$ graft injection immediately under surgery scars in patients who underwent superomedial pedicle breast reduction with wise-pattern skin excision in our clinic in the period from January 2018 to January 2019. The study protocol was approved by the ethics committee at our institution (No. 2018/445) and written informed consent was obtained from all patients. Patients aged 18–55 years, with no additional disease and no smoking history, were included in the study. Three groups were formed in a randomized manner, each group comprising 15 patients. No additional treatment was applied to the surgical incisions in the first group (control group), whereas fat grafts were injected immediately under the surgical incisions in the second group (fat graft group) and nanofat-enriched fat graft in the third group (fat$^n$ graft group).

Scars were evaluated and scored using the Vancouver scar scale (VSS) by three independent blinded reviewers at the postoperative six-month follow-up (Table 1). Scar evaluation was performed on a 4-cm portion of IMF scars at the T-junction to standardize scar comparison between groups (Figure 1). Furthermore, patients were asked to evaluate their scars on a visual analogue scale (VAS) by marking their evaluation results from

CONTACT Cemal Alper Kemaloğlu dralperkemaloglu@yahoo.com Faculty of Medicine, Erciyes University, Köşk Mahallesi Prof. Dr. Turhan Feyzioğlu cad. No. 42, Melikgazi/Kayseri 38039, Turkey

Table 1. The Vancouver scar scale.

| Pigmentation | | |
|---|---|---|
| 0: Normal | | |
| 1: Hypopigmentation or hyperpigmentation not exceeding 5% of the whole | | |
| 2: Hyperpigmentation ranging from 5% to 30% of the whole | | |
| 3: Hyperpigmentation not < 30% of the whole | | |
| Vascularity | Pliability | Height |
| 0: Normal | 0: Normal | 0: Normal |
| 1: Red | 1: Supple | 1: Elevation of 0–1 mm |
| 2: Slightly dark red | 2: Yielding | 2: Elevation of 1–2 mm |
| 3: Dark red | 3: Firm | 3: Elevation of 2–4 mm |
| | 4: Banding | 4: Elevation of > 4 mm |
| | 5: Contracture | |

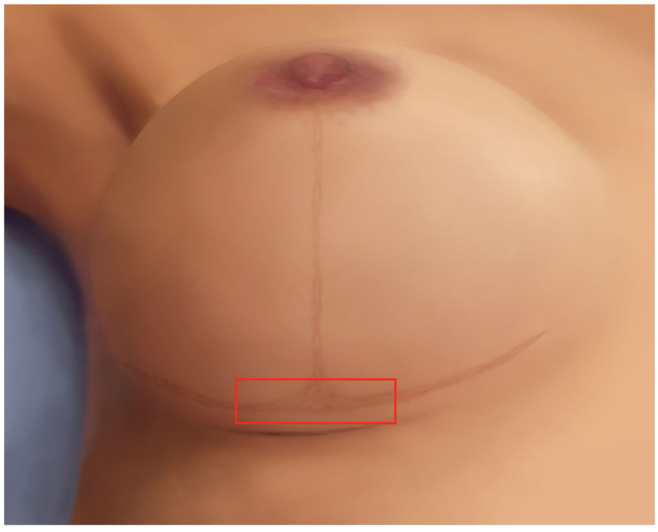

Figure 1. Scar analysis was carried out on a 4-cm portion of inframammary fold (IMF) scars at the T-junction.

1 to 10 (1, best results; 10, worst results) at the postoperative six-month follow-up.

The normality of distribution of continuous variables was tested by the Shapiro–Wilk test. Both Kruskal–Wallis and Dunn multiple comparison tests were used to compare three independent groups for non-normal data. The Mann–Whitney *U* test was used to analyze two independent samples. Statistical analysis was performed using SPSS for Windows, Version 24.0 (SPSS Inc., Chicago, IL), and continuous variables are expressed as means and standard deviations, as well as minimum and maximum values; $p < 0.05$ was considered to be statistically significant.

### Surgical technique

Patients were operated on by one of two surgeons (C. A. K. and İ. Ö.). The pre-operative markings were made when the patients were in the standing position. The new nipple position was created at the IMF level, which was approximately 21 cm away from the sternal notch. Then, markings were made according to an inverted T-scar pattern. The vertical length of the T-scar, from the nipple-areolar complex (NAC) to the IMF, was set to 6 cm in all patients. Before the operation, a mixed solution of 0.5% lidocaine and 1:200,000 epinephrine in lactated Ringer's solution was infiltrated along the incision line and in the area of estimated resection. In the fat and fat$^n$ groups, the fat grafts were harvested from the lateral border of the breast before starting the resection. Then, the pedicle was de-epithelialized and elevated from the chest wall. The resection was conducted according to the preoperative markings. The pedicle was rotated to the new location by exercising care to ensure that no undue tension or kinking was placed on the pedicle. The lateral and medial flaps were brought together in a tension-free manner to prevent delayed wound healing and the skin was closed in layers using 4/0 PDS and 5/0 Monocryl (Ethicon, New Brunswick, NJ) sutures. After the suturing procedure, fat and fat$^n$ grafts were injected under the entire surgical incision line subcutaneously by using a 23-G cannula into the fat and fat$^n$ groups, respectively (0.5 ml of fat or fat$^n$ graft injected for a 2-cm scar) (Figure 2).

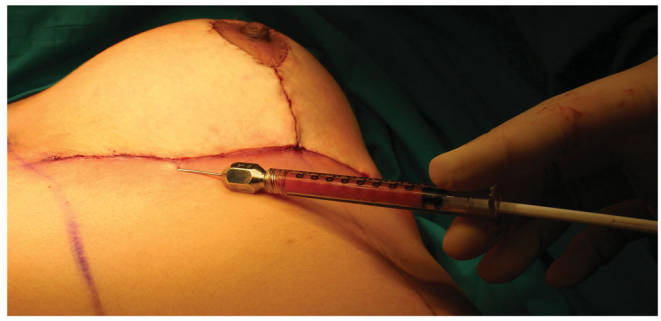

Figure 2. Intraoperative injection of nanofat-enriched fat graft under the surgical scar.

### Obtaining the fat graft and fat$^n$ graft

In the fat and fat$^n$ groups, fat grafts were harvested from the lateral border of the breasts by using a two-hole Coleman harvesting cannula with a blunt tip. The harvesting cannula was attached to a 10-ml syringe and the plunger of the syringe was pulled back to create adequate negative pressure. After harvesting the appropriate quantity of fat into the 10-ml syringe, the fat grafts were transferred from the syringe to a blood collection tube. Then, they were centrifuged at 3000 rpm (1200 *g*) for 3 min in a sterilized centrifuge rotor and spun to separate the tissue components. The supernatant oil on the surface and the liquid portion at the bottom were decanted and the middle layer (fat graft) was aspirated using a 10-ml syringe. To obtain the nanofat graft, emulsification of the fat (10 ml) was achieved by shifting the fat between two connected 10-ml syringes *via* a female-to-female Luer-Lock connector. In this way, the microfat lipoaspirate was processed into nanofat [16]. After 30 passes, the fat became liquid and this was filtered over a sterile nylon cloth to remove the connective tissue and collect the effluent (nanofat graft). Then, 1 ml of the nanofat graft was mixed with 9 ml of the fat graft to obtain the nanofat-enriched fat graft (fat$^n$ graft).

### Evaluation of the fat graft and fat$^n$ graft

To show the difference between the fat graft and the fat$^n$ graft, 12 samples were collected from six patients to conduct cell count and viability analyses. Fat graft and fat$^n$ graft samples of 4 ml each were collected from each patient. The collected samples were submitted to the Genome and Stem Cell Laboratory of our university in a transfer solution containing low-glucose Dulbecco's modified Eagle's medium (DMEM) with penicillin–streptomycin, and after collagenase type II digestion (2.5 mg/ml, Cat No. 6885, Sigma-Aldrich, Darmstadt, Germany) the viability percentages and cell counts in the fat graft and fat$^n$ graft samples were determined using the Muse Cell Analyzer (Merck Millipore, Kenilworth, NJ).

Table 2. Comparison of clinical data, total mass of breast reduction and scar scores.

| | Control group ($n = 15$) | Fat group ($n = 15$) | Fat$^n$ group ($n = 15$) | $p$ |
|---|---|---|---|---|
| Age[a] (years) | 35.3 ± 10.5 | 37.1 ± 12.4 | 37.4 ± 11.2 | 0.75 |
| BMI[a] (kg/m$^2$) | 29.8 ± 3.5 | 31 ± 3.8 | 30 ± 3.7 | 0.20 |
| Total mass of reduction[a] (g) | 1700 ± 285.5 | 1580 ± 235.6 | 1620 ± 255.4 | 0.65 |
| VSS[b] | | | | |
| Pigmentation (0–3) | 2 (1–3) | 2 (1–2) | 1 (0–2) | 0.001* |
| Vascularity (0–3) | 2 (1–3) | 1 (0–2) | 1 (0–2) | 0.002* |
| Pliability (0–5) | 3 (1–4) | 1 (0–2) | 1 (0–2) | 0.001* |
| Height (0–4) | 1 (0–1) | 0 (0–1) | 0 (0–1) | 0.703 |
| VAS[b] (1–10) | 6 (4–8) | 4 (2–6) | 3 (2–4) | 0.001* |

*Significant at $p < 0.05$; Kruskal–Wallis test.
[a]Expressed as mean ± standard deviation.
[b]Expressed as median (min–max).

## Results

All 45 patients included in the study were successfully followed-up for 6 months. Apart from one patient in the control group (who developed partial nipple necrosis), no complications were observed in the study groups. General patient demographics, total mass of breast reduction and scar scores on the VSS and VAS are summarized in Table 2.

The mean age and body mass index (BMI) for the three groups were: 35.3 years and 29.8 kg/m$^2$ in the control group; 37.1 years and 31 kg/m$^2$ in fat graft group; and 37.4 years and 30 kg/m$^2$ in the fat$^n$ graft group. No statistical differences in age or BMI were observed between the groups ($p = 0.75$).

The mean total weight of the resected mass for both breasts was 1700 g in the control group, 1580 g in the fat graft group and 1620 g in the fat$^n$ graft group. No statistical differences were observed between the groups ($p = 0.65$).

Except for scar height, all VSS scores in the fat and fat$^n$ groups were significantly lowered compared to those of the control group (Figure 3). When comparing the fat and fat$^n$ groups, pigmentation scores were significantly lower in the fat$^n$ group ($p = 0.005$); however, there was no significant difference in vascularization, pliability and height score between the fat and fat$^n$ groups ($p = 0.084$, $p = 0.988$, and $p = 0.980$, respectively). The VAS scores were significantly lower in the fat and fat$^n$ groups compared to those in the control group ($p = 0.001$ for both groups) but there was no statistical difference in VAS scores between the fat and fat$^n$ groups ($p = 0.060$; see Figures 3 and 4).

Analytical evaluation of the fat graft and fat$^n$ graft samples revealed no differences in cell viability between these two groups: the mean viability of the cells was 89.4% in the fat graft samples and 87.25% in the fat$^n$ graft samples. However, a statistically different and higher cell number was found in the fat$^n$ graft samples ($40.27 \times 10^6$ ± 30.56 cells) compared to the fat graft samples ($17.93 \times 10^6$ ± 14.93 cells; $p = 0.03$) (see Table 3 and Figure 5).

## Discussion

Reduction mammoplasty is one of the most common operations performed, not only for functional improvement but also to achieve an aesthetically pleasant breast shape. Despite the evolution in surgical techniques for breast reduction and the emergence of various methods over recent years, wise-pattern skin excision using either the inferior or superomedial pedicle is still the most frequently used technique. However, lengthy scar formation along the IMF is a major disadvantage of the wise-pattern skin excision, especially if the scar quality is poor. Manahan et al. reported that untoward scar formation accounts for half of the common complications of breast reduction surgery [17]. Meshulam-Derozon et al. reported that 40% of his reduction mammoplasty patients were dissatisfied with the appearance of their scars [2]. Brown et al. reported that the most frequent cause of dissatisfaction was the scar formation from the patient's perspective [18]. The results here are compatible with the results of previous studies, thus strengthening the results [3,19,20].

Scarring is an unavoidable component of wound healing. Despite performing the surgical technique properly and with care for the tissue, healing can end in an unpleasing appearance. Even though great advances have been introduced in the surgical techniques and adjunctive measures have been developed to decrease scar formation [5,21–23], no treatment modalities have yet been introduced in the medical literature to eliminate the risk of untoward scar formation. In particular, in the wise-pattern skin excision technique the T-junction may show delayed wound healing and undesirable scarring formation. In this regard, we reduced the pedicle as much as possible and left the lateral and medial pillars abundant to create minimal tension on the T-junction. We think this is the most effective method to prevent delayed wound healing complications in our patient series.

In contrast to the scar formation, regeneration is the other side of the healing process, characterized by scarless tissue healing and restoration of the original architecture, organization and function of the tissue. Regenerative healing is observed in the wounds of fetal skin until mid-pregnancy [24,25]. This phenomenon appears to be intrinsic to the unique properties of structures such as the fetal cells, extracellular matrix, cytokines and gene expression [26], which are likely to be efficient particularly in the inflammatory and proliferatory phases. Unlike wounds in adults, fetal wounds have a lower macrophage count and they lack the polymorphonuclear leukocytes in the inflammatory phase [27]. Other striking differences between fetal and adult tissue are observed in fibroblast functions in the proliferative phase, including migration, matrix production and differentiation [28,29]. Finally, growth factors and cytokine levels are highly variable between the wounds of fetal and adult tissue [30–32].

The balance between scar formation and scarless healing seems to be related to the modulation of cells and cytokines in the first two phases of wound healing. In that respect, ADSCs may play a key role in modulating scarring through their various properties, including the amelioration of inflammation, the release of growth factors and the capacity to differentiate into a variety of cell types [21,33,34]. Clinical studies in the literature mostly utilize the adipose tissue to benefit from the aforementioned properties of ADSCs. Several studies in the literature have shown that fat grafting provides a regenerative environment that improves scar qualities and scar-related symptoms in patients with burns and traumatic and surgical scars [35–37].

For scar management, immediate applications to cutaneous wounds have been studied by various authors, notably the use of some opioids and triamcinolone acetonide [38,39], the main mechanism of action being to decrease macrophage density and reduce myofibroblast and fibroblast activity. Although there have been some promising results, delayed wound healing, irreversible subcutaneous atrophy and hypopigmentation remain as major disadvantages of these chemicals.

Immediate fat grafting for scar management is a relatively new concept. Fat grafts contain adipocytes, preadipocytes, tissue macrophages, fibroblasts, vascular smooth muscle cells, pericytes, lymphocytes and ADSCs. In this regard, the idea of immediate fat grafting under the surgical incision is mainly to interfere with the healing process *via* ADSCs located in the fat grafts. Balkin et al.

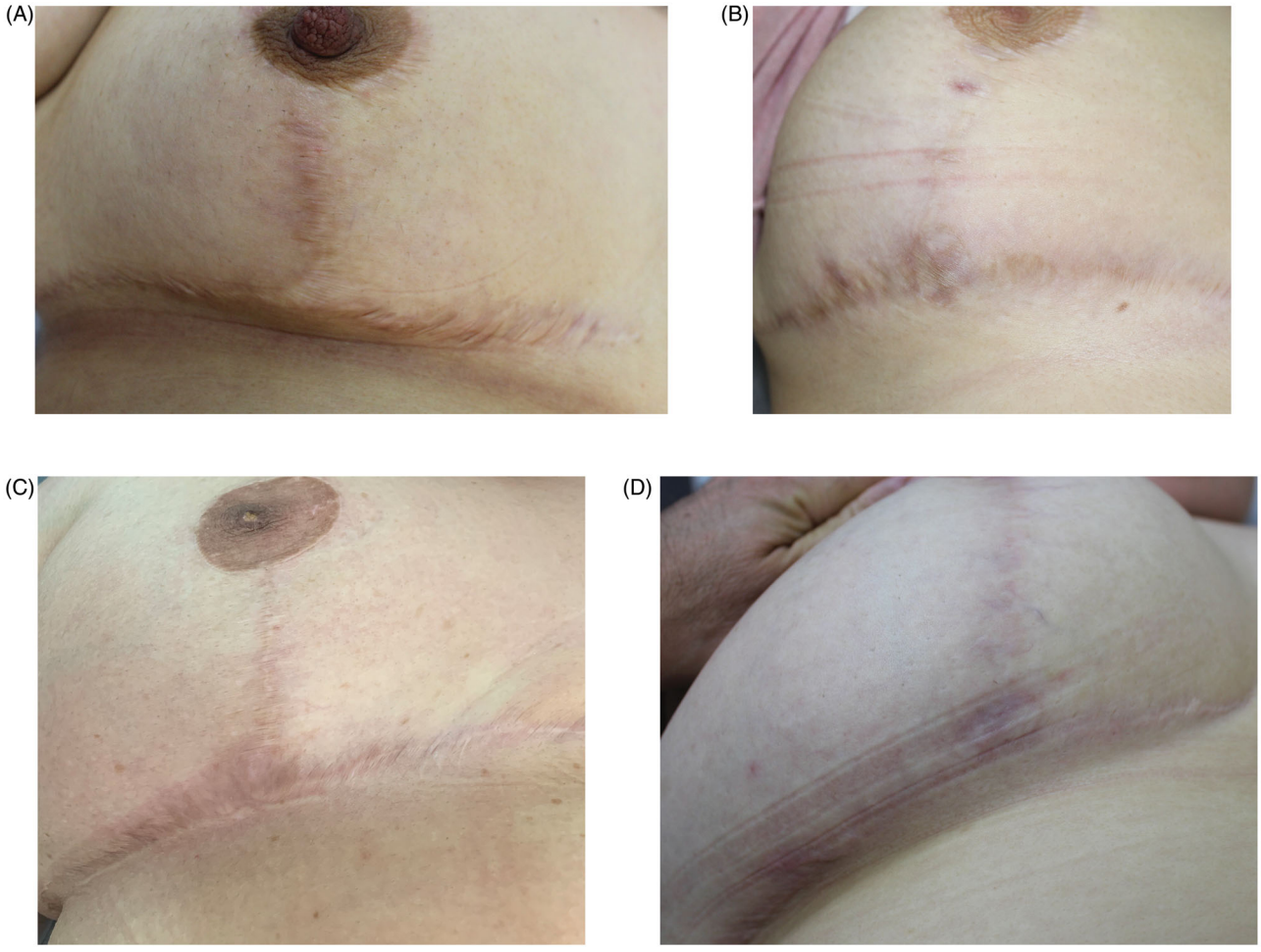


Figure 3. Postoperative photographs (A–D) of patients in the control group six months after surgery.

showed that immediate fat grafting in primary cleft lip patients increased scar quality and minimized scar burden [40]. Similar results have been reported by Zellner et al., who demonstrated that immediate fat grafting in cleft lip patients improved scar quality [41]. Although these results are promising, some limitations exist in these studies. For instance, study participants were selected from the pediatric population, the scars were very short and no information was provided on the cell count in the fat graft.

The term 'nanofat' was introduced by Tonnard et al. for the first time in 2013 to describe a new method to prepare autologous fat grafts to utilize their proposed regenerative properties [16]. It has been demonstrated that nanofat contains ADSCs but no viable adipocytes. Thus, the main clinical application of nanofat is not for filling soft tissue defects but rather to stimulate tissue regeneration and remodeling. For these purposes, nanofat has been used for improving superficial rhytides, skin discolorations and manifestations of photoaging [42–44].

In our study, we used immediate fat and fat$^n$ graft injections for the management of breast reduction surgery scars. The fat and fat$^n$ graft-injected groups scored significantly better on all items of the VSS, except for scar height, compared to the control group. Also, VAS scores were significantly lower in the fat and fat$^n$ graft groups compared to the control group. Our results showed that both fat and fat$^n$ grafts are effective at improving scar quality and patient satisfaction. The potential mechanism of fat grafting on scars is not clear but the action of ADSCs has been suggested to be a major factor. ADSCs have the paracrine ability to secrete immune-modulating and proangiogenic factors such as VEGF, HGF, and TGF-β, which might explain their ability to improve scar quality [45]. Further molecular studies are necessary to gain better insight into the roles of associated factors.

The aim of mixing nanofat and fat grafts was to enrich the fat graft with ADSCs, thus increasing the number of ADSCs per injected volume of graft and obtaining adequate grafts to inject the entire incision line. As we showed in the analytical comparison of fat and fat$^n$ graft samples, the fat$^n$ samples contained a significantly higher number of cells without compromised viability. Heterogeneous fat cell suspensions such as fat$^n$/fat graft samples consist of a heterogeneous mesenchymal population of cells that include not only adherent cell populations (ADSCs, fibroblasts) but also hematopoietic stem cells, monocyte/macrophages, erythrocytes and lymphocytes [46]. The frequency of stromal progenitors such as ADSCs ranges from 1% to 10% relative to the total nucleated cell population [47]. According to our study results, fat$^n$ graft samples contained a significantly higher number of total nucleated cells and, directly, a higher amount of ADSCs. These results are also consistent with the previous study by Banyard et al. that they noted ADSCs constitute 3.11% ± 0.8% of nanofat, which is approximately a 3-fold increase over that in standard lipoaspirate [48].

However, when we look at the clinical results there was no significant difference in VSS scores between the fat and fat$^n$ graft groups, except for pigmentation. Beneficial effects of nanofat injections on skin discoloration have been reported by Uyulmaz [42] and Tonnard [43], but the effect of fat$^n$ grafts on pigmentation changes in fresh scars has been reported for the first time

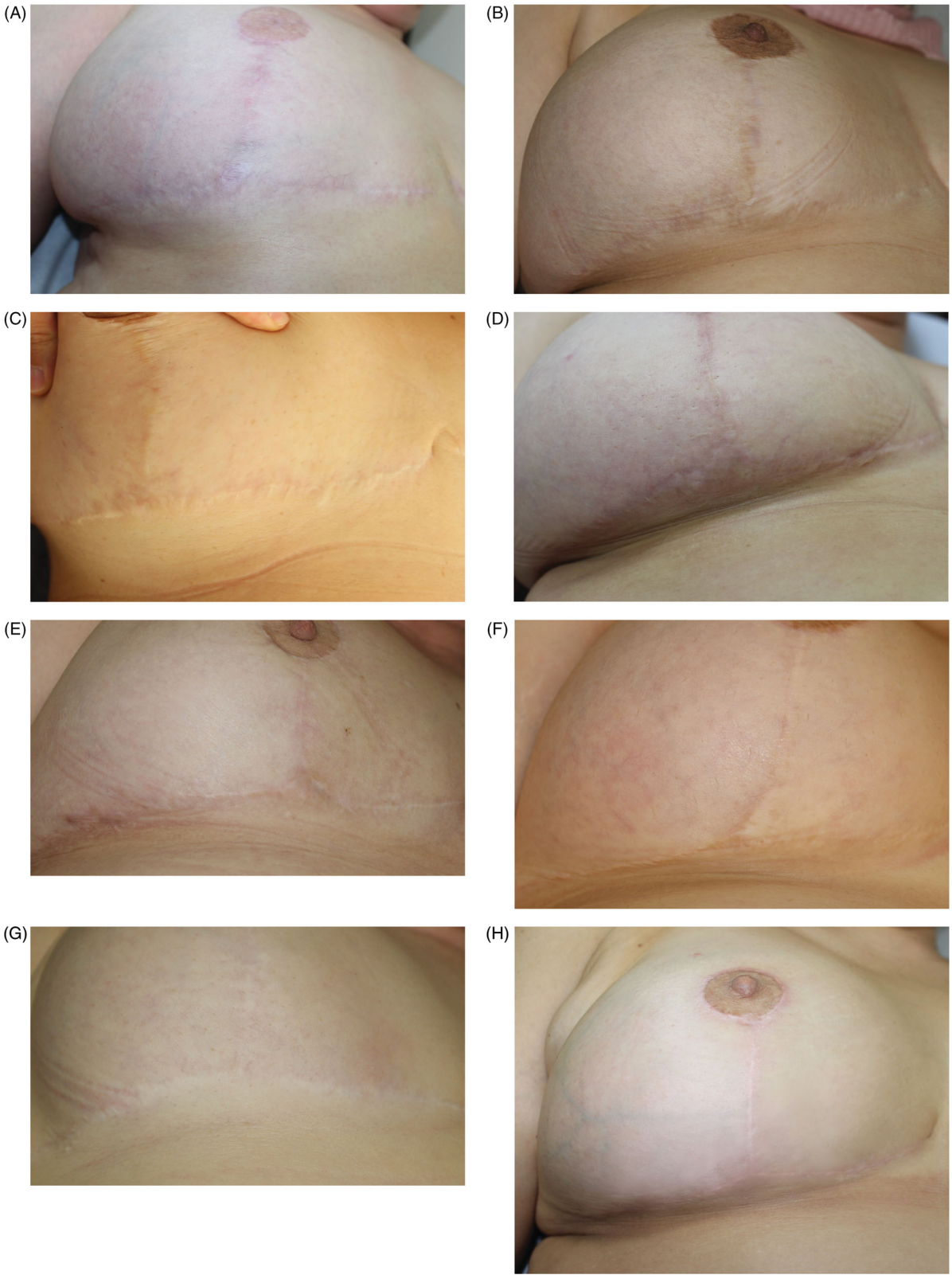


**Figure 4.** Postoperative photographs of patients in the fat graft group (A–D) and nanofat-enriched fat graft group (E–H) six months after surgery. There is no delayed wound healing in any of the groups but note the improvement of cutaneous scars in the fat graft and nanofat-enriched fat graft groups.

**Table 3.** The mean total cell count and viability of fat graft and nanofat-enriched fat graft ($fat^n$ graft) groups.

| | Fat graft ($n = 6$) | $Fat^n$ graft ($n = 6$) | *$p$ Value |
|---|---|---|---|
| Cell count (/ml) (mean ± SD) | $17.93 \times 10^6 \pm 14.93$ | $40.27 \times 10^6 \pm 30.56$ | 0.03 |
| Viability (%) (mean ± SD) | 89.4 ± 45.32 | 87.25 ± 44.80 | 0.41 |

*Mann–Whitney *U* test.

here, as far as we know. This phenomenon needs to be confirmed by other studies.

Our study is the first to use immediate fat and $fat^n$ graft injections for scar management in adults. Although our results are promising, there are some limitations: the short follow-up period (6 months), small patient numbers in the groups and lack of

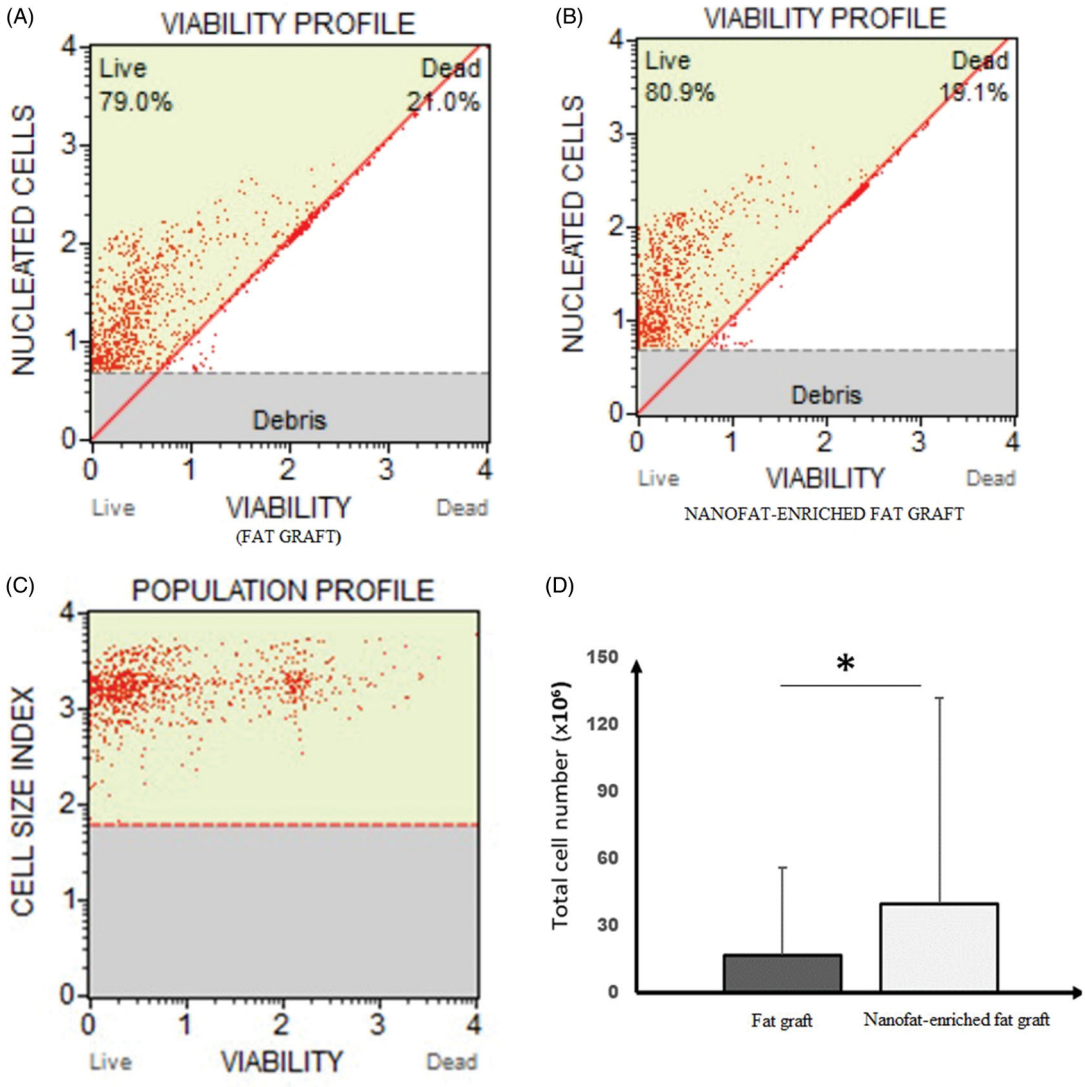


Figure 5. Representative viability profile of the fat graft (A) and nanofat-enriched fat graft (B) groups, with cell population profile (C) and cell count comparisons (D).

molecular analysis results. In addition, a better study design would have been to have a fat injection on one side and no injection on the other side of the same patient. However, for ethical reasons this could not be done.

In summary, we believe that this study provides essential information in terms of scar management after immediate fat and fat$^n$ graft treatment. Only limited data on the clinical results are available at present, but in the future a larger prospective study involving a control and fat graft groups containing different densities and quantities of ADSCs, along with histopathological analysis, may help us to understand more.

## Conclusion

In this study, we demonstrated that simultaneous fat and fat$^n$ grafting under closed surgical incision conveys beneficial effects on scars in breast reduction patients. Fat and fat$^n$ grafting may be a safe alternative to the other wound intervention therapies and without the unwanted side effects.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## References

[1] Hansen JE. Avoiding the unfavorable outcome with wise pattern breast reduction. Clin Plast Surg. 2016;43(2):349–358.
[2] Meshulam-Derazon S, Barnea Y, Zaretski A, et al. Large-volume breast reduction: long-term results. Scand J Plast Reconstr Surg Hand Surg. 2009;43(2):65–70.
[3] Dabbah A, Lehman JA, Parker MG, et al. Reduction mammaplasty: an outcome analysis. Ann Plast Surg. 1995;35(4):337–341.
[4] Niessen FB, Spauwen PH, Schalkwijk J, et al. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg. 1999;104(5):1435–1458.
[5] Sobanko JF, Alster TS. Laser treatment for improvement and minimization of facial scars. Facial Plast Surg Clin North Am. 2011;19(3):527–542.
[6] Mustoe TA. Evolution of silicone therapy and mechanism of action in scar management. Aesthetic Plast Surg. 2008;32(1):82–92.
[7] Fang QQ, Chen CY, Zhang MX, et al. The effectiveness of topical anti-scarring agents and a novel combined process on cutaneous scar management. Curr Pharm Des. 2016;23:2268–2275.

[8] Hietanen KE, Järvinen TA, Huhtala H, et al. Treatment of keloid scars with intralesional triamcinolone and 5-fluorouracil injections- a randomized controlled trial. J Plast Reconstr Aesthet Surg. 2019;72(1):4–11.
[9] Shome D, Khare S, Kapoor R. An algorithm using Botox injections for facial scar improvement in Fitzpatrick Type IV-VI skin. Plast Reconstr Surg Glob Open. 2018;6(8):e18888.
[10] Klinger M, Marazzi M, Vigo D, et al. Fat injection for cases of severe burn outcomes: a new perspective of scar remodeling and reduction. Aesthetic Plast Surg. 2008;32(3): 465–469.
[11] Sardesai MG, Moore CC. Quantitative and qualitative dermal change with microfat grafting of facial scars. Otolaryngol Head Neck Surg. 2007;137(6):868–872.
[12] Caviggioli F, Villani F, Forcellini D, et al. Nipple resuscitation by lipostructure in burn sequelae and scar retraction. Plast Reconstr Surg. 2010;125(4):174e–176e.
[13] Negenborn VL, Groen JW, Smit JM, et al. The use of autologous fat grafting for treatment of scar tissue and scar-related conditions: a systematic review. Plast Surg Nurs. 2016;36(3):131–143.
[14] Pallua N, Baroncini A, Alharbi Z, et al. Improvement of facial scar appearance and microcirculation by autologous lipofilling. J Plast Reconstr Aesthet Surg. 2014;67(8): 1033–1037.
[15] Kim WS, Park BS, Sung JH, et al. Wound healing effect of adipose-derived stem cells: a critical role of secretory factors on human dermal fibroblasts. J Dermatol Sci. 2007; 48(1):15–24.
[16] Tonnard P, Verpaele A, Peeters G, et al. Nanofat grafting: basic research and clinical applications. Plast Reconstr Surg. 2013;132(4):1017–1026.
[17] Manahan MA, Buretta KJ, Chang D, et al. An outcomes analysis of 2142 breast reduction procedures. Ann Plast Surg. 2015;74(3):289–292.
[18] Brown AP, Hill C, Khan K. Outcome of reduction mammaplasty-a patients' perspective. Br J Plast Surg. 2000;53(7): 584–587.
[19] Godwin Y, Wood SH, O'Neill TJ. A comparison of the patient and surgeon opinion on the long-term aesthetic outcome of reduction mammaplasty. Br J Plast Surg. 1998; 51(6):444–449.
[20] Davis GM, Ringler SL, Short K, et al. Reduction mammaplasty: long term efficacy, morbidity, and patient satisfaction. Plast Reconstr Surg. 1995;96(5):1106–1110.
[21] Martin P. Wound healing-aiming for perfect skin regeneration . Science. 1997;276(5309):75–81.
[22] Kim JS, Hong JP, Choi JW, et al. The efficacy of a silicone sheet in postoperative scar management. Adv Skin Wound Care. 2016;29:414–420.
[23] Mustoe TA, Cooter RD, Gold MH, International Advisory Panel on Scar Management, et al. International clinical recommendations on scar management. Plast Reconstr Surg. 2002;110(2):560–571.
[24] Coolen NA, Schouten KCWM, Middelkoop E, et al. Comparison between human fetal and adult skin. Arch Dermatol Res. 2010;302(1):47–55.
[25] Coolen NA, Schouten KC, Boekema BK, et al. Wound healing in a fetal, adult, and scar tissue model: a comparative study. Wound Repair Regen. 2010;18(3):291–301.
[26] Bullard KM, Longaker MT, Lorenz HP. Fetal wound healing: current biology. World J Surg. 2003;27(1):54–61.
[27] Adzick NS, Harrison MR, Glick PL, et al. Comparison of fetal, newborn, and adult wound healing by histologic,enzyme-histochemical and hydroxyproline determinations. J Pediatr Surg. 1985;2:315–319.
[28] Lovvorn HN, Cass DL, Sylvester KG, et al. Hyaluronan receptor expression increases in fetal excisional skin wounds and correlates with fibroplasia. J Pediatr Surg. 1998;33(7): 1062–1069.
[29] Estes JM, Vande Berg JS, Adzick NS, et al. Phenotypic and functional features of myofibroblasts in sheep fetal wounds. Differentiation. 1994;56(3):173–181.
[30] Beanes S, Dang C, Soo C, et al. Down-regulation of decorin, a TGF-beta modulator, is associated with scarless fetal wound healing. J Pediatr Surg. 2001;36(11):1666–1671.
[31] Lorenz HP, Adzick NS. Scarless skin wound repair in the fetus. West J Med. 1993;159(3):350–355.
[32] Hsu M, Peled ZM, Chin GS, et al. Ontogeny of expression of transforming growth factor-beta 1 (TGF-beta 1), TGF-beta 3, and TGF-beta receptors I and II in fetal rat fibroblasts and skin. Plast Reconstr Surg. 2001;107:1787–1794.
[33] Schaffler A, Buchler C. Concise review: adipose tissue-derived stromal cellsebasic and clinical implications for novel cellbased therapies. Stem Cells. 2007;25:818–827.
[34] Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7(2):211–228.
[35] Jaspers ME, Brouwer KM, van Trier AJ, et al. Effectiveness of autologous fat grafting in adherent scars: results obtained by a comprehensive scar evaluation protocol. Plast Reconstr Surg. 2017;139(1):212–219.
[36] Fredman R, Katz AJ, Hultman CS. Fat grafting for burn, traumatic, and surgical scars. Clin Plast Surg. 2017;44(4): 781–791.
[37] Klinger M, Caviggioli F, Klinger FM, et al. Autologous fat graft in scar treatment. J Craniofac Surg. 2013;24(5): 1610–1615.
[38] Rook JM, Hasan W, McCarson KE. Temporal effects of topical morphine application on cutaneous wound healing. Anesthesiology. 2008;109(1):130–136.
[39] Kauh YC, Rouda S, Mondragon G, et al. Major suppression of pro-alpha1(I) type I collagen gene expression in the dermis after keloid excision and immediate intrawound injection of triamcinolone acetonide. J Am Acad Dermatol. 1997;37(4):586–589.
[40] Balkin DM, Samra S, Steinbacher DM. Immediate fat grafting in primary cleft lip repair. J Plast Reconstr Aesthet Surg. 2014;67(12):1644–1650.
[41] Zellner EG, Pfaff MJ, Steinbacher DM. Fat grafting in primary cleft lip repair. Plast Reconstr Surg. 2015;135: 1449–1453.
[42] Uyulmaz S, Sanchez Macedo N, Rezaeian F, et al. Nanofat grafting for scar treatment and skin quality improvement. Aesthet Surg J. 2018;38(4):421–428.
[43] Tonnard P, Verpaele A, Carvas M. Fat grafting for facial rejuvenation with nanofat grafts. Clin Plast Surg. 2020; 47(1):53–62.
[44] Rihani J. Microfat and nanofat: when and where these treatments work. Facial Plast Surg Clin North Am. 2019; 27(3):321–330.
[45] Giri S, Machens HG, Bader A. Therapeutic potential of endogenous stem cells and cellular factors for scar-free skin regeneration. Drug Discov Today. 2019;24(1):69–84.

[46] Han J, Koh YJ, Moon HR, et al. Adipose tissue is an extramedullary reservoir for functional hematopoietic stem and progenitor cells. Blood. 2010;115(5):957–964.

[47] Bourin P, Bunnell BA, Casteilla L, et al. Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: a joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). Cytotherapy. 2013;15(6):641–648.

[48] Banyard DA, Sarantopoulos CN, Borovikova AA, et al. Phenotypic analysis of stromal vascular fraction after mechanical shear reveals stress-induced progenitor populations. Plast Reconstr Surg. 2016;138(2):237e–247e.