

BIOLOGY AND FUNDAMENTALS OF LIPOFILLING: CURRENT STANDINGS ON GRAFT SURVIVAL, REGENERATIVE POTENTIAL AND SAFETY

Hieronymus P.J.D. Stevens and Joep C.N. Willemsen discuss the latest innovations in lipofilling, including graft survival, improvements in harvesting techniques, and oncological safety

ABSTRACT

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KEYWORDS

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Lipofilling is the removal of fat by liposuction, which is then injected into the desired region of the body for volume enhancement. However, the technique is not new and more than 125 years ago the alleged potential of living fat cells as fillers was explored¹. Lipofilling has regained popularity in recent decades. Prior to 1966 there was criticism of the scientific knowledge and personal experience of clinicians advocating lipofilling. An expanding knowledge of adipocyte survival and standardisation of the lipofilling method contributed to the predictability of fat graft take and has expanded its applications.

Despite these developments lipofilling is still labeled as 'experimental' including by the senior authors' own national board (De Nederlandse Vereniging voor Plastische Chirurgie, NVPC). The use of living fat cells as a graft is therefore labeled as 'special medical treatment' and is not recognised as a valid treatment option. The American Society of Plastic Surgeons (ASPS) fat graft task force² agrees that lipofilling for aesthetic breast augmentation is not recommended for reconstruction but is very promising and clinically relevant. More level one and two evidence-based research is required.

The scientific interest in lipofilling received a great boost by the discovery of the pre-adipocyte stem cell in



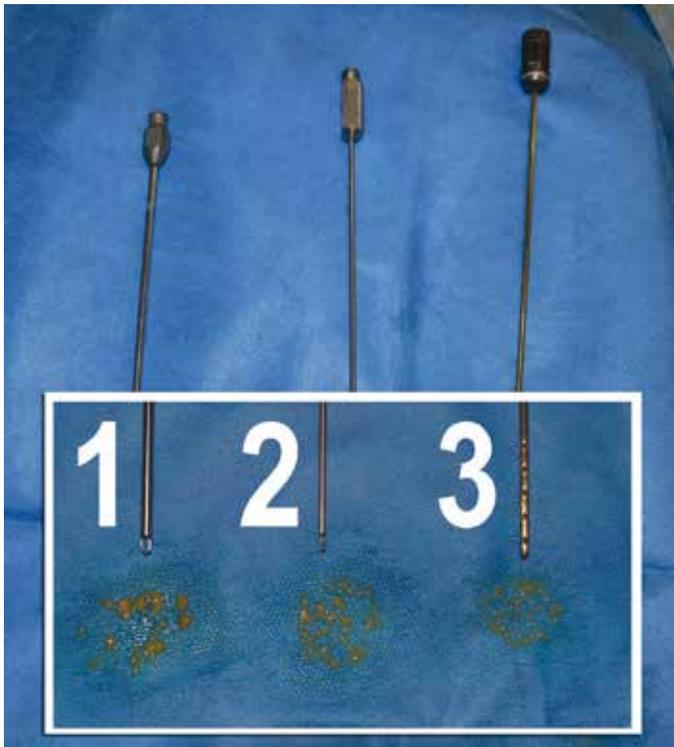


Figure 1 Different generations of lipo-harvesting cannulae and their effect on fat particle size. (1) Classic Coleman (opening diameter 2 mm by 2.8mm, 1986); (2) 'refined harvesting cannula' (opening diameter 1.8mm, KMI® (Innovative Med Inc., Corona, CA, US), 2002); (3) Micro-harvesting cannula (opening diameter 1mm, type Tonnaerd, Tulip® (Tulip Medical Products, San Diego, CA, US), 2010)

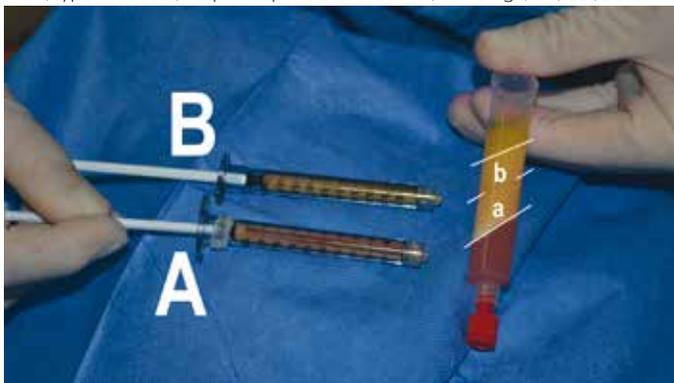


Figure 2 Centrifuging lipoaspirate results in three fractions, clearly visible in a 10cc syringe. From bottom to top: liquid waste (water and blood), (A) hyperdens fat, (B) hypodens fat, and oil from ruptured fat cells. The hyperdens fat (the 1cc syringe marked A) is used for superficial lipofilling since it is rich in adipose-derived stem cells. Hypodens fat (the 1cc syringe marked B) is used for volumetric deep lipofilling

lipoaspirate³. This resulted in an exponential increase in the number of mesh heading-related publications scored on *PubMed*.

In this article, the authors discuss the latest innovations in lipofilling regarding graft survival, safety, and regenerative potentials along with some practical tips.

History of lipofilling

Since the beginning of 'modern' plastic, reconstructive, and aesthetic surgery the potential use of adipose tissue in lipofilling has been examined. Gustav Neuber⁴, just

having completed the construction of the world's first sterile operating theatre in Germany in 1893, was the first to use fat in correcting a scar after osteomyelitis of the orbital rim. In 1895 Vincenz Czerny used a lipoma for breast reconstruction after mastectomy⁵. Eugene Hollander in the *Handbuch der Kosmetik*, showed the first pictures after lipotransfer for lipoatrophy of the face and a retracted defect of the chest⁶. Results at that time were dismissed as 'moderate' and 'highly variable in nature'. Charles Miller, a controversial doctor from Chicago, published in 1907 '*Cosmetic Surgery: The correction of featural imperfections*'⁶, in which he was the first to describe the use of a cannula to inject living fat cells. A newspaper interview from that time (1908) shows how the established order ridiculed him and expressed hostilities to his interest in elective surgery and the use of fat. This led to rejected manuscripts and many years of skepticism because of non-reproducible results. Only in the second half of the 20th century has lipofilling come back into the spotlight. Yves-Gerard Illouz⁷ introduces liposuction but also the reuse of lipoaspirate for lipofilling of the breast. Additionally, Pierre Fournier⁸ propagated harvesting by suction with a sharp syringe. In 2009 they presented together their 25 years of experience with lipofilling at EMAA in Paris. The technique becomes more popular after Sidney Coleman, Plastic Surgeon, New York, improves the reproducibility by centrifuging the lipoaspirate prior to injection [AQ3: do you have a reference for the previous statement?]. Until then, 'decantation' was preferred (the water fraction from the lipoaspirate separates from the fat cell-containing fraction used for injection). The quantity of living fat cells retrieved by this technique was unpredictable, varying from 20-50%. Separation by centrifugation improved this quantity to 85-90%^{9,10}.

Coleman also introduces the word lipostructure in 2006, and injects with blunt cannulae [AQ4: please provide a reference for the previous statement]. Recently, micro-fat grafting (fat particle diameter <1mm) was introduced in combination with less traumatic methods of lipofilling. These innovations undoubtedly improved predictability and enhanced results.

Research indicates three steps should be taken for an optimal result from lipofilling:

- Step 1: keep the adipocytes alive during liposuction
- Step 2: keep adipocytes alive during the method of 'purification' or separation (blood, water, oil)
- Step 3: Optimise adipocytes survival after injection in the target area.

Fat survival

Since the introduction of lipofilling and especially in the last decade, controversy about the 'survival' of transplanted fat has existed. Different methods of fat harvesting, processing, and injection as well as the differences between the host and donor sites have contributed to this¹¹.

It is commonly accepted that the vascular ingrowth starts from day 7 after transplantation¹². Fat necrosis is expected to peak at day 30. Biopsies from lipografts

taken in a number of animal studies 2 months after lipofilling show a well vascularised sample of tissue with living functional cells²²³. The number of human studies that monitor long term fat graft volume is limited. Swanson et al¹⁴ explored the survival of fat grafts in the face by analysing lipograft volume through multiple magnetic resonance imaging (MRI) scans. Although limited by a small number of patients, the study shows a stable lipograft volume after 6 months, with a similar density on the MRI as 'normal' fat tissue. The authors also noted that there was no significant difference in graft volume between 1 and 6 months after lipofilling, suggesting adequate vascularisation of the remaining cells in the lipograft. Additional evidence for fat graft survival is found in the studies by Herold et al¹⁵ and Khouri et al¹⁶. Both studies, measure breast volume after lipofilling using MRI imaging. The study of Herold et al shows 70% lipograft retention (n=10) 6 months post-operatively. Khouri et al reported even higher percentages: 80% (+/- 18%) after 6 months, with volumes up to 277cc per side. It has to be noted that the BRAVA pre-expansion system (Brava, LLC, Miami, FL, US) was used in the study of Khouri et al. The recently published study of Choi et al¹⁷, shows an average volume retention of 52% after 140 days at volumes of 111 cc up to 216cc per breast (n=20). Volume was measured with a 3D photograph system instead of more traditional CT and/or MRI measurements. This study by Choi et al shows relatively low volume retention of only 29% with small volume lipofilling. In a recent retrospective study by our team using photographic analysis, significantly better long term-aesthetic outcomes were measured with MACS-lift and lipofilling (n=42) compared to MACS-lift alone (n=50)¹⁸. These first findings played a key-role in the senior author's development of the one-two-three dimensional face ageing concept.

New insight in fat-survival

It appears plausible that a fat graft will survive in a well-vascularised host target area. Likewise it seems plausible that a fat graft will only partially, or even not, survive in a poorly vascularised host area like scarred or irradiated tissue. Large volume lipofilling in tight compartments shares a similar fate. Studies that aim to improve fat graft survival focus on three steps:

- Step 1: improvement of harvesting techniques
- Step 2: enhancement of the fat graft itself
- Step 3: optimising the donor site.

Step 1: improvement of harvesting techniques

The diameter of the lipofilling cannula has drastically decreased over the last couple of years. The standard Coleman cannula had 2.88mm suction holes, the refined cannulae used by the senior author since 2002 have a diameter of only 1.8mm. From 2010 onward, the diameter decreased even further to 1mm (Figure 1). If you look at the fat graft (or a fat particle) in abstract fashion, and considered it as a sphere, the diffusion area would correlate, with the radius to the third power. Further downsizing the harvesting cannula diameter could, at

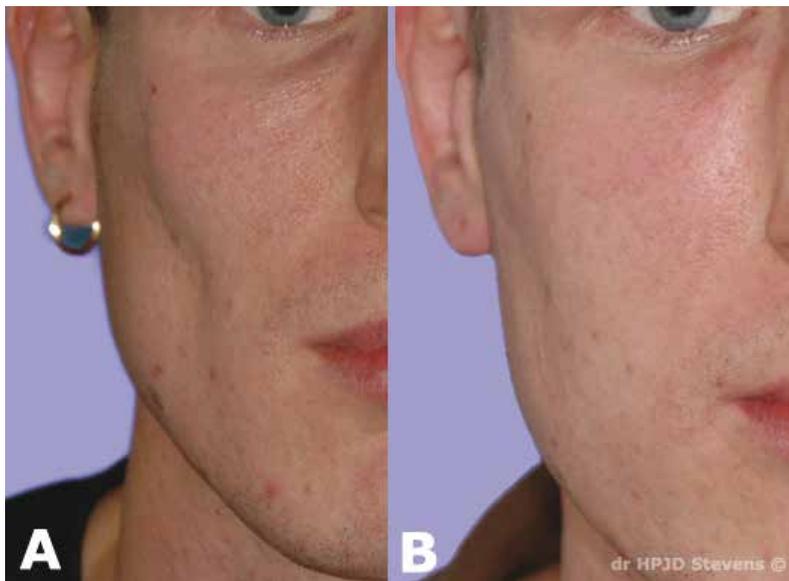
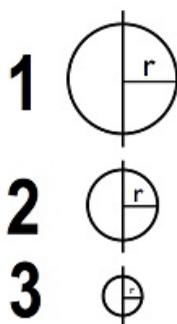


Figure 3 A 26-year-old man with hemifacial atrophy, (A) pre-operative and (B) 24 months postoperative after 33cc of lipofilling on the affected side



radius		r 2		r 3	
mm	%	mm	%	mm	%
1.4	100	1.96	100	2.74	100
0.9	64	0.81	41	0.73	27
0.5	36	0.25	13	0.13	5

Table 1 Practical guideline for lipofilling (personal preferences of the senior author HPJD Stevens after 1067 procedures)

least in theory, increase the diffusion area by 80-95% (Table 1)¹⁹. It is nowadays commonly accepted that graft survival in the first days depends on diffusion and imbibition¹⁹.

Step 2.1

For small volume lipofilling, authors agree with the propagators of centrifugation instead of decantation. Centrifugation of the lipoaspirate results in three fractions: Hyperdense fat, hypodense fat, and waste (Figure 2). The hyperdense fat is rich in precursor fat cells called adipose derived stem cells (ADSC)¹⁹. These precursor cells seem to play an import role in vascularising the fat graft²⁰, and could explain the regenerative properties²²² of fat grafting. By using the high-density fat, and discarding the low-density fraction, we are in fact upgrading the lipoaspirate in comparison to a decanted sample²²³. In theory, high-density fat grafts show a higher percentage of graft retention, and have

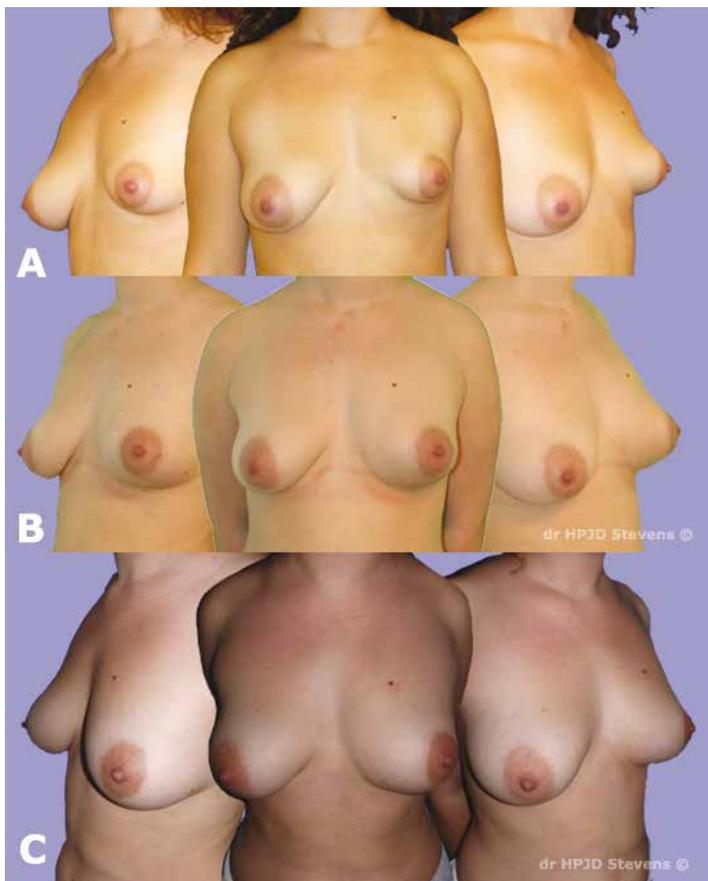


Figure 4 A 24-year old woman with evident breast asymmetry: (A) pre-operative, (B) 4 months post-operative after 320 cc of lipofilling and the BRAVA system, (C) 14 months post-operative, after gaining weight (4kg) both breast increased equally in size.

superior 'regenerative' potential over low-density fat grafts²⁴. The senior author tends to use high density fat for superficial 'regenerative' purposes, and low density fat for deep lipofilling, which focusses more on volume.

Step 2.2

One round of centrifugation (2.5 minutes) only yields 6 times 3-6 cc of viable lipograft, reconstructions requiring a large volume of lipograft, such as those for the breasts or buttocks, would be too time consuming using this method. A number of commercially available systems are on the market that deliver an alternative method of harvesting and processing, these include water assisted liposuction and the lipocollector²⁵. The senior author has put a number of systems to the test, and prefers the Cytori Puregraft® 850 system (Cytori Therapeutics, San Diego, CA, US). This closed system cleans the lipoaspirate of oil, water, and infiltration fluids like adrenaline and lidocaine by osmotic washing. The result is a viable and clean lipoaspirate, with a similar or even superior quality in comparison to centrifuging, in only a fraction of the time²⁶.

Step 2.3

The upgrading of lipoaspirates with a fraction of ADSC is a relatively new but promising technique. As pointed out

earlier on in this article, the ADSCs seem to play a central role in fat graft survival²⁷. In the first days after transplantation, the ADSC have a supporting role for the adipocyte, and later on they play a key role in neo-angiogenesis in the fat graft. Although promising, there are no large placebo controlled human trials to this date. There are a range of devices on the market that can extract ADSC from lipoaspirates, mainly by enzymatic breakdown. Unfortunately, these devices have a high cost and maintenance price, and processing of a lipoaspirate is time consuming. Another fact to take in account is the potential oncogenic potential of these grafts. The technique seems promising but does require more study on both long-term safety and efficacy²⁷.

Step 3.1

Injection of the fat should take place in a 3D fashion in the tissue layers, rather than just placing large lumps. Placement of the fat in a 3D fashion vastly expands the area over which diffusion can take place, which is the key factor in graft survival during the first days. Another commonly accepted fact is that overfilling is counterproductive. Adding extra fat to a host area that is not capable of supporting it leads to less fat retention. Overfilling also increases the pressure in the lipofilling compartment, a finding that has been linked to a high percentage of graft loss²⁸. It is better to build up volume in two or three separate sessions rather than overfilling in one session²⁹.

Step 3.2

Pre- and postoperative expansion of the lipofilling site seems to have a positive effect on survival, as shown by Khouri's BRAVA-system¹⁶. Compartment pressure is lowered by external suction, which in theory lowers liponecrosis. Furthermore, local expansion of the tissue increases vessel formation in the donor area. Pre-treating the donor area increased fat retention with 20%, which was determined through MRI scans. Results of the BRAVA system are exceptional (*Figure 4*), the only significant drawback of using this system is the high patient effort and compliance needed. The latest protocol suggests that patients should wear the brava system for at least 10 hours a day, 4 weeks before and after surgery.

Step 3.3

Platelet rich plasma (PRP), used in orthopaedic medicine for decades³⁰, has now made its introduction into plastic surgery. Adding a high concentration of platelets directly to the lipograft or injecting it in the host area will release a tremendous amount of growth factors. These growth factors are normally associated with wound healing, and in the case of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF)³¹ are pro-angiogenic. Although large prospective human studies are lacking to this date, there are many promising placebo controlled animal studies that show an impressive effect. In the studies of Oh et al³² and Nakamura et al³³ they observed significant higher fat retention with increased vessel formation. The right concentration (4-5 times

Volume	Target	Step 1 Harvesting	Step 2 Processing	Step 3 Injection (technique)
Small (<50cc)	Face, scars, and small defects	Micro-cannula (21cm) <ul style="list-style-type: none"> • type <u>Tonnaerd</u> or type <u>Sorrenson - Tulip</u> • Woman: upper legs • Man: abdomen 	Centrifuge <ul style="list-style-type: none"> • 2.5 min • Maximum 3000rpm 	<ul style="list-style-type: none"> • Blunt curved cannula (13-15cm) • V-dissector • Droplet technique (prevent large lumps) • Deep versus superficial filling • Sharp needle injection of fat (SNIF) • Addition of platelet rich plasma (PRP)
Large (250–800cc)	Breast, buttock, and large defects	Refined-cannula (32cm) <ul style="list-style-type: none"> • type Pyramid or type Settler • Woman: upper legs, abdomen, lower back 	<u>Puregraft®</u> <ul style="list-style-type: none"> • 250 • 850 	<ul style="list-style-type: none"> • Straight cannula (18cm) • Droplet technique (prevent large lumps) • Deep versus superficial filling • Addition of PRP (except breast)

Table 2 Practical guideline for lipofilling (personal preferences of the senior author HPJD Stevens after 1067 procedures)

above baseline) of PRP seems paramount in achieving these effects³⁴. How PRP exactly improves graft take remains unclear, the growth factors may influence the ADSC in the lipograft, the adipocyte, the donor area, or combination of all. Clinically there seems to be an effect: which is further supported by the findings of several retrospective studies on aesthetic outcome and recovery time when using PRP. **[AQ5: can you please reference these studies]**

More than filling alone?

During the last century, it became apparent that multipotent or precursor cells were available in subcutaneous fat³⁵. However, harvesting and classifying these cells proved to be a technical challenge. The introduction of liposuction changed all this and for the first time there was access to large volumes of living human fat cells. Zuk et al³ showed in their study that this indeed was the fact, their findings lead to significant advances in stem cell related tissue engineering and regenerative medicine. The ADSC almost has the same differentiation as other stem cells³⁶, but are readily available, and easy to access³⁷.

With the introduction of superficial lipofilling in plastic surgery, clinical observations soon followed. Coleman in 2006²¹, was one of the first to suggest that 'lipofilling might be more than filling alone' and could have a local rejuvenation effect. In a number of cases of lipofilling of the face, the overlying skin showed changes, small wrinkles disappeared, pore size decreased, and pigmentation improved. Also, scars seemed to fade, and felt more like normal skin (Figure 5).

These first observations led to the initiation of studies that evaluated these rejuvenating properties. In 2007 Rigotti et al²⁹ in their study, *Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells*, introduced a new method in treating irradiated skin. For the first time, lipofilling was used as a therapy to repair the damaged skin instead of using it for volumetric correction. Rigotti suggested that the positive

Figure 5 Close-up of the skin of a 58-year-old female patient; (A) pre-operative there was extensive tissue response on a permanent filler (injected elsewhere) with severe scarring. (B) 12 months post-operative from two sessions of lipofilling (15 cc per session) around the effected area and peri-orally. There was evident improvement of scar colour, elasticity, and general appearance



rejuvenating effect reported in the study might be attributed to the ADSCs present in the lipograft.

More recently, Sultan et al³⁸ showed a similar finding in a placebo controlled animal study. Mice underwent radiation, with one group receiving lipofilling of the damaged area, and one group a placebo. Lipofilling dampened the effects of the acute radiodermatitis. An observation that was further supported by histological findings: there was less fibrosis and SMAD3 expression (fibrosis marker). The authors suggest that these effects might be owing to the ADSC, either by neo-angiogenesis or inhibiting the TGF- β myofibroblast.

The regenerative properties of the lipograft was soon used for other types of skin damage like thermal injuries. Klinger et al³⁹ was the first to present a small case series (n=3) that were treated with lipofilling after hemifacial second and third degree burns. Klinger concluded that, 'lipofilling improves scar quality and suggests a tissue regeneration enhancing process.' The group of Sultan et al⁴⁰ (as described above) also conducted a placebo controlled mice study that explored the possibility of using lipofilling to minimise scarring after thermal injury. The mice that received lipofilling directly after administering the thermal injury showed increased neo-angiogenesis of the area, measured with a duplex Doppler, and cellular expression of related genes. Also, like with the irradiated mice, a lower amount of fibrosis was observed in the lipofilling treated mice. The authors suggest that the ADSC might take over, or assist the endothelial progenitor cells, which are paramount for neo-angiogenesis after thermal injury. It is widely accepted that, with severe thermal injury, the endothelial progenitor cells response from the bone marrow is slow, or even absent⁴¹. The resulting hypoxic tissue will result in a high TGF- β expression that results in severe scarring. Lipofilling might have a place in treating thermal injuries in the future.

Another application for the regenerative properties of the lipograft was presented by Cervelli et al^{42,43}. In a number of pilot studies they show the treatment of post-traumatic and chronic ulcers with a combination of PRP and enhanced stromal vascular fraction lipografts (or ADSC enriched). According to Cervelli et al the clinical results are good, with a high patient satisfaction. Unfortunately, the number of available studies that research this treatment is low. It may well be that this therapy will form an alternative to extensive debridement followed by loco-regional reconstruction or hyperbaric oxygen therapy.

Further research into the cellular interactions between the ADSC and adipocyte, along with the interaction of the ADSC on the local cellular environment will give insights in the reported regenerative effects and lead to new therapies. Most likely, fat graft survival will increase, as well as in bad donor areas like irradiated tissue. Also, tissue engineering with the use of ADSC and scaffolds³⁶ (3D Matrix) is showing great potential *in-vitro*⁴⁴ but also *in-vivo*⁴⁵. Furthermore the down regulating effect of the ADSC on the immune response might be a future therapy for scar prevention, revision, and chronic inflammatory skin diseases. Anecdotally, during the last 3 years, the senior author of this article used superficial lipofilling with PRP successfully for skin rejuvenation of the face, décollete, and hand dorsum. A blind randomised controlled trial is currently underway to further objectify these findings.

Oncological safety of lipofilling

The potential carcinogenic properties of lipofilling has been a point of discussion in many articles. Fundamental studies show that adipocytes placed in hypoxic condition produce large amounts of VEGF and other proliferative growth factors^{46,47}. Furthermore, the aromatase available in adipocytes results in a high local oestrogen concentration⁴⁷. If we take into account that the vascularisation of breast

Key points

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■ xxxxx

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tissue is relatively poor in comparison to the face, both factors have the potential to be a carcinogenic trigger.

In the recently published systematic review by Claro et al⁴⁸ on oncological complications after lipofilling of the breast, the number of mammographic changes were comparable to other forms of reconstructions. However, the number of level one and two trials included in this review was low. The ability to detect changes early in a mammography are not influenced by lipofilling in that breast⁴⁹. The British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) recently updated their guidelines. These updates included: lipofilling is a good alternative for breast reconstruction⁵⁰, and follow-up can take place according to the standard guidelines for oncological breast reconstruction. The US guidelines are less progressive and give no recommendation, but do say that lipofilling is 'promising and clinically relevant'². Further studies with adequate power and long term follow-up are required to draw definite conclusions. In addition, little is known about the role of additives like PRP or ADSC enrichment on the oncogenic potential of the lipograft.

Lipofilling in daily practice

Table 2 shows an overview that could serve as a guideline for the aesthetic and reconstructive surgeon. The experience of the surgeon and his operating team, as well as the expectations of the patient, are important factors in achieving a satisfying result, which sometimes requires multiple procedures. Clinical results are presented in Figures 3-4.

Conclusion and future expectations

The use of living fat cells for reconstructive and aesthetic purposes, harvested and grafted to a donor site within the same individual looks more promising than ever before. The lack of significant level 1 and 2 trials is a reason to be reserved at this time. Lipofilling not only seems interesting for the reconstruction of volumes but also the regenerative potential of the ADSC allows for reconstruction on a cellular level. The technological advances and practical improvements of the last decade makes lipofilling a good or even better alternative than current treatments options. Many other clinicians, such as dermatologists, interventional radiologists, and cardiologists⁵¹ have shown their interest in lipofilling, especially in the regenerative potential of the lipograft. This article's two authors have initiated a number of studies, including a randomised controlled trial and fundamental studies into the effect of PRP on the lipograft.

► **Declaration of interest** Both authors declare to have no potential conflicts of interest with respect to the research, authorship, and publication of this article. None of the authors received financial support for the research, authorship, and publication of this article.

► **Figures 1-5, Tables 1-2** © Dr HPJD Stevens

References

- Holländer E. *Handbuch der kosmetik*. Leipzig: Veit & Comp; 1912
- Gutowski KA, ASPS Fat Graft Task Force. Current applications and safety of autologous fat grafts: A report of the ASPS fat graft task force. *Plast Reconstr Surg* 2009; 124: 272-280
- Zuk PA, Zhu M, Ashjian P et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 2002; 13: 4279-95
- Van De Graaf RC, Korteweg SFS, Gustav Adolf Neuber (1850-1932) and the first report on fat auto-grafting in humans in 1893. *History of Plastic Surgery* 2010; 1(1): 7-11
- Champaneria MC, Wong WW, Hill ME, Gupta SC. The evolution of breast reconstruction: a historical perspective. *World J Surg* 2012; 36(4): 730-42
- Miller C. *The correction of featured imperfections*. Chicago: Oak Printing Co., 1907
- Illouz YG. Body contouring by lipolysis: A 5-year experience with over 3000 cases. *Plast Reconstr Surg* 1983; 72: 591-97
- Fournier PF, Ottent FM. Lipodissection in body sculpturing: The dry procedure. *Plast Reconstr Surg* 1983; 72: 598-609
- Rohrich RJ, Sorokin ES, Brown SA. In search of improved fat transfer viability: A quantitative analysis of the role of centrifugation and harvest site. *Plast Reconstr Surg* 2004; 113: 391-5
- Conde-Green A, de Amorim NF, Pitanguy I. Influence of decantation, washing and centrifugation on adipocyte and mesenchymal stem cell content of aspirated adipose tissue: A comparative study. *J Plast Reconstr Aesthet Surg* 2010; 63: 1375-1381
- Gir P, Brown SA, Oni G, Kashafi N, Mojallal A, Rohrich RJ. Fat grafting: Evidence-based review on autologous fat harvesting, processing, reinjection, and storage. *Plast Reconstr Surg* 2012; 130: 249-258
- Pu LL. Towards more rationalized approach to autologous fat grafting. *J Plast Reconstr Aesthet Surg* 2012; 65: 413-9
- Brucker M, Sati S, Spangenberg A, Weinzwieg J. Long-term fate of transplanted autologous fat in a novel rabbit facial model. *Plast Reconstr Surg* 2008; 122: 749-54
- Swanson E. Malar augmentation assessed by magnetic resonance imaging in patients after face lift and fat injection. *Plast Reconstr Surg* 2011; 127: 2057-65
- Herold C, Ueberreiter K, Cromme F, Busche MN, Vogt PM. [The use of mamma MRI volumetry to evaluate the rate of fat survival after autologous lipotransfer]. *Handchirurgie, Mikrochirurgie, plastische Chirurgie: Organ der Deutschsprachigen Arbeitsgemeinschaft für Handchirurgie: Organ der Deutschsprachigen Arbeitsgemeinschaft für Mikrochirurgie der Peripheren Nerven und Gefässe: Organ der Vereinigung (TRUNCATED)* 2010; 42:129-34
- Khouri RK, Eisenmann-Klein M, Cardoso E et al. Brava and autologous fat transfer is a safe and effective breast augmentation alternative: Results of a 6-year, 81-patient, prospective multicenter study. *Plast Reconstr Surg* 2012; 129: 1173-87
- Choi M, Small K, Levovitz C, Lee C, Fadi A, Karp N. The volumetric analysis of fat graft survival in breast reconstruction. *Plast Reconstr Surg* 2013; 131(2): 185-91
- Willemsen JC, Mulder KM, Stevens HP. Lipofilling with minimal access cranial suspension lifting for enhanced rejuvenation. *Aesthet Surg J* 2011; 31(7): 759-69
- Wang WZ, Fang XH, Williams SJ et al. Analysis for apoptosis and necrosis on adipocytes, stromal vascular fraction, and adipose-derived stem cells in human lipoaspirates after liposuction. *Plast Reconstr Surg* 2013; 131: 77e-85e
- Butala P, Hazen A, Szpalski C, Sultan SM, Coleman SR, Warren SM. Endogenous stem cell therapy enhances fat graft survival. *Plast Reconstr Surg* 2012; 130(2): 293-306
- Coleman SR. Structural fat grafting: More than a permanent filler. *Plastic and reconstructive surgery* 2006; 118: 1085-1205
- Gir P, Oni G, Brown SA, Mojallal A, Rohrich RJ. Human adipose stem cells: Current clinical applications. *Plast Reconstr Surg* 2012; 129: 1277-1290
- von Helmburg D, Hemmrich K, Haydarlioglu S, Staiger H, Pallua N. Comparison of viable cell yield from excised versus aspirated adipose tissue. *Cells Tissues Organs* 2004; 178: 87-92
- Allen RJ, Jr, Canizares O, Jr, Scharf C et al. Grading lipoaspirate: Is there an optimal density for fat grafting? *Plast Reconstr Surg* 2013; 131: 38-45
- Ueberreiter K, von Finckenstein JG, Cromme F, Herold C, Tanzella U, Vogt PM. BEAULI--a new and easy method for large-volume fat grafts. *Handchir Mikrochir Plast Chir* 2010; 42: 379-85
- Zhu M, Cohen SR, Hicok KC et al. Comparison of three different fat graft preparation methods: Gravity separation, centrifugation, and simultaneous washing with filtration in a closed system. *Plast Reconstr Surg* 2013; 131: 873-80
- Castella L, Planat-Benard V, Laharrague P, Cousin B. Adipose-derived stromal cells: Their identity and uses in clinical trials, an update. *World J Stem Cells* 2011; 3: 25-33
- Hovius SE, Kan HJ, Smit X, Selles RW, Cardoso E, Khouri RK. Extensive percutaneous aponeurotomy and lipografting: A new treatment for dupuytren disease. *Plast Reconstr Surg* 2011; 128: 221-228
- Rigotti G, Marchi A, Galie M et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: A healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg* 2007; 119: 1409-22
- Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: A review of the literature. *J Bone Joint Surg Br* 2009; 91: 987-996
- Lacci KM, Dardik A. Platelet-rich plasma: Support for its use in wound healing. *Yale J Biol Med* 2010; 83(1): 1-9
- Oh DS, Cheon YW, Jeon YR, Lew DH. Activated platelet-rich plasma improves fat graft survival in nude mice: A pilot study. *Dermatologic surgery: official publication for American Society for Dermatologic Surgery* 2011; 37: 619-25
- Nakamura S, Ishihara M, Takikawa M et al. Platelet-rich plasma (PRP) promotes survival of fat-grafts in rats. *Ann Plast Surg* 2010; 65: 101-6
- Mazzocca AD, McCarthy MB, Chowanec DM et al. Platelet-rich plasma differs according to preparation method and human variability. *J Bone Joint Surg Am* 2012; 94: 308-16
- Rodbell M. Localization of lipoprotein lipase in fat cells of rat adipose tissue. *J Biol Chem* 1964; 239: 753-55
- Sterodimas A, de Faria J, Nicaretta B, Pitanguy I. Tissue engineering with adipose-derived stem cells (ADSCs): Current and future applications. *J Plast Reconstr Aesthet Surg* 2010; 63: 1886-92
- Ogawa R. The importance of adipose-derived stem cells and vascularized tissue regeneration in the field of tissue transplantation. *Curr Stem Cell Res Ther* 2006; 1: 13-20
- Sultan SM, Stern CS, Allen RJ, Jr et al. Human fat grafting alleviates radiation skin damage in a murine model. *Plast Reconstr Surg* 2011; 128: 363-372
- Klinger M, Marazzi M, Vigo D, Torre M. Fat injection for cases of severe burn outcomes: A new perspective of scar remodeling and reduction. *Aesthetic Plast Surg* 2008; 32: 465-9
- Sultan SM, Barr JS, Butala P et al. Fat grafting accelerates revascularisation and decreases fibrosis following thermal injury. *J Plast Reconstr Aesthet Surg* 2012; 65: 219-27
- Rignault-Clerc S, Biemann C, Delodder F et al. Functional late outgrowth endothelial progenitors isolated from peripheral blood of burned patients. *Burns* 2013; 39(4): 694-704
- Cervelli V, Gentile P, Grimaldi M. Regenerative surgery: Use of fat grafting combined with platelet-rich plasma for chronic lower-extremity ulcers. *Aesthetic Plast Surg* 2009; 33: 340-45
- Cervelli V, Gentile P, Scioli MG et al. Application of platelet-rich plasma in plastic surgery: Clinical and in vitro evaluation. *Tissue engineering* 2009; 15: 625-34
- Tremolada C, Palmieri G, Ricordi C. Adipocyte transplantation and stem cells: Plastic surgery meets regenerative medicine. *Cell Transplant* 2010; 19: 1217-23
- McArthur G. Melbourne scientists poised to begin surgery to help cancer victims regrow breasts. *Melbourne: Herald Sun*, 2009
- Hou WK, Xu YX, Yu T et al. Adipocytokines and breast cancer risk. *Chin Med J (Engl)* 2007; 120: 1592-96
- Bertolini F, Lohsiriwat V, Petit JY, Kolonin MG. Adipose tissue cells, lipotransfer and cancer: A challenge for scientists, oncologists and surgeons. *Biochim Biophys Acta* 2012; 1826: 209-214
- Claro F, Jr, Figueiredo JC, Zampar AG, Pinto-Neto AM. Applicability and safety of autologous fat for reconstruction of the breast. *Br J Surg* 2012; 99: 768-780
- Petit JY, Lohsiriwat V, Clough KB et al. The oncologic outcome and immediate surgical complications of lipofilling in breast cancer patients: A multicenter study--milan-paris-lyon experience of 646 lipofilling procedures. *Plast Reconstr Surg*. 2011; 128: 341-46
- Fatah F, Lee M, Martin L, Sassoon E, Weiler-Mithoff E. Lipomodelling guidelines for breast surgery. London: Association of Breast Surgery, British Association of Plastic, Reconstructive and Aesthetic Surgeons, British Association of Aesthetic Plastic Surgeons, 2012.
- Otto Beitzes J, Oie E, Shahdadfar A et al. Intramyocardial injections of human mesenchymal stem cells following acute myocardial infarction modulate scar formation and improve left ventricular function. *Cell Transplant* 2012; 21: 1697-1709