The effects of facial lipografting on skin quality: a systematic review

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ABSTRACT

Introduction

Autologous lipografting for improvement of facial skin quality was first described by Coleman in 2006. The current dogma dictates that adipose tissue-derived stromal cells (ASCs) which reside in the stromal vascular fraction (SVF) of lipograft contribute to skin rejuvenation *e.g.* increased skin elasticity, a more homogenous skin color and softening of skin texture. Nowadays, many studies have been reported on this 'skin rejuvenation' effect of autologous fat grafting. This systematic review was undertaken to assess the efficacy of autologous lipografting on skin quality.

Material & Methods

MEDLINE, Embase, Cochrane Central, Web of Science and Google Scholar databases were searched for studies evaluating the effect of autologous lipografting on facial skin quality (05-11-2018). Outcomes of interest were skin texture, color and elasticity as well as histological outcomes and number of complications.

Results

Nine studies were included with 301 patients treated in total. No meta-analysis could be performed due to heterogeneity of the metrics and outcomes. Eight studies reported increased skin elasticity, improvement in skin texture as well as a more homogeneous skin color after treatment with lipografting, cellular SVF or Nanofat. One study reported no increased skin elasticity after lipografting. Histological improvement was seen after lipografting and ASCs injections. However, in general, the level of evidence of the included studies was low. No serious complications were reported.

Conclusion

Autologous facial lipografting as well as cSVF and ASCs injections hardly seem to improve facial skin quality but can be considered as a safe procedure.

INTRODUCTION

Aging of the face is characterized by many changes in a broad spectrum of facial skin features *e.g.* increased pigmented spots, increased wrinkle depth and rosacea formation. Aged facial skin can be categorized into two types of aging: intrinsic or programmed aging and extrinsic or photoaged aging. Intrinsic aging is caused by passage of time due to genetic influences, while extrinsic aging is mainly caused by ultraviolet radiation or cigarette smoke.[1,2] Major alterations of both intrinsic as well as extrinsic aging occur in the dermal extracellular matrix.[3,4] In aged skin, there is a reduced collagen syntheses and increased collagen fiber fragmentation resulting in collagen deficiency and therefore a thinner skin.[3,5] Photoaged skin is often histologically characterized by increased epidermal thickness, damaged dermal connective tissue as well as accumulation of disorganized elastin.[1,6] These extracellular matrix changes result in loss of elasticity and therefore formation of wrinkles over time.

In 2006, Coleman was the first to describe that lipografting or lipofilling, the transplantation of adipose tissue, reduced age-related skin changes such as wrinkle depth, pore size and pigmented spots.[7] These "skin rejuvenation" effects were ascribed to the regenerative potential of adipose tissue-derived stromal cells (ASCs). ASCs are attached around vessels as precursor cell types *e.g.* pericytes and supra-adventitial cells in the stroma *i.e.* stromal vascular fraction (SVF) of adipose tissue.[8,9] Adipose tissue comprises of parenchyma *i.e.* adipocytes and SVF that also consists fibroblasts, immune cells and vascular cells.[10,11] ASCs can be enzymatically isolated from large quantities of lipoaspirates and have the ability to remodel extracellular matrix.[12,13]

The enzymatic isolation of ASCs sparked an increase in clinical studies with respect to ASC-enriched lipofilling or cell-assisted lipofilling (CAL).[14-16] However, in many countries the use of enzymes and animal derived products to isolate cells (*e.g.* ASCs) from human tissue for clinical use is forbidden by legislation. Hypothetically, the animal-derived products increase the risk for zoonosis, while these multistep procedures are considered undesirable manipulations. Therefore, new intraoperative isolation procedures of ASC were developed without the use of enzymes and animal derived products, called mechanical isolation procedures.[11] Most of these mechanical isolation procedures isolate SVF that still contains cell-cell and cell-matrix connections (tSVF), in contrast to enzymatically isolated SVF that is a single cell suspension which obviously lack cell-cell connections and extracellular matrix (cSVF).[11,17]

Thus far, no studies have been published using tSVF or tSVF-enriched lipografting for skin rejuvenation purposes. Numerous other publications have described the clinical observation of improved skin quality after

lipografting.[7,18-28] This systematic review now was undertaken to evaluate the effect of lipografting on skin quality.

METHODS

Protocol, information sources and search

This study was performed in accordance with the PRISMA statement.[29] The study was not registered. MEDLINE, Embase, Cochrane Central, Web of Science and Google Scholar databases were searched (08-12-2017). An update search was performed on 05-10-2018. The search was restricted to humans. Keywords used for the search on the effect of lipografting on human facial skin quality can be found in table 1, supplemental content.

Eligibility criteria

Studies were included if lipografting or a component of adipose tissue *i.e.* tSVF, cSVF or ASCs was used to improve human facial skin quality. Changes in skin quality were defined as clinical changes in skin texture, color and elasticity or any histological changes in skin epidermis or dermis (Table 1). Studies were included if adipose tissue was obtained by liposuction. Studies including patients with diseases and trauma that could affect skin quality or subcutaneous adipose tissue *e.g.* burn wounds, scars and disease-caused lipoatrophy were excluded. Studies only evaluating wrinkles or volumetric effect of lipografting or any components of adipose tissue without analyzing the skin elasticity were excluded as well. A decreased wrinkle depth after lipografting can be caused by either a volumetric effect of lipografting or increased skin elasticity. Improved skin elasticity is considered to be a positive effect on skin quality, while a volumetric effect of lipografting does not influence the skin quality. Furthermore, studies evaluating the effect of lipografting on infraorbital dark circles were excluded, because the therapeutic effect is based on reducing transparency of the orbicularis oculi muscle through the lower eyelid skin by increasing subcutaneous volume.[30,31] Additionally, studies analyzing the outcome of facial lipografting or any substance of adipose tissue in conjunction with other surgical procedures *e.g.* botulinum toxin injection or fillers were excluded. Case reports, conference abstracts and reviews were excluded as well *i.e.* only peer-reviewed original research papers were included (Table 1). The literature search was not restricted by date or publication status (Table 1, supplemental content).

Study selection

Two authors (JvD and ML) independently selected prospective and retrospective clinical studies that met the eligibility criteria (Fig. 1). Reference lists of the included studies were hand-searched for relevant studies that were not initially included using the aforementioned inclusion criteria. Inconsistences were discussed during a consensus meeting. In case of disagreement, the senior author (BvdL) gave a binding verdict.

Assessment of quality of included studies

The included studies were graded on quality of evidence using the Oxford Center for Evidence-Based Medicine (OCEBM) criteria.[32] Disclosure agreements were reviewed for each study.

Outcomes

Outcomes of interest were clinical outcomes *i.e.* skin texture, skin color as well as skin elasticity, histological outcomes and number of complications. No meta-analysis could be performed due to the diversity of the metrics and outcomes.

Risk of bias in individual studies

The quality of lipografting and ASCs depends on age, comorbidity such as obesity and diabetes mellitus type 2, harvesting and processing techniques of adipose tissue.[33-38] For those reasons, detailed clinical information *e.g.* demographics, harvesting and processing techniques are included.

RESULTS

Included studies

The literature search yielded 4595 publications (Fig. 1). After abstract screening, 2267 articles were excluded. Seventy-three studies were read in full-text and assessed on eligibility criteria. Thirty-eight studies did not describe an outcome of interest and were therefore excluded.[7,26,30,31,39-72] Fourteen publications were reviews and therefore excluded.[7,73-84] Eight studies were excluded based on the use of lipografting or any substances of adipose tissue in combination with other treatments.[85-92] One study was excluded because it was an animal study.[15] Two studies were excluded based on the treatment of disease-caused lipoatrophy.[93,94] One study was excluded for being a letter to the editor.[95]

Quality assessment of included studies

Of the nine included studies; two studies scored a level of evidence of 2[21,25], two studies a level of evidence of 3 [19,96] and five studies a level of evidence of 4 (Table 2).[18,20,22-24] In one study, a disclosure agreement of support by a manufacturer was provided.[25]

Study characteristics

Eight of the nine included studies were prospective clinical trials[19,21,22,96-100], six of these eight were controlled studies and of the latter mentioned six studies[19,21,22,96,98,100], two had been randomized.[21,100] In total, 301 subjects were treated. All studies included a 93% female study population. All studies reported the range of age while four studies reported the mean age too.[19,22,96,100] Willemsen et al. reported an overall Body Mass Index between 20-25, which was already stable for one year (Table 3).[100]

Adipose tissue harvesting and processing

All studies reported which donor site had been used. Eight studies used infiltration prior to liposuction[19,21-23,96,97,99,100] and one study by Charles-de-Sá et al. did not mention any infiltration step (Table 4).[20] Five out of the seven studies that used lipografting used decantation to process the adipose tissue prior to injection.[20-24] Two studies processed the adipose tissue by centrifugation of which one used the standard Coleman technique.[19,25] Three studies used enzymatic isolation to isolate SVF (cSVF).[18,20,22] One study used the so-called Nanofat which essentially is an emulsification procedure of lipoaspirates (Table 4).[96]

Intervention and injection methods

Seven studies used lipografting[19,21-23,98-100], while one study used cSVF[97] and one study used Nanofat as a treatment to improve facial skin quality.[96] Botti et al. compared different adipose tissue processing techniques *i.e,* filtering and washing versus centrifugation.[19] Two studies used cSVF enriched lipografting and compared this with cultured ASCs injection of which Rigotti et al. included a third group using platelet rich plasma (PRP) enriched lipografting.[20,22] Willemsen et al. compared PRP enriched lipografting to saline 0.9% enriched lipografting.[25] Covarrubias et al. compared lipografting with no treatment.[21] Liang et al. compared platelet rich fibrin (PRF) enriched Nanofat with hyaluronic acid injection (Table 5).[96]

The injected fat volumes differed highly among all studies, ranging from 0.05 ml – 43 ml per region of the face (Table 4). In five of the nine studies the same subject was used for both the intervention group as well as the control group.[19,21-23,98] Song et al. compared different adipose tissue injection techniques *i.e.* conventional hand push injection versus an electric injection device (YSZTQ-01, Lanzhou Wenhe Medical Instrument R&D Co., Ltd, Lanzhou).[23] Seven out of the nine studies mentioned the injection plane (Table 5).[21,22,96-100]

Clinical outcome

Skin texture

Skin texture improvement after lipografting was reported in three studies (n=149).[19,24,96] Trivisonno et al. reported 25% improvement in skin texture measured with a non-validated skin surface profilometry analyzer (Antera 3D multispectral analyzer, Miravex Limited, Dublin, Ireland) ninety days postoperative ($p<0.01$).[24] A dermatologist also reported improvement of skin texture with the use of a non-validated 3-grade scale.[24] The skin texture homogeneity score decreased from 2.43 ± 0.68 to 1.19 ± 0.4 and the skin roughness score decreased from 2.33 ± 0.73 to 1.19 ± 0.4 ($P<0.05$). Trivisonno et al. did not use a control group.[24] Liang et al. reported improvement in skin texture after PRF enriched Nanofat measured with a non-validated VISIA skin imaging analyzer (VISIA Canfield Imaging Systems, Fairfield, NJ, USA) one, twelve and twenty-four months postoperative.[96] Botti et al. reported that 68% and 72% of the included subjects scored 'high' on improvement in skin texture for filtered and washed adipose tissue and centrifuged adipose tissue, respectively.[19] The level of improvement in skin texture was measured with a non-validated self-evaluated questionnaire. No statistical analysis was mentioned in this study (Table 6).

Skin color

A more homogeneous skin color was noticed after lipografting in two studies (n=97).[23,24] Trivisonno et al. reported declined concentrations of hemoglobin and melanin measured with a validated skin surface profilometry analyzer (Antera 3D multispectral analyzer, Miravex Limited, Dublin, Ireland), ninety days postoperative ($p<0.05$).[24,101] A dermatologist also reported decreased pigmentation and redness of the skin with the use of a non-validated 3-grade scale.[24] The skin redness score decreased from 2.29 ± 0.64 to 1.14 ± 0.36 and the skin melanin pigmentation score decreased from 2.33 ± 0.58 to 1.24 ± 0.44 ($p<0.05$). Song et al. reported that 80% and 72.2% of the included subjects scored 'high' on improvement in skin pigmentation measured by

visual evaluation of photographs for respectively two different injection techniques: 1) lipografting with an electric injection device and 2) conventional hand push injection ($p>0.05$).[23] However, no statistical analysis was used to analyze this improvement. Amirkhani et al. assessed the effect of cSVF on the skin color (n=16). No difference in pigmentation and melanin production was measured with a validated Mexameter six months postoperative ($p>0.05$) (Table 6).[18,101]

Skin elasticity

Increased skin elasticity was reported in two studies, while another study failed to show increased skin elasticity after cSVF and Nanofat injections as well as lipografting, respectively (n=144).[18,25,96] In a non-controlled study, Amirkhani et al. showed increased skin elasticity after injection of cSVF measured with a validated cutometer (C&K Electronic, Cologne, Germany), six months postoperative compared to preoperative $P<0.001$).[18] Liang et al. reported increased skin elasticity using the non-validated SOFT5.5 in a controlled study following PRF enriched Nanofat one, twelve and twenty-four months postoperative. Although, no comparisons between the intervention and the control group have been made.[96] In a double-blinded, randomized placebo-controlled trial, Willemsen et al. demonstrated no increase in skin elasticity after lipografting with or without the addition of PRP measured with a validated cutometer, twelve months postoperative ($p>0.05$).[25] Yet, reversal of the correlation between true skin elasticity and age (from negative to positive) might suggest a small effect of lipografting. The reversal of this correlation was stronger when using lipografting with PRP in comparison with lipografting alone. However, these results were not significant, most likely due to the small sample size caused by too many dropouts ($p=0.055$) (Table 6).

Histological outcome

Three studies showed histological and/or histomorphometric improvement of skin biopsies after treatment with lipografting, PRP-enriched lipografting, cSVF-enriched lipografting and cultured ASCs.[20-22] All studies used the same patients for the intervention group as well as the control group. In an observer-blinded, randomized clinical trial, Covarrubias et al. compared lipografting with no treatment and demonstrated an increase in dermis thickness, presence of immature collagen and arteries sixty-nine days postoperative (n=16, $p<0.001$).[21] No increase or decrease was seen in the presence of mature collagen.

In two non-blinded, non-randomized studies conducted by the same research group, three different types of treatments were performed: 1) PRP-enriched lipografting; 2) cSVF-enriched lipografting; and 3) injection of cultured ASCs (n=13).[20,22] Three months postoperative skin biopsies were compared with preoperative skin biopsies. The different types of treatment were not compared with each other. After all three types of treatment, the reticular dermis showed a decrease in elastic fiber network with more dissociated elastic fibers, a smoother surface and a smaller diameter.[20,22] Additionally, after cSVF-enriched lipografting and cultured ASCs the reticular dermis showed a decrease in collagen fibers.[20] Additionally, the number of oxytalan elastic fibers in the papillary dermis was increased.[20,22] Moreover, after injection of PRP-enriched lipografting increased inflammatory infiltrates and vasculature was seen (Table 6).

Complications

Six out of the nine studies reported on the occurrence of no significant complications after lipografting, cSVF or Nanofat treatment (n=196, Table 6).[18,19,23-25,96] Liang et al. reported fourteen small complications: five patients had a transient infection, seven patients suffered from temporarily paresthesia and two patients noticed pigmentation changes which lasted for more than twelve months.[96]

DISCUSSION

This systematic review demonstrates that substantial evidence is lacking that the use of lipografting or a component of adipose tissue *i.e.* cSVF or ASCs rejuvenates healthy human facial skin, as was advocated by Coleman.[7] This review also demonstrates that the use of facial lipografting or a substance of adipose tissue can be considered to be a safe procedure.

In general, most included studies of this review reported positive results. However, the level of evidence in five out of nine included studies was low with an OCEBM evidence level of just 4.[18,20,22-24] Therefore, the reported outcomes of these studies should be interpreted with caution. Low levels of evidence were caused by poor study designs: two studies lacked a control group[18,24], four studies used non-validated methods of measurements[19,23,24,96], two studies did not report any quantitative data[20,22] and two studies did not define the outcome of interest *i.e.* skin texture.[19,96] Trivisonno et al. defined improved skin texture as decreased wrinkle depth, folds and fine lines when analysed with the profilometry analyser. The observed improved skin texture might therefore be caused by a volumetric effect of lipografting.[24] The volumetric effect of lipografting can

decrease wrinkle depth and give the patients' face a rejuvenated appearance. Decrease in wrinkle depth is not necessarily related to an improved skin quality. Furthermore, each skin parameter *e.g.* skin texture, wrinkles, pigmentation, pores, is affected by one another. For example, skin texture is defined as softening of the skin which is affected by wrinkles, pores and birthmarks. Hence, the improvement in skin texture is partly caused by a volumetric effect of lipografting due to decreased wrinkle depth. This shows that the definition of "skin rejuvenation" or "skin quality" is rather broad and difficult to confine.

The heterogeneity between studies is high caused by the absence of standardization of fat harvesting and processing techniques of lipoaspirates as well as variation in patient demographics. Cell yield and viability of both lipoaspirate and cSVF depend on age, comorbidity *e.g.* obesity, diabetes mellitus type 2 and probably harvest location and processing techniques such as centrifugation and decantation.[33-38,102] The majority of the included studies did not mention these donor characteristics, which makes comparison of the included study populations difficult.

Animal experiments corroborate the clinical findings that administration of adipose tissue or its components is of little influence on skin quality. Two mice experiments demonstrated increased dermal thickening due to increased numbers of type 1 collagen fibers and angiogenesis after lipografting.[103,104] Another study investigating the effect of lipografting, ASC transplantation and ASC-enriched lipografting on the upper eyelid of pigs showed no increase in epidermal thickening.[105] However, the use of ASC-enriched lipografting resulted in an increased dermal thickening as well as increased epidermal cell proliferation, collagen content and number of arterioles in comparison with placebo.[105]

In aesthetic plastic surgery, it is challenging to design well-defined prospective randomized clinical trials with the use of validated equipment and questionnaires to assess skin quality. A study on the number of publications in three major plastic surgery journals found only 1.83% of the publications to be randomized clinical trials.[106] Plastic surgery literature consists mainly of relatively small sample sized studies, as compared to the general medical literature. Moreover, a small sample size makes it more difficult to establish significant differences between the experimental and the placebo group.[107]. Also, to treat a patient with placebo and subject the patient to all the potential risk of surgery is generally seen as ethically undesirable. However, treating a patient with a non-scientifically proven treatment is ethically undesirable as well. Hence, most clinical trials compare two different treatments, which makes it challenging to establish any significant difference in outcome and real effect of the treatment. To date, the readouts to quantify skin rejuvenation are mainly based on pre-

and postoperative photographic comparisons, which often are not or poorly standardized. These pre- and postoperative photographs are often analysed in a descriptive manner instead of being blinded analysed by an objective and independent third observer or are the result from objective, validated, computer analysis.

To improve future clinical trials using facial lipofilling in aesthetic plastic surgery, we propose a statement for designing a proper randomized clinical trial with validated and objective readouts (Table 7). In this way, comparing outcomes of future clinical trials can draw a definite conclusion on the effect of facial lipofilling on skin quality. The study population should consist of a standardized group with ASA1 classification and a minimum age of 35, because skin elasticity is higher in younger patients.[108] Patients with obesity, systemic diseases, smokers and hormonal fluctuations should be excluded because all of these factors influence adipose tissue quality as well as skin quality.[38,109-111] Moreover, patients with preceding facial interventions within the last twelve months should be excluded because of late effects of priory interventions. Patients with a known history of psychiatric disorder should also be excluded because this could influence patient satisfaction outcomes. To date, there is no consensus on the quality of lipoaspirate harvested from different locations *e.g.* abdomen, upper legs as well as injection volumes and lipoaspirate processing techniques *e.g.* centrifugation, decantation.[33,35,37] Thus, we propose a standard harvesting location in all trial patients and to centrifuge lipoaspirate as first described by Coleman to ensure the right amount of lipoaspirate by losing infiltration fluid.[112] Injection volumes should be standardized during the entire study and there should be a maximum time of 30 min. between harvesting and injection to prevent ischemic cell death. Finally, we propose the use of the validated cutometer as primary outcome since loss of skin elasticity is strongly correlated with ageing.[113] Secondary outcomes should include: patient reported outcome measures *i.e.* satisfaction as measured with the validated FACE-Q questionnaires, clinical photographs analyses (by blinded and independent observers) and complications (number and type).

Nowadays, the indication for lipografting has already proven its efficacy for other clinical applications *e.g.* as a treatment to increase volume for cosmetic and/or oncological breast augmentation as well as anti-scarring treatment for (posttraumatic) scars and burn wounds.[114-117] In a systematic review on lipografting in cosmetic breast augmentation, Groen et al. showed high retention volumes after lipografting after long term follow up (average volume retention 62.4% [range 44.7%-82.6%], mean time follow-up 16.6 months) with high satisfaction rates among patients (92%) and surgeons (89%).[115] Two systematic reviews on lipografting and ASCs in burn wounds showed that autologous lipografting significantly restores volume, improves scar appearance

and scar related pain and itchiness.[116,117] Apparently It seems to be that the severity of the skin trauma/damage plays a key role whether lipografting or ASCs could be effective in skin reparative/ wound reparative effects. In case of low amounts of damage *e.g.* aging of the extracellular matrix in physiological processes such as ageing of the skin, lipografting or ASCs are not or hardly able to remodel the extracellular matrix. However, in case of severe skin damage, as in pathological processes *i.e.* burn wounds or scarring, lipografting or ASCs seem to be highly effective in remodelling the damaged skin.[116,117]

CONCLUSION

This systematic review demonstrates a lack of scientific evidence that autologous facial lipografting or any other substance of adipose tissue *i.e.* cSVF and ASCs improves normal aged facial skin quality but also demonstrates that the procedure can be considered to be safe.

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FIGURE LEGEND

Figure 1. Flow diagram of study selection.

TABLE LEGEND

Table 1. Inclusion and exclusion criteria.

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Table 7. Statement for designing a proper and well-designed clinical trial for facial lipofilling.

SUPPLEMENTAL LEGEND

Table S1. Specific search terms of databases.

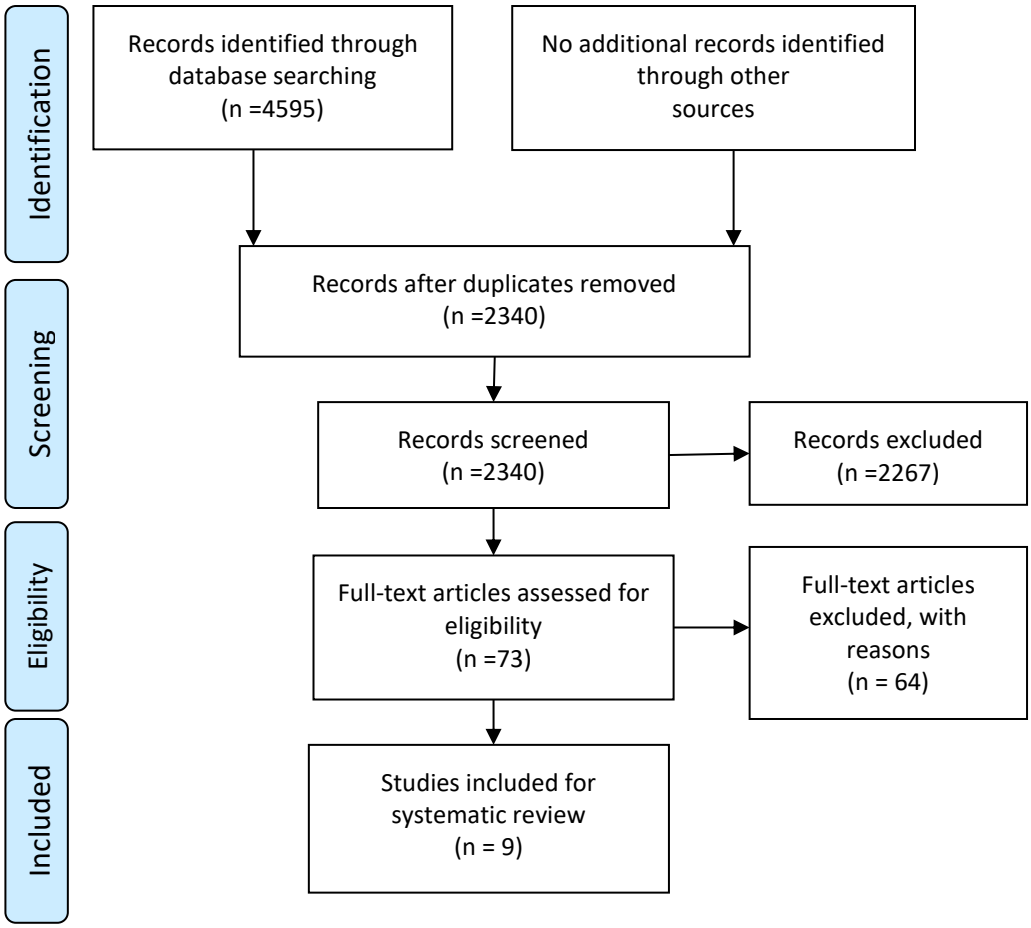

Figure 1. Flow diagram of study selection.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Human skin	Diseases and trauma affecting skin quality *e.g.* burn wounds, scars, disease-caused
Adipose tissue obtained by liposuction	Studies evaluating volumetric effect of lipografting *e.g.* effect on wrinkle depth
Facial lipografting or any components of adipose tissue *i.e.* ASCs, cSVF, tSVF	Studies evaluating effect of lipografting on infraorbital dark circles
Clinical skin changes in texture, color and elasticity	Lipografting in conjunction with other treatments *e.g.* botulinum toxin or fillers
Changes in skin histology	Case reports, conference abstracts and reviews
Prospective and retrospective studies	

ASCs = adipose tissue-derived stromal cells; cSVF = cellular stromal vascular fraction; tSVF = tissue stromal vascular fraction

Table 2. Quality assessment of included studies according to the OCEBM criteria.

Author, year	Level of evidence
Amirkhani et al. 2016	4
Botti et al. 2011	3
Charles-de-Sá et al. 2015	4
Covarrubias et al. 2013	2
Liang et al. 2018	3
Rigotti et al. 2016	4
Song et al. 2017	4
Trivisonno et al. 2017	4
Willemsen et al. 2017	2

OCEBM = Oxford Center for Evidence-Based Medicine

Table 3. Study characteristics and patient demographics.

		Sex				
Author, year	**Study Type**	**Male**	**Female**	**Mean age (y) + sd**	**Range (y)**	**BMI**
Amirkhani et al. 2016	Prospective, non-blinded, non-randomized, non-controlled clinical trial	1	15	-	38-56	-
Botti et al. 2011	Prospective, double-blinded, non-randomized, controlled clinical trial	4	21	46.3	21-72	-
Charles-de-Sá et al. 2015	Prospective, non-blinded, non-randomized, controlled clinical trial	1	5	-	45-65	-
Covarrubias et al. 2013	Prospective, single-blinded, randomized, controlled clinical trial		16	-	40-70	-
Liang et al. 2018*	Prospective, non-blinded, non-randomized, controlled clinical trial	12	91	28.5	24-55	-
Rigotti et al. 2016	Prospective, non-blinded, non-randomized, controlled clinical trial	2	11	56.2	45-65	-
Song et al. 2017	Retrospective, non-blinded, non-randomized, case-control study		76	-	26-53	-
Trivisonno et al. 2017	Prospective, non-blinded, non-randomized, non-controlled clinical trial	2	19	-	35-62	-
Willemsen et al. 2017	Prospective, double-blind, randomized, placebo-controlled clinical trial		25	52 ± 6.75	38-63	20-25 (1 year stable)

** Sex, mean age + sd and range are only given for the experimental group. No demographic data of the control group (n=128) could be extracted.*

Table 4. Adipose tissue harvesting and processing characteristics.

Author, year	Donor site	Infiltration solution	Harvesting cannula	Pressure	Processing method
Amirkhani et al. 2016	Abdominal	Saline solution + epinephrine 0.001%	3 mm	-	Enzymatic isolation of cSVF with collagenase type 1
Botti et al. 2011	Abdomen, knees, or thigh	Saline solution + mepivacaine 0.25% + epinephrine 1:500,000, ratio 1:1 solution:tissue	2 mm two-hole blunt	Manual negative pressure <2 cc	I1: filtering and washing with the use of strainer and 0.9% NaCl I2: centrifugation at 3000 rpm for 3 min.
Charles-de-Sá et al. 2015	Abdominal	-	3 mm	-	I1: non-enzymatic isolation of cSVF by centrifugation at 1286 *xg* for 3 min. cSVF was mixed with decanted lipografting I2: enzymatic isolation of cSVF and subsequent expansion of ASCs for 5 weeks
Covarrubias et al. 2013	Lower hemiabdominal	150 ml of saline solution + adrenaline 0.25g + 20 ml of lidocaine 2%	3 mm	-	Decantation for 15 min.
Liang et al. 2018	Medial and lateral thigh	Tumescent technique	3.5 mm polyporous	Low negative pressure	Centrifugation at 1000 rpm for 2 min., washing with NaCl and subsequently the Nanofat procedure. Nanofat was mixed with PRF.
Rigotti et al. 2016	Infraabdominal	Lidocaine 0.5% + epinephrine 1:500,000	3 mm three-hole	Manual vacuum	I1: non-enzymatic isolation of cSVF by centrifugation at 1286 *xg* for 3 min. cSVF was mixed with decanted lipografting I 2: enzymatic isolation of cSVF and subsequent expansion of ASCs for 4-5 weeks I 3: decanted lipografting was mixed with PRP
Song et al. 2017	Abdominal, thighs and buttocks	Tumescent technique (not specified)	-	Low pressure	Decantation and wicking
Trivisonno et al. 2017	Thighs and hip	Tumescent technique (250 ml saline solution + adrenaline 0.5 mg + lidocaine 20 mg)	2.1 mm multiperforated, rounded-tip	Manual negative pressure	Decantation for 20-30 min.
Willemsen et al. 2017	Upper legs	Standard Coleman procedure	2.4 mm x 22 cm	Manual low negative pressure	Standard Coleman procedure

I= intervention; cSVF = cellular stromal vascular fraction; NaCl = natriumchloride; rpm = rounds per minute; ASCs = adipose derived stromal cells; PRF = platelet rich fibrin; PRP = platelet rich plasma; wicking = inserting a cottonoid strip into the syringe touching the fat graft to wick off any remaining oil.

Table 5. Intervention types and injection characteristics.

Author, year	Intervention type	Injection technique	Injection cannula/needle	Injected volume/ number of cells	Injection site	Injection plane	Number of lipografting sessions
Amirkhani et al. 2016	I1: cSVF	-	18-gauge blunt needle	2×10^7 of cells for each side of the face	Nasolabial fold	Subcutaneous	1
Botti et al. 2011	I1: filtered and washed lipografting I2: centrifuged lipografting	Retrograde and fanning	1-, 1.5-, or 2-mm blunt cannula with a lateral opening	Temporal 2-4 ml, eyelids 1-3 ml, tear-through 0.5-1 ml, malar 3-4 ml, cheek 5-7 ml, nasolabial fold 2-3 ml, mandible 4-6 ml, marionette fold 3-5 ml, chin 2-4 ml, lips 3-6 ml	I1: left side of the face I2: right side of the face	-	1
Charles-de-Sá et al. 2015	I1: cSVF-enriched lipografting I2: cultured ASCs	I1: retrograde and fanning I2: -	I1: 1.5 mm blunt cannula I 2: 30-gauge needle	I1: cSVF + 1 ml of lipografting I2: 2×10^6 of cells in 0.4 ml saline 0.9%	I1: right preauricular area I2: left preauricular area	Subdermal	1
Covarrubias et al. 2013	I: lipografting C: no treatment	Fanning	1 mm blunt cannula	5 ml of lipografting	I: preauricular region on one side of the face C: preauricular region on the other side of the face	Intramuscular and subcutaneous	1
Liang et al. 2018	I: Nanofat + PRF C: hyaluronic acid	Needle hydro lifting	-	4-5 ml	Forehead, cheeks, chin	Intradermal	1
Rigotti et al. 2016	I1: cSVF-enriched lipografting I2: cultured ASCs I3: lipografting + PRP	I1: retrograde and fanning I2: - I3: -	I1: 1.5 mm blunt cannula I2: 30-gauge needle I3: 1.5 mm blunt cannula	I1: - I2: 2×10^6 of cells in 0.4 ml of saline 0.9% I3: 1 ml of lipografting + 1 ml of PRP	I1: right preauricular area I2: left preauricular area 2 cm distal from the tragus I3: left preauricular area 2 cm forward from the lobe	Subdermal	1
Song et al. 2017	I1: lipografting with an electric injection device (YSZTQ-01) I2: lipografting with a conventional hand push injection	I1: retrograde I2: -	-	0.05–26.43 mL of lipografting per region	I1: left side of the face I2: right side of the face	-	1-2
Trivisonno et al. 2017	I: lipografting	-	23-gauge needle	12-18 ml of lipografting	-	Intradermal	1

Willemsen et al. 2017	I: lipografting + PRP C: lipografting + saline 0.9%	Standard Coleman procedure	0.9 mm x 5 cm injectors	*Temporal 2 ml, nasojugal groove 1 ml, central midface 2 ml, nasolabial fold 2 ml, marionette-line/prejowling/chin 3 ml **Temporal/midface 4 ml, lower midface cheek 2 ml, while rolls 2 ml	See column injected volume	Subcutaneous and subdermal	1

*I= intervention; C= control; cSVF = cellular stromal vascular fraction; ASCs= adipose derived stromal cells; PRF = platelet rich fibrin; PRP = platelet rich plasma; YSZTQ-01 = code of an electric lipografting injection device. *Subcutaneous **Subdermal.*

Table 6. Results of lipografting or any substance of adipose tissue on facial skin quality**.**

Author, year	Method of measurement	Follow-up Period	Results	Complications
Amirkhani et al. 2016	Skin thickness, elasticity and pigmentation assessed with a cutometer, and a skin scanner using ultrasound (DUB-TPA).	Preoperative, 15, 30, 60, and 180 days postoperative	An increase in skin elasticity***, dermis thickness**, dermis density*** and epidermis thickness** after 6 months. No difference was seen in epidermis density. There was no difference in pigmentation and melanin production 6 months post-operative.	None
Botti et al. 2011	Subjective patient self-evaluation of skin texture improvement using a non-validated questionnaire.	6 months postoperative	No difference in skin texture between the two groups. Improvement in skin texture was rated 'high' in 68% of the patients of the filtered and washed adipose tissue group vs72% of the patients of the centrifuged adipose tissue group.	None
Charles-de-Sá et al. 2015	Histological and histomorphometric analysis by optical and electron microscopy of skin biopsies.	Preoperative and 3 months postoperative	After both treatments analysis showed a decrease in elastic fiber network and collagen fibers in the reticular dermis. The elastic fibers were more dissociated and reduced in diameter with a smoother surface. An increase of oxytalan elastic fibers was visible in the papillary dermis. No quantitative data was shown and no differences were noticed between both groups.	Not mentioned
Covarrubias et al. 2013	Histological evaluation of skin biopsies.	60-90 days postoperative	An increase in dermis thickness, immature collagen and presence of arteries was found in the intervention group compared to the control group.*** No difference in presence of mature collagen was found between the two groups.	Not mentioned
Liang et al. 2018	Skin texture assessed with the VISIA skin imaging analyser. Skin elasticity assessed with a skin scanner (SOFT5.5).	Preoperative, 1, 6, 12 and 24 months postoperative	Improvement in skin texture and elasticity scores 1, 12 and 24 months postoperative for intervention group**. No comparisons made between intervention group and control group.	5 transient infections, 7 temporarily paraesthesia, 2 pigmentation changes
Rigotti et al. 2016	Histological and histomorphometric analysis by optical and electron microscopy of skin biopsies.	Preoperative and 3 months postoperative	Lipografting + PRP resulted in an increased number of small oxytalan elastic fibers present in an irregular network in the papillary dermis. Reticular dermis showed a decrease of elastic fibers with a reduced diameter and smoother surface. Moreover, an induced inflammatory infiltrates and increased vasculature was visible. No quantitative data was shown.	Not mentioned
Song et al. 2017	Visual evaluation of photographs by a group including the patient, a plastic surgeon and a third party unrelated to the study.	Preoperative, directly postoperative and at 6-24 months postoperative (mean follow-up 10.7 months)	Improvement in skin pigmentation was rated 'high' in 80% vs 72.2% for respectively the use of lipografting with an electric injection device and conventional hand push injection. No difference between the groups.	None
Trivisonno et al. 2017	Skin surface profilometry (Antera 3D® multispectral analyser), clinical assessment by a dermatologist using a 3-grade scale.	Preoperative, 30 and 90 days postoperative	Clinical assessment: improved skin texture, homogeneity and skin colour after treatment.* Skin surface profilometry: 25% improvement in skin texture**, and declined facial haemoglobin and melanin concentrations* after 90 days.	None
Willemsen et al. 2017	Skin elasticity was measured with a cutometer.	Preoperative, 1 week, 3 months and 12 months postoperative	Lipografting with PRP did not improve skin elasticity as compared to lipografting without PRP or compared to the baseline at any follow-up moment.	None

*PRP = platelet rich plasma. * p<0.05, ** p<0.01, *** p<0.001*

Table 7. Statement for designing a proper and well-designed clinical trial for facial lipofilling

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Study design	Patient demographics	Treatment	Outcomes
• *Placebo vs. treatment or Treatment vs. treatment* • *Lipofilling without other treatments** • *Randomized* • *Double-blinded*** • *Follow-up with a minimum of 1 year*	*Inclusion criteria* • *ASA1 with a BMI <30 for at least 1 year* • *Non-smokers: >1-year non-smoking* • *Uniform population of females or males* • *Age: minimum of 35* *Exclusion criteria* • *Diabetes mellitus type 1 or type 2* • *Human immunodeficiency virus* • *Immunological diseases* • *Collagen diseases* • *Interventions of the face 1 year prior to the date of surgery* • *Active child wish* • *Active use of hormone replacement therapy∞* • *History of a psychiatric disorder*	• *Standardized harvesting location* • *Centrifuged adipose tissue as described by Coleman* • *Well documented injection volumes per deep, superficial and intradermal anatomical locationº* • *Number of sessions need to be standardized* • *Maximum time of 30 min. between lipoharvesting and injection*	*Primary outcome* • *Skin elasticity measured with the cutometer* *Secondary outcome* • *Patient satisfaction measured with the FACE-Q* • *Clinical photographs analysed by a blinded and independent observer* • *Number of complications*

**Lipofiling can only be combined with cSVF, tSVF or PRP-like treatments. **Patient as well as investigator performing measurements preoperative and during follow-up. ∞Hormonal birth control treatments are excluded. ºTemporal, nasojugal groove, central midface, nasolabial fold, marionette-line/prejowling/chin. ASA = American Society of Anaesthesiology*

SUPPLEMENTAL CONTENT

Table S1. Specific search terms of databases.

Databases	Search terms
Embase	((('mesenchymal stem cell transplantation'/de OR transplantation/de OR 'tissue transplantation'/de OR 'tissue graft'/de OR injection/de OR 'cell therapy'/de OR 'stem cell transplantation'/de OR 'stem cell'/de) AND ('adipose tissue'/exp OR 'adipose tissue cell'/exp OR fat/de OR 'lipectomy'/de OR liposuction/de)) OR 'lipofilling'/de OR 'fat transplantation'/de OR 'fat injection'/de OR 'adipose tissue transplantation'/de OR 'autologous fat transfer'/de OR 'adipose derived stem cell'/de OR 'fat transfer'/de OR 'fat grafting'/de OR 'stromal vascular fraction'/de OR lipografting/de OR (lipofill* OR Lipograft* OR lipoinject* OR microlipofill* OR Microlipograft* OR microlipoinject* OR ((fat OR dermofat OR microfat OR Nanofat OR adipose OR facelift* OR face-lift* OR lipectom* OR liposuct*) NEAR/6 (transplant* OR graft* OR autotransplant* OR autograft* OR inject* OR stem-cell* OR Progenitor-Cell* OR transfer* OR autolog* OR implant* OR redistribut* OR filler OR filling)) OR (stroma* NEAR/3 vascul* NEAR/3 fraction*)):ab,ti) AND ('rhytidoplasty'/exp OR 'facial rejuvenation'/de OR 'face skin'/de OR 'face'/exp OR 'wrinkle'/de OR 'face surgery'/de OR 'facies'/de OR (Rhytidoplast* OR facelift* OR face-lift* OR midface* OR midfacial* OR face OR facial OR cheek* OR chin OR forehead* OR fore-head* OR periocul* OR periorbit* OR peri-ocul* OR orbit* OR nasolabial* OR wrinkle* OR bucca* OR (Crow* NEAR/3 feet*) OR ((frontal OR frontopariet* OR fronto-orbital*) NEAR/3 area*) OR facies):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim
Medline Ovid	(((Mesenchymal Stem Cell Transplantation/ OR Transplantation/ OR Tissue Transplantation/ OR Injections/ OR Cell- and Tissue-Based Therapy/ OR Stem Cell Transplantation/ OR Cell Transplantation/ OR Stem Cells/) AND (exp Adipose Tissue/ OR Lipectomy/)) OR exp Adipose Tissue/tr OR (lipofill* OR Lipograft* OR lipoinject* OR microlipofill* OR Microlipograft* OR microlipoinject* OR ((fat OR dermofat OR microfat OR Nanofat OR adipose OR facelift* OR face-lift* OR lipectom* OR liposuct*) ADJ6 (transplant* OR graft* OR autotransplant* OR autograft* OR inject* OR stem-cell* OR Progenitor-Cell* OR transfer* OR autolog* OR implant* OR redistribut* OR filler OR filling)) OR (stroma* ADJ3 vascul* ADJ3 fraction*)).ab,ti.) AND (Rhytidoplasty/ OR exp Face/ OR Skin Aging/ OR Facies/ OR (Rhytidoplast* OR facelift* OR face-lift* OR midface* OR midfacial* OR face OR facial OR cheek* OR chin OR forehead* OR fore-head* OR periocul* OR periorbit* OR peri-ocul* OR orbit* OR nasolabial* OR wrinkle* OR bucca* OR (Crow* ADJ3 feet*) OR ((frontal OR frontopariet* OR fronto-orbital*) ADJ3 area*) OR facies).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.
Cochrane CENTRAL	((lipofill* OR Lipograft* OR lipoinject* OR microlipofill* OR Microlipograft* OR microlipoinject* OR ((fat OR dermofat OR microfat OR Nanofat OR adipose OR facelift* OR face-lift* OR lipectom* OR liposuct*) NEAR/6 (transplant* OR graft* OR autotransplant* OR autograft* OR inject* OR stem-cell* OR Progenitor-Cell* OR transfer* OR autolog* OR implant* OR redistribut* OR filler OR filling)) OR (stroma* NEAR/3 vascul* NEAR/3 fraction*)):ab,ti) AND ((Rhytidoplast* OR facelift* OR face-lift* OR midface* OR midfacial* OR face OR facial OR cheek* OR chin OR forehead* OR fore-head* OR periocul* OR

	periorbit* OR peri-ocul* OR orbit* OR nasolabial* OR wrinkle* OR bucca* OR (Crow* NEAR/3 feet*) OR ((frontal OR frontopariet* OR fronto-orbital*) NEAR/3 area*) OR facies):ab,ti)
Web of Science	TS=(((lipofill* OR Lipograft* OR lipoinject* OR microlipofill* OR Microlipograft* OR microlipoinject* OR ((fat OR dermofat OR microfat OR Nanofat OR adipose OR facelift* OR face-lift* OR lipectom* OR liposuct*) NEAR/5 (transplant* OR graft* OR autotransplant* OR autograft* OR inject* OR stem-cell* OR Progenitor-Cell* OR transfer* OR autolog* OR implant* OR redistribut* OR filler OR filling)) OR (stroma* NEAR/2 vascul* NEAR/2 fraction*))) AND ((Rhytidoplast* OR facelift* OR face-lift* OR midface* OR midfacial* OR face OR facial OR cheek* OR chin OR forehead* OR fore-head* OR periocul* OR periorbit* OR peri-ocul* OR orbit* OR nasolabial* OR wrinkle* OR bucca* OR (Crow* NEAR/2 feet*) OR ((frontal OR frontopariet* OR fronto-orbital*) NEAR/2 area*) OR facies))) AND DT=(article) AND LA=(english)
Google Scholar	lipofilling|lipofiller|Lipograft|lipoinjection|"adipose stem|Progenitor cell|cells"|"adipose*stem|Progenitor cell|cells" Rhytidoplasty|facelift|midface|midfacial|face|facial|cheek|chin|forehead|periocular|periorbital|"peri ocular|orbital"|wrinkles|buccal|"Crow's feet"