

Protocol for a Systematic Review of Outcome Measurement Tools for Autologous fat Grafting of the Facial Region

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Keywords: Adipose-derived stem cells, Autologous fat, Cell-assisted lipotransfer, Fat grafting, Lipotransfer, Stromal vascular fraction, outcome methods, measurement tools, safety, effectiveness, Systematic review

Posted Date: November 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-99448/v1>

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Abstract

Background

Autologous fat grafting has become an established therapeutic entity in several regions of the body. Especially in the facial region, AFG has been widely applied in the field of plastic and reconstructive surgery. Indications include reconstructive purposes such as primary genetic disorders in maxillofacial development, or secondary asymmetries following primary reconstructive surgery. In addition, AFG has found several applications in the field of aesthetic surgery, such as skin rejuvenation. In addition to conventional AFG, recently several alternative strategies of grafting have been developed. Examples for these are transplantation of a graft including adipose derived stem cells (ADSC's), cell-assisted lipofilling (CAL), and grafting with stromal vascular fraction (SVF). Until today, there is no common consensus on how to measure a successful outcome of autologous graft transplantation in the facial region. This systematic review aims to critically evaluate the current available outcome measurement methods, and compare them with regards to accuracy, cost-effectiveness, safety and validation in the clinical setting. The quality of evidence of included publications will be assessed using the GRADE strategy.

Methods

A comprehensive, structured literature search of published articles will be conducted. This is designed by authors and performed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P). The literature search will be performed using the electronic databases MEDLINE (PubMed), EMBASE and Cochrane Library, including publications from inception to May 2020. Two independent authors will conduct the search, screen the articles, and complete data collection. The main outcome will be which methods are currently used to determine a successful fat grafting procedure in the face. We propose to review the current methods used to establish their overall performance in several domains. In addition, patients measured via the 3D volumetric photography method will be further analysed with regards to accuracy of the camera and retention of fat per method and ml injected.

Discussion

Autologous fat grafting in the facial region has gained significant attention in the field of plastic and reconstructive surgery in the past decades. In light of the growing public interest in this topic, a systematic review of the outcome measurement tools is of essence. We will critically evaluate all approaches currently in practice and give a recommendation regarding several aspects of use. A common approach to measurement and reporting of results fosters an environment of high-standard healthcare delivery and promotes future research and informed clinical practice. In addition, we will further analyse the outcomes of different grafting methods using 3D volumetric photography as measurement tool.

PROSPERO registration number: CRD42020213407

Background

Autologous fat grafting (AFG) has become an established method in the field of plastic-reconstructive surgery over the past two decades. Since the beginning of structural fat grafting, where Coleman et al. (1–3) first described a standardised method which is still broadly in use today, different types of harvesting, processing and grafting methods have emerged. In addition to that, the lipoaspirate can be used in combination with other biological products. These include cell assisted lipofilling (CAL), where fat is combined with adipose-derived stem cells (ADSC) which have been reported to improve fat survival rate (4), ADSC transfer only, fat plus stromal vascular fraction (SVF) transfer, which contains ADSC's, endothelial cells, endothelial progenitor cells, pericytes, preadipocytes and hematopoietic cells (5) and fat plus platelet rich plasma (PRP), which is claimed to support angiogenesis and reduce absorption of fat (6, 7).

AFG has a broad spectrum of applications in several regions of the human body, including the female breast and the face. Facial AFG indications include reconstructive purposes defects and asymmetries after primary reconstructive surgery, congenital maxillofacial deficits (8) and aesthetic indications including lipofilling for facial rejuvenation. Although facial fat grafting has gained an undeniable amount of attention recently, there is still no widely accepted consensus over the measurement tools to assess the outcome.

The diversity of ways to define and quantify an objectively good outcome of AFG in the facial region creates difficulties in validation of research results and challenges in comparing the outcome among different studies.

Popular measurement methods include subjective parameters such as patient satisfaction surveys, and scores given by a jury voting on pre- and postoperative photographs.

Objective methods include volumetric measurements via 3D-photography, magnetic resonance imaging or computed tomography. In the aesthetic field common parameters include skin quality, more specifically skin texture, skin colour, elasticity and histological outcomes. (9) The purpose of this systematic review is to better understand and compare the objective and subjective outcome measurement tools currently used following fat grafting in the facial region and to propose a core of outcome set (COS) to be used in facial fat grafting. This will help create reproducible studies and experiments and comparability of outcomes. A more detailed analysis of the studies using 3D volumetric photography as outcome measurement method will be undertaken. In addition, grafting methods CAL, ADSC only, SVF enriched graft and fat only will be compared where primary empirical evidence exists.

Methods

This protocol has been submitted to the PROSPERO database and is currently under review for registration (ID: 213407). A comprehensive, structured literature search of published articles will be

conducted. This is designed by authors S.S. B.L. and A.A., and performed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) (10).

Search Strategy

The literature search will be performed using the electronic databases MEDLINE (PubMed), EMBASE and Cochrane Library, including publications from inception to May 2020. The keywords used in the search will be selected from key papers and are described in Table 1. Search strings 1 and 2 will be combined using the Boolean term AND, then the limits are applied. Furthermore, a 'MeSH term' search will be conducted, and the reference lists of included articles are reviewed for any additional articles. The full search strategy is provided in the **appendix**. Study selection will be independently assessed by 2 reviewers (S.S. and B.L.), any persisting disagreements were reviewed and adjudicated by a third reviewer (A.A.).

Table 1

Number	Search terms
String 1	"Fat graft" or "Fat grafting" or "Fat transplant" or "Fat transplantation" or "Fat transfer" or "Fat augmentation" or "Fat injection" or "Lipoinjection" or "Lipotransfer" or "Lipofilling" or "Lipograft" or "Autologous fat" or "Autogenous fat" or "lipoaspirate" or "nanofat" or "microfat"
String 2	"face" or "facial" or "midface" or "head and neck" or "maxillofacial" or "facial reconstructive" or "facial asymmetry" or "facial hemiatrophy" or "lipodystrophy" or "facelift" or "rhytidectomy" or "facial rejuvenation" or "rhinoplasty" or "cheek" or "eyelid" or "nose" or "forehead" or "glabella" or "chin" or "nasolabial" or "buccal" or "periocular" or "periorbital" or "mouth"

Study selection criteria

Articles are eligible for inclusion if they provide primary empirical evidence of patient outcomes after fat grafting. Outcome measures reported are categorized as either objective or subjective and reported separately. The full inclusion and exclusion criteria are detailed in Table 2. Inclusion: Patients of any age and any gender, regardless of ethnicity, who have undergone autologous fat grafting (AFG) to the facial region one or several times. This can be out of various reasons including but not limited to: reconstructive purposes such as reduction of defects and asymmetries after head and neck cancer surgery, congenital maxillofacial deficits and aesthetic indications including lipofilling for facial rejuvenation.

Exclusion: Patients who have undergone AFG in any other region than the face, or where no outcomes are reported.

Table 2

Inclusion Criteria
<ol style="list-style-type: none"> 1. Original publications 2. Human subjects 3. Case Series, Retrospective Data Analyses, Clinical Trials, Controlled Clinical Trials, Prospective Studies
Exclusion Criteria
<ol style="list-style-type: none"> 1. Publication type does not match inclusion criteria (Review articles, Mixed methodology studies without subgroup data, Animal studies, Conference Articles, Case studies) 2. The paper is about fat grafting undertaken at sites other than the Maxillofacial and Head and Neck region 3. The paper is not about treatment 4. The paper is not about a surgical intervention (but included if terms such as reconstruction or rehabilitation, or flap or graft, are mentioned).

Participants

Patients undergoing autologous fat grafting (AFG) in the facial region for various reasons, including reconstructive purposes such as reduction of defects and asymmetries after head and neck cancer surgery, congenital maxillofacial deficits and aesthetic indications including lipofilling for facial rejuvenation.

Intervention

Autologous fat grafting in the facial region for reconstructive and aesthetic purposes

Comparator

Other methods of autologous grafting in the facial region for reconstructive and aesthetic purposes including:

- - Cell assisted lipofilling (CAL)
- - Stromal vascular fraction (SVF) only grafting
- - Adipose derived stem cell (ADSC) only grafting
- - Lipotransfer mixed with platelet rich plasma (PRP)

Outcome

The main outcome will be which methods are currently used to determine a successful fat grafting procedure in the face. We will then compare these methods regarding accuracy, cost-effectiveness, safety

and validation in the clinical setting. The accuracy will be analysed by comparison of ml of injected fat to measurement of pre- to postoperative and long-term follow up outcomes.

The cost effectiveness will be evaluated by comparison of cost of acquisition of machine divided by number of measurements achieved by this machine.

The safety will be measured by adverse events.

The tools will also be rated by status of validation (validated y/n)

In addition, we will analyse

- - amount of fat injected by facial subunit in ml
- - the subset of patients measured via volumetric methods will be further analysed with regards to retention of fat per method and ml injected.
- - The comparison of fat per subunit injected to amount of fat retained in %
- - Which subunit retains most fat in %
- - Which device has the most accurate measurements by measuring amount of fat injected versus amount of volume difference when comparing preoperative to postoperative photographs in ml

Data extraction

Articles are scanned, analysed and data extracted using a predesigned data collection sheet. This data collection template is tested in two randomly chosen publications, before being used on all included articles. Data extracted include patient demographics (gender, age, comorbidities), the details of the fat grafting protocol used (donor site, processing methodology, graft volume) and any outcome measures reported including time to outcome measurement and any complications.

Subgroup analyses

Assuming that sufficiently robust patient groups can be identified from the studies, the different fat grafting methods and patient aetiologies (reconstructive/aesthetic) will be considered separately.

Methodological Quality and risk of bias assessment

Included studies are assigned a level of evidence based on the Oxford Centre for Evidence Based Medicine (11). In addition, randomized control trials are rated for bias using the GRADE approach. This includes the RoB version 2.0 tool for RCTs and ROBINS-I for Comparative studies (12).

Data analysis and synthesis

Data are analysed using IBM SPSS statistics version 24. Primary and secondary outcome measures will be evaluated using simple descriptive statistics. Where appropriate, we will provide pooled estimates with corresponding measures of dispersion.

We will only perform a meta-analysis if a sufficient number of studies (minimum ≥ 3) with consistent characteristics are included. In the first instance, we will combine all AFG techniques into a single intervention group. If ≥ 3 comparable studies are available for one or more intervention subtypes (namely lipotransfer, CAL, SVF- or ADSC-only), we will perform individual subgroup meta-analyses to statistically evaluate how these techniques compare to one another regarding the fat retention rate.

We will explore all sources of potential heterogeneity related to study design, participants, interventions, comparators and outcomes. Statistical heterogeneity will be assessed using the χ^2 test and quantified with the I^2 statistic. The thresholds for interpretation of the I^2 value will be in accordance with those presented in the Cochrane Handbook for Systematic Reviews of Interventions. An evaluation of between study heterogeneity will inform our decision as to whether a fixed or random effects model is more appropriate for the dataset. If sufficient studies are included in the meta-analysis, we will interrogate the accuracy of our overall outcome estimate using a sensitivity analysis.

Continuous outcomes will be analysed using either mean differences or standardised mean differences (with 95% confidence intervals (CIs)); dichotomous data will be analysed using risk ratios (with 95% CIs); time-to-event data will be analysed using hazard ratios (with 95% CIs).

In the event that a meta-analysis is not appropriate, we will combine the results of all included studies in a qualitative synthesis with reference to our primary and secondary outcomes. In this narrative evaluation, we will comment on whether the efficacy and safety of AFG outcome measurement methods appear to vary according to the intervention subgroups defined above.

Discussion

Autologous fat grafting in the facial region has gained significant attention in the field of plastic and reconstructive surgery in the past decades. Up to today, there is no single best measurement method of practice to determine a successful outcome of AFG to the face. In light of the growing public interest in this topic, a systematic review of the outcome measurement tools is of essence. We will critically evaluate all approaches currently in practice and give a recommendation regarding several aspects of use. In addition, we will further analyse the outcomes of different grafting methods using 3D volumetric photography as measurement tool. We hope to identify the most effective method with regards to accuracy of the camera and retention of fat per method and ml injected. Should one tool be observed to have the highest ratings in all domains tested, we will give a recommendation for future use. We also hope to identify which grafting technique is superior and whether this varies according to facial subunit injected or time to follow-up. Combined, we hope the conclusions will help shape the clinical decision-making process with aspects of finding the ideal transplantation technique for their patient and validating a successful result. We will discuss the generalisability and robustness of our results in light of the level of evidence and overall risk of bias of each summary outcome measure observed. A common approach to measurement and reporting of results fosters an environment of high-standard healthcare delivery and promotes future research and informed clinical practice.

Abbreviations

AFG- Autologous fat grafting

CAL- Cell-assisted lipofilling

ADSC's- Adipose derived stem cells

SVF- Stromal vascular fraction

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Dr. Sophie Speiser^{b,c*}, BA, BSc.: First reviewer, design of study, data analysis, data interpretation, manuscript preparation

Miss Aurora Almadori^{a,b,c} MBChB, MSc: Second reviewer, design of study, data interpretation, manuscript preparation

Mr Benjamin Langridge^{a,b,c*} MBBS MA(Cantab.) MRCS FHE: Third reviewer, design of study, data interpretation, manuscript preparation

Professor Peter EM Butler^{a,b,c} MD FRCS (Plast): Design of study, data interpretation, manuscript preparation

BL, SS and WR designed the study in cooperation. SS and HK planned the original review protocol, which was revised by WR. MB and SS conducted the pilot literature searches, SS built and carried out the final search. SS drafted the manuscript with inputs by BL. WR and HK contributed to manuscript revision. All authors read and approved the final manuscript prior to submission. SS is the primary author and guarantor of this protocol.

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Supplementary Files

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- [Appendix.docx](#)
- [PRISMAPchecklist.docx](#)