IBEROAMERICAN JOURNAL OF MEDICINE
iberoamericanjm
Journal homepage: www.iberoamjmed.com

Review

Use of stem cell-enriched fat grafts in facial reconstruction: have they demonstrated superiority over autologous fat grafting?

Gerardo Jesus Farley Reina Gonzalez [a], *Maria Daniela del Pilar Zambrano Arenas* [b], *Daniel Hernandez Cabarcas* [c], *German Daniel Matiz* [b], *Wilmer Giovanny Galvis Ballesteros* [d], *Miguel Andres Montalvo Clavijo* [e], *Rodrigo Alberto Caicedo* [f], *Michael Gregorio Ortega-Sierra* [g,*]

[a] *School of Medicine, Universidad del Tolima, Ibagué, Colombia*
[b] *School of Medicine, Universidad El Bosque, Bogotá, Colombia*
[c] *School of Medicine, Universidad del Norte, Barranquilla, Colombia*
[d] *School of Medicine, Universidad de Pamplona, Pamplona, Colombia*
[e] *School of Medicine, Universidad Ciencias Médicas de la Habana, La Habana, Cuba*
[f] *School of Medicine, Universidad Libre, Cali, Colombia*
[g] *Universidad Centrooccidental Lisandro Alvarado, Hospital Centro Antonio María Pineda, Barquisimeto, Venezuela*

ARTICLE INFO

Article history:
Received 27 July 2023
Received in revised form 23 August 2023
Accepted 10 September 2023

Keywords:
Transplants
Stem cells
Face
Plastic surgery procedures

ABSTRACT

Since the 1990s, big strides have been made in plastic and reconstructive surgery, thanks to the implementation of new techniques and resources for its execution. In cases where restoration is sought for small defects, biosurgery, involving the utilization of stem cells, biomaterials, chemical engineering, and tissue engineering, can be employed. The potential to stimulate the innate regenerative capacity of tissue and generate a persistent response over time, minimizing surgical trauma and re-interventions, lies in stem cell transplantation. However, the evidence published on this matter is very scarce, leading to divergence of opinions, suggestions, and recommendations. The aim of this review is to analyze the most recent evidence concerning the outcomes of using fat grafts enriched with stem cells in facial reconstruction, as compared to autologous fat grafts. The review of the literature demonstrates a marked trend suggesting that fat grafts enriched with stem cells may be superior to autologous grafts in facial reconstruction, with potential benefits in medium-term volume retention and faster attainment of results.

* *Corresponding author.*
E-mail address: mortegas2021@gmail.com
ISSN: 2695-5075 / © 2023 The Authors. Published by Iberoamerican Journal of Medicine. This is an open access article under the CC BY license (http://creativecommons. org/licenses/by/4.0/).
https://doi.org/10.53986/ibjm.2023.0028

Uso de injertos de grasa enriquecidos con células madre en la reconstrución facial: ¿han demostrado superioridad sobre los injertos de grasa autólogos?

INFO. ARTÍCULO

Historia del artículo:
Recibido 27 Julio 2023
Recibido en forma revisada 23 Agosto 2023
Aceptado 10 Septiembre 2023

Palabras clave:
Trasplante
Células madre
Cara
Procedimientos cirugía plástica

RESUMEN

La cirugía plástica y reconstructiva, ha dado pasos agigantados desde la década de los años 90, con la implementación de nuevas técnicas y recursos para su realización. En los casos de defectos pequeños donde se busca la restauración, se puede hacer uso de la biocirugía, que involucra el uso de células madre, biomateriales, ingeniería química y de tejidos. El trasplante de células madre, tiene el potencial de estimular la capacidad innata regenerativa del tejido, así como de generar una respuesta persistente a lo largo del tiempo, minimizando el trauma quirúrgico y la reintervención. A pesar, de la ventaja plausible, la calidad y cantidad de la evidencia publicada al respecto es muy escasa, ocasionando divergencia de opiniones, sugerencias y recomendaciones. Con base en lo anterior, el objetivo de esta revisión consiste en realizar un análisis de la evidencia más reciente sobre los resultados en el uso de injertos de grasa enriquecidos con células madre en la reconstrucción facial, comparado a los injertos de grasa autólogos. A través de la revisión de la literatura, se pudo evidenciar que, aunque la evidencia es heterogénea a la fecha, existe una tendencia marcada en que el uso de injertos de grasa enriquecidos con células madre, podría ser superior a los injertos autólogos en la reconstrucción facial, con potenciales beneficios en la retención de volumen a mediano plazo y mayor celeridad en la obtención de resultados.

HOW TO CITE THIS ARTICLE: Farley Reina Gonzalez GJ, del Pilar Zambrano Arenas MD, Hernandez Cabarcas D, Matiz GD, Galvis Ballesteros WG, Montalvo Clavijo MA, Caicedo RA, Ortega-Sierra MG. Use of stem cell-enriched fat grafts in facial reconstruction: have they demonstrated superiority over autologous fat grafting?. Iberoam J Med. 2023;5(4):170-175. doi: 10.53986/ibjm.2023.0028.

1. INTRODUCTION

Enormous progress has been made in plastic and reconstructive surgery since the 1990s, with the implementation of new techniques and resources for its performance [1, 2]. For instance, facial reconstruction, being one of the most complex interventions in this discipline due to the involvement of numerous structures and organs, as well as functional and aesthetic outcomes, has rapidly evolved with the inclusion of new grafts [2, 3]. Autologous fat grafts have traditionally been one of the options used because of their good tissue tolerability and satisfactory outcomes. However, the response during the rehabilitation and anatomical normalization phase, as well as the extent and severity of the defect to be reconstructed, also plays a crucial role [4, 5].

In cases of small defects requiring restoration, biosurgery can be employed, involving the utilization of stem cells, biomaterials, chemical engineering, and tissues [6-10]. The potential to stimulate the innate regenerative capacity of tissue and generate a persistent response over time, minimizing surgical trauma and reoperation, lies with stem cell transplantation [10]. Despite its plausible advantage, the quality and quantity of published evidence on this matter are very limited, resulting in divergent opinions, suggestions, and recommendations.

However, the most recent and high-quality evidence seems to offer a broader perspective on the trend of outcomes obtained when comparing the use of fat grafts enriched with stem cells to the use of autologous fat grafts [11]. Given the need for a scientifically sound basis to facilitate decision-making in clinical practice, especially in severe cases requiring extensive reconstruction, the objective of this review is to analyze the most recent evidence regarding the outcomes of using fat grafts enriched with stem cells in facial reconstruction, as opposed to autologous fat grafts.

2. MATERIAL AND METHODS

A literature search was conducted using the terms 'stem cell-enriched fat grafts,' 'autologous fat grafting,' and 'facial reconstruction,' along with their synonyms, which were combined using Boolean operators, in the PubMed and Scopus databases. Any full-text articles that compared the outcomes of using fat grafts enriched with stem cells in

facial reconstruction to autologous fat grafts were included, with priority given to original studies and systematic reviews and meta-analyses. Articles published up to the year 2023 were included. A total of 34 articles were identified, including some describing basic theoretical concepts. The estimated values and calculations found were reported in their original measurements, including frequencies, percentages, confidence intervals (CI), difference of means (DM), relative risk (RR), odds ratio (OR), or hazard ratio (HR).

3. RESULTS

3.1. USE OF STEM CELLS IN PLASTIC SURGERY: ADVANTAGES OVER TRADITIOAL APPROACHES

With the advent of technology in health research involving stem cells, the potential of these cells has been demonstrated through tissue engineering based on their properties [12, 13]. Achieving their purification requires various processes, starting with the extraction of these cells from the epidermal tissue. Initially, cellular cultures, enzymatic restoration, and purification are performed, and growth factors, physical, and chemical factors are added to facilitate their appropriate adaptation when applied to the skin [13-15].

Consequently, different cellular subtypes can be obtained, allowing for more effective tissue reconstruction and promoting a healthier cellular transition. As a result, the transplantation of these cells has the capacity to induce immunomodulation, recruit keratinocytes and fibroblasts, and promote angiogenesis, nerve regeneration, synthesis of elastin and collagen, and even hair regeneration [12, 13, 15-17]. In contrast, achieving these advantages using traditional techniques is very difficult or even impossible when working with tissue lacking prior regeneration and differentiation. In such cases, only the facial structure is restored without addressing crucial details that significantly contribute to the patient's aesthetics [15]. The administration of stem cells can initiate an anti-aging mechanism through cellular reprogramming, reducing cell wear and senescence, and restoring the proteodynamics of previous cells. These benefits extend to soft tissues, bone, cartilage, and more [15-17]. Thus, they can be applied during bone reconstruction, wound healing, augmentation and regeneration of soft tissues, peripheral nerve, and cartilage (Figure 1). These benefits are particularly associated with the specific use of mesenchymal stem cells [18].

However, it is essential to consider some limitations when using these cells. The U.S. Food and Drug Administration (FDA) has reported concerns about the inherent risk of contamination and damage to cultivated and distributed cells [19]. Therefore, strict and restricted regulation is necessary in the commercialization of stem cell-based products to ensure patient safety. This is primarily due to a significant gap in the evidence from trials that thoroughly studied the factors associated with potential harmful effects

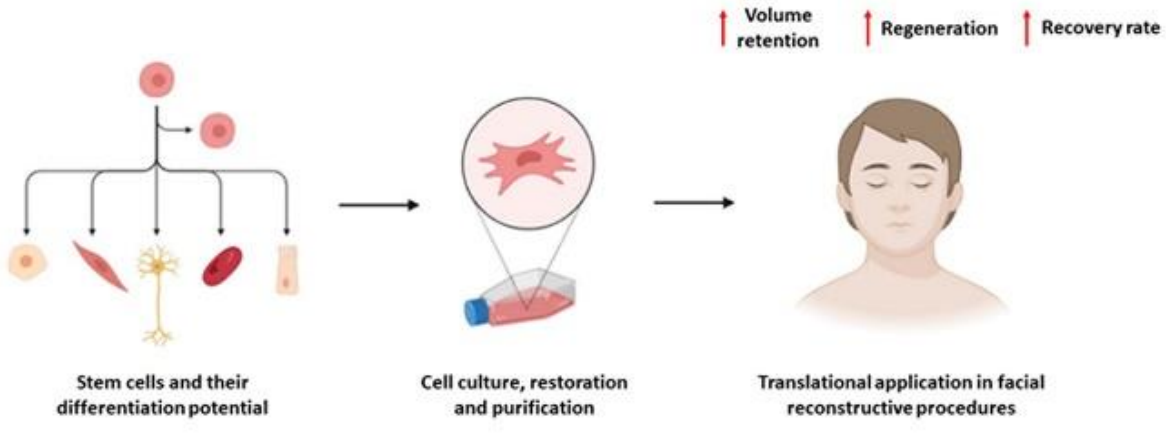

***Figure 1**: Potential benefits of the use of stem cell-enriched biotissues in the reconstruction of facial defects in plastic surgery.*

of stem cells during cultures or translational applications [12, 16]. This risk begins with the extraction of tissue and donor cells, continues through laboratory manipulation, and extends to eventual administration. Even the use of substrates and compounds in cultures should be of the highest quality. Thus, it is essential to always verifying that the provider possesses all certifications and discloses the actual components of their products [12-14].

Another risk lies in the potential for these reprogrammed cells to undergo malignant transformation. Undoubtedly, like all pluripotent cells, they are susceptible to mutagenesis and the eventual acquisition of malignant properties, especially mesenchymal stem cells. However, specific evidence studying this phenomenon is currently unknown [15, 20]. Nevertheless, the benefits of using these cells and the impact they can have on health outcomes, such as morbidity, functional capacity, and quality of life, are evident.

3.2. CLINICAL EVIDENCE ON THE USE OF STEM CELL-ENRICHED FAT GRAFTS VS. AUTOLOGOUS FAT GRAFTS

To date, clinical evidence studying the use of stem cell-enriched fat grafts versus autologous fat grafts is scarce. However, there is a marked trend favoring the benefit of using grafts enriched with stem cells.

Among the most recent studies, Bourne et al [21] conducted a randomized controlled trial with 12 subjects who had at least two craniofacial deficiencies and underwent surgery for correction using stem cell-enriched fat grafts compared to traditional grafts. They found no statistically significant differences in volume retention between the intervention group and the control group, both overall (50.3% vs. 57.3%; p=0.269) and in the malar region (51.4% vs. 56.7%; p=0.494). No association was found between any sociodemographic or clinical factor and volume retention. The cellular subpopulation was predominantly composed of adipocytes derived from stem cells (60.1% ± 11.2%), and a strong correlation was only found between the presence of pericytes and volume retention (p = 0.027) [21]. The authors concluded that although both interventions were effective and safe (due to the absence of adverse events), there was no significant advantage in favor of using stem cells.

In previous years, these same researchers evaluated surgical outcomes in the transfer of autologous fat for craniofacial deformity reconstruction in a prospective cohort study of 20 subjects [22]. The authors did not observe adverse events but identified that volume retention at three months significantly predicted volume retention at nine months (p <0.001). Those undergoing a second intervention had similar retention to the first intervention (p=0.05), and as in the previous study, there was no association between any sociodemographic or clinical factor and retention, except for smoking, which was associated with higher retention (74.4% vs. 56.2%; p=0.009). Physical appearance (p=0.002), social relationships (p=0.02), and functionality (p=0.05) significantly improved at nine months. Considering that there were no significant differences between this intervention and the use of stem cells, it is presumed that these outcomes are similar to those that can be achieved with the use of stem cells, with a notable impact on the patient's functional capacity and self-image [22]. Importantly, without the presence of serious adverse or secondary events.

Sasaki et al [23], through a case-control study, evaluated the efficacy and safety of cell-assisted fat grafts versus traditional grafts, using 3D evaluation. Volunteer candidates selected their preferred technique for facial volume augmentation. The study determined that graft enrichment with stem cells significantly improved the mean volume retention at nine months (p <0.01) [23].

Rasmussen et al [24], through a systematic review, evaluated the effect, viability, and clinical relevance of using stem cell-enriched fat grafts in large interventions, including 38 studies. The researchers observed that the use of stem cell-enriched grafts increased volume retention by more than 1.5 times compared to other techniques. However, they stated that the evidence was highly heterogeneous, making it difficult to determine the clinical relevance, although the results are promising [24].

Sterodimas et al [25], in a randomized controlled trial involving 20 participants with facial defects, compared the performance of autologous fat grafts to stem cell-enriched fat grafts. They found that the entire stem cell-enriched graft group required only one treatment session to achieve aesthetically acceptable results and high levels of satisfaction. In contrast, in the control group, only three patients achieved these results during the first session. It should be highlighted that at 18 months, there were no statistically significant differences between both groups, leading to the conclusion that the benefit of using stem cell-enriched grafts lies in obtaining favourable results more quickly [25].

In China, Yin et al [26] also conducted a randomized controlled trial with 50 patients (equally divided into two groups) to evaluate the effect of stem cell-enriched grafts versus standard fat grafts in facial reconstruction. They

demonstrated that the survival rate of stem cell-enriched grafts was significantly higher than that of the control group (77.6% vs. 56.2%; p <0.001). Additionally, skin quality based on texture was significantly better in the intervention group at 6 months post-surgery (15.8 vs. 10.3; p <0.01). Satisfaction was similar at the end of the study in both groups [26]. Interestingly, studies using platelet-rich plasma-added grafts and assessing the same outcomes as previously mentioned evidence have obtained very similar results, showing an added benefit to the cellular modification of the transplanted tissue [27]. Bashir et al [28] in Pakistan evaluated outcomes in the use of traditional grafts versus stem cell-enriched grafts for facial deformity reconstruction in 25 individuals, observing that the use of enriched grafts had similar outcomes in terms of soft tissue thinning at 6 months post-intervention, with equal satisfaction [28].

Krastev et al [29], through a systematic review and meta-analysis of 52 studies with 1568 patients, evaluated the safety and efficacy of autologous fat transfer, showing that patient satisfaction and surgeon satisfaction were approximately 91% and 88%, respectively. The number of sessions required to achieve.

3.3. FUTURE PERSPECTIVES

In the field of plastic surgery, particularly in the utilization of biomaterials enriched with stem cell properties, research lines and future perspectives warrant deep translational application evaluation due to the scarcity of evidence regarding marker expression or tissue changes in this technique, and its associated factors [30, 31]. Several authors [32], who emphasize the significant gap, especially in low and middle-income countries, where evidence pertaining to this subject is nearly absent, have supported this viewpoint. Importantly, it should be emphasized that the advancement of these techniques and biomaterials extends beyond the mere aesthetics of the procedure. The primary objective is the restoration of the patient's quality of life and functional capacity [32]. Consequently, this area could be defined as a research priority in the reconstruction of congenital or acquired facial defects, especially in children and adolescents, where the emotional impact of the defect could be greater and could affect other domains of their lives [33, 34]. Particularly, because the evidence related to this topic that has exclusively studied children is very limited [34].

The potential of bioprinting and regenerative medicine lies in surpassing organ regeneration and ensuring the preservation of all the functionality and organic properties of the tissue. This implies a remarkable progress in tissue engineering and regeneration. The utilization of 3D tools and regeneration may revolutionize the traditional paradigm and prognosis for managing burned patients or healing extensive wounds [35, 36]. The establishment of more research centers and specialized care in plastic and reconstructive surgery is necessary to enable the inclusion of patients as research subjects and overcome the barrier of sample size limitation observed in previous studies.

4. CONCLUSIONS

Despite the heterogeneity of the evidence to date, a pronounced trend suggests that the utilization of fat grafts enriched with stem cells may be superior to autologous grafts in facial reconstruction, offering potential benefits in mid-term volume retention and faster achievement of results.

5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

6. REFERENCES

1. Menick FJ. Facial reconstruction with local and distant tissue: the interface of aesthetic and reconstructive surgery. Plast Reconstr Surg. 1998;102(5):1424-33. doi: 10.1097/00006534-199810000-00015.

2. Wallace CG, Wei FC. The current status, evolution and future of facial reconstruction. Chang Gung Med J. 2008;31(5):441-9.

3. Degner DA. Facial reconstructive surgery. Clin Tech Small Anim Pract. 2007;22(2):82-8. doi: 10.1053/j.ctsap.2007.03.009.

4. Guntinas-Lichius O, Genther DJ, Byrne PJ. Facial Reconstruction and Rehabilitation. Adv Otorhinolaryngol. 2016;78:120-31. doi: 10.1159/000442132.

5. Elegbede A, Mermulla S, Diaconu SC, McNichols C, Liang Y, Liang F, et al. Patient-reported Outcomes in Facial Reconstruction: Assessment of FACE-Q Scales and Predictors of Satisfaction. Plast Reconstr Surg Glob Open. 2018;6(12):e2004. doi: 10.1097/GOX.0000000000002004.

6. Zeiderman MR, Pu LLQ. Contemporary reconstruction after complex facial trauma. Burns Trauma. 2020;8:tkaa003. doi: 10.1093/burnst/tkaa003.

7. Jaiswal R, Pu LL. Reconstruction after complex facial trauma: achieving optimal outcome through multiple contemporary surgeries. Ann Plast Surg. 2013;70(4):406-9. doi: 10.1097/SAP.0b013e3182853f45.

8. Rose EH. Aesthetic reconstruction of the severely disfigured burned face: a creative strategy for a "natural" appearance using pre-patterned autogenous free flaps. Burns Trauma. 2015;3:16. doi: 10.1186/s41038-015-0014-8.

9. Klimczak J, Helman S, Kadakia S, Sawhney R, Abraham M, Vest AK, et al. Prosthetics in Facial Reconstruction. Craniomaxillofac Trauma Reconstr. 2018;11(1):6-14. doi: 10.1055/s-0037-1603459.

10. Mao JJ, Stosich MS, Moioli EK, Lee CH, Fu SY, Bastian B, et al. Facial reconstruction by biosurgery: cell transplantation versus cell homing. Tissue Eng Part B Rev. 2010;16(2):257-62. doi: 10.1089/ten.TEB.2009.0496.

11. Karam M, Abul A, Wood B, Kahlar N, Naik A, Tay J, et al. Stem Cell-Enriched Fat Grafts Versus Autologous Fat Grafts for Facial Reconstruction:

A Systematic Review and Meta-analysis. Ann Plast Surg. 2023;90(5):487-93. doi: 10.1097/SAP.0000000000003553.

12. Salibian AA, Widgerow AD, Abrouk M, Evans GR. Stem cells in plastic surgery: a review of current clinical and translational applications. Arch Plast Surg. 2013;40(6):666-75. doi: 10.5999/aps.2013.40.6.666.

13. McArdle A, Senarath-Yapa K, Walmsley GG, Hu M, Atashroo DA, Tevlin R, et al. The role of stem cells in aesthetic surgery: fact or fiction? Plast Reconstr Surg. 2014;134(2):193-200. doi: 10.1097/PRS.0000000000000404.

14. Nayar HS, Caplan AL, Eaves FF, Rubin JP. The Ethics of Stem Cell-Based Aesthetic Surgery: Attitudes and Perceptions of the Plastic Surgery Community. Aesthet Surg J. 2014;34(6):926-31. doi: 10.1177/1090820X14539971.

15. Atiyeh BS, Ibrahim AE, Saad DA. Stem cell facelift: between reality and fiction. Aesthet Surg J. 2013;33(3):334-8. doi: 10.1177/1090820X13478944.

16. Atiyeh B, Ghieh F, Oneisi A. Nanofat Cell-Mediated Anti-Aging Therapy: Evidence-Based Analysis of Efficacy and an Update of Stem Cell Facelift. Aesthetic Plast Surg. 2021;45(6):2939-47. doi: 10.1007/s00266-021-02353-w.

17. Tonnard P, Verpaele A, Peeters G, Hamdi M, Cornelissen M, Declercq H. Nanofat grafting: basic research and clinical applications. Plast Reconstr Surg. 2013;132(4):1017-26. doi: 10.1097/PRS.0b013e31829fe1b0.

18. Rigotti G, Charles-de-Sá L, Gontijo-de-Amorim NF, Takiya CM, Amable PR, Borojevic R, et al. Expanded Stem Cells, Stromal-Vascular Fraction, and Platelet-Rich Plasma Enriched Fat: Comparing Results of Different Facial Rejuvenation Approaches in a Clinical Trial. Aesthet Surg J. 2016;36(3):261-70. doi: 10.1093/asj/sjv231.

19. Dwivedi S, Sharma P. Stem Cell Biology: A New Hope in Regenerations and Replenishments Therapy. Indian J Clin Biochem. 2018;33(4):369-71. doi: 10.1007/s12291-018-0792-4.

20. Tran DK, Phuong TNT, Bui NL, Singh V, Looi QH, Koh B, et al. Exploring the Potential of Stem Cell-Based Therapy for Aesthetic and Plastic Surgery. IEEE Rev Biomed Eng. 2023;16:386-402. doi: 10.1109/RBME.2021.3134994.

21. Bourne DA, Egro FM, Bliley J, James I, Haas GL, Meyer EM, et al. Stem Cell Therapy Enriched Fat Grafting for the Reconstruction of Craniofacial Deficits. Plast Reconstr Surg Glob Open. 2023;11(6):e5056. doi: 10.1097/GOX.0000000000005056.

22. Bourne DA, Bliley J, James I, Donnenberg AD, Donnenberg VS, Branstetter BF 4th, et al. Changing the Paradigm of Craniofacial Reconstruction: A Prospective Clinical Trial of Autologous Fat Transfer for Craniofacial Deformities. Ann Surg. 2021;273(5):1004-11. doi: 10.1097/SLA.0000000000003318.

23. Sasaki GH. The Safety and Efficacy of Cell-Assisted Fat Grafting to Traditional Fat Grafting in the Anterior Mid-Face: An Indirect Assessment by 3D Imaging. Aesthetic Plast Surg. 2015;39(6):833-46. doi: 10.1007/s00266-015-0533-5.

24. Rasmussen BS, Lykke Sørensen C, Vester-Glowinski PV, Herly M, Trojahn Kølle SF, Fischer-Nielsen A, et al. Effect, Feasibility, and Clinical Relevance of Cell Enrichment in Large Volume Fat Grafting: A Systematic Review. Aesthet Surg J. 2017;37(suppl_3):S46-S58. doi: 10.1093/asj/sjx008.

25. Sterodimas A, de Faria J, Nicaretta B, Boriani F. Autologous fat transplantation versus adipose-derived stem cell-enriched lipografts: a study. Aesthet Surg J. 2011;31(6):682-93. doi: 10.1177/1090820X11415976.

26. Yin Y, Li J, Li Q, Zhang A, Jin P. Autologous fat graft assisted by stromal vascular fraction improves facial skin quality: A randomized controlled trial. J Plast Reconstr Aesthet Surg. 2020;73(6):1166-73. doi: 10.1016/j.bjps.2019.11.010.

27. Picard F, Hersant B, La Padula S, Meningaud JP. Platelet-rich plasma-enriched autologous fat graft in regenerative and aesthetic facial surgery: Technical note. J Stomatol Oral Maxillofac Surg. 2017;118(4):228-31. doi: 10.1016/j.jormas.2017.05.005.

28. Bashir MM, Sohail M, Bashir A, Khan FA, Jan SN, Imran M, et al. Outcome of Conventional Adipose Tissue Grafting for Contour Deformities of Face and Role of Ex Vivo Expanded Adipose Tissue-Derived Stem Cells in Treatment of Such Deformities. J Craniofac Surg. 2018;29(5):1143-7. doi: 10.1097/SCS.0000000000004367.

29. Krastev TK, Beugels J, Hommes J, Piatkowski A, Mathijssen I, van der Hulst R. Efficacy and Safety of Autologous Fat Transfer in Facial Reconstructive Surgery: A Systematic Review and Meta-analysis. JAMA Facial Plast Surg. 2018;20(5):351-60. doi: 10.1001/jamafacial.2018.0102.

30. Moltaji S, Alkhatib AH, Liu H, Murphy J, Gallo L, Karpinski M, et al. Introducing Knowledge Translation to Plastic Surgery: Turning Evidence into Practice. Plast Reconstr Surg. 2018;142(5):760e-769e. doi: 10.1097/PRS.0000000000004891.

31. Mason W, Levin AM, Buhl K, Ouchi T, Parker B, Tan J, et al. Translational Research Techniques for the Facial Plastic Surgeon: An Overview. Facial Plast Surg. 2023. doi: 10.1055/a-2113-5023.

32. Dedhia R, Hsieh TY, Tollefson TT, Ishii LE. Evidence-based Medicine in Facial Plastic Surgery: Current State and Future Directions. Facial Plast Surg Clin North Am. 2016;24(3):265-74. doi: 10.1016/j.fsc.2016.03.005.

33. Dreher R, Blaya C, Tenório JL, Saltz R, Ely PB, Ferrão YA. Quality of Life and Aesthetic Plastic Surgery: A Systematic Review and Meta-analysis. Plast Reconstr Surg Glob Open. 2016;4(9):e862. doi: 10.1097/GOX.0000000000000833.

34. Del Rio A, Rinaldi R, Napoletano S, di Luca NM. Cosmetic surgery for children and adolescents. Deontological and bioethical remarks. Clin Ter. 2017;168(6):e415-e420. doi: 10.7417/T.2017.2044.

35. Shimizu Y, Ntege EH, Sunami H. Current regenerative medicine-based approaches for skin regeneration: A review of literature and a report on clinical applications in Japan. Regen Ther. 2022;21:73-80. doi: 10.1016/j.reth.2022.05.008.

36. Bashiri Z, Rajabi Fomeshi M, Ghasemi Hamidabadi H, Jafari D, Alizadeh S, Nazm Bojnordi M, et al. 3D-printed placental-derived bioinks for skin tissue regeneration with improved angiogenesis and wound healing properties. Mater Today Bio. 2023;20:100666. doi: 10.1016/j.mtbio.2023.100666.