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Potential use of bio-stimulators and the successful process of cervicofacial liposculpture: a systematic review

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Abstract

Introduction: In the liposculpture scenario, and at the cellular and molecular level, tissue engineering has numerous advantages that meet the needs of the injured tissue or organ for the regeneration process or fillings and contours. Biological microenvironments enable cell recognition and signaling cascades for neovascularization and stabilization of fat grafting. **Objective:** A systematic review was conducted on the use of potential bio-stimulators (cells and molecules) and the biochemical and physiological mechanisms that can contribute to the successful process of cervicofacial liposculpture, to promote neovascularization and stabilization of fat grafting or fat reduction. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from June to August 2024 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 110 articles were found. A total of 41 articles were fully evaluated and 25 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies at high risk of bias and 28 studies that did not meet the GRADE. The present study showed that the use of potential bio stimulators such as stromal vascular fraction cells and mesenchymal stem cells from adipose tissue, exosomes, microRNA, and PRP, as well as the molecules secreted by these cells, can contribute to the successful process of cervicofacial liposculpture, to promote neovascularization and stabilization of fat grafting or fat reduction. Furthermore, studies have shown that the use of adipose tissue plus PRP led to the presence of more pronounced inflammatory infiltrates and greater vascular reactivity, increased vascular permeability, and certain reactivity of the nervous component, noting that the addition of 20% PRP activated with calcium to adipose tissue grafts can enhance the results of regenerative and aesthetic facial surgeries.

Keywords: Facial liposculpture. Vascular stromal fraction. Mesenchymal stem cells. Platelet-rich plasma. Exosomes. MicroRNA.

Introduction

In the liposculpture scenario, and at the cellular and molecular level, tissue engineering offers numerous advantages that meet the needs of the damaged tissue or organ for the regeneration process or for filling and contouring [1]. To achieve this, it is necessary to understand the chemical, physical, and biological processes of both the biological material and the target biological niche [2,3].

In this sense, biological microenvironments enable cellular recognition and signaling cascades for neovascularization and stabilization of fat grafting [4]. Another advantage is the minimally invasive surgical intervention, which allows the use of faster surgical techniques that cause less risk to the patient [5,6]. Furthermore, adult stem cells, such as mesenchymal stem cells from adipose tissue (ADSCs), are an

alternative for cell therapy and human tissue engineering, since it has been found that they have a high degree of plasticity, with the capacity for self-renewal and differentiation into specialized progenitors [7].

In this aspect, ADSCs are primordial mesodermal cells present in all tissues and are capable of differentiating in vitro and in vivo into different cell types. Their therapeutic potential is mainly explained by the production of bioactive molecules, which provide a regenerative microenvironment in injured tissues [8]. Furthermore, ADSCs secrete a cascade of cytokines and growth factors with paracrine, autocrine and endocrine activities, such as Il-6, Il-7, Il-8, Il-11, Il-12, Il-14, Il-15, macrophage colony-stimulating factor (M-CSF), Flt-3 ligand and Stem Cell Factor (SCF), leukemia inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). When combined, these factors can produce a series of responses from the local immune system, stimulating angiogenesis and inducing the proliferation and differentiation of mesenchymal stem cells in the desired tissue [9].

In addition, ADSCs induces the expression of junction proteins and increases microvascular integrity and the production of nitric oxide (NO) by macrophages [8]. The vascular stromal fraction (VSF) derived from ADSCs is a heterogeneous mixture of cells, including fibroblasts, pericytes, endothelial cells, blood cells, and stem cells derived from adipose tissue.

Also, fibrin-rich plasma (FRP) developed in France by Choukroun et al. (1993) [10] can be highlighted, presenting most of the leukocytes, platelets, and growth factors. It is the second generation of platelet concentrate with a high potential for wound repair. In this context, with progressive polymerization, the incorporation of circulating cytokines increases in the fibrin network, implying a longer life for these cytokines, since they will be released and used only in the remodeling of the initial scar matrix, which is long-term. Cytokines are thus kept in situ for a convenient period when the cells begin remodeling the matrix [11,12].

In biostimulation, adipose tissue stands out as an ideal filler for cosmetic surgery, as it is cheap and easy to obtain, has a natural appearance and texture, is immunologically compatible and long-lasting, and has a low risk of infection. By most metrics, autologous adipose tissue grafts perfectly meet these criteria. Facial fat grafting is a commonly accepted surgical procedure, and recent studies are working on optimizing this technique, with a greater supply of cells and molecules for aesthetic improvement [4].

Therefore, this study conducted a systematic review of the use of potential biostimulators (cells and molecules) and the biochemical and physiological mechanisms that can contribute to the successful process of cervicofacial liposculpture, to promote neovascularization and stabilization of fat grafting or liposuction.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/11/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 07/11/2024.

Research Strategy and Search Sources

The literary search process was carried out from June to August 2024 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The Health Sciences Descriptors (DeCS /MeSH Terms) were used: *"Facial liposculpture. Vascular stromal fraction. Mesenchymal stem cells. Platelet-rich plasma. Exosomes. MicroRNA"*, and using the Boolean "and" between the terms MeSH and "or" between historical discoveries.

Study Quality and Risk of Bias

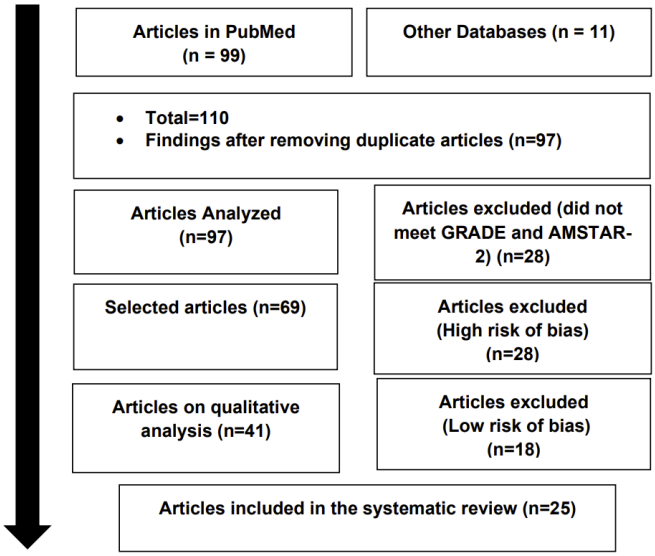
Study quality was based on the GRADE instrument [13] and risk of bias was analyzed according to the Cochrane instrument [14].

Results and Discussion

Summary of Literature Findings

A total of 110 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the theme of this article, resulting in 69 articles. A total of 41 articles were evaluated in full and 25 were included and developed in the present systematic review study (Figure 1). According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=93.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Main Biostimulators for Liposculpture

Adipose-derived mesenchymal stem cells (ADSCs) are characterized by adhesion and proliferation properties, the ability to differentiate into osteocytes, chondrocytes, and adipocytes in vitro, positive for CD73, CD90 and CD105, and negative for major histocompatibility complex class II (MHC-II), CD11b, CD14, CD31, CD34, and CD45. Due to their capacity for differentiation, in vitro expansion, and release of trophic materials, together with immunoregulatory properties, ADSCs are strong candidates for tissue repair [7-9].

Notably, due to the non-invasive isolation method, no ethical concerns, lower immunogenicity, faster self-renewal capacity, more stable doubling time, and higher proliferation potency, ADSCs are the preferred candidates for cell-based and adipose tissue-based therapies in regenerative medicine [4]. In addition, platelet-rich plasma (PRP) contains numerous growth factors that are responsible for its efficacy. The growth factors are released after endogenous or exogenous platelet activation and then have a chemotactic effect and act directly and indirectly on tissue regeneration. Some platelets are activated by mechanical influences during centrifugation. Collagen activates platelets in vivo endogenously, while needle bleeding induced by injection may further contribute to coagulation. Exogenous activation by the addition of calcium has become less popular in recent years [15].

The addition of PRP to adipose tissue grafts has many advantages with a simple, economical, and safe method [4]. In addition to its potentiating effect on adipose tissue grafts, PRP has a rejuvenating capacity. Thus, the addition of 20% PRP to adipose tissue grafts is considered to provide better fat graft survival, less bruising and inflammation, and easier application of adipose tissue grafts due to the liquefaction effect of PRP [16].

In addition, exosomes stand out along with ADSCs. Exosomes are extracellular vesicles measuring 40-100 nm in diameter and with a density of 1.13-1.19 g/mL, containing proteins, mRNAs, miRNAs, and DNAs. Exosomes change the biochemical characteristics of recipient cells through the delivery of biomolecules and play a role in cellular communication. These vesicles are produced from body fluids and different cell types. Evidence suggests that ADSCs-derived exosome (ADSCs -EXO) exhibits similar functions to ADSCs with low immunogenicity and no tumorization [17].

In this regard, the composition of exosomes differs based on their sources. The protein and lipid content of exosomes has been measured by various methods such as fluorescence-activated cell sorting, Western blotting, mass spectrometry, and immunoelectron microscopy. In this regard, Rabs and Annexin, including Annexin I, II, V, and VI, are cytosolic proteins present in exosomes that contribute to the formation of exosome docking, membrane fusion, and kinetic regulation of cytoskeletal membranes. In addition, adhesion molecules such as intercellular adhesion molecule-1, CD11a, CD11b, CD11c, CD18, CD9, adipose tissue globule EGF-factor VIII (AGM-E8), CD58, CD146, CD166 have also been identified in exosomes [18]. Exosomes also contain heat shock proteins (Hsp70 and Hsp90), which facilitate the loading of peptides onto MHC I and II [19,20].

Also, exosomes contain non-coding RNAs or fragments, including overlapping RNA transcripts, protein-coding region, structural RNAs, transfer RNA fragments, YRNAs, short hairpin RNAs, small interfering RNAs (siRNAs), microRNA (miRNA), messenger RNA (mRNA), and DNA [21]. Regarding miRNA, exosomes contain miR-1, miR-15, miR-16, miR-17, miR-18, miR-181, and miR-375 [22]. Furthermore, several cytokines, such as Tumor Necrosis Factor-α (TNF-α), Granulocyte-Macrophage Colony-Stimulating Factor (GMCSF), Interleukin (IL)-2, IL-6, IL-8, IL-10, IL-15, IL-1β, are expressed in exosomes [23].

Key Clinical Findings

Adipose tissue grafts enriched with stromal vascular fraction (SVF) were first reported by Moseley and colleagues in 2006 [24]. It was later further described by Matsumoto and colleagues [25], and the technique was soon termed "cell-assisted lipotransfer" (CPL). Since then, numerous preclinical animal studies have demonstrated improvements in adipose tissue graft volume with CPL [26], giving rise to translational studies in humans.

In this regard, authors evaluated adipose tissue grafts enriched with CPL in 10 patients with Parry-

Romberg hemifacial atrophy and found that volume retention was substantially improved in the group receiving CPL (47% resorption in control subjects versus 21% in CAL) [27]. In a randomized, triple-blind clinical trial of 10 patients, authors found better retention in the group receiving SVF-enriched adipose tissue grafts compared with standard adipose tissue grafting in the control group [28]. Furthermore, five human cohort studies have also been published examining SVF-enriched adipose tissue grafts in the face and chest. Four of the five studies showed improvement with LPC [29-32].

Furthermore, a clinical trial was conducted on 13 patients who were candidates for facelift. Patients underwent adipose tissue harvesting by liposuction of the abdomen and underwent one of three protocols: injection of SVF-enriched adipose tissue or expanded adipose tissue-derived stem cells, or adipose tissue plus PRP in the preauricular areas. As a result, the use of adipose tissue plus PRP led to the presence of more pronounced inflammatory infiltrates and greater vascular reactivity, increased vascular permeability, and some reactivity of the nervous component. The addition of PRP did not improve the regenerative effect. Therefore, the use of PRP did not show significant advantages in skin rejuvenation compared to the use of stem cells derived from expanded adipose tissue or adipose tissue enriched with SVF [33].

To corroborate these findings with greater scientific evidence, a meta-analysis study investigated the effect of PRP on the survival rate of fat grafting. Eleven studies with 1,125 patients were analyzed. Patients were followed up from 3 to 24 months post-fat grafting (LE). The adipose tissue survival rate ranged from 20.5% to 54.8% in the LE alone and from 24.1% to 89.2% in the PRP + LE groups. The survival rate was significantly higher and the recovery time was significantly shorter in the PRP + LE group than in the LE alone group [34].

Thus, the aim of adding platelet-rich plasma (PRP) to autologous LE is to increase the graft survival rate. After activation, platelets release some important growth factors. As a result, PRP can increase the proliferation and differentiation of ADSCs into adipocytes, improve the vascularization of the adipose tissue graft, and can block the apoptosis of grafted adipocytes. The other expected benefit of adding PRP to the adipose tissue graft is the improvement of skin trophicity above the grafted areas. After the comprehensive analysis of 11 clinical studies in humans and 7 in animals, a significant increase in the survival rate of adipose tissue grafts was observed, highlighting that the addition of 20% PRP activated with calcium hydrochloride to adipose tissue grafts can enhance the results of regenerative and aesthetic facial surgeries [35].

Finally, a study investigated the safety and efficacy of PRP in 10 patients who received equal volumes of adipose tissue on opposite cheeks with plication of the lateral submuscular fascia system or without a facelift. Comparable adipose tissue retention/baseline assessments by 3D Vectra Analysis were performed. The mean percent change in mean volume assessments at adipose tissue/PRP sites from baseline demonstrated a higher but statistically nonsignificant value over 1 year than the percent value changes at adipose tissue/normal saline sites on the opposite cheek. Volume restorations of the malar fat pad, nasojugal fold, and nasolabial fold were evaluated. No adverse events were observed during the 1-year study. Perioperative edema, erythema, bruising, and tenderness lasted up to 1 to 2 weeks at most [36].

Conclusion

It was concluded that the use of potential bio-stimulators such as stromal vascular fraction cells and mesenchymal stem cells from adipose tissue, exosomes, microRNA, and PRP, as well as the molecules secreted by these cells, can contribute to the successful process of cervicofacial liposculpture, to promote neovascularization and stabilization of fat grafting or fat reduction. Furthermore, studies have shown that the use of adipose tissue added to PRP led to the presence of more pronounced inflammatory infiltrates and greater vascular reactivity, increased vascular permeability, and some reactivity of the nervous component, highlighting that the addition of 20% PRP-activated with calcium hydrochloride to adipose tissue grafts can enhance the results of regenerative and aesthetic facial surgeries.

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