Applications of Biotissues in Plastic Surgery: A Systematic Review

Aplicações dos biotecidos na cirurgia plástica: Uma revisão sistemática

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Abstract

Introduction Biotissues are defined as organized combinations of synthetic and/or biological substances that interact with complex biological systems to treat, replace, or remodel tissues and organs. Tissue bioengineering employs a variety of methods, including the use of biological and synthetic scaffolds, along with interactions involving stem cells and cytokines. The present review evaluates the techniques and methods for biotissue synthesis, as well as their efficacy in both animal and human models.

Materials and Methods A systematic literature review was conducted using the PubMed, Lilacs, Scielo, and Cochrane databases, employing specific descriptors. The analysis focused on identifying the countries of origin of the studies and categorizing the techniques and resources utilized, with the aim of informing the selection of strategies for the application of biotissues in reconstructive plastic surgery.

Results Among the 37 selected articles, 15 focused on in vitro experimentation, 14 on in vivo experimentation, and 8 employed both approaches. The studies were further categorized into 3 primary subtopics: adipogenesis (18 articles), angiogenesis (10 articles), and chondrogenesis (9 articles), all relevant to tissue reconstruction.

Conclusion Advances in the use of biomaterials in regenerative medicine are promising, with experimental results aligning well with contemporary plastic surgery practices. While human application remains limited, the potential of stem cells and growth factors suggests significant future developments, warranting further focused studies. The present review elucidates the technologies and progress in the use of biomaterials, highlighting their impact on the technical evolution of reconstructive plastic surgery.

Keywords
- biomaterials
- reconstructive plastic surgery
- scaffolds

Resumo

Introdução Biotecidos são combinações organizadas de substâncias sintéticas e/ou biológicas que interagem com sistemas biológicos complexos para tratar, substituir ou remodelar tecidos ou órgãos. A bioengenharia de tecidos emprega diversos métodos,

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incluindo *scaffolds* biológicos e sintéticos, com interação com células-tronco e citocinas. Esta revisão examina técnicas e métodos para a síntese de biotecidos, além de sua eficácia em modelos animais e humanos.

Materiais e Métodos Foi realizada uma revisão sistematizada da literatura nas plataformas PubMed, Lilacs, Scielo e Cochrane, utilizando descritores específicos. A análise focou na identificação dos países de origem dos estudos, categorização das técnicas e recursos empregados, visando auxiliar na escolha de estratégias para o uso de biotecidos na cirurgia plástica reconstrutiva.

Resultados Dos 37 artigos selecionados, 15 abordaram experimentação *in vitro*, 14 *in vivo*, e 8 utilizaram ambas as abordagens. Os estudos foram classificados em 3 subtemas principais: adipogênese (18 artigos), angiogênese (10 artigos) e condrogênese (nove artigos), todos voltados para reconstruções teciduais.

Conclusão Os avanços no uso de biomateriais na medicina regenerativa são promissores, com experimentos satisfatórios alinhados à cirurgia plástica contemporânea. Embora a aplicação em humanos seja limitada, o potencial das células-tronco e fatores de crescimento sugerem avanços significativos que devem ser melhor desenvolvidos isoladamente em estudos futuros. Esta revisão esclarece as tecnologias e progressos no uso de biomateriais, destacando seu impacto na evolução técnica da cirurgia plástica reconstrutiva.

Palavras-chave
- biomateriais
- cirurgia reconstrutiva
- *scaffolds*

Introduction

Plastic surgery has seen numerous advancements in the field of reconstructive surgery. Since Sir Harold Delf Gillies' studies during World War I, various strategies have been developed focusing on the reconstructive ladder. However, the current gold standard for such procedures involves autologous surgical flaps, which present several disadvantages, including limited donor sites, donor site morbidity, and complex, prolonged operations with associated risks. To overcome these challenges, bioengineering offers the potential for unlimited resources through the use of biotissues, providing a safer alternative to restricted autologous flaps.[1]

Biotissues are defined as any combination of synthetic and/or biological substances that, when organized and integrated, can interact with complex biological systems to treat, replace, or remodel tissues or organs of the studied organism.[2] Such biotissues must meet specific criteria: they must allow for appropriate cellular proliferation for the target tissue, match the biodegradation rates and biological evolution of the host organism, and avoid provoking immunological-inflammatory rejection, thereby ensuring viability.[3]

However, the ideal use of biotissues for creating viable tissues in human reconstructive and aesthetic surgeries, aiming to achieve the correct proportion and function of the replaced organ, still faces limitations within the current scientific knowledge. These challenges include inadequate nourishment of engineered tissues and limited materials available for scaffold production.[4] The basic building blocks of tissue engineering are the extracellular matrix (ECM) or scaffold, viable cells, and the appropriate homeostatic maintenance of tissues.[1]

The objective of the current systematic review is to initially present the fundamental principles underlying tissue engineering and subsequently analyze the main techniques and innovations in the field.

Materials and Methods

The research was conducted using the MEDLINE, LILACS, Scielo, and Cochrane databases, employing descriptor terms obtained from DECS/MESH. The descriptors used to select the desired articles in the databases were: *plastic surgery* AND *biomaterials* AND *tissue engineering* AND *scaffold* AND *stem cells*. The search was restricted to articles published between 2010 and 2023, in English, Portuguese, and Spanish, and included only systematic reviews, meta-analyses, and clinical and experimental studies, resulting in a total of $n = 257$ articles. The selection of articles was performed using the Rayyan platform (Rayyan Systems, Cambridge, MA, USA) for the development of systematic and systematized literature reviews. Two different reviewers were involved in the study. In cases of uncertainty regarding the inclusion of an article, a third reviewer was consulted (►**Fig. 1**).

The evaluation of the article started with the title and abstract, and there was primary exclusion in case of inadequacy to the subject. Secondary exclusion was conducted after complete reading of the articles, followed by a second filtering to obtain the articles that were in fact consistent with the methodology, objectives, practical application, and discussion compatible with the objectives of the present review.

In the first exclusion, duplicated articles were removed as well as those that focused on: dental treatment, osteogenesis, specific biochemical approach, narrative reviews and articles without a focus on plastic surgery. In the second exclusion, articles were removed that exposed: only biochemical focus, did not consider practical applicability,

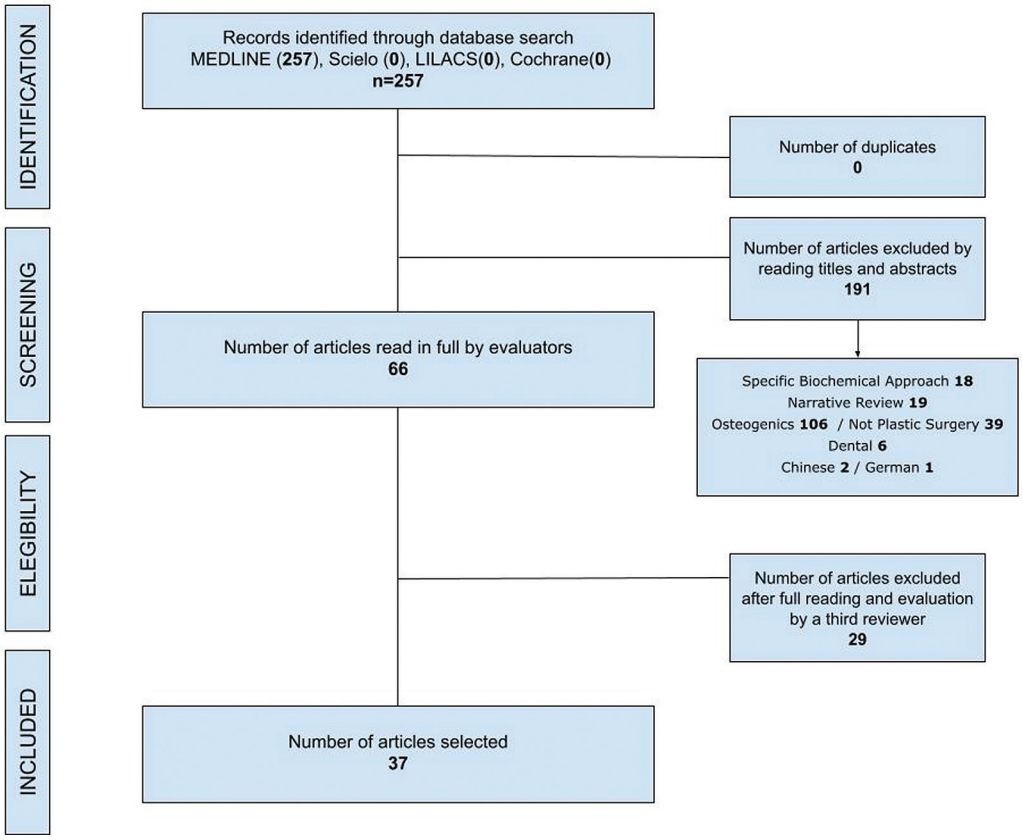

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart of the selection of articles.

protocols of exclusive reproduction of the scaffold, and articles that had no applicability in reconstructive plastic surgery. Experiments with incomplete results were not considered, and those selected were read in full.

For the elaboration of results and discussion, the articles were categorized into specific themes of their approach. Articles that did not use animals to experiment with grafts were considered in vitro, while the ones that considered its respective use were considered in vivo. The focus was considered: adipogenic for articles that aimed at the reconstruction of soft tissues involving techniques for collecting adipose tissue associated with the respective tissue stem cells as the main objective; angiogenic for those who proposed neovascularization and homeostatic maintenance of the graft as a goal; and chondrogenic for those who aimed at the formation of neocartilage. The terms *scaffold*, *vehicle* and *hydrogel* were used as synonyms given the specific context determined at the time of use. For distribution of articles according to nationality, the accredited service and country of origin of the first author were considered (►**Fig. 2**).

Results

Thirty-seven articles were selected, among which 15 performed an experimental approach in an exclusive in vitro model; 14 performed an experimental approach in an exclusive in vivo model; and 8 performed experimentation with both approaches in the same study (►**Tables 1**–**3**).[5–41] The countries that most published on the subject were China (nine articles), Germany (five articles), Belgium (five articles), and the United States (four articles).

In general, the most frequently encountered concerns in the reviewed studies were based on the analysis of integration, compatibility, and adhesion of stem cells or biomaterial/graft at the target site (scaffold or animal). Analyses related to tissue maintenance, inflammatory reactions, and adverse reactions in in vivo testing models were also reported. In turn, in in vitro testing models, analyses related to the way of production of the scaffold and the culture of stem cells were also observed. Only one of the reviewed articles did not use stem cells.

In the thematic division and objectives of the studies, it was observed that 18 studies focused on adipogenesis, 10 studies focused on angiogenesis, and 9 focused on chondrogenesis.

In the articles on adipogenesis, the use of adipose tissue-derived stem cells (ASCs) was observed in all selected cases—alternating between cells of xenogeneic or human origin. Applications aimed at remodeling large excisional wounds and treating soft-tissue wounds were also noteworthy in this block.

In articles on angiogenesis, majority use of ASCs was observed, followed by MSCs. Applications aimed at maintaining grafts and tissues through neovascularization and paracrine signaling to promote angiogenesis also stood out in this block.

In articles on chondrogenesis, majority use of mesenchymal stem cells (MSCs) was observed, generally taken from xenogeneic or human bone marrow (BMSCs). One of the

Table 1 Techniques, advantages, and limitations in adipogenesis

Author and year	Technique	Benefits	Limitations
Flynn et al. (2010)[5]	hASCs were seeded onto DAT scaffold in an in vitro model	Highly favorable compatibility, integration, and cellular adhesion	Need for further studies on DAT scaffold
Wu et al. (2012)[6]	hASCs were seeded onto DAT scaffold in an in vitro model. Subsequently, the biofabricated tissue was implanted into the subcutaneous tissue of mice	Highly favorable compatibility, integration, and cellular adhesion	Need for further studies on DAT scaffold
Alharbi et al. (2013)[7]	hASCs were seeded in Matriderm carrier in an in vitro model	Comparison of cannulas for liposuction for graft survival	It does not assess long-term tissue maintenance
Garg et al. (2014)[8]	rASCs were seeded onto a hydrogel scaffold (collagen-pullulan) in an in vitro model and then circularly inserted into superficial wounds on the backs of mice	Four graft production methods were analyzed, with rapid production and observed angiogenesis	Need for human studies
Cheung et al. (2013)[9]	hASCs were seeded on scaffold (DAT + MGC or DAT + MCS) in a 3D in vitro model. Subsequently, the graft was created using rASCs and implanted into the subcutaneous tissue of rats	The encapsulation method offers a minimally invasive technology for irregular defects in soft tissues	There is a need for further studies that analyze the long-term maintenance of cellular density in the implanted graft
Gugerell et al. (2015)[10]	hASCs were seeded onto PLLG + Gel-MA scaffolds under static conditions. Subsequently, they were placed in a bioreactor in an in vitro model	Dynamic conditions and observed angiogenesis	Production time
Pati et al. (2015)[11]	hASCs were seeded onto a 3D printed scaffold (DAT) in an in vitro model	Highly favorable compatibility, integration, and cellular adhesion	Need for further studies on DAT scaffold
Zeng et al. (2015)[12]	hASCs were seeded in microgel (PMMA) cultured in both 2D and 3D in an *in vitro* model. Subsequently, the grafts were inserted into superficial wounds on the backs of mice	The major advantage of the 3D structure is the ease of injecting the hydrogel solution for grafting and for cellular viability	There is a need for further studies on PMMA microgels
Wahl et al. (2015)[13]	hASCs were seeded onto 4 different commercial scaffolds (BioPiel, Smart Matrix, Integra DRT, Strattice) in both an in vitro and in vivo model using the amniotic membrane of chicken eggs	The major advantage of bovine collagen and fibrin matrices lies in their efficiency in wound healing	There is a need for further studies to corroborate any inefficiency of chitosan scaffold or porcine DAT
Lequeux et al. (2015)[14]	hASCs were injected along with the Cytocare vehicle into the subcutaneous tissue of mice	Highly favorable compatibility, integration, and cellular adhesion	It does not assess long-term tissue maintenance
Hanken et al. (2016)[15]	hASCs were seeded on silk scaffolds with and without growth factors in an in vitro model	Graft maintenance and neovascularization achieved through growth factors	There is a need for further studies on silk scaffolds and longer graft periods
Zhu et al. (2019)[16]	rASCs were seeded onto a scaffold (porcine ADM) in an in vitro model. Subsequently,	Highly favorable tissue compatibility and maintenance	There is a need for further studies on ADM scaffolds

Table 1 (*Continued*)

Author and year	Technique	Benefits	Limitations
	the grafts were inserted into the subcutaneous fascia of rats		
Buschmann et al. (2019)[17]	rASCs were seeded onto a PLGA scaffold and injected into the chest wall of mice	Highly favorable compatibility, integration, and cellular adhesion Neovascularization observed	Some inflammatory reaction observed
Tytgat et al. (2019a)[18]	hASCs were seeded onto a Gel-SH/Gel-NB scaffold in an in vitro model	An alternative candidate to the use of Gel-MA	The mechanical strength of the scaffold is still to be assessed in future studies
Tytgat et al. (2019b)[19]	hASCs were seeded onto a 3D printed scaffold (Gel-MA/Car-MA) in an in vitro model	Highly favorable compatibility, integration, and cellular adhesion Mechanical properties similar to native breast tissue	Lower differentiation potential compared with Gel-MA
Colle et al. (2020)[20]	hASCs were encapsulated and seeded onto a 3D printed scaffold (Gel-MA) in an in vitro model	Ease of scaffold replication through 3D mold printing	There is a need for further studies on spheroids (microcapsules)
Benmeridja et al. (2020)[21]	Microspheres of hASCs + HUVECs were seeded and molded into a 3D structure in an in vitro model	Ease of scaffold replication through 3D mold printing. Neovascularization observed	There is a need for further studies on spheroids (microcapsules)
Pu et al. (2021)[22]	hASCs were injected along with DAT-gel into the subcutaneous tissue of mice	Ease of injecting the hydrogel solution for grafting and for cellular viability	The short in vivo experimentation time necessitates further studies with long-term grafts

Abbreviations: 3D, three-dimensional; ADM, acellular dermal matrix; BioPiel, chitosan piofilm; Car-MA, methacrylated K-carrageenan; Cytocare, hyaluronic acid; DAT, decellularized adipose tissue; Gel-MA, methacrylamide gelatin; Gel-NB, norbornene gelatin; Gel-SH, thiolated gelatin; hASCs, human adipose-derived stem cells; HUVECs, human umbilical vein endothelial cells; Integra DRT, bovine collagen; matriderm, collagen and elastin; MCS, chondroitin sulfate methacrylate; MGC, glycol chitosan methacrylate; PGLA, poly(lactic-co-glycolic acid); PMMA, poly(methyl methacrylate); rASCs, murine adipose-derived stem cells; Smart Matrix, fibrin matrix; Strattice, decellularized porcine dermis.

Table 2 Techniques, advantages, and limitations in angiogenesis

Author and year	Technique	Benefits	Limitations
Wang et al. (2010)[23]	SMCs were derived from hASCs and seeded onto PGA mesh. Subsequently, the mesh was placed in a pulsatile bioreactor in an in vitro model	Successfully formed small-diameter three-dimensional vessel. Tissue biomechanics enhanced by pulsatile conditions of the bioreactor	Lack of in vivo testing
Zhang et al. (2011)[24]	Cardiac-derived VR-EPCs were seeded onto an Integra Matrix carrier in an in vitro model. Subsequently, the bioengineered tissues were inserted into full-thickness skin wounds in mice	Utilization of an alternative source of stem cell types	There is a need for further studies involving the use of VR-EPCs and the facilitation of their acquisition
Mestak et al. (2013)[25]	rASCs were seeded onto a scaffold of porcine ADM in an in vitro model. Subsequently, partial excision of the abdominal wall of mice was performed, and the graft was sutured in place	It evaluates the use of cultured meshes for abdominal wall repair, which raises reservations regarding their clinical benefit	The complexity of the graft extraction, cultivation, and maintenance process still makes the technique distant from clinical application

(*Continued*)

Table 2 (*Continued*)

Author and year	Technique	Benefits	Limitations
Han et al. (2014)[26]	hUCMSCs were seeded and differentiated in vitro into fibroblasts. Subsequently, the cells were cultured on a scaffold (ADM + collagen-chitosan) and inserted into full-thickness skin wounds on the backs of pigs	Efficiency in the superficial treatment of ischemic wounds and chronic ulcers	There is a need for further studies to ensure a favorable final clinical application
Zhang et al. (2015)[27]	PLGA/PEG microspheres containing VEGF were impregnated into collagen-chitosan scaffolds seeded with hASCs in an in vitro model. Subsequently, the biofabricated tissue was inserted around the vascular pedicle of mice	Significant neovascularization, promoting graft maintenance and nutrient availability.	There is a need for more preclinical studies that analyze graft/flap maintenance over longer periods of time
Freiman et al. (2016)[28]	PLLA/PLGA scaffolds were combined with four different combinations of stem cells (hASCs, HAMECs, HUVECs, and HNDFs)	Observed neovascularization enhances graft integration into the host as well as its maintenance	There is a need for an analysis of the graft over a period longer than 14 days to obtain more information about its long-term maintenance and nutrition
Du et al. (2017)[29]	Rabbit BMSCs were seeded onto sheets and subsequently decellularized to form the graft (BMSC-MEC). The grafts were inserted into mice with full-thickness skin wounds	Maturation of granulation tissues, rapid reepithelialization, and angiogenesis were observed at the graft site	There is a need for further studies involving chemical conditioning of the ECM as a strategy for its better adhesion and in vivo maintenance
Steiner et al. (2018)[30]	ADA-GEL microcapsules (with or without BMSCs) were aggregated in a Teflon chamber and inserted into the groin area of rats along with a created arteriovenous loop	The use of microcapsules alongside the vascular loop promoted favorable vascularization	There is a need for more studies involving the use of microcapsules as a vehicle, as well as the utilization of looped vessels for angiogenesis
Duisit et al. (2018)[31]	ADM was obtained from the human ear + pedicle. rASCs were seeded on the scaffold for an in vitro experimental model. Subsequently, they were inserted into wounds on the backs of mice	It considers the use of *post-mortem* human tissues (complex structures with vascularization) to obtain ECM	A scaffold that is challenging to obtain. Further studies are needed for advancements in the proposed vascular graft
Griffin et al. (2019)[32]	rASCs were seeded (with and without PRP) on polyurethane scaffolds and inserted into the subcutaneous tissue on the backs of mice	Adhesion and vascularization were observed	In the study, there is a lack of evidence to establish the causality of argon plasma usage as a direct factor responsible for improved tissue adhesion
Dash et al. (2020)[33]	hiPSCs derived from human vascular smooth muscle cells were seeded onto the Matrigel scaffold in the described in vitro model	A detailed description facilitates the replication of the methods used	It hinders a more in-depth evaluation due to the expository content in the protocol

Abbreviations: ADA-Gel, aldehyde dialdehyde gelatin; ADM, acellular dermal matrix; BMSCs, bone marrow stromal cells; HAMECs, human adipose tissue-derived microvascular endothelial cells; hASCs, human adipose-derived stem cells; hiPSCs, human-induced pluripotent stem cells; HNDFs, human neonatal dermal fibroblasts; hUCMSCs, human umbilical cord mesenchymal stem cells; HUVECs, human umbilical vein endothelial cells; Integra Matrix, cross-linked bovine collagen + glycosaminoglycans; Matrigel, protein + collagen IV; MEC, decellularized extracellular matrix; PEG, polyethylene glycol; PGA, polyglycolic acid; PGLA, poly(lactic-co-glycolic acid); PLLA, poly-L-lactic acid; PRP, platelet-rich plasma; rASCs, murine adipose-derived stem cells; SMCs, vascular smooth muscle cells; VEGF, vascular endothelial growth factor; VR-EPCs, vascular resident endothelial progenitor cells.

Table 3 Techniques, advantages, and limitations in chondrogenesis

Author and year	Technique	Benefits	Limitations
Liu et al. (2010)[34]	Porcine BMSCs and chondrocytes were cultured on a PLGA scaffold. Subsequently, the bioengineered tissue was inserted into the subcutaneous tissue of mice	Paracrine induction observed favored chondrogenesis	There is a need for more studies on paracrine chondroinduction and mixed culture
Xue et al. (2012)[35]	Porcine BMSCs were cultured in ACSs, and cultures on a PLGA scaffold were considered as a control. Subsequently, the bioengineered tissues were inserted into the subcutaneous tissue of mice	ACSs have antiangiogenic activity that promotes the stabilization of newly formed cartilage	There is a need for a comparative analysis with other synthetic biomaterials
Patel et al. (2013)[36]	Human BMSCs were cultured on a POSS-PCU scaffold in the shape of a human auricle in an experimental in vitro model	Chondrogenesis was observed in vitro with cell differentiation induced by added growth factors	Further studies involving the POSS-PCU scaffold and in vivo testing are needed
Mendelson et al. (2014)[37]	Hydrogel microspheres loaded with human growth factors were inserted into a PLGA scaffold. The hydrogel graft was placed over the native nasal cartilage of mice	Graft formed without the need for the use of stem cells	There is a need for further studies on the chondroinduction of native tissues on grafts without stem cell cultivation
Zhang et al. (2014)[38]	Human chondrocytes and goat BMSCs were cultured on a PGLA scaffold in an in vitro model	uman chondrocytes retained a strong initial capacity for cartilage formation, potentially promoting ectopic chondrogenesis of BMSCs in vitro	Lack of in vivo testing
Herrero-Mendez et al. (2015)[39]	The use of a decellularized scaffold with sGAG for tissue repair. The analyzed scaffolds were a 50:50 mixture and another one of 90:10 of HR007 enriched with HÁ	The scaffolds demonstrated important biological properties in vitro for clinical use in promoting the repair of chondral or dermal defects	Lack of in vivo testing
Ding et al. (2016)[40]	Pig BMSCs and auricular cartilage were obtained and cultured with a PGLA scaffold in separate groups and together. The bioengineered tissues were inserted into pig subcutaneous tissue	It was demonstrated that BMSC-based engineered cartilage can suppress inflammation in vivo when cultured without chondrocytes	There is a need for further studies on the application of long-term cultured BMSC grafts
Rajabian et al. (2017)[41]	"Rabbit BMSCs were seeded on a chitosan scaffold. Subsequently, the bioengineered tissues were inserted into superficial wounds on the backs of these animals	Promotion of reepithelialization through paracrine factors	Chitosan dressings with or without BMSCs, when without proliferation stimuli, worsened wound healing

Abbreviations: ACSs, acellular cartilage sheets; BMSCs, bone marrow stromal cells; PGLA, poly(lactic-co-glycolic acid); POSS-PCU, poly (hexanolactone/carbonate) urethane/urea-modified polyhedral oligomeric silsesquioxane poly (carbonate urethane); sGAG, sulfated glycosaminoglycans.

articles did not use stem cells. This block also highlighted applications aimed at remodeling/healing of dermal wounds and paracrine signaling for chondrogenic differentiation.

Discussion

Tissue bioengineering has the potential to become one of the foundations of regenerative medicine in the 21st century. The techniques described approach practical applicability as the study of the interaction of the graft with the in vivo environment progresses.[24] Thus, the present study discusses the applications, advantages, and disadvantages of the reviewed articles as well as their relationship with the scientific literature in the following subtopics

Scaffold/Scaffolding/Vehicle

The use of hydrogels was observed in 23 articles, as an attempt to promote greater integration capacity of the

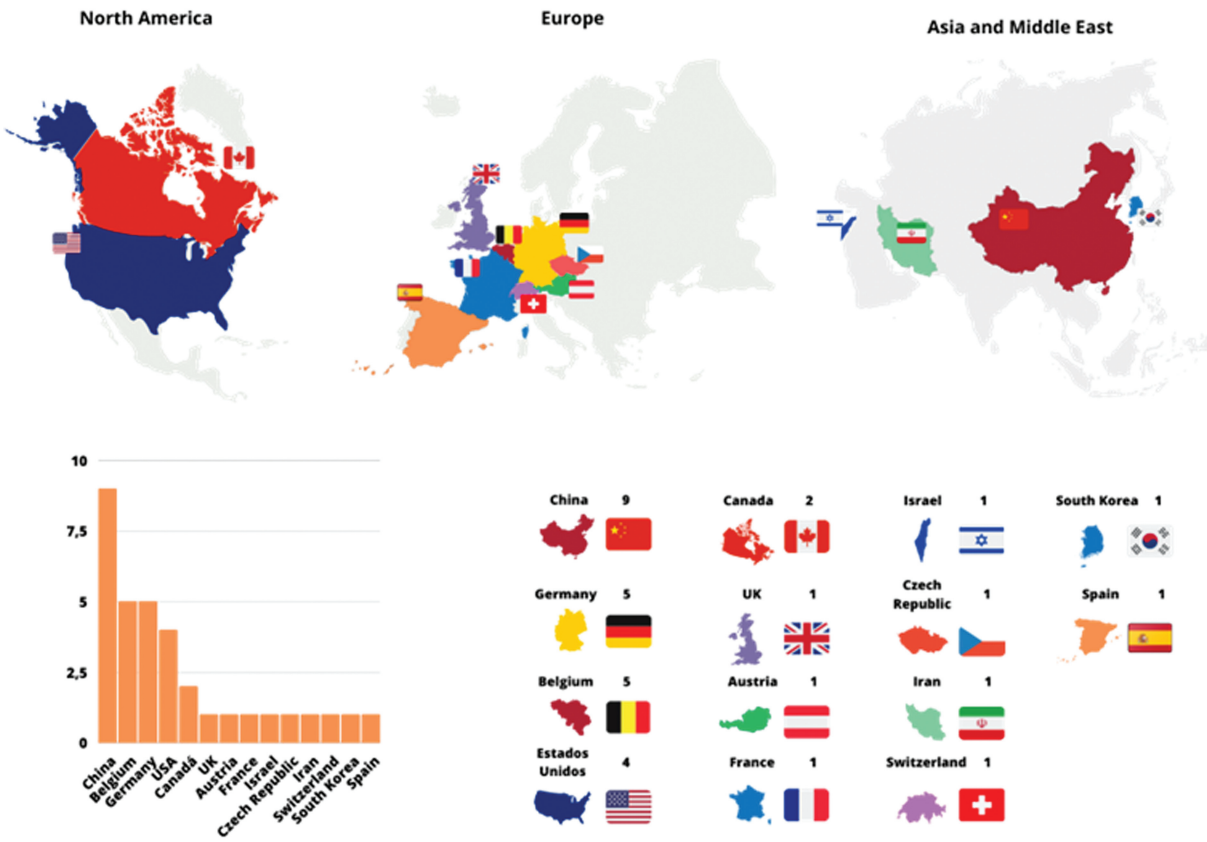

Fig. 2 Worldwide distribution map of reviewed articles on biotissues.

acellular biomaterial into the host. In line with the study by Gierek et al., 2022, these studies reported ease of implantation and handling of the proposed biotissue, as well as mechanical properties capable of simulating the native adipose tissue.[36,42] Regarding the applicability of the methods, the use of hydrogels was considered to be a potential means of guaranteeing mechanical properties without compromising the natural biodegradation of the in vivo graft, since it guarantees the diffusion and support of the biological components.[25,31,38]

According to Gierek et al., 2022, the use of ROMs has considerable reconstructive potential in human surgery, thanks to their biocompatibility and structure.[42] Accordingly, the vast use of ADMs, in the reviewed studies, shows an advance in studies that refer to the potential of these scaffolds with emphasis on xenogeneic techniques or through human liposuction. The use of DAT has shown to be promising thanks to the ease of obtaining and low morbidity in the donor area in liposuctions, see use for obtaining scaffolding and ASCs through previously discarded surgical residues.[5,9,13]

Three-dimensional printing and planning technologies are already widely used in reconstructive surgery to prepare interventions and produce customized implants as recognized by the Royal College of Surgeons in the Commission on the Future of Surgery.[43] This is shown in this review in five articles [21,36–38,40] which use this technique to obtain "leaked" structural scaffolds for the injection of cellular and biological contents that can compose the final graft. This type of method proved to be efficient in guaranteeing graft viability when compared with the non-impression technique; with favorable biomechanics and mimetic tissue capacity.[37]

Based on Salehi-Nik et al., 2013, perfusion bioreactors can provide near-in vivo physical and environmental stimuli to cultured tissues.[44] In this sense, it compares favorably with the pulsatile experimentation obtained in the formation of small caliber vessels with biomechanics and elasticity similar to the human saphenous vein. This approach can be used not only in the improvement of reconstructive techniques in plastic surgery, but also in the engineering of other types of elastic muscular conduits of small diameters, such as: ureter, cystic duct and ovarian duct.[6]

Stem Cells

The management of ASCs and their use in clinical studies has been practiced for many years with favorable results.[45–47] Accordingly, 23 studies considered its use due to the ease of obtaining this type of cell and its history in the literature. In this sense, the xenogeneic acquisition aimed at a low morbidity of the donor area.[24,35,37] There was also the use of liposuction as a way of using hospital waste that was previously discarded.[11] This reflects the ease of handling and applicability of the techniques, since these methods take advantage of a tissue that has a considerable proportion of stem cells, with a frequency ranging from 0.01% to 5% of the liposuction, depending on the extraction method.[48] On this matter, a congruence with Wu et al., 2012, was reported, which highlighted a higher rate of adherence and concentration of ASCs obtained with

micro harvest (blunt cannula 2 mm in diameter) compared with conventional techniques.[6]

According to Solchaga et al., 2011, the management of BMSCs is still complex for application in reconstruction techniques, requiring further advances.[49] Accordingly, this review highlights the difficulties encountered in the nine studies that used this cell type to control the inflammatory response and successfully form cartilaginous tissues without a considerable rate of fibrosis.[7,10,17,26,27,30,31] However, satisfactory and alternative results were obtained from co-transplantation with human microtia cells and the use of cytokines for paracrine differentiation, which reflects advances in academic research on their use.[7,17,27]

It is also worth mentioning, in the comparison between the cell types described in the article, that ASCs have potential advantages over BMSCs. This is evident not only in its simplified way of obtaining and managing it, but also in its ability to rapidly proliferate and secrete high levels of pro-angiogenic cytokines.[50–52]

Graft Maintenance

Considering the study by Colazo et al., 2019, it is known that vascularization is considered a major challenge in tissue engineering and regeneration, especially within the scaffold used.[53] In this context, to ensure the maintenance of in vivo tissue for long periods, a series of criteria had to be guaranteed, such as: the formation of capillary networks, nutrition, hydration, and biocompatibility of the inserted graft.[17] In this sense, the presence of immunoregulatory factors (such as TGF-β, Cox-2, CD45 and CD68) and pro-angiogenic agents (such as VEGF, HGF, bFGF and CD31) is proposed as a form of adequate dynamic regeneration of the tissue, based also on the speed and efficiency of the evaluated healing.[18,23,33–35]

Adipogenesis

Evidence of the regenerative properties of autologous fat transplantation has encouraged research on the clinical use of ASCs.[54] In the articles referred to, with this regenerative focus, there was extensive use of ASCs as the standard choice for collection and cultivation of stem cells (►**Table 2**). This reflects not only the ease of handling and collection of this cell type, but also the increasing use of fat grafting and liposuction in aesthetic and reconstructive procedures in plastic surgery today—since the purified (or atraumatic) period that followed Coleman's work (1994 to date).[55]

According to Rupnick et al., 2002, adipose tissue is highly vascularized, as each adipocyte is surrounded by an extensive capillary network.[56] Thus, angiogenesis is closely related to the maintenance and remodeling of adipose tissue. Accordingly, the results obtained highlight the same potential described in the literature: a low degree of graft fibrosis and pro-angiogenic capacity[19,28,35,40]—which can be better achieved with the co-culture of cell types from vascular tissues (for example, HAMECs and HUVECs).[26,35]

Angiogenesis

According to Chen et al., 2017, traditional grafts that do not account for homeostatic maintenance and final tissue integration limit the effectiveness of treatments.[57] This way, tissue-engineered vascular grafts serve as the next best alternative to the applicability of the methods.[58] Accordingly, the articles reviewed in this block highlighted the degree of graft incorporation and the measurement of growth factors and paracrine secretion of the cell types involved.[26,40] In this context, favorable results were obtained in the treatment of ischemic wounds and ulcers.[15]

Directly related to the principles of reconstructive plastic surgery and the need for microvascular techniques to maintain grafts,[41] the use of biotissues and techniques that ensure tissue perfusion stood out: the formation of small-caliber three-dimensional vessels 6 and the use of arteriovenous loops for graft irrigation.[31]

Chondrogenesis

In articles with this regenerative focus, there was extensive use of BMSCs as a choice of stem cells. In this case, this preference does not reflect ease of handling and collection, since the need for bone marrow cell isolation can be a complex and invasive procedure, although widely documented.[59] Also noteworthy is its difficult handling due to the lack of advanced knowledge about its differentiation mechanisms.[60] Thus, the choice is based on the known differentiation potential of these cells in the formation of neocartilage when in a three-dimensional environment.[61–63] Accordingly, the increasing formation of irregular fibrotic tissue around the implant was evaluated in Ding et al., 2016, which made it difficult to maintain it in vivo for long durations, which distances the clinical application of these methods.[27]

As a way to get around this lack of differentiation control, the use of growth factors, such as TGF-ßs, IGF-1, and BMPs to initiate chondrogenesis, elucidated promising results in a coordinated way.[7] Another way to circumvent inflammation was the use of acellular cartilage sheets (ACSs), which showed favorable results for the maintenance of cartilaginous tissue considering its anti-angiogenic activity, which stabilizes the manipulated cartilage in vivo, a beneficial factor for handling the final graft.[10] Mendelson et al., 2014, described the satisfactory reconstruction of the cartilage of the nasal dorsum of mice without the use of stem cells, which through a dose-dependent system of TGF-β3, avoided the adverse reactions discussed here.[16]

Limitations

Although the results prove to be quite promising, several limitations that have been universally found in the studies can be highlighted, which still distance the reality of clinical applicability, since it must be reproducible, controllable, and feasible. In addition to a limited collection of similar studies, one of the limitations found in this systematic review was the scarcity of randomized controlled clinical studies, which are considered the gold standard for evaluating the efficacy and safety of any medical intervention. Most of the studies found consist of animal studies and in vitro research.

Conclusion

The techniques and procedures described in this review hold significant potential for future practical application in reconstructive plastic surgery as more studies progress in this field. Notable advancements include the use of stem cells and growth factors as fundamental resources for promoting tissue regeneration and graft biocompatibility. Consequently, this review fulfills its role in elucidating the current evidence on the topic, making the key techniques and innovations in the use of biomaterials in reconstructive plastic surgery and its fundamental principles accessible to plastic surgeons.

Authors' Contributions

RSA: analysis and/or data interpretation, conception and design study, conceptualization, data curation, final manuscript approval, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft preparation, and Writing—review & editing; MGVBM: analysis and/or data interpretation, conceptualization, data curation, formal analysis, methodology, and writing—original draft preparation; NTS: analysis and/or data interpretation, conception and design study, conceptualization, formal analysis, investigation, project administration, resources, validation, and writing—original draft preparation; EBG: supervision, visualization, and writing—review & editing; LMF: Conception and design study, supervision, validation, visualization, writing—review & editing.

Clinical Trials

None.

Ethics Committee

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Conflict of Interests

The authors have no conflict of interests to declare.

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