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Review article

Soft tissue fillers for adipose tissue regeneration: From hydrogel development toward clinical applications

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A B S T R A C T

There is a clear and urgent clinical need to develop soft tissue fillers that outperform the materials currently used for adipose tissue reconstruction. Recently, extensive research has been performed within this field of adipose tissue engineering as the commercially available products and the currently existing techniques are concomitant with several disadvantages. Commercial products are highly expensive and associated with an imposing need for repeated injections. Lipofilling or free fat transfer has an unpredictable outcome with respect to cell survival and potential resorption of the fat grafts. Therefore, researchers are predominantly investigating two challenging adipose tissue engineering strategies: *in situ* injectable materials and porous 3D printed scaffolds. The present work provides an overview of current research encompassing synthetic, biopolymer-based and extracellular matrix-derived materials with a clear focus on emerging fabrication technologies and developments realized throughout the last decade. Moreover, clinical relevance of the most promising materials will be discussed, together with potential concerns associated with their application in the clinic.

Contents

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1. Introduction

From an application point-of-view, the development of biomaterials for adipose tissue regeneration has recently gained increasing attention because of the exponential growth of adipose tissue reconstructions performed in modern health care [1–4]. In addition to cosmetic considerations, these reconstructions are also attempted for patients suffering from congenital defects, trauma or surgical resections including third-degree burn victims and women undergoing lumpectomies after breast cancer treatment. The latter case is highly relevant as breast cancer is the most prominent cancer striking women worldwide [5,6]. However, there remains a clear and urgent medical need to develop materials that outperform both the commercially available soft tissue fillers and the current techniques as these are concomitant with several disadvantages.

For aesthetic surgeries, surgeons generally implement soft tissue fillers that are commercially available and Food and Drug Administration (FDA)-approved including hyaluronic acid (HA), collagen and poly(methyl methacrylate) [7–10]. Most often, cosmetic or aesthetic surgery aims to fill small facial depressions or folds requiring volumes of approximately 1–2 ml [7,10,11]. The cost associated with these products is rather high, even for very small volumes, as indicated in Table 1. It would not be feasible to apply these fillers for larger volumes (e.g. breast reconstructions), as this would imply a cost, solely related to the material, of 245,000 € (considering a volume of 350 ml and approximately 700 €/ml material). Moreover, these fillers are associated with some adverse effects such as foreign body reaction and inflammation, shape distortion and the need for repeated injections due to absorption of the filler material [11–15]. Reconstructive procedures focus on the treatment of larger defects due to burns, post-traumatic loss of tissue or full breast amputation. For the latter, much greater volumes are required, ranging between 200 and 400 ml [16]. These soft tissue reconstructions are either performed by implantation of a prosthesis or by applying autologous tissue through microsurgical free tissue transplantation (i.e. the so-called "free flaps"), or another technique, called lipofilling [17–23]. Lipofilling is the free transfer or transplantation of the patient's own, autologous fat harvested through liposuction and transferred as a free graft. This new therapy has been introduced into daily clinical treatments since the discovery of a stem cell population within the subcutaneous adipose tissue, namely the adipose tissue-derived mesenchymal stem cells (ASCs) [24]. However, both non-autologous and autologous approaches are concomitant with major drawbacks. First, tissue transplantation is very expensive with the total cost varying from 15,000 to 25,000 € per patient. In addition, secondary procedures are often required for additional corrections such as nipple reconstruction. The cost of a lipofilling treatment ranges between 2000 and 5000 €, while multiple sessions are generally required to optimize the final result. The greatest concern associated with autologous fat grafting is the unpredictable rate of resorption. Free fat grafting rarely results in sufficient tissue augmentation because of delayed neo-vascularization associated with subsequent cell necrosis, fibrosis and graft volume shrinkage. Moreover, survival of the transplanted fat is very unpredictable. Resorption generally occurs within 4–6 months after the lipofilling procedure [16]. The rate of resorption amounts up to 90% in experimental studies but is limited to 40–60% in clinical trials [25–29]. Although lipofilling is well accepted in daily clinical practice, the latter disadvantage remains a major issue. One of the main concerns when applying a prosthesis, which is most often silicone-based, is the occurrence of potential rupture [22,23,30]. Rupture can result in leakage, capsular contracture and infection [31,32].

To date, no solution has been provided to counteract all the problems associated with soft tissue fillers and free fat grafting techniques. As a result, an increasing interest from material scientists has emerged focusing on the development of superior materials for adipose tissue engineering purposes and addressing the existing limitations. These new approaches should ideally aim for a more predictable outcome and an improved cost-effectiveness. The latter, for instance, can be achieved by increasing the volume retainment after lipofilling thereby reducing the overall treatment time, the number of surgical procedures and accordingly, the cost of the procedure.

Several review articles have already been published within the research field of adipose tissue engineering. However, their focus was mostly on the application of stem cells and their cell source [33,34] or on the applied materials and their properties [35–37]. The present review tackles recent developments in the field of adipose tissue regeneration with special attention given to material development along with emerging fabrication strategies elaborated during the last decade. In the first part, the ideal design specifications are discussed according to the appropriate fabrication technologies. Furthermore, promising biomaterials applied through an *in situ* injectable approach or as porous 3D printed scaffolds are covered. Within both approaches, relevant material classes will be discussed along with their advantages and limitations toward their potential in modern health care. Both synthetic, biopolymer-based and extracellular matrix (ECM)-derived materials will be discussed.

Table 1
Overview of the currently existing techniques and available soft tissue fillers in the clinic. All soft tissue fillers mentioned are FDA-approved.

Soft tissue fillers for aesthetical surgeries		
	Commercial product(s)	Cost (€/ml)
Calcium hydroxylapatite	*Radiesse©*	350–700
hyaluronic acid	*Juvederm©*	350–700
	Restylane©	450–600
Collagen	*Cosmoderm/ Cosmoplast©*	270–540
Poly-L-lactic acid poly(methyl methacrylate)	*Sculptra©*	700–900
(PMMA microspheres) + collagen	*Artefill©*	900
Reconstructive methods		
	Product	Cost (€)/ unilateral surgery
Free flap	*Autologous tissue*	15,000–20,000
Lipofilling	*Processed lipoaspirate*	2000–5000*
Prosthesis	*Silicone*	5000–8000

* Price per session.

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