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Review

State of Research on Tissue Engineering with 3D Printing for Breast Reconstruction

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Abstract

This review investigates the intersection of tissue engineering and 3D printing technologies in the realm of breast reconstruction, underscoring the transformative potential these approaches offer for enhancing post-mastectomy outcomes. It encompasses a detailed examination of current methodologies, focusing on the creation of biocompatible, bioabsorbable scaffolds that adeptly mimic the extracellular matrix to promote tissue integration and regeneration. A significant portion of the analysis draws from a search conducted on PubMed, which aimed to collate relevant preclinical and clinical studies in this domain. This search underscored the nascent stage of many applications, highlighting a critical need for more comprehensive preclinical trials to validate the efficacy and safety of these innovative solutions. Our search revealed that many studies have studied alternatives for breast reconstruction using tissue engineering; with a significant proportion of these modalities focusing on using flaps inside 3D-printed chambers. Moreover, although some studies have shown significant adipose tissue growth, their results still do not approximate breast dimensions. Specifically, the review identifies a limited range of polymers that have been explored in preclinical and clinical studies for breast reconstruction, including tissue-engineering chambers and scaffolds for the reconstruction of the breast mound made of poly-lactic acid, poly-glycolic acid, poly-lactic-co-glycolic acid, poly-4-hydroxybutyrate, polycarbonate, and polycaprolactone. For nipple reconstruction, two studies assessed scaffolds made of poly-4-hydroxybutyrate and poly-lactic acid. The review highlights the utilization of bioabsorbable materials in these devices, indicating the potential for performing one-stage surgeries. Moreover, it elaborates on the biomechanical properties of these materials, aligning them with the specific goals of breast reconstruction. The review acknowledges the complexity of navigating regulatory landscapes, suggesting that overcoming these obstacles is essential for clinical translation. Despite these challenges, the convergence of 3D printing and tissue engineering is presented as a paradigm shift in breast reconstruction, offering the potential to significantly enhance aesthetic and functional outcomes, minimize post-surgical complications, and improve patients' quality of life.

Keywords: breast reconstruction; 3D printing; tissue engineering

1. Introduction

Breast cancer presents an important challenge to global health care and significantly impacts on the quality of life of countless woman, necessitating advancements in treatment and post-surgical care. Within this framework, breast reconstruction emerges as a beacon of hope, offering a path to regain physical and emotional well-being. While substantial strides have been made in reconstruction techniques, a gap persists in accessibility, affordability, and safety, underscoring a pressing need for innovation and improvement.

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In 2020, the U.S. reported 239,612 new female breast cancer cases with 42,273 deaths, equating to 119 new cases and 19 deaths per 100,000 women (1). Beyond its devastating health impact, breast cancer imposes a significant financial burden on the U.S. healthcare system. A recent nationwide study revealed that cancer patients experience almost 4 times higher mean expenditures per person ($16,346) compared to those without cancer ($4,484) (2). This financial strain is mirrored in the field of breast reconstruction, where the costs of current methods, coupled with the need for specialized surgical skills, often place these critical procedures out of reach for many.

Moreover, the burden of breast cancer transcends beyond the numbers, profoundly affecting women's quality of life. Survivors often struggle in their cognitive, sexual, and emotional well-being, underscoring the broader challenges that come with recovery (3). In this context, breast reconstruction after mastectomy is a key element in the journey towards recovery, improving emotional functioning and social functioning scores, especially in younger patients. Furthermore, breast reconstruction positively impacts body image and sexual functioning, especially when an immediate breast reconstruction is offered (4).

Current options—alloplastic and autologous—each carry their own set of complications. Alloplastic or implant-based breast reconstruction can lead to complications such as capsular contracture, implant failure, rupture, and cancer (5).The FDA has reported new cases of cancers, including squamous cell carcinoma and lymphomas, in the capsule surrounding breast implants, distinct from the previously recognized Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) (6, 7). Moreover, although Acellular Dermal Matrices (ADMs) have emerged as a tool to reduce such risks of capsular contracture in prepectoral approaches, their high cost remains a barrier.

Alternatively, autologous breast reconstruction has been associated with higher satisfaction compared to implant-based reconstruction (8). Still, patients with autologous breast reconstruction may suffer complications including flap failure, mastectomy flap necrosis, donor site morbidity, and emergent reoperations (9, 10). Moreover, it is essential to highlight that autologous breast reconstruction is often challenging, requiring highly trained microsurgeons and microsurgery-equipped hospitals, which are often lacking in developing countries (11, 12).

Autologous fat grafting for breast reconstruction is globally accepted, with its safety and efficacy confirmed by many clinical studies (13, 14). Nevertheless, fat grafting for breast reconstruction is constrained by the limited volume it can provide and the inconsistent retention rates, often necessitating multiple sessions to attain a satisfactory final volume (15, 16).

With the challenges posed by conventional methods, the medical community has eagerly sought innovative solutions. The fields of tissue engineering and 3D printing are two domains that have shown promise in revolutionizing medical treatments across various sectors (17, 18). These innovative methods offer the possibility of reconstructions tailored to an individual's anatomy, using the patient's own cells and host response towards tissue regeneration, thereby promising better functional and aesthetic outcomes (19).

With the ability to customize the structure, composition, and mechanical properties of biomaterials, 3D printing has opened doors for the development of implants that mimic the natural extracellular matrix, facilitating cellular integration and tissue regeneration (20). Furthermore, such advancements might pave the way for improved functional and aesthetic outcomes in breast reconstruction.

This review focuses on the latest developments in tissue engineering and 3D printing for breast reconstruction. We aim to identify current research gaps, guide future studies in this domain, and critically evaluate the potential of these emerging technologies to transform breast reconstruction procedures in medical practice.

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2. Biomaterials and Tissue Bioengineering for Breast Reconstruction.

A. The current state of research on reconstructive materials

The field of tissue engineering has seen a noticeable surge recently, particularly in the development of ideal biomaterials for breast reconstruction. In the past, substances like hydrogels, ceramics, and biopolymers showed great promise for fostering cellular growth and directing tissue rejuvenation (21). The primary objective of research has been to develop materials that mimic the extracellular matrix found naturally in breast tissue while promoting cell adhesion, development, and specialization (22, 23).

Tissue engineering combines cells, biomaterials, and advanced methodologies to develop biological structures that both mirror and augment the inherent functionalities of human organs and tissues (24). Over time, this domain has significantly advanced, now emphasizing not just the regeneration of in vivo tissues without innate self-repair capabilities, but also the creation of in vitro models that illuminate cellular dynamics (25-28). These models also provide platforms for cutting-edge applications like organs-on-a-chip and medication screening (29, 30).

In the world of 3D printing microvascular networks, current methodologies exhibit limitations in precisely emulating the native cellular composition and functionality of vascular structures. Additionally, these techniques often lack the capacity to control hierarchical dimensions accurately (31). Consequently, the complete replication of native microvascular networks via 3D printing remains unfeasible at this juncture.

B. Role of biodegradable materials in tissue engineering

Biodegradable materials are of particular interest in tissue engineering for breast reconstruction. Over time, a process of gradual degradation ensues, concomitantly with the progressive integration of native tissues during the regenerative phase, removing the necessity for subsequent surgical intervention aimed at implant removal. This feature allows the preservation of the regenerated tissue's structural integrity while minimizing the long-term complications linked to non-biodegradable components. (32). The degradation rate, however, must be carefully tuned to match the rate of tissue regeneration (33).

C. Advantages and limitations of biodegradable materials

While biodegradable materials present an exciting frontier for breast tissue engineering, striking a balance between their evident benefits and inherent challenges remains critical. One key advantage is that, unlike traditional implants, they are designed to be reabsorbed by the body, avoiding the consequences of long-term inflammation of permanent implants (34, 35)

Although surgical insertion of biodegradable materials can still lead to surgical infections, researchers have suggested that biodegradable materials carry a lower risk (36). The degradation rate of these materials needs careful calibration to provide sufficient support without triggering complications. Other concerns include the potential loss of mechanical strength over time and the long-term impact of degradation byproducts in the body (37).

3. Preclinical Studies on Reconstructive Materials with Tissue Engineering

A. Overview of preclinical research in tissue engineering for breast reconstruction (Table 1)

Table 1. Overview of preclinical research in tissue engineering for breast reconstruction.

Author, Year	Study Objective	Methodology	Materials Used	Key Findings	Limitations
Huss, 2001 (44)	Examine co-culture of mammary cells	Human mammary epithelial cells and preadipocytes co-	Collagen gel matrix	Both cell types expanded through multiple subcultures,	Limited to in vitro environment

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	and adipocytes in 3D collagen	cultured in 3D collagen gel matrix		maintained normal cell distribution and growth patterns	
Huss, 2002 (45)	Enhance adipocyte survival for lipo-injection	Selective in vitro culturing of preadipocytes	Preadipocytes	Increased proliferation and survival in cell cultures	Limited to in vitro environment
Krause, 2008 (46)	Study stromal-epithelial interactions	Cocultures of human mammary epithelial cell line (MCF10A) and human mammary fibroblasts embedded in type I collagen or mixed Matrigel-collagen matrix	MCF10A, fibroblasts, type I collagen, Matrigel-collagen matrix	Formation of ductal and alveolar structures confirmed histologically	Limited to in vitro environment
Findlay, 2011 (47)	Upscale small-animal adipose tissue-engineering models to a large animal (pig)	Large-volume (78.5 ml) subcutaneous chambers enclosing fat flap in pigs	Dome-shaped perforated polycarbonate TEC, poly(L-lactide-co-glycolide) sponge	Significant fat flap growth up to 56.5 ml from initial 5 ml by 22 weeks	Limited translation to human models
Findlay, 2009 (48)	Evaluate longevity of tissue-engineered adipose tissue	Chambers implanted in mice groins, filled with Matrigel and heparin; varied configurations (autograft, open, fat flap)	Matrigel, heparin, autologous fat	Higher adipose tissue volumes and vascularization, especially in fat flap group	Animal model; limited human applicability
Dolderer, 2007 (49)	Generate adipose tissue from vascularized fat flap inside a chamber	Rat model, chambers with or without PLGA scaffolds	Polycarbonate chambers, PLGA scaffolds	Significant adipose volume increase in all chamber groups	Animal model; unclear mechanism for human scaling
Dolderer, 2011 (50)	Evaluate long-term stability of chamber-generated adipose tissue	Rat model, perforated vs. nonperforated chambers	Polycarbonate chambers	Volume growth, greater in perforated chambers	Animal model limitations, unclear scalability to humans
Wan, 2016 (51)	Assess external suspension device for adipose tissue growth	Rabbit model, external suspension vs. traditional chamber	External suspension device (negative pressure)	Larger volume growth with external suspension (81 ml vs 31 ml over 36 weeks)	Animal model, device usability in human scenarios unclear
Cleret, 2022 (52)	Effects of irradiation on fat flap growth	Rat model, bioresorbable PLGA-based TEC	PLGA-based bioresorbable TEC	Radiation reduced fat flap growth, introduced fibrosis	Animal model; limited

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		implantation; irradiation pre- or post-implantation		and histological changes; viable as adjunct in breast reconstruction despite irradiation	clinical translation
Faglin, 2020 (53)	Influence of TEC design on adipose tissue growth	Rat and pig models, TECs (perforated vs. nonperforated), 3D-printed bioresorbable scaffolds	PLA (rat), PGA (pig) scaffolds	Perforated TEC superior, rapid adipose growth, bioresorbable TEC achieved >140% volume growth in pigs	Animal models; unclear full clinical translation potential
Dong, 2022 (54)	Evaluate nipple projection retention using 3D scaffolds	Nude rat model, 3D-printed scaffolds filled with human cartilage	3D-printed P4HB scaffolds, human costal cartilage	Improved nipple projection and tissue growth, regenerative response	Small animal model; uncertain scalability
Samadi, 2021 (55)	Preserve nipple geometry using scaffolded cartilage	Nude rat model, external scaffolds with autologous cartilage	3D-printed PLA external scaffolds, autologous cartilage	Maintained superior nipple volume, viable cartilage tissue with biomechanical similarity to human nipples	Animal model; limited human applicability
Bao, 2021 (56)	Enhance fat graft retention with scaffold support	Nude mice model, fat graft injected into scaffold	3D-printed polycaprolactone scaffolds	Improved graft retention, angiogenesis observed; superior cellular preservation initially	Short-term animal study
Chhaya, 2016 (57)	Scaffold pre-vascularization for breast reconstruction	Minipig model, pre-vascularized scaffold compared to immediate grafting	Polycaprolactone scaffolds	Pre-vascularized scaffolds improved adipose tissue retention significantly	Limited animal study duration, scalability unclear
Baek, 2019 (58)	Hybrid scaffold approach to improve fat graft survival	Male mice model, hybrid devices combining implants + scaffolds + inguinal fat grafts	Polycaprolactone scaffolds, electrospun nanofibers, silicone implants	Improved adipocyte morphology at early stage; limited overall retention benefits	Small animal model; unclear human translation

Preclinical studies serve as a foundation in medicine, ensuring that medical interventions, especially in the domain of tissue engineering, are safe, efficient, and offer positive prognostic value.

As breast reconstruction techniques evolve, preclinical studies have seen significant advancements, such as fat grafting techniques, acellular dermal matrices, nerve reconstruction, monitoring and imaging techniques, and the understanding of physiology (38-43). However, when delving into tissue bioengineering specific to breast reconstruction, there is a noticeable scarcity of published research.

We performed a review of the available literature of preclinical research in tissue engineering for breast reconstruction in PubMed on 04/16/2025 using the following search strategy:

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"("Mammaplasty"[Mesh]) AND "Tissue Engineering"[Mesh]." The search yielded 39 results published between 2001 and 2025, and 10 articles were deemed relevant and are reviewed below.

Many efforts have been made to understand the capability of enhancing tissue growth in vitro. From the earliest efforts, we found Huss et al (44) in a study where human mammary epithelial cells and preadipocytes were co-cultured in a 3-D collagen gel matrix, demonstrating the potential for growing human-like breast tissue in the laboratory (44). The same authors later conducted an in-vitro study selectively culturing preadipocytes, showing increased proliferation and survival in cell cultures (45), this finding would open expectations on the engineering of autologous fat tissue with the aim of enhancing lipoinjection retention rates. Moreover, in a study conducted by Krause et al (46), human mammary epithelial cells and fibroblasts were cultured in a 3D matrix, resulting in cellular growth and the development of complex ductal and alveolar structures in the first weeks (46). These authors have been encouraged to culture breast-harvested cells in 3D Cultures to provide growing cells with an environment resembling in vivo structures.

On the other hand, other authors have focused their preclinical research on in vivo studies with different animal models using polycarbonate-made tissue engineering chambers (TECs) with varied results. In a notable study, researchers scaled up small-animal adipose tissue-engineering models to a pig model. They inserted in the pig's groin large-volume dome-shaped chambers made of hollow, perforated chambers enclosing a fat flap. By 6 weeks, all chambers had new tissue, with the initial 5 ml of fat expanding to volumes of up to 56.5 ml in 22 weeks. This growth persisted for 22 weeks after chamber removal, with one sample even relocated to a nearby submammary pocket (47).

Furthermore, although the aims and fundamentals of most of these studies were not clearly stated as addressing challenges in breast reconstruction, their results are highly translatable to the breast reconstruction field (48-50).

In a study examining the longevity of tissue-engineered adipose tissue, researchers implanted chambers into the groins of 8-week-old male mice. These chambers, filled with Matrigel and heparin, came in three configurations: autograft, which incorporated a small fat autograft; open, designed with a 1-mm hole for external adipose tissue interaction; and fat flap, which allowed for a segment of external adipose tissue to be wedged into one end. After one year, the results indicated that chambers in closer proximity to vascularized adipose tissue, particularly the fat flap group, showcased the highest volumes of adipose tissue growth. All specimens displayed new blood vessels, pointing to successful vascularization. Notably, the autograft group demonstrated a higher concentration of fibrous tissue. Compared to data taken at 6 weeks, adipose tissue percentages at the 1-year mark were significantly higher across all chamber configurations (48).

Dolderer et al. also assessed the growth of pedicled fat flap tissue located in rat groins along the milk line using subcutaneously implanted polycarbonate chambers. The study involved a variety of solid or perforated chambers, with placement or not of a PLGA scaffold inside them. Interestingly, the resulting flaps increased their volume in all the groups with the chambers (49). Later, the authors in another similar study used pedicle tissue flaps in either perforated or nonperforated chambers. Over 20 weeks, volume analysis indicated growth within the chambers, with perforated chambers showing greater volume, while transferred tissues with no chambers maintained their volume (50). Interestingly, in both studies, connective and fat were the tissues occupying most of the internal chamber area, with breast gland cells remaining the minority.

Notably, the manufacturing methods for the polycarbonate chambers in these in-vivo studies were not described. Regarding the PLGA scaffolds used, the fabrication involved thermally induced phase separation techniques (49).

Other authors have researched new tissue engineering methods, such as Jinlin et al., who used an external suspension device to generate negative pressure, enhancing adipose tissue flap growth and eliminating the need for implanting the foreign material of the TEC. When tested on rabbits, the adipose flaps produced by this device showcased a typical tissue structure similar to the chamber group. However, the group with the external suspension device yielded a significantly larger flap volume, growing from 5 ml to 81 ml over 36 weeks; in contrast, the group with the chamber increased

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from 5 ml to 31 ml. Both methods displayed similar structural and cellular changes throughout development, but at the initial stage, the group with the chambers exhibited a thicker capsule surrounding the flaps. Furthermore, the authors highlight the potential of external suspension devices to mold flaps into specific shapes using the implant chamber externally (51).

In a study conducted at the University of Lille, authors investigated the effects of irradiation on fat flap growth in a rat TEC-based adipose tissue-engineering model. Utilizing a 3D-printed bioresorbable PLGA-TEC made from PLGA, the experiment divided 28 female Wistar rats into three groups: non-irradiated controls, post-TEC implantation irradiation, and pre-TEC implantation irradiation groups. The results revealed no significant macroscopic or physicochemical changes in the PLGA-based TEC following irradiation. However, while the non-irradiated control group experienced substantial fat flap growth, the irradiated groups exhibited decreased growth and histological differences, such as emerging fibrosis and reduced adipose tissue regeneration. Despite these differences, the study suggests that integrating TECs during radiotherapy may be a viable approach for breast reconstruction, offering potential new avenues for treatment (52).

Another study (53) delved into the influence of the TEC design on adipose tissue growth. Researchers utilized two TEC variants, one with perforations and the other without, to analyze their effectiveness in fostering adipose tissue expansion in rats. These TECs were 3D-printed from polylactic acid (PLA). Simultaneously, the study assessed the potential of bioresorbable polymers for TEC design, emphasizing polyglycolic acid (PGA) in pigs. Through a series of methods, including histological analysis, metabolic profiling, and MRI imaging, findings indicated that perforated TECs outperformed their nonperforated counterparts, resulting in 3 to 5 times faster adipose tissue growth within 90 days. This growth involved functional adipocytes surrounded by a moderate fibrous capsule infiltrated by inflammatory cells and new microvasculature predominantly at the flap's periphery. Notably, a flat base in the TEC design enhanced the overall fat volume growth. Transitioning to the pig model, the bioresorbable PGA-based TEC led to a remarkable fat flap growth of over 140% (75,000 mm3) by day 90, and the TEC underwent significant resorption. Notably, there was no systemic inflammation, and histological data identified the adipose tissue expansion as a consequence of an increased number of adipocytes rather than individual cell hypertrophy (53).

Several studies have studied alternatives for breast reconstruction using tissue engineering; however, most of these modalities have focused on using flaps inside 3D-printed chambers. Moreover, although some studies have shown significant adipose tissue growth, it still does not approximate breast dimensions, further limiting its utility in breast reconstruction, especially in those patients desiring bigger breast sizes.

Another search was performed to review the current state of research, especially for 3D printing tissue engineering methods for breast reconstruction. The search was conducted in PUBMED on 08/20/2023 using the following search strategy: ("Printing, Three-Dimensional"[Mesh]) AND ("Mammaplasty"[Mesh]). This time, the search resulted in only 9 results, and only 2 were found relevant and were targeted to nipple reconstruction.

One study focused on the challenge of maintaining long-term nipple projection following breast reconstruction post-mastectomy. Researchers utilized 3D-printed scaffolds made of P4HB polymer measuring 1 x 1 cm with a domed top incorporating 2.0 mm pores. In addition, some scaffolds incorporated an internal 3D lattice. Human costal cartilage was processed and filled into these scaffolds and implanted into twenty-five nude rats. Results indicated that nipples with 3D-printed scaffolds maintained better projection and volume over six months post-surgery compared to controls. Significant tissue growth within the scaffold was observed, and a shift from inflammatory to regenerative tissue response was noted. Regarding the P4HB scaffold's degradation, a quicker rate was observed in the group with the internal 3D lattice, with a decrease in stiffness over time (54).

Other researchers proposed a novel technique using discarded costal cartilage from autologous flap breast reconstructions. They processed the costal cartilage and placed it within 3D-printed external scaffolds made of PLA to create tissue constructs that resemble the shape and biomechanical properties of a human nipple. After implanting these constructs in nude rats for three months, results

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showed superior preservation of the nipple's volume and projection compared to the non-scaffolded costal cartilage construct. Furthermore, histologic and mechanical analyses showed viable cartilage tissue with biomechanical properties similar to native human nipple tissue (55).

These studies underscore the potential of 3D-printed scaffolds in outperforming traditional nipple reconstruction methods by maintaining nipple projection.

Delving further into the literature, it is evident that some innovators seek further solutions for the creation of breast mound with 3D printing technologies. For instance, Bao et al. (56) investigated the effects of a 3D printed polycaprolactone scaffold on human fat grafting in nude mice. Their scaffold, 1.5 mm in diameter with a porous, mesh-like structure, showed higher retention of the grafted fat's volume and weight over 8 weeks, compared to the control group without a scaffold. Histologically, the scaffold group preserved cellular structure more effectively, particularly notable in the first 4 weeks. Fibrosis levels were comparable between groups. Interestingly, the study found increased angiogenesis in the scaffold group's sample periphery, although the internal areas showed higher angiogenesis in controls at 8 weeks, likely due to prolonged hypoxia stimulating blood vessel formation. Nonetheless, no significant difference in mature vessel formation was observed at week 8 in any group. Fat viability in the scaffold group was superior until week 4, but by week 8, a shift occurred, likely from vacuole resorption leading to denser viable fat (56).

Angiogenesis plays a crucial role in the success of fat grafting procedures, serving as a vital host response to ensure graft viability. A study by Chhaya et al. (57)explored the concept of scaffold pre-vascularization using hemisphere-shaped polycaprolactone scaffolds of 75 cc volume in minipigs over 24 weeks. The study results highlighted that the scaffolds, implanted empty and then undergoing a 2-week pre-vascularization stage before the addition of a fat graft, showed a significantly higher adipose tissue area (48%) compared to the scaffolds where the fat graft was injected during the implantation procedure (40%) (57). This study underscores the challenges that large scaffolds intended for humans could face due to the limited rate of angiogenesis from the periphery to the graft's center.

Other works in the field have been conducted with composite methods, combining implants with tissue engineering strategies to enhance fat graft retention. Baek et al. (58) developed a hybrid 3D printed device made with polycaprolactone and coated with electrospun nanofibers. In their study on male mice, the devices were placed on silicone implants, with inguinal fat grafts placed on the nanofiber-coated surface. They compared the results with fat grafts on implants alone or with the polycaprolactone scaffold with no nanofibers. The findings showed no significant difference in capsule thickness and adipocyte retention between groups. However, at the 4-week mark, the group with the scaffold plus nanofibers exhibited improved adipocyte morphology compared to the other groups (58). This finding underscores the critical role of surface characteristics, such as nanofiber-mediated topography mimicking the extracellular matrix, in promoting superior fat cell structure.

B. Evaluation of biodegradable materials in preclinical models: biocompatibility, degradation kinetics and biomechanical properties (Table 2)

Table 2. Evaluation of biodegradable materials in preclinical models: biocompatibility, degradation kinetics and biomechanical properties.

Material	Biocompatibility	Degradation Kinetics	Biomechanical Properties	Key Points and Considerations
PLA (Polylactic Acid)	Moderate; can trigger inflammatory responses due to acidic degradation products (lactic acid).	6 to 12 months	Good initial mechanical properties but tends to become brittle.	Widely utilized; concern about inflammation due to acidic degradation byproducts.
PGA (Polyglycolic Acid)	Good biocompatibility; broadly accepted in	Rapid degradation within weeks to months, breaking	High initial strength, diminishes	Beneficial for short-term applications; degradation may be

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	medical applications such as sutures.	down into glycolic acid.	quickly due to rapid degradation.	too rapid for prolonged structural support.
PLGA (Poly(lactic-co-glycolic acid))	Generally good; however, inflammatory concerns exist due to acidic degradation products.	Adjustable degradation time from weeks to months depending on the PLA to PGA ratio.	Mechanical properties adjustable through composition ratio (versatile).	Highly customizable; requires careful formulation to balance degradation rate and inflammatory response.
P4HB (Poly-4-hydroxybutyrate)	Excellent biocompatibility with minimal inflammatory response.	Degrades over approximately 12 to 18 months into 4-hydroxybutyric acid.	Flexible, robust mechanical strength suited for soft tissue implants.	Ideal for long-term, flexible support; more complex and costly due to exclusive fermentation-based synthesis.
Poly(D,L-lactide)	Moderate biocompatibility; inflammatory response potential similar to PLA.	Similar to PLA; adjustable by altering blend ratio of stereoisomers.	Properties depend on stereoisomer ratios; can exhibit brittleness.	Mechanical and degradation profiles can be customized, yet inflammatory potential remains a concern.

Biocompatibility is a common concern in tissue engineering; hence, studies must ensure that introduced materials interact safely with host tissues. For breast reconstruction and other medical uses, materials must be both physiologically and immunologically compatible to prevent adverse reactions and ensure natural integration.

Many biomaterials used in medical implants and regenerative medicine often develop foreign body reactions upon implantation (59). The foreign body reaction to biomaterials progresses through five phases: protein adsorption, acute and chronic inflammation, and the formation of foreign body giant cells and fibrous capsules (60).

Biodegradable materials are promising because they allow the creation of devices with the ability to provide temporary structure and mechanical support as the tissue regenerates until device resorption, minimizing long-term foreign body presence (61).

Much has been researched about the use of biodegradable materials for drug delivery systems (62), orthopedic devices (63, 64), stents (65), and wound healing (66-68). However, only a few bioabsorbable polymers have been tested for breast reconstruction, including PLA, PGA, PLGA, P4HB, and poly(d,l)-lactide polymer.

PLA is an aliphatic polyester with degradation products of lactic acid, typically degrading over 6 to 12 months. It is prized for good mechanical properties but can be brittle and produce inflammatory acidic products upon degradation (69, 70). PGA is used widely in sutures and degrades into glycolic acid within weeks to a few months. It is recognized for its strength and biocompatibility, though its quick degradation can sometimes pose challenges (71, 72). PLGA, a mix of PLA and PGA, degrades to release both lactic and glycolic acids over weeks to several months. It is versatile compared to PGA and PLA since the composition ratio can control its resorption time (73). P4HB is known for flexibility and strength, degrading into 4-hydroxybutyric acid in about 12 to 18 months; however, unlike other resorbable polyesters such as PLA, PGA, and PLGA, its production is complex since it is exclusively synthesized in the fermentation process; therefore, it is less readily available and more costly (74, 75). Finally, Poly(D, L)-lactide combines two PLA stereoisomers and shares a similar degradation rate and product with PLA; its blend ratio influences its properties but can produce inflammatory products (76, 77).

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The degradation rate of biomaterials plays a pivotal role in determining the success of tissue regeneration. For breast reconstruction, it is paramount that the material degrades at a rate that allows the concurrent growth and maturation of the new tissue, ensuring the maintenance of structural integrity. Rapid degradation could lead to tissue collapse and inadequate support. In contrast, slow degradation might hinder natural tissue formation, causing prolonged foreign body reactions or fibrotic encapsulation.

A developmental scaffold should be biocompatible with controlled degradation, have a 3D interconnected pore design, offer structural support, and promote positive cell interactions(78).

One common issue found in the preclinical studies for breast reconstruction using 3D printing is the mechanical properties of the TEC or scaffolds per se, as they are made of stiff materials, which do not align with the mechanical properties of the breasts.

Breast tissue, being highly vascular and glandular, has specific needs for elasticity, sensation, and aesthetics (79). Therefore, Biodegradable materials for breast reconstruction should ideally emulate the biomechanical properties of native breast tissue to meet patients' needs.

C. Gaps in preclinical testing: lack of specific preclinical studies on reconstructive materials for breast reconstruction and Implications.

The rapid advancements in reconstructive surgery, particularly breast reconstruction, are commendable. However, a significant concern arises from the lack of comprehensive preclinical studies targeting reconstructive materials. Without abundant reproducible and robust preclinical research, the understanding of how these materials might interact within the body remains limited, keeping the door closed to potential unanticipated outcomes.

The implications of this data gap hinder clinicians from understanding the safety and the overall behavior of the materials and their consequences. Biocompatibility and integration with native tissues are primary concerns when implanting any new reconstructive material. The body's response must be gauged to predict long-term outcomes (80, 81).

Beyond safety, the performance of these materials, like their aesthetic results or longevity, remains unpredictable. Ethically, exposing patients to potential risks without comprehensive prior testing challenges the medical principle of "do no harm"(82, 83).

The varied levels of success rate documented in preclinical studies for breast reconstruction regarding the utilization of tissue-engineered scaffolds or chambers, whether 3D printed or not, as highlighted in earlier cited studies, amplifies a critical issue of publication bias. The underrepresentation of studies yielding negative results could lead to the misallocation of funding in project investments and obstruct the exploration of alternative, potentially more effective approaches for breast reconstruction (84).

In essence, while innovation in breast reconstruction is crucial, it must be underpinned by rigorous preclinical testing to ensure superior outcomes, maintain ethical standards, and empower informed decision-making.

4. Clinical Indicators for Reconstructive Materials

A. Identification and evaluation of clinical indicators of success for breast reconstruction

Clinical indicators are measurable metrics used to assess the quality and outcomes of healthcare services. These can relate to the structure, process, or results of care. They serve as benchmarks that guide healthcare professionals and organizations in enhancing care quality. They must be valid, sensitive, and clearly defined to gauge healthcare performance effectively. While optimal indicators are evidence-based, some may be based on professional consensus (85).

Breast-Q, developed in 2009, is a comprehensive tool designed to capture patient views on breast surgeries, with modules focused on specific procedures like augmentation, reduction, and reconstruction. Developed with substantial patient feedback, it evaluates surgical outcomes and their impact on health and quality of life (86).

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Since its development, BREAST-Q has been used extensively in breasts to measure the influence of oncoplastic treatment on patient-reported outcomes. Questionnaires of patient-reported outcome measures need to demonstrate validity and reliability. Consequently, the BREAST-Q has become the gold standard patient-reported outcome measures instrument for breast surgery (87, 88). However, these quality assessment tools are based on patient quality of life rather than objective measurements, making them useless for preclinical research.

Currently, there is no standardized objective measurement tool for breast reconstruction assessment (89). Some surgeons rely on the overall assessment of objective indicators to assess reconstruction success. These indicators include survival, complications, and aesthetic outcomes such as breast symmetry, volume, color differences, scar appearance, and nipple-areolar complex (89-91).

Regarding preclinical research of reconstructive materials, most studies primarily focus on assessing fat volume retention/growth. However, there is oversight of some other aesthetic indicators other than volume, such as symmetry, color differences, and scar appearance.

On the other hand, bioabsorbable materials hold a significant advantage of their potential to gear toward 1 stage surgery, consequently decreasing the hospital burdens and exposure to the inherent risk of surgical procedures.

B. Assessment of existing clinical studies on reconstructive materials (Table 3)

Table 3. Clinical studies on reconstructive materials.

Author, Year	Study Objective	Methodology	Materials Used	Key Findings	Limitations
Rehnke, 2020 (92)	Evaluate effectiveness of composite strategy combining absorbable mesh with autologous fat grafting	Retrospective review, 22 patients, 28 reconstructed breasts, mean follow-up 19 months	Lotus scaffold (TIGR Matrix, SERI Scaffold, PHASIX mesh), Autologous fat graft	High elasticity, natural feel; histology: PHASIX mesh had superior fat structuring and milder foreign body response	Small sample size, retrospective design, limited follow-up period
Morrison, 2016 (93)	Assess clinical feasibility of TEC for adipose tissue growth	Case series, 5 patients, TEC with TAP flaps, follow-up up to 6-12 months	Acrylic chambers, thoracodorsal artery perforator (TAP) flaps	One patient achieved significant tissue expansion (210 ml); others no significant growth	Small sample size, limited success, patient discomfort led to early removal
Clinical trial NCT05460780 (94,95)	Safety and efficacy of bioabsorbable TEC with LICAp/LTAp flap	Ongoing trial, immediate reconstruction post-mastectomy	Bioabsorbable TEC, LICAp or LTAp pedicled flaps	Preliminary results: successful implantation in first human case (as reported)	Awaiting comprehensive data and long-term follow-up results
van Turnhout, 2018 (96)	Evaluate SERI surgical scaffold for direct-to-implant reconstruction	Retrospective review, 16 patients, 22 breasts; literature review included	SERI surgical scaffold	High complication rate (seroma 45%, scaffold integration issues 14%)	Retrospective, small sample, potential product-associated bias
Clinical trial NCT05437757 (97)	Safety and efficacy of fat grafting within	Prospective trial, recruiting 20 participants	3D-printed polycaprolactone	Ongoing, preliminary safety and	Awaiting results, small planned sample

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	3D-printed scaffolds	scaffold, autologous fat	effectiveness assessment in progress

The need for new methods in breast reconstruction has prompted significant research contributions on the clinical front.

One study introduced a method combining a three-dimensional absorbable mesh construct, referred to as the "Lotus scaffold", with autologous fat grafting. Researchers conducted a retrospective review of 22 patients with a total of 28 breasts reconstructed using the Lotus scaffold coated by 50-100 cc of autologous fat grafting obtained by liposuction, with an average follow-up period of 19 months. Different FDA-approved meshes were trialed, including TIGR Matrix Surgical Mesh (copolymer of glycolide, lactide, and trimethylene carbonate), SERI Surgical Scaffold, and PHASIX mesh (Poly-4-Hydroxybutyrate). Patients underwent an average of two additional fat grafts after implantation with an average volume of 458 ml. Histological assessments confirmed fat tissue surrounding the scaffold. The TIGR® mesh triggered a robust foreign body reaction with dense collagen and scattered fat cells.

In contrast, the PHASIX® mesh had a milder response with less dense connective tissue and better structured fat tissue. Furthermore, compression tests determined that the scaffold exhibited a highly elastic profile. Safety-wise, 25% presented at least 1 adverse event; notably, one case presented a subdermal cancer recurrence one year post-mastectomy. All but two respondents to a satisfaction survey were pleased with their outcomes, reporting soft, naturally reconstructed breasts (92).

Other authors explored breast reconstruction using dome-shaped acrylic chambers with perforated walls and internal capacities ranging from 140 to 360 ml. In this study, 5 participants underwent thoracodorsal artery perforator (TAP) flaps, with volumes ranging from 6-50 ml. These flaps were placed inside the TEC. Patients were then monitored post-surgery for up to six months until chamber removal, except for 1 patient showing notable tissue growth, who was followed up for 6 additional months which resulted in filling a 210 ml space. Three other patients exhibited no tissue growth beyond the initial flap's dimensions, resulting in silicone implant reconstructions. Lastly, one patient had her chamber removed early due to discomfort. Histological analyses after chamber removal confirmed the presence of viable, well-vascularized fat inside the chamber for certain patients (93). Notably, patient-reported and aesthetic outcomes were not assessed in this study.

This same approach is being studied by the clinical trial NCT05460780, which aims to assess the safety and efficacy of Matisse®, a TEC implant-based method for immediate breast reconstruction in Georgia (country). This method, however, involves a bioabsorbable TEC implantation with a pedicled LICAp or LTAp flap within it to support a flap growth (94). Although no preliminary results have been published, a recent press report released in 2022 claimed that they achieved the first successful breast reconstruction with their device (95).

Other tools have been developed and tested in the field of breast reconstruction with 3D printing, such as surgical meshes, to provide breast support for implants and tissue expanders. One study investigated the outcomes of using SERI Surgical Scaffold conducted in The Netherlands. This retrospective study included 16 patients (22 breasts) and found no intraoperative issues. However, postoperative complications such as bleeding (5%), seroma (45%), and infection (9%) were observed. Significantly, 14% lacked scaffold integration, resulting in skin ulcerations. The authors also conducted a systematic literature review, pinpointing the scarcity and potential bias in existing studies, with many authors affiliated with the product's producer (96).

Another clinical trial (NCT05437757) investigates an approach for breast reconstruction where patients' fat tissue is harvested using liposuction and then injected into 3D printed scaffold implants made of polycaprolactone, a material approved for skull bone restoration by Australian regulatory authorities. Currently, the trial is seeking around 20 participants, primarily to determine the safety and efficacy of this approach (97).

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Some patient-oriented concerns when assessing the TEC or scaffolds used for breast reconstruction are the biomechanical properties of the materials. Since these TECs provide a hard shell to enhance flap growth, they must maintain their mechanical properties for an acceptable period. However, such properties could lead to discomfort and unnatural breast shapes for relatively long periods, discouraging patients from undergoing this type of reconstruction. Indeed, in Morrison et al.'s (93) study, one out of 5 subjects underwent early removal of the TEC due to discomfort (93).

5. Direction of Research and Limitations

A. Current trends and advancements in tissue engineering and 3D printing.

The increasing popularity and advancements in 3D printing technology have ushered in a new era of tissue engineering. The latest 3D printers offer improved precision, allowing for the creation of more complex tissue structures.

In addition, 3D bioprinters have emerged as a promising tool for tissue engineering. 3D bioprinting uses stem cells and bioinks to create 3D structures. These structures eventually integrate with a patient's tissue, thanks to the bioinks' support for cell growth and adhesion (98). One limitation of bioprinters is the high costs, with prices ranging from $5000 to over $1,000,000 (99). However, many conventional low-cost 3D printers have been proven to be able to shift to bioprinters by modifying some factors (100-102).

There is still a considerable journey ahead in research involving bioprinters. While bioink has been utilized to construct various breast cancer models (103, 104), its application in the context of breast reconstruction remains unexplored.

B. Identification of research gaps and areas for future exploration

This paper has already delved into the research gaps. It goes without saying that given the relatively emerging nature of this field, there exists a vast array of unexplored territories.

Artificial Intelligence has the potential to revolutionize 3D printing in healthcare by precisely adapting designs to complex body structures using sensory data, making real-time adjustments during the printing process, and predicting and adapting to rapid changes, like organ movements (105, 106). In breast reconstruction, AI could enable the creation of more tailored implants and offer real-time adaptability to patient-specific anatomies, enhancing the overall precision and outcomes of the procedure.

Another field that needs to be explored, both in the preclinical and the clinical phases, is the use of growth factors and mesenchymal stem cells that can aid in fat growth and replication to expand fat flaps and fat grafts. However, contrary to the philosophy of 3D printing in healthcare, which promises simplicity, this would add further steps and obstacles, including concerns about the oncological potential of fat grafts.

Moreover, it remains to be determined whether the implantation of 3D printed devices, based on each design and polymer, might interfere with monitoring breast cancer recurrence.

C. Regulatory Considerations and Future Perspectives

Research has been focused on simplifying breast reconstruction through 1 or 2-stage reconstructions using specific materials. However, the properties of these scaffolds are yet to be improved to achieve mechanical properties resembling natural breasts, allowing for comfortability and wellness of patients during the first months before the polymer reabsorbs. To attain this goal, more materials and designs for breast TEC or scaffolds need to be tested.

Further limitations regarding materials that may be used for breast reconstruction arise based on FDA regulations. The FDA's Center for Devices and Radiological Health regulates medical devices in the U.S., including those created using 3D printing. Based on regulatory control level, devices are categorized into Class I, II, and III. Most Class I medical devices are exempt from Premarket Notification 510(k), whereas Class II devices usually require it, and Class III devices, the highest risk category, need Premarket Approval (PMA) (107, 108). For a device to gain FDA clearance through

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510(k), it must demonstrate substantial equivalence to a predicate device that is legally marketed (109). Currently, breast implants are classified as Class III devices (110); furthermore, since the FDA has not yet approved or cleared any devices utilizing tissue bioengineering methods for breast reconstruction, new devices for this purpose will automatically require the more stringent PMA process before they can be legally marketed in the US.

In 2016, the FDA introduced draft guidance for 3D printed devices, providing advice on design, manufacturing, and testing. This guidance, still under review, details technical requirements and information expectations for premarket submissions (107).

The future of breast reconstruction with 3D printing methods envisions a scenario where the patient's breasts are imaged, and the corresponding implants are manufactured directly within the healthcare facility, ensuring rapid availability at reduced costs. To support Point of Care manufacturing, the FDA is currently exploring regulatory frameworks for 3D printing of medical devices at the Point of Care. This initiative involves gathering stakeholder feedback to address the unique challenges of integrating 3D printing technologies in healthcare settings, focusing on managing risks and ensuring safety and effectiveness (111).

The regulatory landscape for 3D printing in breast reconstruction is intricate. While 3D printing offers tailored solutions vital for individual patient needs, it challenges traditional FDA frameworks designed for standardized devices. Balancing innovation and safety is critical. Defining responsibility becomes complex as 3D printing blurs the lines between manufacturers and healthcare providers. Transparent communication between innovators and regulatory bodies is crucial to navigate these challenges.

D. Challenges and requirements for clinical translation

Challenges in clinical translation from animal models to humans in breast reconstruction arise due to the inherent biological differences between species, especially in tumor development and physiology (112). Animal surgical models demonstrate limited success in translating to human clinical research, emphasizing an urgent need to explore alternative surgical research models.

Successful procedures in animal models might need significant modifications when applied to the larger and complex human anatomy. These changes are essential to ensure long-term outcomes, safety, and efficacy.

Concerning translational research in breast reconstruction using 3D printing, most studies perform reconstructions in healthy animal models, disregarding the impact of breast cancer resection, chemotherapy, and radiotherapy in such procedures. In contrast, studies in clinical trials are usually done on patients immediately after cancer resection.

E. Future prospects and potential impact of tissue engineering in breast reconstruction

In the evolving field of breast reconstruction, tissue engineering stands poised to revolutionize treatment paradigms. Harnessing the synergy of advanced biomaterials, 3D printing, and regenerative medicine, the prospect of creating personalized, biocompatible reconstructions that mimic the native breast tissue's form and function is on the horizon. This transition promises enhanced aesthetic and functional outcomes and a potential reduction in post-surgical complications. By addressing current limitations and intricacies of traditional reconstructive procedures, tissue engineering could elevate the standard of care, offering patients natural-feeling results and enhancing the quality of life.

6. Conclusions

tissue engineering and 3D printing technologies represent significant potential to address existing limitations in breast reconstruction following mastectomy. The integration of biodegradable biomaterials, such as PLA, PGA, PLGA, and P4HB, offers promising strategies to mimic the native structure and function of breast tissue, aiming for enhanced aesthetic and functional outcomes. However, critical gaps persist, notably in the biocompatibility, degradation kinetics, and biomechanical properties of these materials, as revealed by current preclinical evidence.

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Future research should prioritize overcoming these limitations by refining scaffold designs to align more closely with natural breast tissue mechanics, enhancing vascularization strategies through prevascularization techniques, and incorporating advanced technologies such as real-time adaptive 3D bioprinting and artificial intelligence-driven customization. Furthermore, rigorous preclinical and clinical evaluations are crucial to ensuring safety, efficacy, and regulatory compliance for successful clinical translation.

Ultimately, advancements in tissue engineering and 3D printing technologies have the potential not only to improve patient satisfaction through personalized, natural-feeling reconstructions but also to increase accessibility and reduce the healthcare burden associated with traditional reconstructive procedures. As research progresses, these innovative approaches are anticipated to revolutionize post-mastectomy care, significantly enhancing the quality of life for breast cancer survivors.

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