

Scaffolds—The Ground for Regeneration: A Narrative Review

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ABSTRACT

Aim: The aim of this study was to comprehensively review the various biomaterials used as scaffolds, rates of biodegradability of natural, artificial and composite hybrid scaffolds, and the role of controlled biodegradability in tissue engineering. **Materials and Methods:** An electronic search for systematic review was conducted in PubMed/MEDLINE (www.ncbi.nlm.nih.gov), Cochrane (www.cochrane.org), Scopus (www.scopus.com) databases, and dental journals related to endodontics and pediatric dentistry to identify the research investigations associated with the degradation profiles, factors relating to degradation, rates of biodegradability and the role of controlled biodegradability of natural, artificial and composite scaffolds. A sample of 17 relevant studies and case reports were identified in our search of 100 using simple random sampling. **Results:** Naturally derived scaffolds degrade at a much higher rate than artificial and composite scaffolds. The degradation profiles of composite scaffolds can be much better controlled than naturally derived scaffolds. **Conclusion:** Composite scaffolds are more favorable as compared to natural or artificial scaffolds, as it has superior mechanical properties, minimal immune response, and a controlled rate of degradation and consequent tissue regeneration.

KEYWORDS: Artificial, degradation profiles, natural, scaffolds, tissue engineering

INTRODUCTION

People and animals have a natural scaffold that surrounds cells and provides structural support for the formation of tissues and organs.^[1] Tissue engineering is a discipline that collaborates cell behavior and the technique of growing them on a substrate known as the “scaffold” along with suitable biochemical factors that promote regeneration.^[2] Scaffolds are designed to create a 3D environment that promotes tissue development of cells that are placed on or within the scaffold.^[3,4] One of the most important properties of a scaffold is its biodegradability. The degradation timeline of a scaffold is very important and should closely follow the rate of tissue regeneration. When taking into consideration natural scaffolds, they may degrade before the tissue regeneration occurs. However with synthetic materials, it must be considered that the release of acidic products will reduce

the pH of the surrounding tissues and will thereby affect the tissues. Some of the other applications in dentistry include regenerative endodontic procedures, guided tissue regeneration in the field of periodontics, and correction of disease affected temporo mandibular joint.

This narrative review aimed to describe the various biomaterials used as scaffolds, rates of biodegradability of natural, artificial and composite hybrid scaffolds, and the role of controlled biodegradability in tissue engineering.

MATERIALS AND METHODS

Articles for this systematic review were searched using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.^[5]

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ELIGIBILITY CRITERIA

For deciding the inclusion criteria, the PICOS Guidelines were followed.^[6] Annexure Table 1 shows the strategy for deciding the inclusion criteria, which were as follows: (1) randomized controlled trials, prospective and retrospective studies, (2) studies (*in vivo* and *in vitro*) that evaluated degradation profiles, factors relating to degradation, rates of biodegradability, role of controlled biodegradability of natural, artificial and composite scaffolds, (3) studies published in the English language, and (4) animal studies.

Exclusion criteria of the study included any letters to editor, reviews, abstracts, and article published in foreign language.

OUTCOME

The outcomes of this review were to assess rates of biodegradability of natural, artificial and composite hybrid scaffolds, the role of controlled biodegradability in tissue engineering, and as to which scaffold works best in dentistry.

STRATEGY OF SEARCH

Information sources

An electronic search for the narrative review was conducted in PubMed/MEDLINE (www.ncbi.nlm.nih.gov), Cochrane (www.cochrane.org), and Scopus (www.scopus.com) databases to identify studies related to the degradation profiles, factors relating to degradation, rates of biodegradability, and the role of controlled biodegradability of natural, artificial, and composite scaffolds. The search structure followed the pediatric and endodontics journals: *Dental Traumatology*, *International Journal of Pediatric Dentistry*, *Pediatric Dentistry*, *Journal of Endodontics*, *International Endodontic Journal*, *Journal of American Dental Association*, and *Australian Endodontic Journal*. The keywords included were as follows: “tissue engineering,” “scaffolds,” “degradation profiles,” “natural,” and “artificial.” The search includes all the articles from start date of each source until February 15, 2020 [Annexure Tables 1 and 2]. The articles searched were selected based on the quality of literature.

RISK OF BIAS

Cochrane Collaboration’s Tool for Assessing Risk of Bias in Randomized Trials was used to evaluate the risk of bias.^[7] Critical assessments were made separately for different domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each domain, the risk of bias was graded as high, low, or unclear based on criteria described in the Cochrane

Handbook for Systematic Reviews of Interventions 5.1.0.^[7]

Various biomaterials both natural and artificial scaffolds that are most commonly used have been described briefly as follows [Annexure Table 3].^[1-3,8-13]

COMPOSITE SCAFFOLDS

Composite materials with polymeric matrices also defined as polymer-based composite materials have emerged as suitable candidates for load-bearing applications in several fields.^[2] For example, polymer materials lack adequate stiffness. Addition of stiff materials such as glasses and ceramic overcomes the inherent weakness of polymers making it suitable for dental tissue regeneration.

BIODEGRABILITY OF SCAFFOLDS: THE CONCEPT^[14,15]

Various groups have stated that degradation of the scaffolds happens due to infiltrating phagocytes. Phagocytes adhere to the scaffold and synthesize large amounts of hydrolytic enzymes. Macrophages are the predominant cells and remain present at the biomaterial interface until the degradation process is finalized. In the presence of large scaffold remnants, macrophages fuse to form foreign body giant cells (FBGCS) and undertake phagocytosis. Ultimately, they release large quantities of ROS, degradative enzymes, and acids in the final attempt to break down the scaffold.

RESULTS

From the characteristic table [Annexure Table 4], it was clear that naturally derived scaffolds degrade at a much higher rate than artificial and composite scaffolds. The degradation profiles of composite and synthetic scaffolds can be better controlled than naturally derived scaffolds. A sample of 17 relevant studies was identified in our search of 100. The variables were authors/journal, type of study, scaffolds considered, tests used, and conclusion.

DISCUSSION

In this narrative review, all *in vitro*, *in vivo* animal models as well as case reports were included. The aim was to evaluate the literature to describe biodegradation as an individual property, and the rate of degradation of commonly used scaffolds. Our article also described the various natural, artificial, and composite scaffolds commonly used. In all of the records evaluated, the method of measurement of biodegradability was done by two of the following methods: either by measuring mass loss in *in vitro* studies or by histologic evaluation at certain intervals in *in vivo* study models. In *in vitro* testing, testing is done according to ISO 10993-14: 2009.^[16]

In most of our evaluated studies, PBS (phosphate buffered saline) or SBF (simulated body fluids) were the solutions used. The samples were placed in a closed test tube in either of these solutions at 37°C. Mass loss was measured after washing with deionized water and dehydration.^[16-19]

Among synthetic membranes, the degradation rate is relatively slow (12–24 months).^[20] Naturally derived membranes without cross-linking show a rapid degradation profile of approximately 7–10 days. Cross-linked membranes show a slow rate of degradation. Controlled degradation was seen with Mg-based bioceramics doped with Zn or Cu ions. The samples doped with Cu showed a faster rate of degradation as well as consequent hydroxyapatite formation as compared to the Zn doped samples. Another example of controlled degradation of natural scaffolds was given by Park *et al.*,^[18] who concluded that aqueous silk fibroin scaffolds showed 95% mass loss. However, the scaffolds prepared with hexafluoroisopropanol (HFIP) showed only 7% mass loss after dehydration, which showed that HFIP could be used to control and slow the rate of degradation of silk fibroin scaffolds.

CONCLUSION

From the above narrative review, it is clear that composite scaffolds are more favorable as they have superior mechanical properties, minimal immune response, and a controlled rate of degradation and consequent tissue regeneration.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHORS CONTRIBUTIONS

Not applicable.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

PATIENT DECLARATION OF CONSENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

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ANNEXURE

Table 1: PICOS guidelines

P (participants/ population)	Biomaterials used in tissue engineering
I (intervention)	Subject to degradation tests
C (comparison)	Comparison of degradation profiles of natural, artificial, and composite hybrid scaffolds
O (outcome)	Primary outcome: To compare and evaluate the degradation profiles of different materials used in the making of scaffolds. Secondary outcome: The role of controlled biodegradability in tissue engineering. The best biomaterial to be used in dental tissue engineering
S (study design)	Randomized controlled trials as well as prospective and retrospective studies: <i>In vivo</i> and <i>in vitro</i> studies that evaluated degradation profiles, factors relating to degradation, rates of biodegradability, studies published in English language, and animal studies.

Table 2: Search strategy

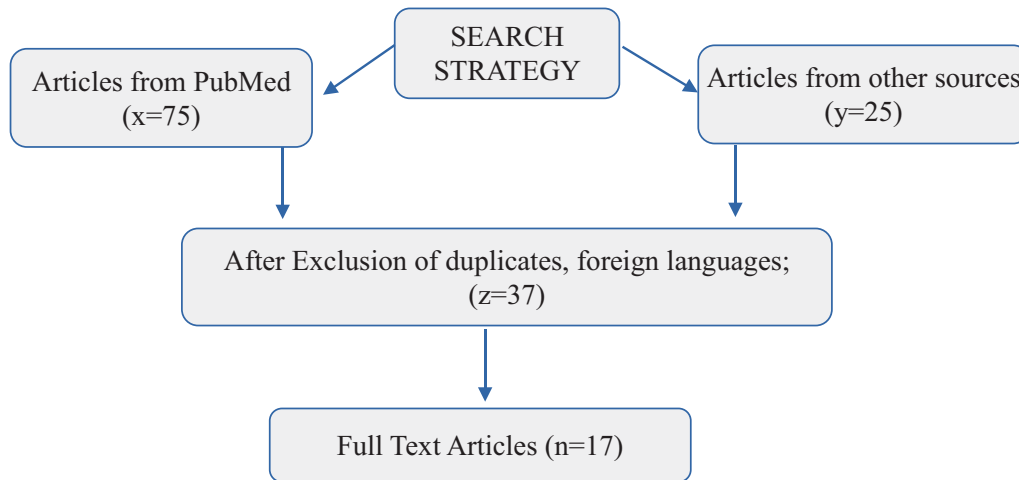


Table 3: Characteristics of natural and artificial scaffolds

Type of scaffold	Name	Characteristics
Natural	Blood clots	First approach to regeneration rich in growth factors.
	Platelet-rich plasma	First generation autologous platelet concentrate Concentration: 1 million/mL
	Platelet-rich fibrin	Second generation autologous platelet concentrate Also known as Choukroun’s PRF. Blood is collected and centrifuged at 300 rpm for 12 min. Three layers: Red cells at the bottom, PRF in the middle layer, and PPP in the top layer.
	Collagen	Major component of ECM membrane: Guided tissue regeneration Sponges: Bone defects
	Chitosan	Production: Deacetylation of chitin. Biocompatible, biodegradable, and antimicrobial
	Silk	Biocompatibility, nontoxicity, and diverse physical characteristics. Use: Periodontal and maxillofacial therapies.
	Hyaluronic acid	Low immunogenic potential Poor mechanical strength Rapid <i>in vivo</i> degradation Injectable gels
Artificial	Poly(ethylene glycol)	Nontoxic Low immunogenicity Undergoes <i>in vivo</i> degradation
	PLLA	Used: Where structural strength is important
	PGA	Used: Cell transplantation
	PLA	Similar to PGA but more hydrophobic.
	PCL	Used: Tissue engineering in bone.

Table 4: Characteristic table

No.	Author/journal	Name and study type	Scaffolds considered	Test used/time taken for complete degeneration	Conclusion
1	Singhal <i>et al.</i> ^[21]	Salient degradation features of a 50:50 PLA/PGA scaffold for tissue engineering (<i>in vitro</i> study)	PLA/PGA (poly lactic acid/ poly glycolic acid) 50:50 ratio; (artificial)	Gel permeation chromatography. Wt reduction over a period of 8 weeks was measured. 2 weeks: bright chalkish white color 4 weeks: cracks/ cavities 8 weeks: Complete Disintegration	Complete disintegration: 8 weeks
2	Fu <i>et al.</i> ^[22]	Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and <i>in vitro</i> degradation (<i>in vitro</i> study)	Bioactive glass (artificial)	The scaffold was put in a solution of PBS and incubated at 37°C. Weight loss measured: 200 h (1 week approx.)	Rapid wt loss occurred: 50 h. Between 50 and 200 h: slow After 200 h: constant
3	Theodorou <i>et al.</i> ^[23]	Sol-gel derived Mg-based ceramic scaffolds doped with zinc or copper ions: preliminary results on their synthesis, characterization, and biocompatibility (<i>in vitro</i> study)	Magnesium-based bioceramics doped with copper or zinc ions (artificial)	Test performed according to the ISO 10993-14: 2009 After 120 h in Tris buffer solution: ZnA ₂ : 5% CuA ₂ : 7% (degradation percentage)	Cu-doped ceramics formed hydroxyapatite: 7 days Zn-doped ceramics did not form hydroxyapatite even after 21 days
4	Lam <i>et al.</i> ^[16]	Evaluation of polycaprolactone scaffold degradation for 6 months <i>in vitro</i> and <i>in vivo</i>	Poly capro lactone scaffold (artificial)	<i>In vitro</i> : Scaffolds were placed in 10-mL PBS and incubated at 37°C. % mass loss measured <i>In vivo</i> : scaffolds implanted in rabbits, mass loss measured: 6 months average wt loss: 0.72%–2.13%	Maximum degradation took place <i>in vivo</i> via the bulk degradation pathway
5	Hafeman <i>et al.</i> ^[24]	Injectable biodegradable polyurethane scaffolds with release of platelet-derived growth factor for tissue repair and regeneration (<i>in vivo</i> study)	Polyurethane scaffolds (artificial)	Scaffold degradation <i>in vitro</i> measured; 4 and 8 weeks: measuring weight loss	Degradation takes place in a controlled manner.

Table 4: Continued

No.	Author/journal	Name and study type	Scaffolds considered	Test used/time taken for complete degeneration	Conclusion
6	Smidt <i>et al.</i> ^[25]	A nouveau collagen scaffold to simplify lateral augmentation between natural teeth (case report)	Collagen membrane (ossix volumax) (natural)	Complete degradation: 6 weeks	Stable clinical outcome for lateral augmentation of a deficient ridge.
7	Moses <i>et al.</i> ^[26]	Biodegradation of three different collagen membranes in the rat calvarium: a comparative study (<i>in vivo</i> study)	One membrane disk of each type (noncross-linked [NCL], glutaraldehyde cross-linked [GCL], and ribose cross-linked [RCL]) was implanted on the calvaria of 20 Wistar rats. (natural)	Histological layers measured: 14 and 28 days.	GCL degraded faster than NCL which degraded faster than RCL.
8	Kozlovsky <i>et al.</i> ^[27]	Biodegradation of a resorbable collagen membrane (Bio-Gides) applied in a double-layer technique in rats (<i>in vivo</i> study)	One layer of collagen compared two layers of collagen (natural)	Similar rate of degradation at 60%—4 weeks and 80%—8 weeks	The use of a double layer of BG membrane results in a barrier of increased collagen area and thickness
9	Gilbert <i>et al.</i> ^[28]	A quantitative method for evaluating the degradation of biologic scaffold materials (<i>in vitro</i> study)	Extracellular matrix scaffold implanted in pigs (natural)	Injection of ¹⁴ C into the pig specimens. Dissection of tissue and placement in 10-mL PBS. Radioactivity measured by LSC	Highest ¹⁴ C content measured: 4 weeks. Complete disintegration: 4 weeks
10	Kawase <i>et al.</i> ^[20]	The heat-compression technique for the conversion of platelet-rich fibrin preparation to a barrier membrane with a reduced rate of biodegradation (<i>in vitro</i> study, <i>in vivo</i> animal model)	PRF normally takes less than 10 days (natural)	Follows hydrolytic degradation. Hot compression increases degradation time up to 2 weeks	Heat compression was able to control the rate of degradation
11	Lundquist <i>et al.</i> ^[17]	Bioactivity and stability of endogenous fibrogenic factors in platelet-rich fibrin (<i>in vivo</i> study)	PRF (platelet-rich fibrin) (natural)	Complete disintegration: 24 h	Proteinases help in faster degradation
12	Wang <i>et al.</i> ^[29]	<i>In vivo</i> degradation of three-dimensional silk fibroin scaffolds (<i>in vivo</i> study)	Silk fibroin scaffolds (composite)	Complete degradation: 6–12 months	No cross-linking required for improving properties
13	Park <i>et al.</i> ^[18]	Relationships between degradability of silk scaffolds and osteogenesis (<i>in vitro</i> study)	Silk fibroin scaffolds (composite) aqueous solution compared to HFIP	Mass loss calculated before and after dehydration day 7: Aq: 5% left HFIP: 93% left	HFIP can control the rate of degradation of SF scaffold
14	Shah <i>et al.</i> ^[30]	Optimization of degradation profile for new scaffold in cartilage repair (<i>in vivo</i> study)	PCL-based polyester polyurethane – urea (PSPU-U) short-term scaffold compared to long-term scaffold (composite)	Histological findings: 4 and 8 and 16 weeks. Cartilage defect was measured	Complete integration: 16 weeks. Short term scaffolds showed better chondrocyte proliferation than long term scaffolds

Table 4: Continued

No.	Author/journal	Name and study type	Scaffolds considered	Test used/time taken for complete degeneration	Conclusion
15	Magno <i>et al.</i> ^[31]	Synthesis, degradation and biocompatibility of tyrosine-derived polycarbonate scaffolds (<i>in vitro</i> study)	Poly (DTE carbonate) with PEG backbone molecules (composite)	Discs of the scaffold incubated in 10-mL PBS, mass loss, and mol wt loss were seen.	Poly (DTE carbonate) with PEG backbone molecules degrade faster than polycarbonate (DTE) scaffolds.
16	Mobini <i>et al.</i> ^[32]	Comparative evaluation of <i>in vivo</i> biocompatibility and biodegradability of regenerated silk scaffolds reinforced with/without natural silk fibers (<i>in vivo</i> study)	Regenerated 2%, 4% wt silk-based composite scaffolds with/without embedded natural degummed silk fibers (composite)	Subcutaneous implantation of scaffolds in nude mice. Histological findings; 14 and 28 days	Silk embedded fibers took more time for degradation and could be controlled as compared to non embedded scaffolds.
17	Gomes <i>et al.</i> ^[17]	Starch–poly(ϵ -caprolactone) and starch–poly(lactic acid) fiber-mesh scaffolds for bone tissue engineering applications: structure, mechanical properties and degradation behavior (<i>in vitro</i> study)	SPCL (starch with ϵ -polycaprolactone, 30:70%) SPLA [starch with poly(lactic acid), 30:70%] fiber-meshes (composite)	Enzymatic degradation, 2 weeks	With increasing degradation time, the diameter of the SPCL and SPLA fibers decreases significantly, increasing the porosity and consequently the available space for cells and tissue in-growth during implantation time.