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

Received: 20-04-20
Revised: 02-05-20
Accepted: 16-10-20
Published: 24-11-20

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.

INTRODUCTION

People and animals have a natural scaffold that surrounds cells and provides structural support for the formation of tissues and organs. 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. Scaffolds are designed to create a 3D environment that promotes tissue development of cells that are placed on or within the scaffold. 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.

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How to cite this article: Joshi SR, Pendyala GS, Shah P, Mopagar VP, Padmawar N, Padubidri M. Scaffolds—the ground for regeneration: A narrative review. J Int Soc Prevent Dent Dent 2020;10:692-9.
ELIGIBILITY CRITERIA
For deciding the inclusion criteria, the PICO5 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.

BIODEGRADABILITY 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 doped with Cu showed a faster rate of degradation than Mg-based bioceramics. The samples showed 95% mass loss. However, the scaffolds prepared with hexaflouroisopropanol (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.

**ACKNOWLEDGEMENT**

Not applicable.

**FINANCIAL SUPPORT AND SPONSORSHIP**

Nil.

**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: In vivo and in vitro studies that evaluated degradation profiles, factors relating to degradation, rates of biodegradability, studies published in English language, and animal studies |

Table 2: Search strategy

![Flowchart showing the search strategy with arrows for Articles from PubMed (x=75), Articles from other sources (y=25), After Exclusion of duplicates, foreign languages; (z=37), and Full Text Articles (n=17)]

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                                  |
|                  |                                           | Able to bind to growth factors.                                                 |
|                  | Silk                                      | Biocompatibility, nontoxicity, and diverse physical characteristics.             |
|                  |                                           | Use: Periodontal and maxillofacial therapies.                                   |
|                  | Hyaluronic acid                           | Low immunogenic potential                                                       |
|                  |                                           | Poor mechanical strength                                                        |
|                  |                                           | Rapid in vivo degradation                                                        |
|                  |                                           | Injectable gels                                                                 |
| Artificial       | Poly(ethylene glycol)                     | Nontoxic                                                                        |
|                  |                                           | Low immunogenicity                                                              |
|                  | PLLA                                      | Undergoes in vivo degradation                                                    |
|                  | PGA                                       | Used: Where structural strength is important                                    |
|                  | PLA                                       | Used: Cell transplantation                                                      |
|                  | PCL                                       | Similar to PGA but more hydrophobic.                                            |
|                  |                                           | 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 et al. [21] | Salient degradation features of a 50:50 PLA/PGA scaffold for tissue engineering (*in vitro* study) | PLA/PGA (poly lactic acid/poly glycolic acid) 50:50 ratio; (artificial) | Gel permeation chromatography. | Complete disintegration: 8 weeks |
| 2   | Fu et al. [22] | Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and *in vitro* degradation (*in vitro* 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. |
| 3   | Theodorou et al. [23] | Sol-gel derived Mg-based ceramic scaffolds doped with zinc or copper ions: preliminary results on their synthesis, characterization, and biocompatibility (*in vitro* study) | Magnesium-based bioceramics doped with copper or zinc ions (artificial) | Test performed according to the ISO 10993-14: 2009 | Cu-doped ceramics formed hydroxyapatite: 7 days. Zn-doped ceramics did not form hydroxyapatite even after 21 days. |
| 4   | Lam et al. [18] | Evaluation of polycaprolactone scaffold degradation for 6 months *in vitro* and *in vivo* | Poly capro lactone scaffold (artificial) | After 120 h in Tris buffer solution: ZnA_2: 5% CuA_2: 7% (degradation percentage) | Maximum degradation took place *in vivo* via the bulk degradation pathway |
| 5   | Hafeman et al. [24] | Injectable biodegradable polyurethane scaffolds with release of platelet-derived growth factor for tissue repair and regeneration (*in vivo* study) | Polyurethane scaffolds (artificial) | Scaffold degradation *in vitro* measured: 4 and 8 weeks: measuring weight loss | Degradation takes place in a controlled manner. |
| No. | Author/journal | Name and study type | Scaffolds considered | Test used/time taken for complete degeneration | Conclusion |
|-----|----------------|---------------------|----------------------|-----------------------------------------------|------------|
| 6   | Smidt et al.[25] | A noveau 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 et al.[26] | Biodegradation of three different collagen membranes in the rat calvarium: a comparative study (in vivo 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 et al.[27] | Biodegradation of a resorbable collagen membrane (Bio-Gides) applied in a double-layer technique in rats (in vivo 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 et al.[28] | A quantitative method for evaluating the degradation of biologic scaffold materials (in vitro study) | Extracellular matrix scaffold implanted in pigs (natural) | Injection of 14C into the pig specimens. Dissection of tissue and placement in 10-mL PBS. Radioactivity measured by LSC | Highest 14C content measured: 4 weeks. Complete disintegration: 4 weeks |
| 10  | Kawase et al.[29] | The heat-compression technique for the conversion of platelet-rich fibrin preparation to a barrier membrane with a reduced rate of biodegradation (in vitro study, in vivo 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 et al.[17] | Bioactivity and stability of endogenous fibrogenic factors in platelet-rich fibrin (in vitro study) | PRF (platelet-rich fibrin) (natural) | Complete disintegration: 24 h | Proteinases help in faster degradation |
| 12  | Wang et al.[28] | In vivo degradation of three-dimensional silk fibroin scaffolds (in vivo study) | Silk fibroin scaffolds (composite) | Complete degradation: 6–12 months | No cross-linking required for improving properties |
| 13  | Park et al.[18] | Relationships between degradability of silk scaffolds and osteogenesis (in vitro 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 et al.[30] | Optimization of degradation profile for new scaffold in cartilage repair (in vivo 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 |
| No. | Author/journal | Name and study type | Scaffolds considered | Test used/time taken for complete degeneration | Conclusion |
|-----|----------------|---------------------|----------------------|-----------------------------------------------|------------|
| 15  | Magno et al.[31] | Synthesis, degradation and biocompatibility of tyrosine-derived polycarbonate scaffolds (*in vitro* 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 et al.[32] | Comparative evaluation of *in vivo* biocompatibility and biodegradability of regenerated silk scaffolds reinforced with/without natural silk fibers (*in vivo* 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 et al.[17] | Starch–poly(ε-caprolactone) and starch–poly(lactic acid) fiber-mesh scaffolds for bone tissue engineering applications: structure, mechanical properties and degradation behavior (*in vitro* 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. |