

# Three dimensional printed scaffolds and biomaterials for periodontal regeneration-an insight

## Abstract

Periodontal applications of three dimensional(3D) printing included education models, scaffolds, socket preservation, and sinus and bone augmentation and guided implant placement. 3D scaffolds have been recently investigated in the field of dentistry and periodontics as a bone graft substitutes which could overcome the drawbacks of routinely employed grafting materials. In this review, we highlight different biomaterials suitable for 3D scaffold fabrication, with a focus on “3D-printed” ones as bone graft substitutes that might be convenient for various applications related to periodontal regeneration and implant therapy.

**Keywords:** three dimensional printing, scaffolds, alveolar bone, periodontal ligament, regeneration

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## Introduction

Three dimensional (3D) printing has promising application in various fields of dentistry such as periodontics, implantology, orthodontic, endodontic, prosthodontics, maxillofacial surgery, and restorative dentistry. In the field of periodontology and implant dentistry, 3D scaffolds in the form of bone graft substitutes overcomes the disadvantages of commonly used grafting materials. Scaffold properties are influenced by the used biomaterials and must be specific for the application while in harmony with the native environment to ensure that the defect area is replaced with a healthy, functional tissue matching the original one, without reparative scar formation. In this review, we focus on different biomaterials suitable for 3D scaffold fabrication, with a focus on “3D-printed” ones as bone graft substitutes that might be convenient for various applications related to periodontal regeneration and implant therapy. A review by Farah et al presented an excellent compilation of 3D printed scaffold and biomaterial.<sup>1</sup> In a recent literature review by Gul et al discussed about the applications of 3D printing in periodontology which includes use of 3D printed scaffold for socket preservation, periodontal regeneration, sinus and bone augmentation and maintenance of peri-

implant. Use of 3D printed surgical guide has increased the accuracy, reduced complications and working time. The only drawback of the 3D printing is its cost effectiveness and the time required for manufacturing.<sup>2</sup> There are limited literature on the 3d printed scaffolds on the medline search using keywords Three dimensional printing, scaffolds, alveolar bone, periodontal ligament and regeneration. Hence, in this review an attempt is made to brief the biomaterials used in regeneration of alveolar bone and periodontal ligament.

## 3d scaffold biomaterials for alveolar bone regeneration

The cellular affinity of a scaffold influences its overall properties<sup>3</sup> such as adhesion, proliferation and regeneration outcome. Intergrins are known to influence the adhesion. The first biomaterials are natural polymers such as proteins and polysaccharides which are utilized in the clinical applications. These biocompatible have the cell recognition and cellular interactions in the tissue environment<sup>4</sup> and hydrophilicity.<sup>5</sup> In the tissue engineering, the hydrophilicity property that is hydrogels are responsible for cell encapsulation leading to successful outcomes.<sup>6-10</sup> The scaffold materials can be made up of natural materials, synthetic materials, bioceramics and metals. The various natural materials used for scaffold are presented in Table 1.

**Table 1** Natural biomaterials utilized for scaffolds

| Natural material | Properties  |
|------------------|---|
| Collagen         | <p>Most commonly expressed protein. Structural strength and stability is provided to several tissues such as bone and skin.</p> <p>In vitro cell adhesion, proliferation and osteogenic differentiation of bone marrow stromal cells are demonstrated.<sup>39</sup></p> <p>Gelatin is the denatured collagen which facilitates osteoblastic migration, adhesion and mineralization due to presence of many biological and functional molecules present in it.<sup>40</sup></p> <p>In Bone Tissue Engineering (BTE) application, collagen which is the major component of ECM serves as an important biomaterial.</p> <p>Collagen is preferred to be used in combination with bioceramic which has close resemblance to ECM of bone specially in non-bearing areas.<sup>41</sup></p> |
| Chitosan         | <p>A polysaccharide is a popular biomaterial with antibacterial, antifungal activities, analgesic properties and rapid formation of clot property, rendering chitosan as a wound healing accumulation biomaterial.<sup>42</sup> This property of Chitosan minimizes contamination of scaffold thus preventing postoperative infections, exposure and failure of scaffold.</p>   |
| Alginate         | <p>The use of alginate is common because it can be highly processed into different types of scaffold and cell encapsulation property<sup>43</sup> helping in regenerative medicine for BTE.<sup>44</sup></p> <p>Both Chitosan and alginate are not present in the human body but have structural similarities to glycosaminoglycans in the ECM of human bone<sup>45</sup> which makes them impressive candidates in BTE.</p>  |

## Disadvantages of natural polymers

Even though there is good biologic characters, the bioactivity is not present in these natural polymers which is required for hard tissue formation.<sup>11</sup> Additional drawbacks are, weak mechanical property and fast degradation time<sup>12-14</sup> through enzymatic reaction.<sup>15</sup>

The undesirable or disadvantages of natural polymer are overcome by use of bioceramics or synthetic polymers or metals which are mechanically strong ones depending on the area of scaffold application

such as non-load bearing or load bearing. Although mechanically weak, bioceramics increase the compressive strength of natural polymer scaffolds.<sup>16</sup> The low cost and possibility of its production in large quantities with longer shelf life than natural polymers are the main advantages of synthetic scaffold biomaterial.<sup>17</sup> Various aliphatic polyesters used are Polycaprolactone(PCL), Polylactic acid(PLA), Polyglycolic acid(PGA) ,Poly lactic co-glycolic acid( PLGA) which are described in Table 2.

**Table 2** Biodegradable polymers and its features as scaffold material

| Synthetic scaffold materials  | Properties  |
|---|---|
| Polycaprolactone (PCL)  | It is the most popular material used in medical devices over 30 years <sup>46</sup> which is used in craniofacial repair. <sup>47</sup><br><br>It is biocompatible, suitable to fabricate various scaffold technique, slow degradation rate and mechanically stable. The maintenance of regenerated bone volume and its outcome is possible owing to slow degradation rate and mechanical stability. <sup>48</sup><br><br>The hydrophobic nature of PCL <sup>49</sup> is responsible for the poor cell affinity and inferior cellular responses and surface interactions. <sup>50</sup> |
| Polylactic acid (PLA), Polyglycolic acid (PGA) ,Poly (lactic-co-glycolic) acid( PLGA) | These are hydrophobic except the PGA which is hydrophilic .These have higher degradation rates as compared to PCL. <sup>51</sup>  |

## Degradation of synthetic aliphatic polymers

Generally they exhibit slow degradation as compared to natural polymers and bio ceramics.<sup>18</sup> They degrade by hydrolysis either as bulk degradation or erosion of surface. Most often, the interior aspect of biomaterial degrade and leaves an empty shell formation by maintaining the size for a significant time period.<sup>19</sup> This characteristic feature is suitable when used for BTE than drug delivery treatment.

Acidic products released during its degradation cause necrosis of tissue and later scaffold exposure.<sup>20</sup> The acidic byproducts can

be counteracted and pH buffering can be achieved by combining polyesters with bioceramics<sup>21</sup> and metals.<sup>22</sup> Good moldability of polyesters into any shape and mechanical properties are best suitable despite their acid by products and lack of bioavailability.

## Bioceramics

These are inorganic materials namely calcium phosphate bioceramics and bioactive glass that are used as bone fillers in dentistry<sup>23</sup> as described in Table 3.

**Table 3** Bioceramics and its characteristic features

| Material                                      | Properties   |
|---|--|
| Calcium phosphate bioceramic                  | It consists of hydroxyapatite (HAP), tricalciumphosphate( $\alpha$ -TCP and $\beta$ -TCP ) and biphasic calcium phosphate (BCP) in the injectable form of cement material (pastes) which are easily moldable ,easy to handle and harden when left in place. There is an intimate adaptation of moldable calcium phosphate materials to complex defects which is not possible with conventional bone grafts. <sup>52</sup>  |
| Hydroxyapatite (HAP)                          | It is the popular material used in BTE because it shows the same chemical composition of native bone minerals , which influences adhesion and osteoblast proliferation positively. <sup>53</sup> The main disadvantage is its prolonged degradation in the crystalline form which impedes the complete bone formation and thus increasing the risk for infection and exposure in oral surgical situations. <sup>54</sup> This disadvantage of crystalline HAP form is overcome by amorphous hydroxyapatite. <sup>55</sup> The crystalline HAP degradation can be modified by addition of the natural polymers with faster kinetics. <sup>56</sup>  |
| $\beta$ -tricalcium phosphate ( $\beta$ -TCP) | The second commonly used is $\beta$ -TCP due to its faster rate of degradation and ability to form a strong calcium phosphate band in bone. Biphasic calcium phosphate (BCP) is formed by combining $\beta$ -TCP with HAP <sup>57</sup> The controlled bioactive and stability. Significant advantages when large bone defects require bone in growth <sup>47</sup> in a controllable degradation rate <sup>58</sup> as BCP is known to have higher rate of degradation than HAP and slower than the $\beta$ -TCP. <sup>59</sup>   |
| Bioactive glass                               | It is a silicon oxide with calcium being substituted. A calcium phosphate layer is formed on the bioactive glass surface after getting exposed to body fluids and this gets chemically bound to bone. <sup>60</sup> The synthetic bioglass and specifically in intra oral application bioglass. <sup>61</sup> It has a slow degradation rate as it sets to a converted HAP like material in internal physiologic situation. <sup>62,63</sup> The mechanism of bioceramic degradation are multiple ways: Dissolution physiochemically accompanied by possible phase transformation, multinucleated cell-mediated degradation and mechanical fragmentation due to structural integrity loss by the above two mechanisms. <sup>64</sup> |

## Mechanism of action of bioceramics

Various biologic activities that is gaining attention in bone reconstruction are due to bioactivity, biocompatibility, hydrophilicity similar to native inorganic bone composition and its unlimited availability.<sup>24</sup>

It has osteoconductive and potential osteoinductive property that is the potential to induce bone formation ectopically by stimulation of the immediate in vivo environment.<sup>25</sup> The osteoinductive activity is attributed either to the bioceramics surface which absorbs osteoconductive exhibiting factor or stimulating the differentiation of osteoprogenitor cell into osteoblasts by gradual release of calcium and phosphate ions into the surrounding environment.<sup>26</sup> The incorporation of calcium phosphate in 3D scaffolds for regeneration of alveolar bone already exists in literature.<sup>27</sup>

## Disadvantages of bioceramics

The required structure is difficult to shape due to extreme brittleness, stiffness, low flexibility and molding property.<sup>28</sup> The mechanical strength is weak,<sup>29</sup> fracture toughness<sup>30</sup> which restricts its usage in non loading ones. The above disadvantages are overcome by addition of synthetic polyesters or metals.<sup>31,32</sup>

## Metals

In the field of dentistry and orthopaedics, the bone replacement is extensively treated by using metallic biomaterials, due to its mechanical properties.<sup>33,34</sup> They are suitable for load bearing areas due to its high strength, toughness and hardness in comparison to polymers and ceramics. The size of scaffold is enhanced by metals to improve the mechanical properties. Various metals used as biomaterials are described in Table 4.

**Table 4** Various metals used as biomaterials

| Metal- biomaterial            | Properties   |
|-------------------------------|--|
| Titanium alloy                | These are used commonly on the basis of good biocompatibility, mechanical properties and elasticity. <sup>65</sup> The major disadvantage is its nondegradability which requires to be removed. This could affect patient satisfaction and enhance the cost of health care. <sup>66</sup>  |
| Magnesium and its alloy       | These have good potential in BTE special orthopaedic application. Their biodegradability by corrosion and the biocompatibility of its degraded products which doesn't involve adverse reactions in surrounding tissues. There is no need for its retrieval through second surgery making it a popular material for scaffold construction. <sup>64,67</sup> These are osteoconductive so as to increase expression of osteogenic marker invitro. <sup>68</sup> The faster in vivo biodegradability of pure magnesium can be controlled by use of magnesium alloy or coated with titanium <sup>69</sup> or ceramics. <sup>70</sup> There is no bioactivity by this metal, magnesium.   |
| Composite or hybrid scaffolds | To incorporate the advantage and restriction of limitation of various biomaterial, two or more materials are combined to produce synergistic effect in the overall combined properties <sup>71</sup> so as to enhance the biological mechanical and scaffold degradation kinetics. <sup>72</sup> The synergistic property can also simulate the complex target bone tissue characteristics which is otherwise not possible with single biomaterial. The term ternary can be used when three biomaterial are used.<br><br>Composite scaffolds for BTE can be divided in to polymer/ceramic, ceramic/metal and polymer/ metal. The polymer/ceramic is the most commonly used in recent five years in orthopaedic field. Various composite scaffold maintain the shape of newly formed bone and favour osteoblast attachment, proliferation and its differentiation. <sup>73</sup> The composite scaffold comprise of matrix which is less than 50% of the total content and a filler which is minor component ( less than 50% of the content). <sup>74</sup> |

## Periodontal regeneration using scaffold

For the GTR applications, a dual role is served by scaffold that is a membrane and a grafting material. To serve as membrane a mechanically strong scaffold should be used. PCL is not used as a scaffold because of its slow degradation which can lead to wound dehiscence and failure of tissue regeneration. Magnesium/ PLGA can be applied in socket preservation. Chitosan, natural polymer is the best choice as GTR which has antibacterial properties. Gelatin can also serve the purpose but has decreased mechanical weakness.

In case of alveolar bone regeneration, augmentation and socket preservation, scaffolds made of bioceramics are used. In load bearing areas, collagen should be preferred. Collagen along with hydroxyapatite helps in bone tissue regeneration due to the compositional similarities and reasonable degradation rate. The effect of 3D scaffolds in blood clot stabilization should be looked at as a factor in alveolar bone regeneration. Scaffold stabilization is also an important and compromised regeneration outcome.

In periodontics, 3D printed scaffolds studies have concentrated on biomatrix, functional formation and spatial organization when multiple tissues for regeneration is attempted. However, the related issues that needs to be thoroughly addressed are vascularization, landscape to geographic analysis, degradation profile to kinetics.<sup>35</sup> In periodontal regeneration, use of 3D scaffold requires critical evaluation of

biologic and mechanical properties as well the degradation kinetics. The blood clot stabilization effect by the 3D scaffold requires to be assessed which serves as an important prognostic factor in bone regeneration.<sup>36</sup> Along with bone regeneration technique for soft tissue management plays an important role in regenerative outcome.<sup>37</sup> The scaffold fabrication technique needs further investigation to develop required scaffolds to suit the type of tissue regeneration. The scaffold stabilization without micro movement is an important issue to prevent compromised regenerative results/outcomes. To overcome the compromise integrity of scaffold in large defects caused by screws and pins could be further investigated with fibrin glue or press fit graft.

Currently, multi-layered 3D scaffold are being experimented in periodontal regeneration using non dental (bone marrow) stem cells along with platelet rich plasma (PRP). In such situations, the role played by non dental stem cells and PRP in periodontal regeneration cannot be discriminated. Instead, use of autologous PDLSCs along with its niche, a natural scaffold is being tried in human rat and has proved to be successful in both clinical and radiographic measurements in SAIPRT procedure.<sup>38</sup> The use of this technique to be incorporated into 3D scaffolds could serve a constructive avenue in 3D scaffold related stem cell approach in periodontics. There is a scarcity of clinical trials literature on 3D scaffolds in bone regeneration/periodontal regeneration. Those published animal studies are not a representation or validated due to the small defect areas and graft size which hinders the extrapolation of the animal study results to human studies.

## Conclusion

3D printing has revolutionized the field of periodontology. A scaffold should be biocompatible, biodegradable, and bioactive and should be made of a hybrid of biomaterials, as the combination of different biomaterials is superior to a pure material. 3D-printed scaffolds show predictable outcome for bone and tissue regeneration as well as sinus and bone augmentation.

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## Conflicts of interest

The author declares there are no conflicts of interest.

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