

# A Systematic Review on Polyester Scaffolds in Dental Three-dimensional Cell Printing: Transferring Art from the Laboratories to the Clinics

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## ABSTRACT

**Objective:** The purpose of this systematic review is to describe developments in three-dimensional (3D) cell printing in the formation of dental pulp tissue using polyester as a scaffold to revitalize the damaged dental pulp tissue.

**Materials and methods:** A literature search for all the data published in PubMed and Google Scholar from January 2000 to April 2022 was conducted. Articles with the keywords 3D cell printing, scaffolds, polyester, dental pulp, and dentistry were used. Inclusion criteria consisted of any publication in electronic or print media directly studying or commenting on the use of polyester scaffolds in 3D cell printing technology in the regeneration of dental pulp. A total of 528 articles were selected, of which 27 duplicates and 286 irrelevant articles were discarded. A total of 215 articles were finally included in the systematic review.

**Result and conclusion:** For dental pulp regeneration, several scaffolds have been discovered to be appealing. Polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers are nontoxic and biocompatible synthetic polyesters that degrade by hydrolysis and have received Food and Drug Administration (FDA) approval for a variety of applications. This review paper is intended to spark new ideas for using a certain scaffold in a specific regenerative approach to produce the desired pulp-dentin complex.

**Keywords:** Dental pulp, Dentistry, Polyester, Scaffolds, Three-dimensional cell printing.

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## INTRODUCTION

Modern manufacturing techniques, known as 3D printing, use digital models created by computer-aided design to automatically create unique 3D things. For approximately 30 years, they have been extensively utilized in the manufacturing, engineering, design, and industrial sectors. Several dental specialties can benefit from the use of 3D printing. It is beneficial to be able to precisely place cells such as odontoblasts on the periphery of the scaffold *via* 3D printing.<sup>1</sup> Due to the tremendous potential of this 3D cell printing technology in dentistry, we decided to conduct a systematic review of the synthetic polyester scaffold materials used currently. Hence the review was undertaken from the year 2000 till date to analyze the trends being followed in synthetic scaffold materials, primarily emphasizing polyester materials.<sup>1</sup>

## HISTORY

In 1986, Charles unveiled the first 3D printing technology.<sup>2</sup> Hull built and developed a 3D printing technique and obtained a patent for stereolithography in 1986. A lot has changed with 3D printing since then.<sup>2</sup>

Additive manufacturing is a cutting-edge manufacturing method. Digital computer-aided design models are used to build it, which are utilized to create customized 3D objects using prepackaged components and automated processes.<sup>3</sup>

Professionals from different fields work in the multidisciplinary field of tissue engineering. The field primarily uses porous 3D scaffolds to create the perfect environment for tissue and organ regeneration. These scaffolds are frequently seeded with cells and occasional growth factors. These cell-seeded scaffolds can either be transplanted directly into the injured location, or they

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can be grown *in vitro* to yield tissues that can be implanted into an injured site.

## WHAT IS 3D CELL PRINTING?

Three-dimensional (3D) printing, often referred to as additive production or solid freeform manufacture, has become more and more popular in recent years.<sup>4</sup> A unique 3D object can be produced using 3D printing technology using a variety of materials and computer-aided design. The ability to incorporate living cells into the process has raised 3D printing to new levels in the medical field and created a plethora of new opportunities for tissue creation.<sup>5</sup> The new possibilities are opening the road for patient-specific therapy. There are many reasons why 3D printing is becoming more popular. The development of a range of printed biomaterials has made it feasible to have more precise control over the scaffold's internal architecture and external

shape. Digital analytical tools are available for the rapid and accurate capture and 3D documenting of the patient's unique conditions. The expiration of important 3D printing patents has significantly reduced printer costs. These technologies are rapidly evolving, bringing new and interesting methods to all medical sectors, including dentistry. The cost decrease and size reduction of the end product are not without certain drawbacks, though. This technology has increased novelties in a variety of sectors, including engineering, dentistry, orthopedics, cardiology, and others.<sup>6</sup>

## SCAFFOLDS

The term "scaffold" has been used in scientific literature to describe a biomaterial that can give support. During the course of the healing process, a "support" is a biomaterial that serves as a biological platform for the proper repair and restoration of the physiological and histological features of damaged tissues.<sup>7,8</sup> An appropriate scaffold must be used in tissues, which are 3D structures, to promote cell formation and differentiation. Extracellular matrix (ECM) molecules are known to influence the formation of stem cells, and a suitable scaffold may be able to detect and bind cells with specificity, contain growth hormones, and disintegrate over time.<sup>9</sup> The current breakthroughs in tissue engineering scaffolds are largely the result of advances in material science. When increasingly versatile and sophisticated biomaterials are created, scaffolds undergo a change from biocompatible cell transporters and straightforward delivery vehicles to biofunctional and directing matrices. Moreover, technological developments have made it possible to regulate and modify every aspect of material behavior for use.<sup>10,11</sup> As a result, the work on using pulp-derived stem cells to regenerate the pulp-dentin complex has continuously advanced.

The requirement is that scaffolds have interconnected porosity, biocompatibility, the capacity to promote the differentiation of committed cells, and conductivity for attachment. Biodegradability is one of the challenges in the development of new treatments for tissue regeneration. The first condition for every scaffold designed for tissue engineering purposes is that it must pass all biocompatibility tests. Cells must adhere to the scaffold, expand through it, and proliferate before a new matrix can form. The body's immune system should have no reaction to the biomaterials that have been implanted. The architecture of prepared scaffolds for engineering diverse tissues is one of the most important properties. Scaffolds with a large number of interconnected porosities allow for cellular penetration as well as the diffusion of oxygen and nutrients. Conductive properties of scaffolds allow tissue-forming cells and additional inductive elements to migrate across and into scaffolding to generate new tissue. Tissue engineering is based on the use of a biodegradable scaffold that is eventually replaced with new tissue. Implanted scaffolds, in this view, should serve as a temporary structure that declines at a rate that is in sync with tissue growth. The ideal scaffold must be biodegradable to enable cells to build their own ECM. Byproducts of the breakdown of the scaffold should not be poisonous and should leave the body without endangering nearby tissues.

### Types of Scaffolds

To provide cells with a carrier surface on which to attach, proliferate, and spatially organize themselves, scaffolds are frequently utilized. Making a microenvironment that closely resembles the interactions

between cells in the pulp-dentin complex, including cell-ECM, cell-cell, and cell-soluble factor interactions, is the goal of choosing a biomaterial for a scaffold. It is, therefore, essential to address the various types of scaffolds utilized in pulp regeneration.

There are two types of scaffolds—naturally derived and synthetic scaffolds. Naturally derived materials are chitosan, alginate, fibronectin, collagen, and hyaluronic acid. Natural scaffolds produce a more accurate representation of the ECM, which regulates cell proliferation and improves cell attachment.<sup>12</sup>

Although natural materials are useful to biological processes, synthetic polymers such as polylactic-polyglycolic acid (PLGA) and poly (ε-caprolactone) (PCL), PLGA has superior processability, mechanical strengths, and predictable rates of degradation for scaffolding.<sup>13</sup> Inorganic sources are used to make synthetic polymers in the industrial sector. They are divided into two categories—nonabsorbable and absorbable polymers. Among synthetic polymers, resorbable polyesters are the most common. PLA, polylactic-polyglycolic acid (PLGA), PGA, polyethylene glycol (PEG), PCL, and PEG-PLGA are among them (PCL).<sup>14</sup>

Synthetic polymers with outstanding biomaterial properties include PLA and PGA.<sup>15</sup> They can be produced indefinitely and are eliminated from the body chemically rather than through cell-mediated processes.

### Naturally Derived Scaffolds

Natural materials can be used to create scaffolds; for example, the ability of various ECM derivatives to assist cell growth has been tested. Protein-based biomaterials (such as gelatin, collagen, and silk), polysaccharide-based biomaterials (such as chitin/chitosan, cellulose, and glucose), and decellularized tissue-derived biomaterials (blood vessels, decellularized heart valves, and liver) are only a few examples of naturally derived biomaterials.<sup>16</sup>

One of the glycosaminoglycans that might be employed as a scaffold material is hyaluronic acid, perhaps in conjunction with cross-linking agents. In order to enhance cell adhesion, a nonbioactive molecule can be linked to a piece of an ECM protein, such as the arginine-glycine-aspartic acid (RGD) peptide.<sup>17</sup> Although they are biocompatible, biodegradable, and structurally sound, they can be challenging to digest and run the risk of dispersing germs or igniting an immune response.<sup>18</sup> Collagen has piqued interest and has been used in a variety of tissue engineering applications, including tooth and bone regeneration. However, it has low mechanical strength and degrades quickly.<sup>19</sup>

### Limitations of Natural Scaffolds

Collagens, glycosaminoglycans, starch, chitosan, and chitin are natural polymers that have been used to heal skin, cartilage, nerves, and bone.<sup>20</sup> While naturally occurring biomaterials are the closest to the native cellular milieu, their general applicability is limited by considerable batch-to-batch differences when isolated from biological tissues.

Poor mechanical performance is also a disadvantage for transplanting scaffolds consisting of natural polymers such as collagen and chitin, which are difficult to melt with heat and require a specific solvent. Natural polymers are generally challenging to control and run the risk of activating the immune system and spreading diseases.

Obtainable from red algae, alginate is a polymer that can be cross-linked *via* Ca<sup>2+</sup> to create a mild gelation process. However, it is difficult to keep track of its decomposition, and calcium-chelating chemicals can readily cause it to dissolve.<sup>21</sup>

## Synthetic Scaffolds

Synthetic polymers such as PLA, PGA, poly-L-lactic acid (PLLA), PCL, and PLGA have been used as scaffolds for pulp regeneration.<sup>22</sup> The synthetic polymers are biodegradable and nontoxic, and they enable exact control of physicochemical features such as degradation rate, mechanical stiffness, porosity, and microstructure.<sup>23,24</sup> PLLA is an extremely strong polymer that has a wide range of applications requiring structural strength.<sup>25</sup> PGA is less hydrophobic than PLA, an aliphatic polyester. After 3–4 months, PLGA was used as a scaffold to demonstrate the formation of dentin-like tissue and the regeneration of pulp-like tissue.<sup>26</sup> In a 50:50 mixture, PLGA takes around 8 weeks to degrade.<sup>27</sup> Bone tissue engineering has used PCL, a slow-degrading polymer, either alone or in conjunction with hydroxyapatite.<sup>28</sup>

## Poly(lactic acid) Scaffold (PLA)

Undifferentiated dental pulp cells and ex vivo cells can bind to one another, thanks to biodegradable polyester PLA.<sup>29</sup> To investigate the growth of adult human dental pulp tissue, three different kinds of tissue engineering scaffolds were used by Chandrasha et al.—(1) open-PLA scaffolds, (2) calcium phosphate (CaP) bioceramic scaffolds, and (3) scaffolds made of bovine collagen. It has a number of attractive characteristics, including biocompatibility, biodegradability, a minimal inflammatory response, low cost, and repeatability. Additionally, successful angiogenesis and cell proliferation have been demonstrated by the interdependent pore structure of the nanofibrous PLA scaffolds.<sup>30,31</sup> PLA scaffolds are ideal options for pulp tissue engineering because of their excellent mechanical qualities and regulated breakdown rate.<sup>32</sup> When stem cells from human exfoliated deciduous teeth or human dermal microvascular endothelial cells were injected into immunodeficient mice, the PLA scaffold was able to produce tissue that was equivalent in architecture and cellularity to the dental pulp tissue.

## Polycaprolactone (PCL) Scaffold

The FDA has authorized PCL, a substantial polymer, due to its favorable mechanical properties, biocompatibility, miscibility with a variety of other polymers, and biodegradability (Labet & Thielemans, 2009). PGA and PLLA are other members of the family of biodegradable polyesters, which also include PCL. It is an aliphatic semicrystalline polymer with an abovebody temperature melting range of 59–64°C and a glass transition temperature of 60°C. Due to its great toughness and outstanding mechanical properties, the semicrystalline PCL develops a rubbery condition at physiological temperatures.<sup>33</sup> It is tissue friendly and nontoxic, making it a popular choice for resorbable sutures, regenerative treatment scaffolds, and drug delivery applications. In physiological conditions, PCL is hydrolyzed by bacteria or loses its aliphatic ester bond, which has the greatest degradation time (2–3 years).<sup>34</sup>

Poly (ε-caprolactone) (PCL) is a synthetic polymer that is less well-known than other aliphatic polyesters. It has good mechanical properties and has a lengthy resorption period (up to 3 years), and it dissolves *via* ester bond hydrolysis.

## Poly(lactic acid)–Poly(glycolic acid) Scaffold (PLGA)

Polyglycolic (PGA) is a synthetic polymer with good biomaterial properties that is reliant on the capacity to manage its synthesis, which affects the final surface properties.<sup>16</sup> Its production is uncontrolled in amount, and chemical processes rather than cell-mediated ones are used to remove it in the body.<sup>35</sup> The PGA

polymers are broken down into their monomers (glycolic acid), which are then removed through several metabolic pathways. Another drawback is that it degrades quickly, which increases the likelihood that the graft will fail too soon. In addition, intracellular acid breakdown might trigger an inflammatory response.<sup>16</sup> Hybrid scaffolds combining PGA and PLA with bioactive glasses and CaP have been developed to alleviate inflammation.<sup>36</sup> These polymers also have a number of drawbacks, including low mechanical strength, production challenges, and an unknown interaction with cells. PLA degrades at a faster rate than PGA. Both, however, disintegrate too quickly to allow for bone repair. Because of this, they are never used alone but rather in the form of PLGA 12:13.<sup>37</sup>

The ester bonding of glycolic and lactic acids results in the copolymer known as PLGA. Once the composite polymer is applied *in situ*, the final polymer chain composition will affect the degradation time and lengthen the composite polymer's half-life in the oral cavity.<sup>38</sup>

In order to achieve successful results, this polymeric bone substitute has been combined with growth factors and mesenchymal stem cells and is being used extensively in dentistry for bone regeneration. Moreover, it can be produced in many other forms, such as hydrogels, microspheres, blocks, and fibers.<sup>16</sup>

## Poly(ethylene glycol) (PEG)

The United States of America FDA has approved the use of PEG, in particular therapeutic uses. Also, the field of tissue engineering has shown a lot of interest in it. High hydrophilicity, low toxicity, nonimmunogenicity, and antifouling properties are all characteristics of PEG.<sup>39</sup>

Poly(ethylene glycol) (PEG) is easy to cross-link *via* chemical, physical, or ionic cross-linking techniques because of its high hydrophilicity. Comparing a chemically cross-linked PEG hydrogel to one that is physically and ionically cross-linked, one can see that the latter has a more stable structure and greater mechanical strength. PEG's "stealth characteristic," or antifouling property, has been used to prevent molecules and microorganisms from adhering to the PEG surface. However, because of this property, cell adhesion to the PEG hydrogel is prevented from occurring. Bioactive patterns have been included in the PEG molecule to boost its cellular attraction in order to solve this problem. One such pattern is the RGD peptide.<sup>40,41</sup> The inert bioactivity of the PEG framework can be improved by copolymerizing it with natural polymers such as hyaluronic acid or collagen.<sup>42</sup> One drawback of PEG as an injectable hydrogel is that it is not biodegradable.

## SCAFFOLD IMPLANTATION

For numerous decades, it has been recognized that tooth pulp has regenerative properties. Odontoblasts become more active in response to stimuli like tissue damage or bacterial toxins, and these cells create reparative dentin as an active defense mechanism to keep the soft tissue away from the injury site. The use of drugs such as calcium hydroxide or mineral trioxide aggregate, which disinfect because of a high pH, cause necrosis in the adjacent cell layer, stimulate defense mechanisms, and cause reparative dentin formation, makes regeneration possible even when pulp tissue is exposed in deep cavities, and the odontoblast layer is disrupted.<sup>43</sup> The power of pulp to regenerate, on the other hand, is restricted until we can develop ways to better leverage its inherent healing potential. Nonregenerative endodontic therapy can keep a tooth functional if regeneration fails and inflammation persists, but it



also delays dentin growth and root maturation, making the tooth fragile and vulnerable. The development of dental pulp engineering techniques has started in several groups. Synthetic polymers such as PLA and PGA,<sup>44</sup> as well as matrices generated from biological sources such as reconstituted collagen, are the most often utilized materials in tissue engineering.<sup>45</sup>

In conclusion, among the materials tested for this application, collagen I and synthetic polymers produced the best outcomes. Regarding biocompatibility and degradation, all of the aforementioned materials perform admirably. FDA-approved for a number of applications, PLA, PGA, and their copolymers are synthetic polyesters that degrade by hydrolysis and are harmless and biocompatible.<sup>46</sup> Whereas natural polymers are risky to handle, alter, and pose the risk of spreading animal-associated illnesses or triggering an immunological response, collagen is biocompatible and enzyme degradable. A gentle form of cell encapsulation can be achieved by cross-linking the red algae-derived polymer alginate with calcium ion (Ca<sup>2+</sup>). Unfortunately, the substance dissolves uncontrollably as it degrades because it is sensitive to compounds that chelate calcium. Chitosan is made from the carbohydrate chitin, which is found in crustaceans. Due to its biocompatibility and capacity to breakdown utilizing naturally occurring enzymes, it has been utilized in a range of tissue engineering applications.<sup>47</sup>

## SUMMARY

For dental pulp regeneration, several scaffolds have been discovered to be appealing. Complex inductive matrices with specific material behavior have emerged from conventional inert scaffolds that just act as passive cell carriers. Each scaffold type has its own set of characteristics that may favor one regenerative method over another. PCL polyester can be used without suffering a major loss of characteristics by changing its biological and chemical properties, physiochemical state, mechanical strength, and degradability. It is easily accessible, cheaply priced, and can be altered in this way. Due to its prolonged decomposition period, it is frequently used to replace hard tissues, load-bearing tissues by boosting stiffness, and soft tissues by reducing molecular weight and degradation time. Understanding their characteristics and how they might be used in clinical dental pulp regeneration treatments is still a work in progress. This review paper is intended to spark new ideas for using a certain scaffold in a specific regenerative approach to produce the desired pulp–dentin complex.

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