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Research review paper

Powder-based 3D printing for bone tissue engineering

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Bone tissue engineered 3-D constructs customized to patient-specific needs are emerging as attractive biomimetic scaffolds to enhance bone cell and tissue growth and differentiation.
The article outlines the features of the most common additive manufacturing technologies (3D printing, stereolithography, fused deposition modeling, and selective laser sintering) used to fabricate bone tissue engineering scaffolds. It concentrates, in particular, on the current state of knowledge concerning powder-based 3D printing, including a description of the properties of powders and binder solutions, the critical phases of scaffold manufacturing, and its applications in bone tissue engineering. Clinical aspects and future applications are also discussed.

Contents

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1. Introduction

Reconstruction of complex bone defects continues to pose a considerable challenge in patients with inadequate vertical and horizontal bone dimensions requiring alveolar bone augmentation to enable dental implant placement (Tonetti and Hämmerle, 2008; Chiapasco and Zaniboni, 2009). While autogenous bone grafts harvested from intra- or extra-oral sites are still generally considered the gold standard for bone repair, their use is limited in clinical practice given high donor site morbidity and graft resorption rates and circumscribed bone availability (Felice et al., 2009a, 2009b; Araújo et al., 2002; Chiapasco et al., 2007).

Some natural and synthetic biocompatible bone substitutes have been developed to promote bone regeneration as alternatives to autogenous bone grafts (Esposito et al., 2009).

Bone tissue engineering has, moreover, emerged as a promising approach to bone repair and reconstruction (Rezwan et al., 2006, Gardin et al., 2015; Fiocco et al., 2015; Bressan et al., 2013, 2014; Sivolella et al., 2012; Gardin et al., 2012; Kumar et al., 2016a).

Scaffolds play a crucial role in bone tissue engineering. Scaffolds are biocompatible structures of natural or synthetic origin, which can mimic the extracellular matrix of native bone and provide a tridimensional (3D) environment in which cells become attached and proliferate. An ideal scaffold should be biocompatible, biodegradable and have adequate physical and mechanical properties. Interconnected porosity of the scaffold allows cell spreading and effective transport of nutrients, oxygen, waste, as well as growth factors, favouring continuous ingrowth of bone tissue from the periphery into the inner part of the scaffold. Finally, a scaffold should be replaced by regenerative tissue, while retaining the shape and form of the final tissue structure (Zavan et al., 2011; Ferroni et al., 2015; Bose et al., 2013).

Although bone regeneration procedures have taken great strides in recent decades (Esposito et al., 2009), one of the primary challenges that remains is optimizing predictable patient-specific treatment strategies.

Bone blocks must fit into anatomical bone defects. Usually cut and shaped manually at the time of surgery to fit the bone defect and to guarantee the graft's mechanical stability, the process of creating bone blocks is a long and complex one (Markiewicz and Bell, 2011; Smith et al., 2007; Oka et al., 2010). Anatomically shaped bone blocks can be fabricated using computer-aided design and computer aided manufacturing (CAD/CAM) technology that mills scaffolds into the exact shape of the bone reconstruction (Oka et al., 2010; Mangano et al., 2014). The porous architecture of the scaffold is thought to mimic cancellous bone structures thus providing an optimal environment for stem cell spreading and differentiation (Gardin et al., 2012; Bressan et al., 2013).

Additive manufacturing (AM), which refers to various processes including three-dimensional printing (3DP), is a fabrication method using 3D multi-layered constructs to build porous biocompatible scaffolds of pre-defined shapes with excellent mechanical and osteoconductive properties (Vaezi et al., 2013). AM technologies, also known as Rapid Prototyping (RP) or Solid Free-form Fabrication (SFF) techniques, have been receiving considerable attention in view of the fact that customized patient-specific 3D bone substitutes can be manufactured for bone tissue regeneration procedures. The combined use of 3D image analysis and computed tomography (CT) techniques can provide components that precisely match patients' bone defects (Lee et al., 2013; Yao et al., 2015; Temple et al., 2014; Xu et al., 2014).

A variety of AM techniques including 3DP, stereolithography (SLA), fused deposition modeling (FDM), and selective laser sintering (SLS) have been developed for tissue engineering applications (Lee et al., 2010; Butscher et al., 2011; Bose et al., 2013; Kumar et al., 2016b).

Powder-based 3D printing is considered a particularly promising bone reconstruction technique as the external shape, internal structure, porosity, and material properties of 3D printed bone substitutes can be varied and thus prepared for specific applications. Synthetic bone substitutes, in particular calcium phosphate (CaP) powder, which can be used to generate 3D printed bone scaffolds (Butscher et al., 2013; Castilho et al., 2014a), are considered particularly interesting solutions for bone tissue repair (Habibovic et al., 2008; Tamimi et al., 2008).

A recent promising approach consists in combining growth factors (GFs) or drugs with osteoconductive scaffolds. This strategy promotes a faster and more significant enhancement of new bone formation thanks to GF or drug delivery and because of the tridimensional stability of the scaffold, which provides protection during the gradual replacement of the graft with newly-formed bone. Various materials have been used to this aim, including inorganic bovine bone, porous hydroxyapatite, and demineralized human bone matrix (Sivolella et al., 2013). Calcium phosphates 3D printed scaffolds have also been used for growth factor and drug delivery (Bose et al., 2013).

This article intends to outline the main features of the most common AM technologies (3D printing, stereolithography, fused deposition modeling, and selective laser sintering) used to fabricate porous scaffolds for bone tissue engineering; it will go on to give a brief overview of 3D printing technology, including a description of the properties of powders and binder solutions, the critical phases of scaffold manufacturing, and its applications in tissue engineering. It also addresses current limitations of a technology which should ideally be site-specific. Clinical aspects and future applications of powder-based 3D printed constructs in bone tissue engineering are also discussed.

2. Material and methods

A Medline (PubMed) search was performed in duplicate for studies regarding the application of powder-based three-dimensional printing (3DP) for the production of bone tissue engineering scaffolds. The Medical Subject Heading (Mesh) term "three-dimensional printing" was used together with the term "bone" applying the following search strategy: (("printing, three-dimensional"[MeSH Terms] OR ("printing"[All Fields] AND "three-dimensional"[All Fields]) OR "three-dimensional printing"[All Fields] OR ("three"[All Fields] AND "dimensional"[All Fields] AND "printing"[All Fields]) OR "three dimensional printing"[All Fields]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields])) AND ("2010/01/01"[PDAT]: "2016/02/29"[PDAT]).

The on-line database was searched to find articles published in the English language between January 1st 2010 until February 29th 2016. All *in vitro*, *in vivo*, and human studies regarding the use of powder-based 3DP printing for the synthesis of bone tissue engineering scaffolds were considered. No limitations with regard to sample size or length of follow-up period were applied.

Systematic reviews and meta analyses were not considered. Studies dealing with the following topics were excluded: 3D printed templates for dental implant positioning or osteotomy design, 3D printed anatomic templates for preoperative planning or training.

2.1. Study selection

The titles and abstracts, whenever available, that were identified by the electronic search were independently screened by two of the authors, and any disagreements were resolved by a discussion between them. Full-text articles of studies appearing to meet the inclusion criteria or in those cases in which the title and/or abstract did not provide sufficient data were requested from their authors. The studies that were selected were then screened independently by both of the reviewers, and disagreements were resolved by discussion.