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Review

Design of biocomposite materials for bone tissue regeneration

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ABSTRACT

Several synthetic scaffolds are being developed using polymers, ceramics and their composites to overcome the limitations of auto- and allografts. Polymer–ceramic composites appear to be the most promising bone graft substitute since the natural bone itself is a composite of collagen and hydroxyapatite. Ceramics provide strength and osteoconductivity to the scaffold while polymers impart flexibility and resorbability. Natural polymers have an edge over synthetic polymers because of their biocompatibility and biological recognition property. But, very few natural polymer–ceramic composites are available as commercial products, and those few are predominantly based on type I collagen. Disadvantages of using collagen include allergic reactions and pathogen transmission. The commercial products also lack sufficient mechanical properties. This review summarizes the recent developments of biocomposite materials as bone scaffolds to overcome these drawbacks. Their characteristics, *in vitro* and *in vivo* performance are discussed with emphasis on their mechanical properties and ways to improve their performance.

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1. Introduction

Replacement/regeneration of damaged bone is a major challenge in orthopedic surgery. Bone graft is second only to blood as the most commonly transplanted tissue [1]. Approximately 500,000 bone grafting procedures are performed annually in the United States alone with about 2.2 million procedures worldwide, generating a sale of about $2.5 billion per year [2]. Bone graft transplants are performed for bone defects that arise due to severe trauma and developmental deformities, replacement surgeries to relieve pain or fix joint damages, revision surgeries to replace or compensate for a failed implant, and tumor resection *i.e.*, surgical removal of tumor affected bone tissue [3]. Current gold standard treatment for these defects is the use of autografts (patient's own tissue), which constitutes 58% of the bone grafts used [4]. It suffers from many drawbacks including limited supply, need for additional surgery for bone extraction and donor site morbidity. An alternative to autografts is the use of allografts (tissue from another patient), which accounts for 34% of the current bone grafts [5]. This also has limitations including

Abbreviations: ALP, Alkaline phosphatase; BCP, Biphasic calcium phosphate; BG, Bioactive glass; CMC, Carboxymethyl cellulose; GAG, Glycosaminoglycan; HA, Hydroxyapatite; P3HB, Poly (3-hydroxybutyric acid); PCL, Polycaprolactone; PHA, Polyhydroxyalkanoates; PHBV, Polyhydroxybutyrate-co-(3-hydroxyvalerate); PLGA, Poly(lactic-co-glycolic acid); PLLA, Poly-L-lactide; PS, Phosphatidylserine; PVA, Polyvinyl alcohol; RGD, Arginine–glycine–aspartic acid; SF, Silk fibroin; TCP, Tricalcium phosphate.

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availability, disease transmission and risks of infection. The limitations of these two approaches can be overcome by the use of synthetic bone substitutes/scaffolds.

The evolution of bone graft biomaterials can be categorized into four different generations. The first generation bone grafts are metals and alloys which have excellent mechanical properties but are neither bioresorbable nor bioactive. Their lifetime is limited and hence need to be removed and replaced surgically. The second generation bone grafts include bioactive ceramics and bioresorbable polymers [6]. Polymeric scaffolds lack bioactivity and sufficient mechanical properties while ceramic scaffolds are too brittle to be used for load bearing applications [7]. The third generation bone grafts are made up of composite scaffolds which combine the strength, stiffness and osteoconductivity of ceramics with the flexibility, toughness and resorbability of polymers [8]. Fourth generation bone grafts are polymer–ceramic composite scaffolds with the incorporation of osteogenic cells, growth factors or bone morphogenetic proteins, used alone or in combination [6].

Native bone tissue is a composite composed of hydroxyapatite (HA) crystals (2–5 nm wide and 70 nm long) and collagen fiber matrix (50–500 nm diameter) [9,10]. The latter provides the strength during tension and resistance to bending while the former resists compression [11]. Hence polymer–ceramic composites are considered as ideal material for bone scaffolds. However, nanocomposites are believed to be more advantageous as they have better mechanical properties [12,13] and high cell–surface interaction [14].

Natural polymers comprise of polysaccharides including starch, alginate, chitin/chitosan and hyaluronic acid derivatives or proteins including collagen, soy, fibrin gels and silk. The native extracellular matrix of the body is mostly made up of natural polymers including collagen, fibrinogen and elastin [15]. Natural polymers are biocompatible and have a biological (cell) recognition property which enhances cell adhesion and differentiation [16]. Despite various advantages, synthetic polymers lack cell adhesion signals and hence the current research focus has shifted to natural polymers for bone tissue engineering applications. However, natural polymers have some disadvantages including poor mechanical properties, immunogenicity and limited supply [16].

An ideal bone tissue engineered scaffold must possess several important characteristics including biocompatibility, osteoconductivity, osteoinductivity, bioactivity, good mechanical integrity throughout the bone healing process, a degradation rate such that the strength of the scaffold is maintained until the regenerated tissue can provide the necessary mechanical support, and interconnected porosity with a pore diameter of at least 100 μm, which is necessary for cell penetration, vascularization of the ingrown tissue and transport of nutrient and wastes [17].

This review provides an overview on the commercial biocomposite scaffolds available for bone tissue regeneration and summarizes recent progress in the development of novel natural polymer based composites to overcome the problems faced by the commercial ones. The mechanical strengths achieved by the biocomposite scaffolds fabricated using various methods are compared to that of natural bone and discussed with respect to their porosities. Similar reviews are available which focuses on natural polymer/hydroxyapatite nanocomposites prior to 2010 [18] and natural polymer/calcium phosphate nanocomposites with emphasis on polymer and ceramic properties and detailed processing methods [19].

2. Commercially available composites

The majority of the commercially available natural polymer–ceramic composites (Table 1) comprises of type I collagen and calcium phosphate mineral which mimics the native bone tissue. Animal studies indicate that composite grafts (Collagraft®) show a higher percentage of ingrowth than the other two classes of commercially available bone graft substitutes namely ceramic (ProOsteon®) and demineralized bone matrix (DBX®) [20]. Nonetheless, it has insufficient mechanical stability and can drift away from the implanted site [21]. Collapat® shows five times higher bone regeneration in rabbit femoral defects than those without implant, with complete closure of the defect in four weeks [22].

The performance of Formagraft® in postlateral spinal fusions in a rabbit model was found equivalent to an iliac crest autograft while its biomechanical performance assessed by destructive uniaxial testing at 12 weeks was superior to the same [23]. But Formagraft® is preferred for use along with bone marrow aspirate and an autograft for better results. The harvesting of bone marrow however causes donor site morbidity. This can be avoided by the use of TricOs T® as studies show that without bone marrow it shows bone ingrowth similar to Collagraft® with bone marrow. Also, addition of bone marrow to TricOs T® does not increase the bone ingrowth [24].

Table 1
Commercially available natural polymer–ceramic composites.

Product	Polymer	Ceramic	Recommended use
Collagraft® (*Zimmer/NeuColl*)	Type I (bovine) collagen	HA, TCP	Acute long bone fractures and traumatic osseous defects
Collapat II® (*BioMet Inc.*)	Type I (calf skin) collagen	HA	Aseptic enclosed metaphyseal bone defects
FormaGraft® (*Maxigen Biotech Inc.*)	Type I collagen	HA, TCP	Bone void filler
Integra Mozaik™ (*Integra OrthoBiologics*)	20% type I collagen	80% TCP	Bone void filler
Vitoss® (or) Vitoss® Bioactive (*Orthovita*)	20% collagen	80% β-TCP (or) 70% β-TCP/10% BG	Bone void filler, spinal and trauma surgery
Mastergraft® matrix (*Medtronic*)	Type I (bovine) collagen	BCP	Bone void filler
CopiOs® (*Zimmer*)	Type I (bovine) collagen	Calcium phosphate, dibasic calcium phosphate	Bone void filler
Biostite® (*Vebas*)	Type I (equinine) collagen, chondroitin-6-sulfate	HA	Filling of peridontal defects, pre-prosthetic osseous reconstruction, maxillo-facial reconstructive surgery
Bio-Oss Collagen® (*Geistlich Biomaterials*)	10% (porcine) collagen	HA	Filling of periodontal defects, alveolar ridge reconstruction
TricOs T® (*Baxter*)	Fibrin	BCP	Bone void filler
CycLos® (*Mathys Orthopaedics Ltd.*)	Sodium hyaluronate	β-TCP	Bone void filler
Cerasorb® (*Curasan Regenerative medicine*)	Collagen	β-TCP	Filling, bridging, reconstruction and bone fusion
Healos® (*Depuy Spine*)	Type I collagen	Nano-HA coating	Bone void filler, spinal surgery
RegenOss® (*JRI Orthopaedics*)	Type I collagen fibers	Magnesium-enriched HA nano-crystals	Long bone fractures, revision hip arthroplasty to fill acetabular defects and spinal fusion
NanOss® Bioactive 3D (*Pioneer surgical*)	Collagen	Nano-HA	Bone void filler