Review

Journal of Tissue Engineering
Volume 9: 1–18
© The Author(s) 2018
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/2041731418776819
journals.sagepub.com/home/tej
SAGE

Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management

Gabriel Fernandez de Grado[1,2,3], Laetitia Keller[1,2], Ysia Idoux-Gillet[1,2], Quentin Wagner[1,2], Anne-Marie Musset[1,2,3], Nadia Benkirane-Jessel[1,2], Fabien Bornert[1,2,3]*, and Damien Offner[1,2,3]*

Abstract

Bone replacement might have been practiced for centuries with various materials of natural origin, but had rarely met success until the late 19th century. Nowadays, many different bone substitutes can be used. They can be either derived from biological products such as demineralized bone matrix, platelet-rich plasma, hydroxyapatite, adjunction of growth factors (like bone morphogenetic protein) or synthetic such as calcium sulfate, tri-calcium phosphate ceramics, bioactive glasses, or polymer-based substitutes. All these substitutes are not suitable for every clinical use, and they have to be chosen selectively depending on their purpose. Thus, this review aims to highlight the principal characteristics of the most commonly used bone substitutes and to give some directions concerning their clinical use, as spine fusion, open-wedge tibial osteotomy, long bone fracture, oral and maxillofacial surgery, or periodontal treatments. However, the main limitations to bone substitutes use remain the management of large defects and the lack of vascularization in their central part, which is likely to appear following their utilization. In the field of bone tissue engineering, developing porous synthetic substitutes able to support a faster and a wider vascularization within their structure seems to be a promising way of research.

Keywords

Synthetic, orthopedics, spine, cyst, dentistry, porosity, vascularization

Date received: 23 February 2018; accepted: 24 April 2018

Introduction

Bone defects can develop from different origins like infection, tumor, trauma, surgery, congenital etiology (Figure 1), and so on.[1] For centuries, the idea of replacing missing bone tissue has emerged. Traces of orthopedic treatments have been found in Pre-Columbian and Egyptian civilizations.[2,3] During the 17th century, Dutch surgeon Job Van Meekeren reported the first success in bone grafting. It consisted of the transplantation of a piece of bone from a dog's skull into a cranial defect in a soldier. Nevertheless, the graft had to be removed under the orders of the Church. During the 19th century, Van Merren reported the first autogenic graft success, while cases of allogenic grafts were reported as well.[4] Non osseous materials (wood, marble, etc.) were used during the same period, but the results were not really convincing until Dreesman used plaster of Paris (calcium sulfate) in 1892 and resulted in a success.[5–7]

[1]INSERM (French National Institute of Health and Medical Research), "Regenerative Nanomedicine" laboratory, http://www.regmed.fr, UMR 1260, Faculté de Médecine, FMTS, F-67085 Strasbourg Cedex
[2]Université de Strasbourg, Faculté de Chirurgie Dentaire, 8 rue Ste Elisabeth, F-67000 Strasbourg
[3]Hôpitaux Universitaires de Strasbourg, 1 Place de l'Hôpital, F-67000 Strasbourg

*These authors contributed equally to this work

Corresponding author:
Damien Offner, INSERM UMR 1260- Regenerative NanoMedicine, Rue Humann, 67000 Strasbourg, France.
Email: damien.offner@hotmail.fr

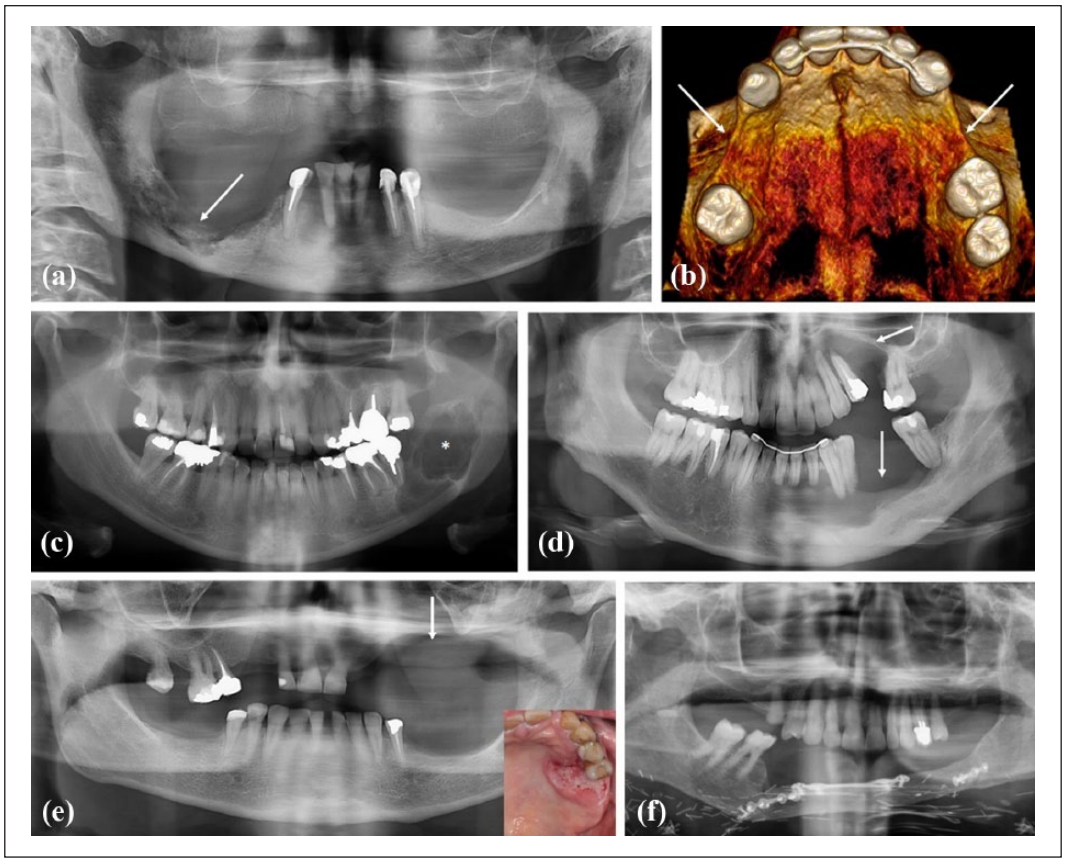

Figure 1. Various origins of bone defects: (a) Panoramic X-ray. Bone defect of the mandible right body corresponding to an osteonecrosis of the jaw in relation to denosumab taking. (b) 3D-reconstructed view of upper jaw. Bilateral bone defect of premolar regions associated to tooth agenesis in a young adult presenting a WNT10A gene mutation. (c) Panoramic X-ray. Bone defect (radiolucency, *) of the mandible right ramus corresponding to an ameloblastoma, an odontogenic aggressive benign tumor. (d) Panoramic X-ray. Bone defect (radiolucency, arrows) of upper and lower jaws corresponding to a trauma. (e) Panoramic X-ray. Bone defect (arrow) of upper jaw after resection surgery of a gingival squamous cell carcinoma (clinical view, left corner). (f) Reconstruction of the mandible by autogenous bone (fibula) following an invasive squamous cell carcinoma of the gingiva.

In 2001, bone grafting represented 500,000 procedures per year in the United States, and more than 2 millions in the world,[8–10] widely using autograft, which is qualified as the gold standard technique. To date, many different materials can be found to fill bone defects. These can be allogenic bone, xenogenic bone, or bone substitutes which are defined as "synthetic, inorganic or biologically organic combinations which can be inserted for the treatment of a bone defect instead of autogenous or allogenous bone."[11,12] The ideal material to replace bone tissue should meet precise specifications, such as being biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, porous, mechanically resistant, easy to use, safe, and cost-effective.[9] If a vast majority of the materials placed on the market are osteoconductive, very few offer osteoinductive properties.[9,13] Regarding the specifications of an ideal material, the only one which seems to meet them is autologous bone. Indeed, autologous bone graft still is the gold standard technique for bone filling for many reasons.[8,9,14–25] First of all, autologous bone meets the mechanical and biological requisites for a filling material. Moreover, its use avoids any immunogenicity or rejection problems[23,24] and any disease transmission risk.[24] Nevertheless, the technique shows many disadvantages as well, and the most important of them is certainly the comorbidity associated with the presence of a second surgical site: the donor site.[15,18,24,25] Complications appear to be chronic pain in a range of 2.5% from 8% of cases, dysesthesia in 6% of cases, or infection in 2% of cases.[26,27] For some surgical procedures that would not require a general anesthesia (e.g. hand surgery), the need to obtain autologous bone (from the iliac crest) makes this anesthesia mandatory, increasing surgical risks for the patient.[16]

The first alternative to autologous bone we can think of is the use of allogenic bone (Figure 2), but a risk of disease transmission exists.[15] Although very rare cases are documented concerning HIV transmission (two cases have been reported since 1989, and the risk is estimated at 1/1.6 million)[28,29] or hepatitis B and C viruses transmission (1 and 2 cases have been reported since 1989, respectively),[28] transmission of other kind of viruses should not be excluded.[28,30,31] Moreover, the high cost of such materials should be

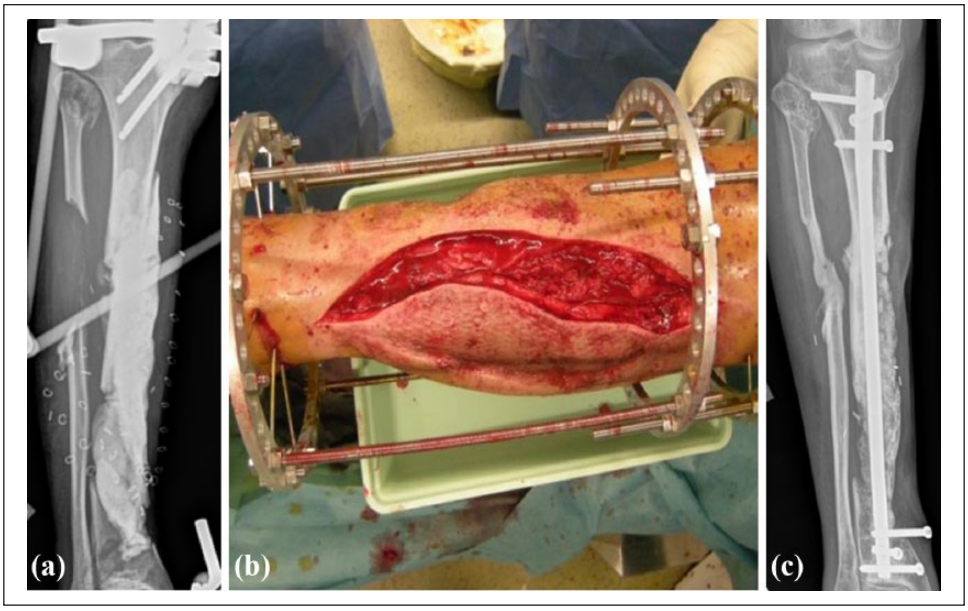

Figure 2. (a) Radiographical view of a right fibula bone loss, after a road traffic accident in a 24year-old woman, with an external fixator. (b) Surgical procedure with the use of allogeneic bone chips. (c) Radiographical view 4months later (courtesy of Dr D. Brinkert).

considered.[23] Indeed, an allogenic bone graft has to be treated and sterilized before it is stored and clinically used, representing a significant cost. On the contrary, an autogenous bone graft procedure allows to overcome any storage issue and is practiced during a single operative time. Another alternative to autograft could be the use of xenogenic bone; however, the same limitations persist with a risk of immunogenicity problems[23] and disease transmission[8] even if the risk is estimated to be very low[32] and mostly concerns the porcine endogenous retrovirus (PERV) and the bovine spongiform encephalopathy (BSE).[8] Furthermore, the medical team needs to deal with the acceptance of this technique by patients, especially regarding their beliefs.[26,33] Thus, to avoid all these limitations, the use of synthetic bone substitutes is becoming increasingly popular.[34,35] However, not all bone substitutes, from biological or synthetic origin, can be used for every application. The aim of our review is to specify the properties of the clinically available most used bone substitutes, according to the literature, to precise some of their clinical use, and to discuss about characteristics that should be developed in order to use them for large bone defects filling.

Bone substitutes

Bone substitutes will be classified in two main categories: bone substitutes derived from biological products and synthetic bone substitutes.

Bone substitutes derived from biological products

Demineralized bone matrix. Demineralized bone matrix (DBM) is bone that has been acid-treated in order to remove the mineral matrix, while maintaining the organic matrix and growth factors such as bone morphogenetic protein (BMP),[24] insulin growth factor (IGF), transforming growth factor (TGF), or fibroblast growth factor (FGF).[8] In proportion, 93% of a DBM is represented with collagen and 5% with growth factors.[24] Since some growth factors are maintained, DBM can show osteoinductive capabilities[36–40] and osteoconductive properties by the presence of a collagen structure.[24,36] Nevertheless, a large rate of the osteogenic capacity of bone is lost during its processing.[41] DBM has been clinically used since the early 1980s[8] after Urist and collegues'[42,43] work and is currently used in 50% of allografts performed in the United States,[39] although evidence for or against its efficacy is still at low level.[19,44] DBM shows no immunological rejections because the antigenic surface structure of the bone is destroyed during its demineralization by acid.[24,45] The use of DBM avoids donor site morbidity, and studies showed a comparable pain intensity after the surgical procedure compared to autograft procedures.[19] DBM is derived from human bone. It presents suitable availability, but this substitute is more expensive than an iliac crest bone autograft procedure,[19] and its mechanical properties are quite low.[8] Thus, DBM is only used for filling purposes and generally not as a stand-alone bone substitute.[8,46]

Platelet-rich plasma. Platelet-rich plasma (PRP) is generally used as a gel that is easily obtained with the patient's blood.[8] Blood is centrifuged through gradient density, and the resulting blood platelets are mixed with thrombin and calcium chloride.[47] Hence, PRP includes an important concentration of platelets and fibrinogen,[47] as well as growth factors such as platelet derived growth factors (PDGF),

vascular endothelial growth factor (VEGF), IGF, and TGF.[8,40,48–50] PRP is expected to show pro-coagulant effects due to platelets;[48] however, there is no evidence in the literature of benefits for the addition of PRP to accelerate bone healing.[40,51] Even if PRP shows limited infectious risks and adverse effects by its origin (autologous blood),[52] it does not present any mechanical resistance and is not validated as a stand-alone bone substitute.[8] PRP is rather used as a supplement to other materials.[47,53–55]

BMPs. Bone morphogenetic proteins (BMPs) are osteoinductive growth factors included in the transforming growth factor β (TGF-β) superfamily.[8] They are produced by osteoblasts and are largely involved in the skeletogenic process,[56] enabling ectopic bone formation.[42] BMP play a role in the recruitment of osteoprogenitor cells in bone formation sites. Genetic engineering allows to synthetize recombinant human BMP (rhBMP-2 and rhBMP-7), which can be produced in large quantities[39,57,58] and limit risks of contamination. rhBMP-2 and rhBMP-7 are allowed by the Food and Drug Administration (FDA) for clinical use.[59,60] The history of the safety of BMP has been eventful: in 2009, a systematic review led by Agarwal et al.[61] including 17 studies for 1342 patients concluded that the use of BMP-2 or BMP-7 did not lead to any adverse effect, whereas recent reviews reported complications up to 50%.[26] After 2 years in 2011, Carragee et al.[62] shared growing reportings linked to the utilization of BMP-2. These studies highlighted unpublished results regarding especially the use of BMP-2. Authors estimated that the risk of complications linked to BMP-2 is 10–50 times higher than the results that were showed in previous studies.[63] Adverse effects then appeared: heterotrophic ossification, osteolysis, infection, and retrograde ejaculation.[39,63] Moreover, paradoxical inhibitory effects of BMP-2 at high concentrations may appear[64] and compromise a successful procedure. Thus, and due to the variability of the needed dosage which is patient- and site-dependant, the use of BMP is still surrounded by a blur. Moreover, BMPs require molecular carriers to deliver and maintain them at their intended osseous targets,[39] their mechanical properties are not biomimetic of the native bone tissue, and their high cost makes their use prohibitive in most settings.[8] However, excluding their adverse effects, BMPs appear to be promising regarding their results in nonunions resolutions,[61] and the decrease in the operating time and blood loss during surgical procedures.[65,66]

Hydroxyapatite. Hydroxyapatite (HA) is part of the apatites family, which are crystalline compounds with crystalline hexagonal lattice. HA has the specific formula ($Ca_{10}(PO_4)_6(OH)_2$) and is the primary mineral component of teeth and bones.[8] Thus, HA is extremely biocompatible[67–69] and does not promote an inflammatory response.[70] Natural HA is porous with a various porosity depending on the bone site that is extracted (for example 65% porosity and pores from 100 to 200 µm for trabecular bone[71]), which allows osteoconductive properties. Indeed, HA resorption is very slow[72] and the material is usually maintained at least up to 3 years after implantation,[69] allowing a slow bone ingrowth progress and cell colonization.[69,71] Since HA offers very good mechanical properties with a compression resistance up to 160 MPa, it is likely to be utilized in small bone defects with low loading condition.[69] Nevertheless, the use of HA alone may be deceiving.[58,73] HA comes in both natural and synthetic forms,[8] and HA-TCP (tri-calcium phosphate) ceramics are usually preferred to HA alone. Some composite materials containing HA and collagen exist as well, and their combination enhances osteoblasts differentiation and accelerates osteogenesis.[74] HA-collagen composites have some mechanical advantages over HA used alone. Indeed, the ductile properties of collagen allow an increase in the poor fracture toughness of hydroxyapatite. Still, the effectiveness of this composite material has to be validated by further clinical studies.[8]

Coral. Corals have interconnected pores and a skeleton quite similar to cortical and spongy bones,[75] and their use as bone substitute has been approved by the FDA in 1992.[58] Coral-based substitutes are mainly calcium carbonate that can be transformed industrially into HA, or they can retain their original state which allows a better resorption by the natural bone.[8] Coralline HA can be used as growth factors carrier, such as BMP, TGF-β, or FGF.[58] It can be found in different aspects like granules or blocks. Despite its slow resorption, it does not induce adverse effects like inflammatory responses.[58,76] Coralline HA is osteoconductive, can show an excellent bone-bonding capacity,[77] avoids donor site morbidities,[58] and is unlikely to promote disease transmissions or risks of deep infections.[78]

Synthetic bone substitutes

Calcium sulfate. The first therapeutic success using calcium sulfate ($CaSO_4$) as a bone substitute was reported in 1892.[5–8] However, this material also called "gypsum" or "plaster of Paris" and has only been FDA accepted in 1996.[58] Calcium sulfate offers many advantages as it presents a structure similar to bone, it is osteoconductive,[34,79] inexpensive,[39,79] and available in different forms (hard pellets and injectable fluids).[17,39] It does not generate allergic reactions.[79] Moreover, calcium sulfate has a crystalline structure that is osteoconductive, onto which bone capillaries and perivascular mesenchymal tissue can invade.[8,80] Calcium sulfate resorbs rapidly in 1–3 months.[8,39,58,79] This resorption creates porosity while stimulating bony ingrowth.[81] Nevertheless, the resorption of calcium sulfate is faster than the rate of new bone deposition,[34,82] and thus, it is rather unsuitable as a material to support early functional rehabilitation.[58,83] Calcium sulfate can be used as a support or a vehicle for local antibiotics or growth factors delivery.[84–87] Although it presents many advantages,

calcium sulfate also shows some disadvantages, in addition to its fast resorption. It is neither osteoinductive nor osteogenic, and in many cases, redness and swelling of the wound can persist after the procedures.[17,58,79] Appearing in 4%–53% of cases,[17,88,89] these kinds of complications are generally managed with local wound care, but just as other bone grafts, infections can appear as well and necessitate sometimes a further surgical intervention.[89]

Calcium phosphate cements. Calcium phosphate cements (CPCs) were invented in 1986 by Brown and Chow[90] and were FDA approved for the treatment of non-load-bearing bone defect in 1996 (concerning tetracalcium phosphate and dicalcium phosphate dihydrate products).[8] This bioresorbable material[91] can stay in the body for long up to 2 years without resorption, depending on its formulation. It consists of a calcium phosphate powder which is mixed with a liquid to form a workable paste.[8] Its isothermic hardening reaction varies from 15 to 80 min depending on the formulation,[92] and this results in nanocrystalline HA, which makes CPC osteoconductive.[8] The main advantage of CPC is the possibility to shape the paste to the complex bone cavity, avoiding gaps between the bone and the implant. Furthermore, some CPC are injectable and can be used in minimal invasive procedures such as vertebroplasty and kyphoplasty. Just like other substitutes (e.g. calcium sulfate and some HA-based grafts), CPC are brittle[8] and can lead to some complications (13% overall complications according to Afifi et al.[93] with 9% major complications and 5% infections). Because clinical outcomes seem not to be better and sometimes worse than the use of methylmethacrylate or autologous bone, CPC should be used selectively.[93]

β-tri-calcium phosphate ceramics. β-tri-calcium phosphate (β-TCP) ($Ca_3(PO_4)_2$) has largely been used as a bone substitute[94–96] for more than 25 years, mainly for orthopedics and dentistry applications,[97] and is considered as the "gold standard" for synthetic bone.[95] It is a biocompatible[98,99] and bioresorbable material[8,58,94,100,101] with properties similar to the inorganic phase of bone. β-TCP is osteoconductive[96,98,102,103] due to its composition and its porosity,[100] which depends on the processing condition. Indeed, its porous structure plays a role in its osteoconductive characteristics.[104] β-TCP gradually resorbs, and although its resorption is unpredictable[105] and slower than the resorption of calcium sulfate,[39,106] β-TCP is meant to be completely resorbed in time[58,100,107] by osteoclasts.[108] β-TCP resorbs in approximately 13–20 weeks after implantation and is then completely replaced by remodeled bone.[103,109] Furthermore, β-TCP with its interconnected pores may accelerate bone remodeling by facilitating the colonization of osteogenic cells and nutrients via an enhanced capillarity[15] and seems to have the potential to influence angiogenesis.[96] In vivo studies showed an incorporation of bone between 45% (in vertebral bodies of apes)[110] and 70% (in piglets' mandibles)[111] 6 months after implantation, and of 95% after 2 years.[100] The use of β-TCP showed very few complications like infection or nonunion.[100] Although its suitable mechanical resistance, it is still inferior to mechanical properties of cancellous bone[39] or of a bone allograft.[112] Therefore, β-TCP should be used selectively.[39,112]

Biphasic calcium phosphates (HA and β-TCP ceramics). β-TCP is mostly used in association with HA.[8,9,23,94,113,114] Synthetic HA can be made by the precipitation of calcium nitrate and ammonium dihydrogen phosphate.[23] This association presents all the advantages of its two components (osteoconductivity,[94,115–118] biocompatibility,[94,113] safe and nonallergen use,[113] and promotion of bone formation[106]). The major gain of using biphasic ceramics (HA and β-TCP mixture) concerns their resorption. Indeed, the resorption of β-TCP is faster than the resorption of HA,[23,72,119] but mechanical properties of HA are slightly better than β-TCP's (average compressive resistances are, respectively, of 160 and 100 MPa).[23] Thus, the association of β-TCP and HA enables a faster and higher bone ingrowth rate than using HA alone[94] while offering better mechanical properties than β-TCP alone.[72,114] Indeed, 12 months after the implantation of the material, 60% of the β-TCP resorbs compared to only 10% for the HA.[94] HA and β-TCP ceramics form a strong direct bond with the host bone.[120] They can be found with different HA/β-TCP ratios and can be associated with bone marrow aspirate which then provides enhanced osteogenic properties to the material.[121] Despite the improvement of mechanical properties of β-TCP by the incorporation of HA, the strength of HA and β-TCP ceramics is still lower than cortical bone compression strength, which is between 150 and 200 MPa.[8] Different preparation methods are available, like a compact form, or a porous form with interconnected macropores equivalent to cancellous bone, which is preferred.[122]

A few studies mention the utilization of composite substitutes of calcium sulfate associated to β-TCP which would lead to very few complications.[34,123] When applied to long bones, the return to full weight bearing and unrestricted activities of daily living is at a mean of 7.3 weeks[34] against 14 weeks when using HA or β-TCP.[23]

Bioactive glasses. Developed for the first time by Hench et al.[124] in the 1970s,[125] bioactive glasses (or bioglasses) are originally silicates that are coupled to other minerals naturally found in the body (Ca, Na_2O, H, and P). The original bioglass composition is 45% silica (SiO_2), 24.5% calcium oxide (CaO), 24.5% sodium oxide (Na_2O), and 6% phosphorous pentoxide (P_2O_5) in weight percentage.[126] When subjected to an aqueous solution or body fluids, surface of bioglasses converts to a silica-CaO/P_2O_5-rich gel layer that subsequently mineralizes into hydroxycarbonate in a few hours.[126–128] Bioglasses are biocompatible, osteoconductive,[58,125,129] and—depending on their processing condition—offer a porous structure which promotes their

resorption and bone ingrowth.[130] The use of bioglasses does not induce an inflammatory response, and their resorption is complete in 6 months for silica-based bioglasses.[131] More recently, phosphate- or borate-based bioglasses have been developed.[132,133] Borate-based bioglasses, which are easily manufacturable, show a faster degradation than silica-based bioglasses, but this degradation rate can be controlled by adjusting its composition. This ability leads to a possible match with the bone regeneration rate.[132] Phosphate-based bioglasses present a controllable solubility by manipulating their composition, and their structure makes them a specific and promising group of bioglasses for hard and soft tissue engineering.[133] When implanted in bone tissues, these materials show a strong bond to bone and withstand removal from the implantation site.[125,129,134] However, bioglasses are quite brittle[58] and present low mechanical strength and decreased fracture resistance.[125] Thus, their utilization should be selective[125] or in association with other bone substitutes.

Polymer-based bone substitutes. Although natural polymers such as collagen exist and are slightly used alone rather than in combination with HA; for example, this section (synthetic bone substitutes) will be focused on synthetic polymers. They can be nondegradable (like poly(methylmethacrylate) or PMMA) or fully biodegradable, thus allowing a total bone replacement in time (e.g. polylactic acid (PLA)) without remaining foreign bodies.[8] Initially used as graft extenders,[135] researches focus on synthetic polymeric bone substitutes, especially in the field of tissue engineering. Polyesters like poly(ε-caprolactone) (PCL), for example, can be synthetized by mimicking the collagenic matrix, offering a structural porosity and osteoconductive properties.[136,137] Most of the polymer-based bone substitutes are suitable to be used as bioactive molecules or growth factors carriers,[138] potentially conferring osteogenetic properties.[139] Since PCL is soluble in a wide range of organic solvents, it is a promising polymer for continuous researches in tissue engineering.[8,140] Actual polymer-based bone substitutes can be found in different forms. Indeed, blocks of acrylic cement (with a similar composition of a prepolymerized PMMA powder mixed with a liquid monomer containing a large amount of methylmethacrylate monomer) can be fashioned into the desired shape,[141] or methacrylate-based products can be used in injectable forms before their polymerisation.[142] PMMA cements are of the most extended used materials for articular prosthesis fixation and vertebroplasty. However, according to a Cochrane review led by Handoll and Watts[143] in 2008, they are materials which few would use to date for specific bone implantation after distal radial fracture, because they do not promote new bone growth and may rather inhibit it.[143,144] Polymer-based bone substitutes are mainly scrutinized for their wide potential in tissue engineering, allowing their fabrication with macropores and micropores and in the shape of thick membranes (e.g. PCL or PLA).[136,138] Clinicians should keep a close eye on outcomes of researches concerning polymer-based bone substitutes as scaffolds for regenerative medicine.

Clinical use

Bone substitutes should be used selectively. According to the literature, here are some directions concerning their clinical use (Table 1).

Spine fusion

Spine fusions represent 200,000 procedures per year in the United States.[145] To date, autograft and allograft are mainly used to promote spine fusion,[146] although other materials seem to fit for this specific use.[15] Indeed, DBM combined with marrow aspirate showed good results in posterolateral spine fusion,[147] and DBM showed good results when used as a graft enhancer of autologous bone either in cervical fusion surgery[37,39] or in lumbar fusion surgery.[148–150] However, there is still no evidence for DBM to be used as a stand-alone material in spine fusion.[37] DBM applied in anterior spinal fusion is currently not recommended in clinical practice[146] because its results have shown a higher rate of graft collapse and pseudarthrosis when compared to autograft.[151] Coralline HA has been studied for spine fusion as a graft enhancer.[76,152] Since the host bleeding bone surface in this area is small, and knowing that coralline HA mixed with local bone and bone marrow needs adequate bleeding to bond to the bone surface, it appeared that coralline HA was inappropriate for intertransverse posterolateral fusion.[76] Although calcium sulfate has been used as a graft expander for spine fusion,[79] there is less evidence of its suitability than there is for β-TCP ceramics. The latter demonstrated efficacy for use as a bone graft extender in posterolateral spinal fusion.[121,146,153] Moreover, β-TCP in a non injectable form showed good radiographic fusion in both single- and double-level lumbar fusion when mixed with local laminar autografts.[154] Thus, many bone graft substitutes are suitable as bone graft extenders, but only osteoinductive proteins (such as rhBMP-2) provide evidence for use as both bone enhancers and bone substitutes[58,146] in spine fusion. Products of tissue engineering (hydrogels or synthetic polymer composites) seem to have the potential to be used for spine fusion though warrants further investigation to be used in clinical practice.[146]

Open-wedge tibial osteotomy

Open-wedge tibial osteotomy (OWTO) is a classical way for treating medial knee osteoarthritis[155] or varus deformity[138] for example. In a review reporting 70 cases, β-TCP ceramics have been used as wedges[101] and showed more than 96% osteointegration and 98.5% of the cases with an achieved bone healing.[101] In accordance with other studies,

Table 1. Clinical use directions of some bone substitutes.

Bone substitute		Clinical use											
		Spine fusion	OWTO	Contained bone defects	Hand surgery	Long bone fracture	Fracture nonunion	Periodontal defects	Sinus augmentation	Osteonecrosis of the jaw	Bone infections (drug carrier)	Cranioplasty	Vertebroplasty/ kyphoplasty
Bone substitutes derived from biological products	DBM	+ (except for anterior spinal fusion)	–	+	NI	NI	++	+	+	NI	NI	+	NI
	PRP	NI	–	NI	NI	NI	NI	–	+/–	+	NI	NI	NI
	BMP	+	NI	–	NI	NI	NI	NI	NI	NI	NI	NI	NI
	HA	NI	+	NI	+ (as a composite graft with calcium sulfate)	NI	NI	NI	NI	NI	+	+	NI
	Coral	–	NI	+	NI	NI	NI	-	NI	NI	NI	NI	NI
	Calcium sulfate	+	NI	+	+ (as a composite graft with HA)	NI	+	NI	NI	NI	+	NI	–
Synthetic bone substitutes	CPC	NI	NI	NI	NI	+	NI	NI	NI	NI	+	+	+/–
	HA and β-TCP ceramics	++	++	++	+	+	NI	+	+	NI	+	NI	NI
	Bioactive glasses	NI	NI	NI	NI	NI	NI	+	+	NI	+	NI	NI
	Polymer-based substitutes	NI	+	–	NI	NI	NI	NI	NI	NI	++	++	++

OWTO: open-wedge tibial osteotomy; DBM: demineralized bone matrix; NI: no literature-related information are given in this review; PRP: platelet-rich plasma; BMP: bone morphogenetic protein; HA: hydroxyapatite; CPC: calcium phosphate cement; TCP: tri-calcium phosphate.
(+) gives good clinical outcomes; (++) gives good clinical outcomes and is largely used; (–) gives bad clinical outcomes; (+/–) both good and bad clinical outcomes are found in the literature.

β-TCP ceramics appear to be a bone replacement material with optimal biocompatibility, resorption characteristics, and bone conduction properties for OWTO,[99,156,157] using indifferently granules or wedge preforms.[158] Using β-TCP ceramics, the results seem to be more similar to those obtained with autologous bone after 6 months, but bone consolidation appears to be a bit longer, so β-TCP ceramics still have to be used selectively.[112] In 2000, Hernigou and Ma[141] obtained clinically satisfying results in OWTO when using acrylic cement wedges. In 2001, Koshino et al.[69] reported a series of 10 cases using HA as a bone substitute for OWTO with good clinical outcomes. However, HA is assumed too frangible to be implanted in bone under mechanical stress or weight bearing,[69,112] but the weak mechanical properties of porous HA might be eliminated once incorporation and bone ingrowth into the pores are achieved.[159] From their retrospective review in 2015 concerning 83 patients having surgery, Giuseffi et al.[160] concluded that allograft mixed with DBM and/or PRP was associated with nonunion.

Contained bone defects (benign tumors and cysts)

Since contained bone defects can occur in many types of bone, a wide range of substitutes has already been clinically used. However, a bone substitute that has been validated in a specific area is not necessarily expected to be validated in another area. Indeed, the setting is different, and the needed characteristics of the bone substitute are different.[9] In some studies, calcium sulfate has successfully been used in filling contained bone defects,[58,79,88,161–163] and results can be comparable to DBM-based allografts,[39] with the advantage to be at lower cost.[164] Calcium sulfate also showed good results in filling unicameral bone cysts in pediatrics, with a rate of healing mostly over 90%.[162,165–167] While polymethylmethacrylate does not seem to be suitable for the filling of bone defects due to primary bone tumors, because it does not preserve bone stock and because the hardened cement does not share the same biomechanical properties as bone,[34,168] the use of a calcium sulfate–calcium phosphate composite was associated with good clinical outcomes (rapid biological integration and early return to activities of daily living) in cavitary bone reconstruction, following intralesional curettage of primary benign bone tumors.[34] Concerning PRP, there are major limitations in the literature in terms of low quality and heterogeneity, which hamper possible beneficial PRP treatments, despite positive preclinical findings on its biological potential to promote bone healing.[169] Moreover, poor evidence mentions the efficacy of PRP in the treatment of traumatic bone cyst in the mandible.[170] Coralline HA, in granules or blocks, seems to be suitable to fill contained bone defects.[58] Although its slow resorption, it does not induce adverse effects.[58] On the contrary, the use of BMP-2 (in the form of rhBMP-2) can lead to a poor healing rate with complications such as an exaggerated inflammatory response, pain, and limb swelling.[171] Finally, β-TCP ceramics are largely used in this purpose[9,23,165] and frequently associated with bone marrow aspirate.[172,173] Using β-TCP, healing rates vary from 90% to 100% with very few complications which resolved uneventfully.[166,172,173]

Hand surgery (hand enchondroma and metacarpal fractures)

Enchondromas are the most common benign tumors of the hand[16,174] appearing usually as solitary, cystic bone tumors.[17] The literature is quite poor regarding the use of bone substitutes for bone filling in hands,[17] as some authors advocate that a simple curettage without filling is a sufficient[175,176] and a less-expensive option.[176] Nevertheless, when bone substitutes are used, β-TCP ceramics seem to be suitable. Indeed, the application of this material gives the same good functional and radiological results compared to autologous bone.[16]

The use of a composite material with 60% calcium sulfate and 40% HA offered good clinical outcomes as well in terms of limited complications (53% redness and swelling lasting up to 10 postoperative days, 8% chronic regional pain syndrome treated successfully with intensive conservative treatment) and an effective return to normal daily activities after 2 months.[17] Furthermore, the use of bone substitutes is especially helpful in the treatment of complicated metacarpal fractures in old multimorbid patients, in whom a general anesthesia or potential donor site morbidities should be avoided,[16,17] allowing a reduced operating time and day-case surgery.[16]

Long bones fracture

Concerning tibial plateau fractures, it has been shown that CPC can provide similar and better mechanical support than autogenous iliac bone graft in the treatment of defects in unstable fractures, preventing subsidence.[91] β-TCP ceramics have been used as well for many decades in long bone fractures, such as tibial plateau fractures.[77] However, their use in distal radial fractures showed no significant benefits in terms of extra stability, compared to the use of internal fixation only, without bone substitute. Moreover, the occurrence of complications did also not show statistical significance.[177] For distal radial fractures, some evidence about bone scaffolding that may improve anatomical outcomes compared with plaster cast immobilization alone exist, but are insufficient on functional outcome and safety.[143]

Fracture nonunion

There is actually no universally accepted definition of nonunion in the orthopedic literature.[178] The FDA defines fracture nonunion as a fracture that is at least 9 months old in which there have been no signs of healing for 3 months.[39]

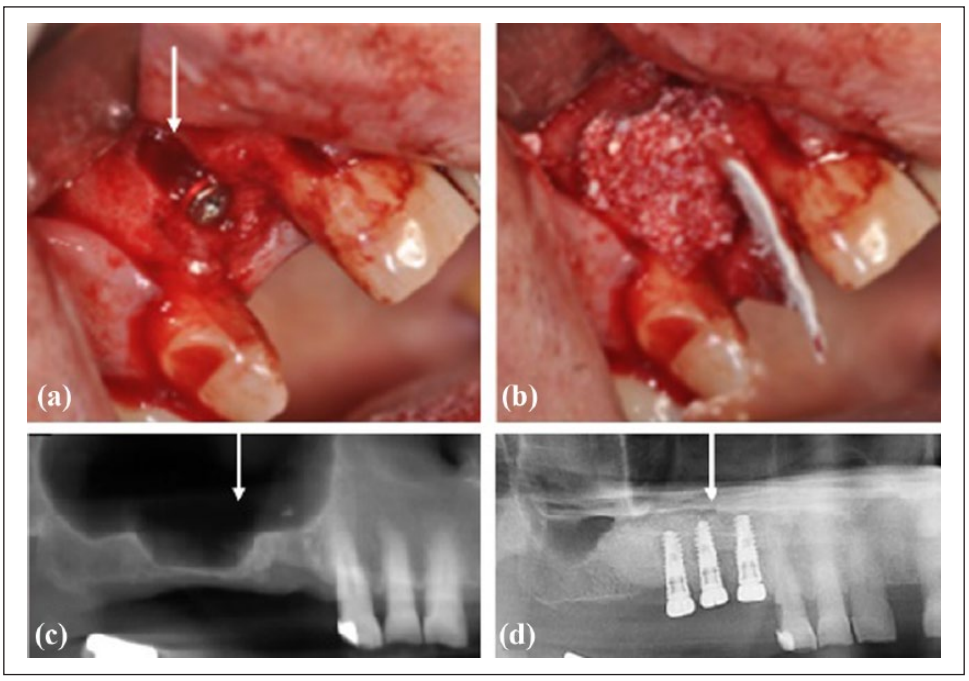

Figure 3. Use of DBM in oral procedures: (a, b) DBM used to fill buccal bone defect (arrow) after implant placement. (c, d) Panoramic X-rays of a maxillary right sinus before (c) and after sinus floor elevation (d) filled with DBM and dental implants placement.

Other definitions mention a fracture in which more than 6 months have elapsed without any improvement toward union,[179] distinguishing these cases from delayed unions. Nonunion appears in 10% of all fractures[180] and are generally treated with an open reduction and internal fixation associated with an augmentation using an autologous bone graft.[19] Since many synthetic bone substitutes are strictly osteoconductive, their biological role in fracture healing is limited,[40] although calcium sulfate has already been used as a graft expander for the treatment of established nonunions with a healing rate of 88%.[181] DBM is a popular bone substitute for the grafting of nonunions.[19,39] It has been compared to autologous bone and led to good results in terms of consolidation (more than 80% success) and a decrease in the adverse effects (especially due to the presence of a donor site).[19] However, the procedure cost was more expensive applying DBM (an average difference of US$190/case).[19] Recently, biphasic calcium phosphate biomaterials have been use associated to autologous, expanded, bone marrow-derived mesenchymal stromal cells. The safety of their use in the treatment of fracture nonunions has been set, but bone healing obtained through this method still has to be determined to compare the efficacy of this strategy with that of current clinical standards such as autograft.[182]

Oral/periodontal procedures

Periodontal diseases are widespread pathologies with 50% of adults suffering from a severe attachment loss problem in France.[183] Dental biofilm provokes an inflammatory response leading to the destruction of attachment tissues of teeth, while creating periodontal pockets whose depth is relative to the severity of the periodontal disease. To treat periodontal defect, the use of bone grafts seems to promote healing compared to open flap debridement alone.[184] Not only the material but also the technique has a role to play as well. Bone grafts in combination with barrier membranes increase clinical attachment level and reduce probing depth compared to graft alone.[184] Granules of β-TCP and HA ceramics can be used with significant pocket depth reduction and clinical attachment gain.[114,185] Bioglasses also have shown good clinical outcomes with a consequent clinical experience.[58,125,185,186] In comparison, other materials are not suitable for the treatment of periodontal defects, such as PRP, which does not demonstrate significant benefit,[187–189] or coralline bone substitutes, which does not yield the desired outcomes.[185] However, even if bone replacement grafts offer clinically satisfying results in terms of bone fill, histologic evidence of periodontal regeneration has only been reported for autogenous bone grafts and DBM.[190] In situations like buccal bone defect filling after a dental implant placement, for example, DBM can also be used (Figure 3).

Concerning sinus elevation, some studies concluded the efficacy of PRP[191] in terms of bone density at 6 months post-grafting,[192] whereas others postulated that PRP did not improve the clinical outcome of sinus lift procedures using autogenous bone or bone substitutes.[47,51,54,193] DBM

can be used with significant results for sinus elevation (Figure 3) as injectable formulation,[194] putty[195,196] or powder form,[196] showing no differences regarding dental implant stability and survival rate in a long-term follow-up.[196] Moreover, using injectable formulation of DBM could allow practical advantages such as a decrease in operative time.[194] The use of bioglasses or a mixture of β-TCP with autologous bone showed suitable results for this procedure;[51] however, the available evidence neither supports nor refutes the superiority of autologous bone over other graft materials for sinus augmentation regarding implant survival or complications at the recipient site.[197]

Osteonecrosis of the jaw

Poor evidence mentions the efficacy of PRP in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ).[198,199] In some studies, however, the use of PRP seems to enhance wound healing and to reduce bone exposure and thus would be an effective treatment protocol to use in BRONJ subjects.[47,200]

Infections

Various bone substitutes can be used as drug carriers in the treatment of bone deep infections.[201] Debridement, and implantation of antibiotic-loaded PMMA granules or beads mostly followed by an implant exchange, is currently the gold standard for this treatment.[201,202] Most commonly used antibiotics are gentamicin, tobramycin, and vancomycin.[201] Other bone substitutes have been used for this purpose, but clinical data in well controlled trials are still very limited:[201] it is the case for β-TCP granules,[203] porous HA blocks,[202,204] calcium sulfate pellets,[202,205] CPC,[206,207] and bioglasses.[208] However, the performance of some bone graft substitutes with antibiotics in one clinical site is not inevitably predictable of their performance in another site.[201] Most infections occur during implantation time and that is why sterile techniques still remain of utmost importance.[26,201]

Cranioplasty

Cranioplasty is performed mostly after traumatic injuries, tumor removal, or decompressive craniectomies[209] in order to protect the brain and achieve a natural appearance.[209,210] Among other characteristics, the ideal material should then be easy to shape, radiolucent, resistant to infections, biocompatible, firm, and stable.[209,210] Apart from some metals (titanium, tantrum, etc.), various bone substitutes are safely used for cranioplasties, such as CPC,[211] HA,[209,211,212] or DBM.[213] But still, PMMA is the most extensively used cranioplasty material,[209,210,214] even if there is still no consensus on which material is better for cranioplasty.[209]

Vertebroplasty and kyphoplasty

Vertebroplasty procedures were designed to stabilize vertebral body compression fracture and to alleviate pain in patients with various etiology such as hemangioma, spine tumor, or osteoporosis.[215,216] Kyphoplasty is a variation of vertebroplasty that usually involves the use of a balloon to create a cavity within the cancellous bone and to elevate or expand the fractured vertebrae toward its original height. The cavity is then filled with bone cement to reinforce the vertebral body.[215,217] The filling material plays a crucial role in the effectiveness of these treatments. It must be applicable in a flowable state due to the percutaneous surgical technique, have an adequate setting time to match the progress of surgeries, and have considerable mechanical strength to withstand cyclic and static complex loading patterns.[215,217] The most popular bone cement used for this purpose is PMMA-based acrylic bone cement, but several disadvantages are mentioned, such as its heat generation during exothermic polymerization, its nonbiodegradability, and a lack of biologic potential to remodel or integrate into the surrounding bone.[215,217] Good clinical results have been reported with PMMA for vertebroplasty and kyphoplasty (over 5° correction for 60% of reducible fractures, with an average of 95% pain reduction within the first week after surgery and improved activity levels for a majority of patients[218,219]). CPCs present interesting characteristics for their use as fillers in vertebroplasty and kyphoplasty. Indeed, they can be easily molded, injected into the defect area, offer the potential for resorption and replacement with new bone, and do not generate heat.[215,217,220] However, there are still some questionings regarding their mechanical strength,[221] and few evidence mentions their use other than in laboratory models.[215,222] To date, it seems that few CPCs are yet readily available for use in vertebroplasty and kyphoplasty.[215] Calcium sulfate has relatively higher mechanical strength than CPC and has been tested, but its fast degradation does not match with the bone formation process and would not allow to support spinal alignment while it is remodeling.[215,217,223]

Miscellaneous

Other surgical uses of bone substitutes are sometimes mentioned in the literature: β-TCP and HA ceramics have been used in hip arthroplasty,[224,225] bioglasses in tympanoplasty,[58] and PMMA in an original creation of a neo-rib for chest wall reconstruction.[226]

For bone defects that are not too large, autologous bone is often preferred. When it comes to large bone defects, the quantity of available autologous bone might not be sufficient, and a wide proportion of bone substitutes is then used as graft expanders,[8,37,47,58,79] rather than as stand-alone grafts. Thus, it appears interesting to discuss about two particular properties—porosity and vascularization—that

should be developed, leading to advances that would allow for a new generation of enhanced bone substitutes to be used for the treatment of large bone defects.

Vascularization, a requirement for bone regeneration

Currently, the use of bone substitutes is limited to relatively restricted bone defects, because they can become atrophic sequesters if they exceed a critical size (up to 60 cm^3)[136] and are not vascularized sufficiently.[227,228] Thus, vascularization is vital for bone defects to heal, and there is a greater need for vascularization at sites where bone substitutes are used because the defects are larger.[96] A lack of vascularization leads to osteonecrosis, which is not a specific disease entity, but the combination of conditions resulting in an impairment of blood supply to the bone tissue.[229] It is also called avascular necrosis.[229]

Indeed, the bridging of bone defects with stable bone substitutes is limited by vascularization as angiogenesis must precede osteogenesis.[106,230] The coupling of osteogenesis and angiogenesis is determinant in the bone healing environment,[231] and osteogenesis, vascularization, and resorption kinetics must be in equilibrium to allow a harmonious bone remodeling process.[232,233] Osteogenic cells will develop into the graft site through the existence of a vascular system[234] that allows to understand why poor vascularity can impede effective osteosynthesis.[39] Besides, studies showed that the presence of VEGF with resorbable carriers influences the ability to promote bone healing.[106,136] Thus, the structure and the composition of bone substitutes must allow vascularization, by presenting an interconnected porosity and a favorable biochemical support. The latter may then accelerate bone remodeling by facilitating colonization and retention of osteogenic cells and nutrients through an enhanced capillarity.[15] The establishment of a vascular network will provide nutrients, soluble factors, and minerals (e.g. calcium and phosphate) which are necessary for the bone healing process.[136] A delayed healing and some nonunions are often attributed to a failure in restoring vasculature rather than a lack of osteogenic potential.[235] That is why vascularization is one of the components of Giannoudis et al.'s[236] diamond concept, which sets the main factors that affect bone regeneration.

To give the capacity to bone substitutes to allow the development of vascularization, pores appear to be essential in their structure.[96] On one hand, the pore size directly plays a role in the bony ingrowth and can improve it when it is from about 80[23,94,237,238] to 200 µm,[58,71,102] ensuring a cell colonization, migration, and transport. Furthermore, porosity fraction in the material in the substitutes plays a role as well in bone ingrowth, allowing more cells to invade and offering a larger surface area that is believed to contribute to a higher bone-inducing protein adsorption.[239] On the other hand, interconnected pores are a crucial characteristic.[15,94] Indeed, dead-end pockets limit vascular supply to the in-growing bone.[23] If 100- to 200-µm pores are enough to support cell migration, 300- to 500-µm pores appear to be recommended to allow the formation of capillaries.[156,232,240,241] However, there is an equilibrium to be found between the decrease in compressive strength and an increased porosity, regarding the desired mechanical properties of bone substitutes.[242]

Nevertheless, even knowing that bone substitutes should be porous to allow vascularization, this biological process takes time. Thus, another approach to promote the quality and speed of bone regeneration is the ability to facilitate the development of a vascular network in the bone tissue during regeneration. For example, this could be achieved by adding growth factors (VEGF) to nanostructured implants,[136] or by creating bone-like structured biodegradable synthetic scaffolds using techniques such as electrospinning.[137,139] This network will provide the nutrients and minerals necessary for cells, conveying cellular waste[243] and therefore avoiding the potential necrosis in the middle of bone defects of a moderate size.[244] Being able to create polymer-based bone substitutes with a given porosity which will support biofunctionalization and promote the establishment of a vascular network[136–139,243,244] are some of the major interests of current researches in bone tissue engineering. That is precisely why clinicians should keep a close eye on these researches.

Conclusion

During the past decades, a plethora of materials have been used as bone substitutes. Some are derived from biological products, others are synthetic. But all of them present advantages and disadvantages and should mainly be chosen selectively. Many surgical procedures call out bone substitutes, such as spine fusion, filling of bone defects, and sinus augmentation, each one being suitable for specific substitutes among others. The main limitations to the use of bone substitutes are large defects and the central osteonecrosis which is likely to appear following their utilization. To avoid this phenomenon, current researches are focusing on the ability to create synthetic scaffolds with a desired porosity and to promote a faster and wider vascularization.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Poirier J, Ribadeau Dumas JL, Catala M, et al. *Histologie: les tissus. Médecine 1ère année*. 2ème éd. Paris: Masson, 2002.

2. Urist MR, O'Conner BT and Burwell RG. *Bone graft, derivatives and substitutes*. Cambridge: Butterworth-Heinemann, 1994.
3. Donati D, Zolezzi C, Tomba P, et al. Bone grafting: historical and conceptual review, starting with an old manuscript by Vittorio Putti. *Acta Orthop* 2007; 78: 19–25.
4. Mainard D and Delagoutte J-P. Les substituts osseux. In: Mainard D, Merle M, Delagoutte J-P, et al. (eds) *Actualités en biomatériaux*. Paris Romilliat, 1990, pp. 128–176.
5. Dreesman H. Über knochenplombierung. *Beitr Klin Chir* 1892; 9: 804–810.
6. Pietrzak WS. *Musculoskeletal tissue regeneration: biological materials and methods*. Human Press, Totowa, 2008, pp. 163–166.
7. Peltier LF and Bickel EY. The use of plaster of Paris to fill defects in bone. *Ann Surg* 1957; 146(1): 161–169.
8. Campana V, Milano G, Pagano E, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mater Sci: Mater Med* 2014; 25: 2445–2461.
9. Faour O, Dimitriou R, Cousins CA, et al. The use of bone graft substitutes in large cancellous voids: any specific needs? *Injury* 2011; 42: S87–S90.
10. Greenwald AS, Boden SD, Goldberg VM, et al. Bone-graft substitutes: facts, fictions and applications. *J Bone Joint Surg Am* 2001; 83: 98–103.
11. Schlickewie W and Schlickewie C. The use of bone substitutes in the treatment of bone defects—the clinical view and history. *Macromol Symp* 2007; 253: 10–23.
12. Pryor LS, Gage E, Langevin CJ, et al. Review of bone substitutes. *Craniomaxillofac Trauma Reconstr* 2009; 2(3): 151–160.
13. Giannoudis PV, Dinopoulos H and Tsiridis E. Bone substitutes: an update. *Injury* 2008; 36(Suppl. 3): S20–S27.
14. Bloemers FW, Blokhuis TJ, Patka P, et al. Autologous bone versus calcium-phosphate ceramics in treatment of experimental bone defects. *J Biomed Mater Res B Appl Biomater* 2003; 66(2): 526–531.
15. Gunzburg R, Szpalski M, Passuti N, et al. *The use of bone substitutes in spine surgery: a state of the art review*. Springer Science+Business Media, Berlin Heidelberg, 2002, 129 pp.
16. Hung YW, Ko WS, Liu WH, et al. Local review of treatment of hand enchondroma (artificial bone substitute versus autologous bone graft) in a tertiary referral centre: 13 years' experience. *Hong Kong Med J* 2015; 21(3): 217–223.
17. Liodaki E, Kraemer R, Mailaender P, et al. The use of bone graft substitute in hand surgery: a prospective observational study. *Medicine* 2016; 95(24): e3631.
18. Delloye C. Is there still a place for bone allografts in orthopedic surgery in 2011? *Bull Mem Acad R Med Belg* 2011; 166: 317–326.
19. Pieske O, Wittmann A, Zaspel J, et al. Autologous bone graft versus demineralized bone matrix in internal fixation of ununited long bones. *J Trauma Manag Outcomes* 2009; 3: 11.
20. Drosos GI, Kazakos KI, Kouzoumpasis P, et al. Safety and efficacy of commercially available demineralized bone matrix preparations: a critical review of clinical studies. *Injury* 2007; 4: S13–S21.
21. Finkemeier CG. Bone-grafting and bone-graft substitutes. *J Bone Joint Surg Am* 2002; 84-A: 454–464.
22. Keating JF and McQueen MM. Substitutes for autologous bone graft in orthopaedic trauma. *J Bone Joint Surg Br* 2001; 83: 3–8.
23. Saikia KC, Bhattacharya TD, Bhuyan SK, et al. Calcium phosphate ceramics as bone graft substitutes in filling bone tumor defects. *Indian J Orthop* 2008; 42(2): 169–172.
24. Tilkeridis K, Touzopoulos P, Ververidis A, et al. Use of demineralized bone matrix in spinal fusion. *World J Orthop* 2014; 5(1): 30–37.
25. Haute Autorité de Santé (HAS). *Substituts osseux. Révision de catégories homogènes de dispositifs médicaux*. Saint-Denis La Plaine: HAS, 2013.
26. Offner D, Wagner Q, Keller L, et al. Complications d'une autogreffe osseuse, et comparaison avec une allogreffe osseuse ou l'utilisation de BMPs (Bone Morphogenetic Proteins): une revue systématique de la littérature. *Le Journal de l'Orthopédie* 2017; 18(65): 3032–3043.
27. Younger EM and Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma* 1989; 3(3): 192–195.
28. Zimmermann G and Moghaddam A. Allograft bone matrix versus synthetic bone graft substitutes. *Injury* 2011; 42(Suppl. 2): S16–S21.
29. Khan SN, Cammisa FPJ, Sandhu HS, et al. The biology of bone grafting. *J Am Acad Orthop Surg* 2005; 13(1): 77–86.
30. Delloye C, van Cauter M, Dufrane D, et al. Local complications of massive bone allografts: an appraisal of their prevalence in 128 patients. *Acta Orthop Belg* 2014; 80: 196–204.
31. Mroz TE, Joyce MJ, Steinmetz MP, et al. Musculoskeletal allograft risks and recalls in the United States. *J Am Acad Orthop Surg* 2008; 16(10): 559–565.
32. Laurencin CT and El-Amin SF. Xenotransplantation in orthopaedic surgery. *J Am Acad Orthop Surg* 2008; 16(1): 4–8.
33. De Vries RBM, Oerlemans A, Trommelmans L, et al. Ethical aspects of tissue engineering: a review. *Tissue Eng Part B Rev* 2008; 14(4): 367–375.
34. Evaniew N, Tan V, Parasu N, et al. Use of a calcium sulfate-calcium phosphate synthetic bone graft composite in the surgical management of primary bone tumors. *Orthopedics* 2013; 36(2): e216–e222.
35. Kirkpatrick JS, Cornell CN, Hoang BH, et al. Bone void fillers. *J Am Acad Orthop Surg* 2010; 18(9): 576–579.
36. Jones CB. Biological basis of fracture healing. *J Orthop Trauma* 2005; 19: S1–S3.
37. Chung HJ, Hur JW, Ryu KS, et al. Surgical outcomes of anterior cervical fusion using deminaralized bone matrix as stand-alone graft material: single arm, pilot study. *Korean J Spine* 2016; 13(3): 114–119.
38. Han B, Tang B and Nimni ME. Combined effects of phosphatidylcholine and demineralized bone matrix on bone induction. *Connect Tissue Res* 2003; 44: 160–166.
39. Roberts TT and Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. *Organogenesis* 2012; 8(4): 114–124.
40. Flynn JM. *Fracture repair and bone grafting. OKU 10: orthopaedic knowledge update*. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2011, pp. 11–21.
41. Wang JC, Alanay A, Mark D, et al. A comparison of commercially available demineralized bone matrix for spinal fusion. *Eur Spine J* 2007; 16: 1233–1240.

42. Urist M. Bone: formation by autoinduction. *Science* 1965; 150: 893–899.
43. Urist M, Mikulski A and Boyd S. A chemosterilized antigen-extracted autodigest alloimplant for bone banks. *Arch Surg* 1975; 110(4): 416–428.
44. De Long WG Jr, Einhorn TA, Koval K, et al. Bone grafts and bone graft substitutes in orthopaedic trauma surgery. *J Bone Joint Surg Am* 2007; 89: 649–658.
45. Tuli SM and Singh AD. The osteoninductive property of decalcified bone matrix. An experimental study. *J Bone Joint Surg Br* 1978; 60: 116–123.
46. Kinney RC, Ziran BH, Hirshorn K, et al. Demineralized bone matrix for fracture healing: fact or fiction? *J Orthop Trauma* 2010; 24(Suppl. 1): S52–S55.
47. Albanese A, Licata ME, Polizzi B, et al. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. *Immun Ageing* 2013; 10: 23.
48. Nikolidakis D and Jansen JA. The biology of platelet-rich plasma and its application in oral surgery: literature review. *Tissue Eng Part B Rev* 2008; 14: 249–258.
49. El-Sharkawy H, Kantarci A, Deady J, et al. Platelet rich plasma: growth factors and pro- and anti-inflammatory properties. *J Periodontol* 2007; 78: 661–669.
50. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost* 2004; 91: 4–15.
51. Rickert D, Huddleston Slater JJR, Meijer HJA, et al. Maxillary sinus lift with solely autogenous bone compared to a combination of autogenous bone and growth factors or (solely) bone substitutes. A systematic review. *Int J Oral Maxillofac Surg* 2012; 41: 160–167.
52. Sanchez AR, Sheridan PJ and Kupp LI. Is platelet-rich plasma the perfect enhancement factor? A current review. *Int J Oral Maxillofac Implants* 2003; 18: 93–103.
53. Ozdemir B and Okte E. Treatment of intrabony defects with betatricalciumphosphate alone and in combination with platelet-rich plasma. *J Biomed Mater Res B Appl Biomater* 2012; 100: 976–983.
54. Cabbar F, Güler N, Kürkcü M, et al. The effect of bovine bone graft with or without platelet-rich plasma on maxillary sinus floor augmentation. *J Oral Maxillofac Surg* 2011; 69: 2537–2547.
55. Arenaz-Búa J, Luaces-Rey R, Sironvalle-Soliva S, et al. A comparative study of platelet-rich plasma, hydroxyapatite, demineralized bone matrix and autologous bone to promote bone regeneration after mandibular impacted third molar extraction. *Med Oral Patol Oral Cir Bucal* 2010; 15: 483–489.
56. Wu X, Shi W and Cao X. Multiplicity of BMP signaling in skeletal development. *Ann N Y Acad Sci* 2007; 1116: 29–49.
57. Cochran DL, Schenk R, Buser D, et al. Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants. *J Periodontol* 1999; 70(2): 139–150.
58. Chai F, Raoul G, Wiss A, et al. Bone substitutes: classification and concerns. *Rev Stomatol Chir Maxillofac* 2011; 112(4): 212–221.
59. Porter JR, Ruckh TT and Popat KC. Bone tissue engineering: a review in bone biomimetics and drug delivery strategies. *Biotechnol Prog* 2009; 25(6): 1539–1560.
60. Burks MV and Nair L. Long term effects of bone morphogenetic protein-based treatments in humans. *J Long Term Eff Med Implants* 2010; 20(4): 277–293.
61. Agarwal R, Williams K, Umscheid CA, et al. Osteoinductive bone graft substitutes for lumbar fusion: a systematic review. *J Neurosurg Spine* 2009; 11(6): 729–740.
62. Carragee EJ, Hurwitz EL and Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J* 2011; 11(6): 471–491.
63. Epstein NE. Complications due to the use of BMP/INFUSE in spine surgery: the evidence continues to mount. *Surg Neurol Int* 2013; 4(Suppl. 5): S343–S352.
64. Castro FPJ. Role of activated growth factors in lumbar spinal fusions. *J Spinal Disord Tech* 2004; 17(5): 380–384.
65. Tressler MA, Richards JE, Sofianos D, et al. Bone morphogenetic protein-2 compared to autologous iliac crest bone graft in the treatment of long bone nonunion. *Orthopedics* 2011; 34(12): e877–e884.
66. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. *J Bone Joint Surg Am* 2001; 83-A(Suppl. 1 Pt2): S151–S158.
67. Ghosh SK, Nandi SK, Kundu B, et al. In vivo response of porous hydroxyapatite and beta tricalcium phosphate prepared by aqueous solution combustion method and comparison with bioglass scaffolds. *J Biomed Mater Res B Appl Biomater* 2008; 86: 217–227.
68. Nandi SK, Kundu B, Ghosh SK, et al. Efficacy of nanohydroxyapatite prepared by an aqueous solution combustion technique in healing bone defects of goat. *J Vet Sci* 2008; 9: 183–191.
69. Koshino T, Murase T, Takagi T, et al. New bone formation around porous hydroxyapatite wedge implanted in opening wedge high tibial osteotomy in patients with osteoarthritis. *Biomaterials* 2001; 22: 1579–1582.
70. Okazaki A, Koshino T, Saito T, et al. Osseous tissue reaction around hydroxyapatite block implanted into proximal metaphysis of tibia of rat with collagen-induced arthritis. *Biomaterials* 2000; 21: 483–487.
71. Daculsi G. Biphasic calcium phosphate concept applied to artificial bone, implant coating and injectable bone substitute. *Biomaterials* 1998; 19: 1473–1478.
72. Spivak JM and Hasharoni A. Use of hydroxyapatite in spine surgery. *Eur Spine J* 2001; 10: S197–S204.
73. Johnson KD, Frierson KE, Keller TS, et al. Porous ceramics as bone graft substitutes in long bone defects: a biomechanical, histological, and radiographic analysis. *J Orthop Res* 1996; 14: 351–369.
74. Xie J, Baumann MJ and McCabe LR. Osteoblasts respond to hydroxyapatite surfaces with immediate changes in gene expression. *J Biomed Mater Res A* 2004; 71(1): 108–117.
75. Chiroff RT, White EW, Weber KN, et al. Tissue ingrowth of replamineform implants. *J Biomed Mater* 1975; 9: 29–45.
76. Korovessis P, Koureas G, Zacharatos S, et al. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. *Eur Spine J* 2005; 14: 630–638.

77. Bucholz MP, Carlton A and Holmes RE. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop* 1989; 240: 53–62.
78. Khan SN, Tomin E and Lane JM. Clinical applications of bone graft substitutes. *Orthop Clin North Am* 2000; 31: 389–398.
79. Beuerlein MJS and McKee MD. Calcium sulfates: what is the evidence? *J Orthop Trauma* 2010; 24: S46–S51.
80. Blaha JD. Evolving technologies: new answers or new problems? Calcium sulfate bone void filler. *Orthopedics* 1998; 21: 1017–1019.
81. Urban RM, Turner TM, Hall DJ, et al. Increased bone formation using calcium sulfate-calcium phosphate composite graft. *Clin Orthop Relat Res* 2007; 459: 110–117.
82. Hak DJ. The use of osteoconductive bone graft substitutes in orthopaedic trauma. *J Am Acad Orthop Surg* 2007; 15: 525–536.
83. Podaropoulos L, Veis AA, Papadimitriou S, et al. Bone regeneration using beta-tricalcium phosphate in a calcium sulfate matrix. *J Oral Implantol* 2009; 35(1): 28–36.
84. Ostermann PA, Seligson D and Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg B* 1995; 77: 93–97.
85. Keating JF, Blachut PA, O'Brien PJ, et al. Reamed nailing of open tibial fractures: does the antibiotic bead pouch reduce the deep infection rate? *J Orthop Trauma* 1996; 10: 298–303.
86. Ferguson JY, Dudareva M, Riley ND, et al. The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. *Bone Joint J* 2014; 96-B(6): 829–836.
87. Thomas MV, Puleo DA and Al-Sabbagh M. Calcium sulfate: a review. *J Long Term Eff Med Implants* 2005; 15(6): 599–607.
88. Kelly CM, Wilkins RM, Gitelis S, et al. The use of a surgical grade calcium sulfate as a bone graft substitute. Results of a multicenter trial. *Clin Orthop Relat Res* 2001; 382: 42–50.
89. Ziran BH, Smith WR and Morgan SJ. Use of calcium-based demineralized bone matrix/allograft for nonunions and posttraumatic reconstruction of the appendicular skeleton. *J Trauma* 2006; 63: 1324–1328.
90. Brown WE, Chow LC. A new calcium phosphate water-setting cement, In: Brown WE Ed., Cements Research Progress, Westerville, 1986, pp. 352–379.
91. Russell TA and Leighton RK; on behalf of the Alpha-BSM Tibial Plateau Fracture Study Group. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. *J Bone Joint Surg Am* 2008; 90: 2057–2061.
92. Burguera EF, Xu HHK and Weir MD. Injectable and rapid-setting calcium phosphate bone cement with dicalcium phosphate dihydrate. *J Biomed Mater Res B Appl Biomater* 2006; 77(1): 126–134.
93. Afifi AM, Gordon CR, Pryor LS, et al. Calcium phosphate cements in skull reconstruction: a meta-analysis. *Plast Reconstr Surg* 2010; 126(4): 1300–1309.
94. Galois L and Mainard D. Bone ingrowth into two porous ceramics with different pore sizes: an experimental study. *Acta Orthop Belg* 2004; 70: 598–603.
95. Galois L, Mainard D and Delagoutte JP. Beta-tricalcium phosphate ceramic as a bone substitute in orthopaedic surgery. *Int Orthop* 2002; 26: 109–115.
96. Malhotra A and Habibovic P. Calcium phosphates and angiogenesis: implications and advances for bone regeneration. *Trends Biotechnol* 2016; 34(12): 983–992.
97. Shigaku S and Katsuyuki F. Beta-tricalcium phosphate as a bone graft substitute. *Jikeikai Med J* 2005; 52: 47–54.
98. Cheung HS and Haak MH. Growth of osteoblasts on porous calcium phosphate ceramic: an in vitro model for biocompatibility study. *Biomaterials* 1989; 10: 63–67.
99. Daculsi G and Passuti N. Effect of the macroporosity for osseous substitution of calcium phosphate ceramics. *Biomaterials* 1990; 11: 86–87.
100. Gaasbeck RDA, Toonen HG, van Heerwaarden RJ, et al. Mechanism of bone incorporation of β-TCP bone substitute in open wedge tibial osteotomy in patients. *Biomaterials* 2005; 26: 6713–6719.
101. Koerten HK and van der Meulen J. Degradation of calcium phosphate ceramics. *J Biomed Mater Res* 1999; 44: 78–86.
102. Dehoux E, Madi K, Fourati E, et al. High tibial open-wedge osteotomy using a tricalcium phosphate substitute: 70 cases with 18 months mean follow-up. *Rev Chir Orthop Reparatrice Appar Mot* 2005; 91: 143–148.
103. Bohner M. Calcium orthophosphates in medicine: from ceramics to calcium phosphate cements. *Injury* 2000; 31(Suppl. 4): 37–47.
104. Frayssinet P, Mathon D, Lerch A, et al. Osseointegration of composite calcium phosphate bioceramics. *J Biomed Mater Res* 2000; 50: 125–130.
105. Nery EB, LeGeros RZ, Lynch KL, et al. Tissue response to biphasic calcium phosphate ceramic with different ratios of HA/βTCP in periodontal osseous defects. *J Periodontol* 1992; 63: 729–735.
106. Geiger F, Beverungen M, Lorenz H, et al. Bone substitute effect on vascularization and bone remodeling after application of phVEGF165 transfected BMSC. *J Funct Biomater* 2012; 3: 313–326.
107. Daculsi G, LeGeros RZ, Heughebaert M, et al. Formation of carbonate-apatite crystals after implantation of calcium-phosphate ceramics. *Calcif Tissue Int* 1990; 46: 20–27.
108. LeGeros RZ, Parsons JR, Daculsi G, et al. Significance of the porosity and physical chemistry of calcium phosphate ceramics. Biodegradation-bioresorption. *Ann NY Acad Sci* 1988; 523: 268–271.
109. Chazono M, Tanaka T, Komaki H, et al. Bone formation and bioresorption after implantation of injectable beta-tricalcium phosphate granules-hyaluronate complex in rabbit bone defects. *J Biomed Mater Res A* 2004; 70(4): 542–549.
110. Eggli PS, Muller W and Schenk RK. Porous hydroxyapatite and tricalcium phosphate cylinders with two different pore size ranges implanted in the cancellous bone of rabbits. A comparative histomorphometric and histologic

study of bony ingrowth and implant substitution. *Clin Orthop Relat Res* 1988; 232: 127–138.
111. Buser D, Hoffmann B, Bernard JP, et al. Evaluation of filling materials in membrane—protected bone defects. A comparative histomorphometric study in the mandible of miniature pigs. *Clin Oral Implants Res* 1998; 9(3): 137–150.
112. Gouin F, Yaouanc F, Waast D, et al. Open wedge high tibial osteotomies: calcium-phosphate ceramic spacer versus autologous bone graft. *Orthop Traumatol Surg Res* 2010; 96(6): 637–645.
113. Bansal S, Chauhan V, Sharma S, et al. Evaluation of hydroxyapatite and beta-tricalcium phosphate mixed with bone marrow aspirate as a bone graft substitute for posterolateral spinal fusionIndian. *J Orthop* 2009; 43(3): 234–239.
114. Bansal R, Patil S, Chaubey KK, et al. Clinical evaluation of hydroxyapatite and β-tricalcium phosphate composite graft in the treatment of intrabony periodontal defect: a clinico-radiographic study. *J Indian Soc Periodontol* 2014; 18(5): 610–617.
115. Matsumine A, Myoui A, Kusuzaki K, et al. Calcium hydroxyapatite implants in bone tumour surgery: a long term follow up study. *J Bone Joint Surg Br* 2004; 86: 719–725.
116. Reddy R and Swamy MK. The use of hydroxyapatite as a bone graft substitute in orthopedic conditions. *Indian J Orthop* 2005; 39: 52–54.
117. Oh KJ, Ko YB, Jaiswal S, et al. Comparison of osteoconductivity and absorbability of beta-tricalcium phosphate and hydroxyapatite in clinical scenario of opening wedge high tibial osteotomy. *J Mater Sci Mater Med* 2016; 12: 179.
118. Rojbani H, Nyam M, Ohya K, et al. Evaluation of the osteoconductivity of α-tricalcium phosphate, β-tricalcium phosphate, and hydroxyapatite combined with or without simvastatin in rat calvarial defect. *J Biomed Mater Res A* 2011; 98(4): 488–498.
119. Lee KS, Chang JS, Kim JH, et al. The role of osteoclast in resorption of hydroxyapatite and β-tricalcium phosphate coating layer. *Key Eng Mater* 2009; 396–398: 81–84.
120. Schwarz F, Herten M, Ferrari D, et al. Guided bone regeneration at dehiscence-type defects using biphasic hydroxyapatite + beta tricalcium phosphate or a collagen coated natural bone mineral: as immunohistochemical study in dogs. *Int J Oral Maxillofac Surg* 2007; 36: 1198–1206.
121. Muschik M, Ludwig R, Halbhubner S, et al. B-tricalcium phosphate as a bone substitute for dorsal spinal fusion in adolescent idiopathic scoliosis: preliminary results of a prospective clinical study. *Eur Spine J* 2001; 10: S178–S184.
122. Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. *Clin Orthop Relat Res* 1981; 157: 259–278.
123. Fillingham YA, Lenart BA and Gitelis S. Function after injection of benign bone lesions with a bioceramic. *Clin Orthop Relat Res* 2012; 470(7): 2014–2020.
124. Hench LL, Splinter RJ, Allen WC, et al. Bonding mechanisms at the interface of ceramic prosthetic materials. *J Biomed Mater Res* 1971; 5: 117–141.
125. Krishnan V and Lakshmi T. Bioglass: a novel biocompatible innovation. *J Adv Pharm Technol Res* 2013; 4(2): 78–83.
126. Hench LL and Wilson J. Surface-active biomaterials. *Science* 1984; 226: 630–636.
127. Wallace KE, Hill RG, Pembroke JT, et al. Influence of sodium oxide content on bioactive glass properties. *J Mater Sci Mater Med* 1999; 10: 697–701.
128. Neo M, Nakamura T, Ohtsuki C, et al. Ultrastructural study of the A-W GC-bone interface after long-term implantation in rat and human bone. *J Biomed Mater Res* 1994; 28: 365–372.
129. Zhang H, Ye XJ and Li JS. Preparation and biocompatibility evaluation of apatite/wollastonite-derived porous bioactive glass ceramic scaffolds. *Biomed Mater* 2009; 4(4): 045007.
130. De Aza PN, Luklinska ZB, Santos C, et al. Mechanism of bone-like formation on a bioactive implant in vivo. *Biomaterials* 2003; 24: 1437–1445.
131. Moimas L, Biasotto M, Di LR, et al. Rabbit pilot study on the resorbability of three-dimensional bioactive glass fibre scaffolds. *Acta Biomater* 2006; 2: 191–199.
132. Rahaman MN, Day DE, Bal BS, et al. Bioactive glass in tissue engineering. *Acta Biomater* 2011; 7(6): 2355–2373.
133. Knowles J. Phosphate based glasses for medical application. *J Mater Chem* 2003; 13: 2395–2401.
134. Hench LL and Paschall HA. Histochemical responses at a materials interface. *J Biomed Mater Res* 1974; 5: 49–54.
135. Nandi SK, Roy S, Mukherjee P, et al. Orthopaedic applications of bone graft and graft substitutes: a review. *Indian J Med Res* 2010; 132: 15–30.
136. Wagner Q, Offner D, Idoux-Gillet Y, et al. Nanostructured implant combining mesenchymal cells and VEGF nanoparticles for enhanced engineered tissue vascularization. *Nanomedicine* 2016; 11: 2419–2430.
137. Eap S, Ferrand A, Palomares CM, et al. Electrospun nanofibrous 3D scaffold for bone tissue engineering. *Biomed Mater Eng* 2012; 22(1–3): 137–141.
138. Eap S, Keller L, Schiavi J, et al. A living thick nanofibrous implant bifunctionalized with active growth factor and stem cells for bone regeneration. *Int J Nanomedicine* 2015; 10: 1061–1075.
139. Ferrand A, Eap S, Richert L, et al. Osteogenetic properties of electrospun nanofibrous PCL scaffolds equipped with chitosan-based nanoreservoirs of growth factors. *Macromol Biosci* 2014; 14(1): 45–55.
140. Porter JR, Henson A and Popat KC. Biodegradable poly(epsilon-caprolactone) nanowires for bone tissue engineering applications. *Biomaterials* 2009; 30(5): 780–788.
141. Hernigou P and Ma W. Open wedge tibial osteotomy with acrylic bone cement as bone substitute. *Knee* 2001; 8: 103–110.
142. Laurencin C, Khan Y and El-Amin SF. Bone graft substitutes. *Expert Rev Med Devices* 2006; 3(1): 49–57.
143. Handoll HHG and Watts AC. Bone grafts and bone substitutes for treating distal radial fractures in adults. *Cochrane Database Syst Rev* 2008; 2: CD006836.

144. Carson JS and Bostrom MP. Synthetic bone scaffolds and fracture repair. *Injury* 2007; 38(Suppl. 1): S33–S37.
145. Rajaee SS, Bae HW, Kanim LE, et al. Spinal fusion in the United States: analysis of trends from 1998 to 2008. *Spine* 2012; 37: 67–76.
146. Gupta A, Kukkar N, Sharif K, et al. Bone graft substitutes for spine fusion: a brief review. *World J Orthop* 2015; 6(6): 449–456.
147. Vaccaro AR, Stubbs HA and Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. *Orthopedics* 2007; 30: 567–570.
148. Kang J, An H, Hilibrand A, et al. Grafton and local bone have comparable outcomes to iliac crest bone in instrumented single-level lumbar fusions. *Spine* 2012, 37: 1083–1091.
149. Cammisa FP, Lowery G, Garfin SR, et al. Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. *Spine* 2004; 29: 660–666.
150. Schizas C, Triantafyllopoulos D, Kosmopoulos V, et al. Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study. *Arch Orthop Trauma Surg* 2008; 128: 621–625.
151. An HS, Simpson JM, Glover JM, et al. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine* 1995; 20: 2211–2216.
152. Mashoof AA, Siddiqui SA, Otero M, et al. Supplementation of autogenous bone graft with coralline hydroxyapatite in posterior spine fusion for idiopathic adolescent scoliosis. *Orthopaedics* 2002; 25: 1073–1076.
153. Vaz K, Verma K, Protopsaltis T, et al. Bone grafting options for lumbar spine surgery: a review examining clinical efficacy and complications. *SAS J* 2010; 4(3): 75–86.
154. Epstein NE. A preliminary study of the efficacy of Beta Tricalcium Phosphate as a bone expander for instrumented posterolateral lumbar fusions. *J Spinal Disord Tech* 2006; 19: 424–429.
155. Brouwer R, Jakma T, Bierma-Zeinstra S, et al. Osteotomy for treating knee osteoarthritis. *Cochrane Database Syst Rev* 2005; 1: CD004019.
156. Meynet JC. Ostéotomie tibiale de valgisation par ouverture interne: place des substituts osseux. *Ann Orthop Ouest* 1998; 30: 171–174.
157. Romanet JP, Benoit J and Nordin JY. Utilisation de céramique d'hydroxyapatite de calcium comme substitut de greffe osseuse (Endobon*). Résultats sur 62 cas revus à 1 an. *Rev Chir Orthop* 1996; 87(Suppl. II): 17.
158. Van Hemert WLW, Willemms K, Anderson PG, et al. Tricalcium phosphate granules or rigid wedge preforms in open wedge high tibial osteotomy: a radiological study with a new evaluation system. *Knee* 2004; 11: 451–456.
159. Holmes RE, Bucholz RW and Mooney V. Porous hydroxyapatite as a bone graft substitute in metaphyseal defects. *J Bone Joint Surg* 1986; 68-A: 904–911.
160. Giuseffi SA, Replogle WH and Shelton WR. Opening-wedge high tibial osteotomy: review of 100 consecutive cases. *Arthroscopy* 2015; 31(11): 2128–2137.
161. Yu B, Han K, Ma H, et al. Treatment of tibial plateau fractures with high strength injectable calcium sulphate. *Int Orthop* 2009; 33(4): 1127–1133.
162. Mik G, Arkader A, Manteghi A, et al. Results of a minimally invasive technique for treatment of unicameral bone cysts. *Clin Orthop Relat Res* 2009; 467(11): 2949–2954.
163. Mirzayan R, Panossian V, Avedian R, et al. The use of calcium sulfate in the treatment of benign bone lesions. A preliminary report. *J Bone Joint Surg Am* 2001; 83(3): 355–358.
164. Kim JH, Oh JH, Han I, et al. Grafting using injectable calcium sulfate in bone tumor surgery: comparison with demineralized bone matrix-based grafting. *Clin Orthop Surg* 2011; 3: 191–201.
165. Werier JM. *Bone graft substitutes in oncology, paediatrics, and hip arthroplasty*. Canadian Orthopaedic Association's COA Bulletin, Ottawa 2011, p. 95.
166. Joeris A, Ondrus S, Planka L, et al. ChronOS inject in children with benign bone lesions: does it increase the healing rate? *Eur J Pediatr Surg* 2010; 20: 24–28.
167. Hou HY, Wu K, Wang CT, et al. Treatment of unicameral bone cyst: a comparative study of selected techniques. *J Bone Joint Surg Am* 2010; 92: 855–862.
168. Campanacci M, Capanna R, Fabbri N, et al. Curettage of giant cell tumor of bone, reconstruction with subchondral grafts and cement. *Chir Organi Mov* 1990; 75(1 Suppl.): 212–213.
169. Roffi A, Di Matteo B, Krishnakumar GS, et al. Platelet-rich plasma for the treatment of bone defects: from preclinical rational to evidence in the clinical practice. A systematic review. *Int Orthop* 2017; 41(2): 221–237.
170. Subramaniam P, Kumar K, Ramakrishna T, et al. Bone regeneration with plasma-rich-protein following enucleation of traumatic bone cyst. *Eur J Dent* 2013; 7(3): 377–381.
171. MacDonald KM, Swanstrom MM, McCarthy JJ, et al. Exaggerated inflammatory response after use of recombinant bone morphogenetic protein in recurrent unicameral bone cysts. *J Pediatr Orthop* 2010; 30(2): 199–205.
172. El-Adl G, Mostafa MF, Enan A, et al. Biphasic ceramic bone substitute mixed with autogenous bone marrow in the treatment of cavitary benign bone lesions. *Acta Orthop Belg* 2009; 75: 110–118.
173. Siegel HJ, Baird RC 3rd, Hall J, et al. The outcome of composite bone graft substitute used to treat cavitary bone defects. *Orthopedics* 2008; 31(8): 754.
174. Payne WT and Merrell G. Benign bony and soft tissue tumors of the hand. *J Hand Surg* 2010; 35: 1901–1910.
175. Schaller P and Baer W. Operative treatment of enchondromas of the hand: is cancellous bone grafting necessary? *Scand J Plast Reconstr Surg Hand Surg* 2009; 43: 279–285.
176. Bachoura A, Rice IS, Lubahn AR, et al. The surgical management of hand enchondroma without postcurettage void augmentation: authors' experience and a systematic review. *Hand* 2015; 10(3): 461–471.
177. Jakubietz MG, Gruenert JG and Jakubietz RG. The use of beta-tricalcium phosphate bone graft substitute in dorsally plated, comminuted distal radius fractures. *J Orthop Surg Res* 2011; 6: 24.
178. Fayaz HC, Giannoudis PV, Vrahas MS, et al. The role of stem cells in fracture healing and nonunion. *Int Orthop* 2011; 35: 1587–1597.
179. Russell AT, Taylor CJ and Lavelle DG. Fractures of tibia and fibula. In: Bucholz RW, Heckman JD and Court-Brown CM (eds) *Rockwood and Green's: Fractures in*

adults, Lippincott Williams & Wilkins, Philadelphia vol. 3, 1991, pp. 1915–1982.
180. Einhorn TA: Enhancement of fracture-healing. *J Bone Joint Surg Am* 1995; 77: 940–956.
181. Borrelli J, Prickett WD and Ricci WM. Treatment of nonunions and On the contrary, allogenic osseous defects with bone graft and calcium sulfate. *Clin Orthop Relat Res* 2003; 411: 245–254.
182. Gómez-Barrena E, Rosset P, Gebhard F, et al. Feasibility and safety of treating non-unions in tibia, femur and humerus with autologous, expanded, bone marrow-derived mesenchymal stromal cells associated with biphasic calcium phosphate biomaterials in a multicentric, non-comparative trial. *Biomaterials*. Epub ahead of print 19 March 2018. DOI: 10.1016/j.biomaterials.2018.03.033.
183. Bourgeois D, Bouchard P and Mattout C. Epidemiology of periodontal status in dentate adults in France, 2002–2003. *J Periodontal Res* 2007; 42(3): 219–227.
184. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, et al. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Ann Periodontol* 2003; 8(1): 227–265.
185. Bayerlein T, Mundt T, Mack F, et al. Bone graft substitutes in periodontal and peri-implant bone regeneration. *Folia Morphol* 2006; 65(1): 66–69.
186. Froum SJ, Weinberg MA and Tarnow D. Comparison of bioactive glass synthetic bone graft particles and open debridement in the treatment of human periodontal defects. A clinical study. *J Periodontol* 1998; 69: 698–709.
187. Del Fabbro M, Bortolin M, Taschieri S, et al. Is platelet concentrate advantageous for the surgical treatment of periodontal diseases? A systematic review and meta-analysis. *J Periodontol* 2011; 82: 1100–1111.
188. Piemontese M, Aspriello SD, Rubini C, et al. Treatment of periodontal intrabony defects with demineralized freeze-dried bone allograft in combination with platelet-rich plasma: a comparative clinical trial. *J Periodontol* 2008; 79: 802–810.
189. Keceli HG, Sengun D, Berberoğlu A, et al. Use of platelet gel with connective tissue grafts for root coverage: a randomized-controlled trial. *J Clin Periodontol* 2008; 35: 255–262.
190. Hanes PJ. Bone replacement grafts for the treatment of periodontal intrabony defects. *Oral Maxillofac Surg Clin North Am* 2007; 19(4): 499–512.
191. Poeschl PW, Ziya-Ghazvini F, Schicho K, et al. Application of platelet-rich plasma for enhanced bone regeneration in grafted sinus. *J Oral Maxillofac Surg* 2012; 70: 657–664.
192. Khairy NM, Shendy EE, Askar NA, et al. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation (randomized clinical trial). *J Oral Maxillofac Surg* 2013; 42(2): 249–255.
193. Esposito M, Grusovin MG, Rees J, et al. Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. *Cochrane Database Syst Rev* 2010; 17: CD008397.
194. Irinakis T. Efficacy of injectable demineralized bone matrix as graft material during sinus elevation surgery with simultaneous implant placement in the posterior maxilla: clinical evaluation of 49 sinuses. *J Oral Maxillofac Surg* 2011; 69: 134–141.
195. Sohn DS, Bae MS, Choi BJ, et al. Efficacy of demineralized bone matrix paste for maxillary sinus augmentation: a histologic and clinical study in humans. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 108: e30–e35.
196. Aly LAA and Hammouda NI. Evaluation of implant stability simultaneously placed with sinus lift augmented with putty versus powder form of demineralized bone matrix in atrophied posterior maxilla. *Future Dental Journal* 2017; 3: 28–34.
197. Nkenke E and Stelzle F. Clinical outcomes of sinus floor augmentation for implant placement using autogenous bone or bone substitutes: a systematic review. *Clin Oral Impl Res* 2009; 20(Suppl. 4): 124–133.
198. Bocanegra-Perez S, Vicente-Barrero M, Knezevic M, et al. Use of platelet-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw. *Int J Oral Maxillofac Surg* 2012; 41: 1410–1415.
199. Mozzati M, Gallesio G, Arata V, et al. Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: a report of 32 cases. *Oral Oncol* 2012; 48(5): 469–474.
200. Coviello V, Peluso F, Dehkhargani SZ, et al. Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients. *J Biol Regul Homeost Agents* 2012; 26: 151–155.
201. Geurts J, Chris Arts JJ and Walenkamp GH. Bone graft substitutes in active or suspected infection. Contraindicated or not? *Injury* 2011; 42(Suppl. 2): S82–S86.
202. Lalidou F, Kolios G and Drosos GI. Bone infections and bone graft substitutes for local antibiotic therapy. *Surg Technol Int* 2014; 24: 353–362.
203. Silverman LD, Lukashova L, Herman OT, et al. Release of gentamicin from a tricalcium phosphate bone implant. *J Orthop Res* 2007; 25(1): 23–29.
204. Takigami I, Ito Y, Ishimaru D, et al. Two-stage revision surgery for hip prosthesis infection using antibiotic-loaded porous hydroxyapatite blocks. *Arch Orthop Trauma Surg* 2010; 130(10): 1221–1226.
205. Mousset B, Benoit MA, Bouillet R, et al. Biodegradable implants for potential use in bone infection. *Int Orthop* 1995; 19: 157–161.
206. Ginebra MP, Canal C, Espanol M, et al. Calcium phosphate cements as drug delivery materials. *Adv Drug Deliv Rev* 2012; 64(12): 1090–1110.
207. Espanol M, Perez RA, Montufar EB, et al. Intrinsic porosity of calcium phosphate cements and its significance for drug delivery and tissue engineering applications. *Acta Biomater* 2009; 5: 2752–2762.
208. Lindfors NC, Hyvönen P, Nyyssönen M, et al. Bioactive glass S53P4 as bone graft substitute in treatment of osteomyelitis. *Bone* 2010; 47(2): 212–218.
209. Aydin S, Kucukyuruk B, Abuzayed B, et al. Cranioplasty: review of materials and techniques. *J Neurosci Rural Pract* 2011; 2(2): 162–167.
210. Cho YJ and Kang SH. Review of cranioplasty after decompressive craniectomy. *Korean J Neurotrauma* 2017; 13(1): 9–14.
211. Piitulainen JM, Kauko T, Aitasolo KM, et al. Outcomes of cranioplasty with synthetic materials and autologous bone grafts. *World Neurosurg* 2015; 83: 708–714.

212. Gosain AK. Hydroxyapatite cement paste cranioplasty for the treatment of temporal hollowing after cranial vault remodeling in a growing child. *J Craniofac Surg* 1997; 8: 506–511.
213. Plum AW and Tatum SA. A comparison between autograft alone, bone cement, and demineralized bone matrix in cranioplasty. *Laryngoscope* 2015; 125: 1322–1327.
214. Gladstone HB, McDermott MW and Cooke DD. Implants for cranioplasty. *Otolaryngol Clin North Am* 1995; 28: 381–400.
215. Lieberman IH, Togawa D and Kayanja MM. Vertebroplasty and kyphoplasty: filler materials. *Spine J* 2005; 5: 305S–316S.
216. Gangi A, Kastler BA and Dietemann JL. Percutaneous vertebroplasty guided by a combination of CT and fluoroscopy. *AJNR Am J Neuroradiol* 1994; 15: 83–86.
217. He Z, Zhai Q, Hu M, et al. Bone cements for percutaneous vertebroplasty and balloon kyphoplasty: current status and future developments. *J Orthop Translat* 2015; 3: 1–11.
218. Phillips FM, Ho E, Campbell-Hupp M, et al. Early radiographic and clinical results of balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Spine* 2003; 28: 2260–2265.
219. Garfin SR, Yuan HA and Reily MA. New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. *Spine* 2001; 26: 1511–1515.
220. Khairoun I, Magne D, Gauthier O, et al. In vitro characterization and in vivo properties of a carbonated apatite bone cement. *J Biomed Mater Res* 2002; 60: 633–642.
221. Low KL, Tan SH, Zein SH, et al. Calcium phosphate-based composites as injectable bone substitute materials. *J Biomed Mater Res B Appl Biomater* 2010; 94: 273–286.
222. Turner TM, Urban RM, Singh K, et al. Vertebroplasty comparing injectable calcium phosphate cement compared with polymethylmethacrylate in a unique canine vertebral body large defect model. *Spine J* 2008; 8(3): 482–487.
223. Vlad MD, Sindilar EV, Marinoso ML, et al. Osteogenic biphasic calcium sulphate dihydrate/iron-modified alpha-tricalcium phosphate bone cement for spinal applications: in vivo study. *Acta Biomater* 2010; 6: 607–616.
224. Blom AW, Wylde V, Livesey C, et al. Impaction bone grafting of the acetabulum at hip revision using a mix of bone chips and a biphasic porous ceramic bone graft substitute. *Acta Orthop* 2009; 80: 150–154.
225. McNamara IR. Impaction bone grafting in revision hip surgery: past, present and future. *Cell Tissue Bank* 2010; 11: 57–73.
226. Suzuki K, Park BJ, Adusumilli PS, et al. Chest wall reconstruction using a methyl methacrylate neo-rib and mesh. *Ann Thorac Surg* 2015; 100(2): 744–747.
227. Kujala S, Raatikainen T, Ryhanen J, et al. Composite implant of native bovine bone morphogenetic protein (BMP) and biocoral in the treatment of scaphoid nonunions—a preliminary study. *Scand J Surg* 2002; 91: 186–190.
228. Koo KT, Polimeni G, Qahash M, et al. Periodontal repair in dogs: guided tissue regeneration enhances bone formation in sites implanted with a coral-derived calcium carbonate biomaterial. *J Clin Periodontol* 2005; 32: 104–110.
229. Fondi C and Franchi A. Definition of bone necrosis by the pathologist. *Clin Cases Miner Bone Metab* 2007; 4(1): 21–26.
230. Glowacki J. Angiogenesis in fracture repair. *Clin Orthop Relat Res* 1998; 355: S82–S89.
231. Gotz W, Reichert C, Canullo L, et al. Coupling of osteogenesis and angiogenesis in bone substitute healing—a brief overview. *Ann Anat* 2012; 194: 171–173.
232. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. *Clin Orthop Relat Res* 2002; 395: 81–98.
233. Axelrad TW, Kakar S and Einhorn TA. New technologies for the enhancement of skeletal repair. *Injury* 2007; 38: S49–S62.
234. Muschler GF, Nitto H, Boehm CA, et al. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. *J Orthop Res* 2001; 19: 117–125.
235. Schmidt-Bleek K, Schell H, Schulz N, et al. Inflammatory phase of bone healing initiates the regenerative healing cascade. *Cell Tissue Res* 2012; 347: 567–573.
236. Giannoudis PV, Einhorn TA, Schmidmaier G, et al. The diamond concept—open questions. *Injury* 2008; 39(Suppl. 2): S5–S8.
237. Karageorgiou V and Kaplan D. Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials* 2005; 26: 5474–5491.
238. Hulbert SF, Cooke FW, Klawitter JJ, et al. Attachment of prostheses to the musculoskeletal system by tissue in growth and mechanical inter locking. *J Biomed Mater* 1973; 7: 1–23.
239. Yuan H, Kurashina K, de Bruijn JD, et al. A preliminary study on osteoinduction of two kinds of calcium phosphate ceramics. *Biomaterials* 1999; 20(19): 1799–1806.
240. Lu JX. Role of interconnections in porous bioceramics on bone recolonization in vitro and in vivo. *J Mater Sci Mater Med* 1999; 10: 111–120.
241. Tsuruga E, Takita H, Itoh H, et al. Pore size of porous hydroxyapatite as the cell-substratum controls BMP-induced osteogenesis. *J Biochem* 1997; 121(2): 317–324.
242. Le Huec JC, Schaeverbeke T, Clement D, et al. Influence of porosity on the mechanical resistance of hydroxyapatite ceramics under compressive stress. *Biomaterials* 1995; 16: 113–118.
243. Guerrero J, Catros S, Derkaoui SM, et al. Cell interactions between human progenitor-derived endothelial cells and human mesenchymal stem cells in a three-dimensional macroporous plysaccharide-based scaffold promote osteogenesis. *Acta Biomater* 2013; 9: 8200–8213.
244. Offner D, Wagner Q, Idoux-Gillet Y, et al. Hybrid collagen sponge and stem cells as a new combined scaffold able to induce the re-organization of endothelial cells into clustered networks. *Biomed Mater Eng* 2017; 28(S1): S185–S192.