Good general review of bone grafts

Review

Journal of Tissue Engineering
Volume 9: 1–18

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

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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]

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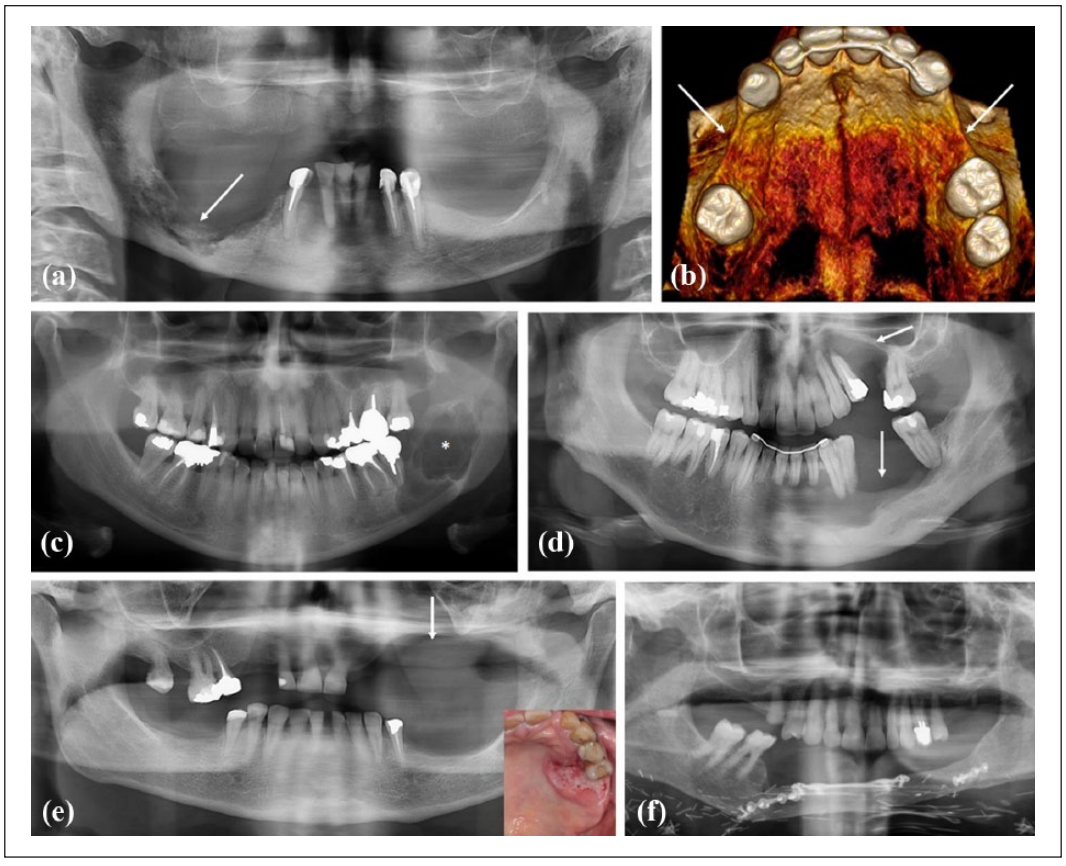

Figure 1. Various origins of bone defects: (a) Panoramic X-ray. Bone defect of the mandible right body corresponding to an osteonecrosis of the jaw in relation to denosumab taking. (b) 3D-reconstructed view of upper jaw. Bilateral bone defect of premolar regions associated to tooth agenesis in a young 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

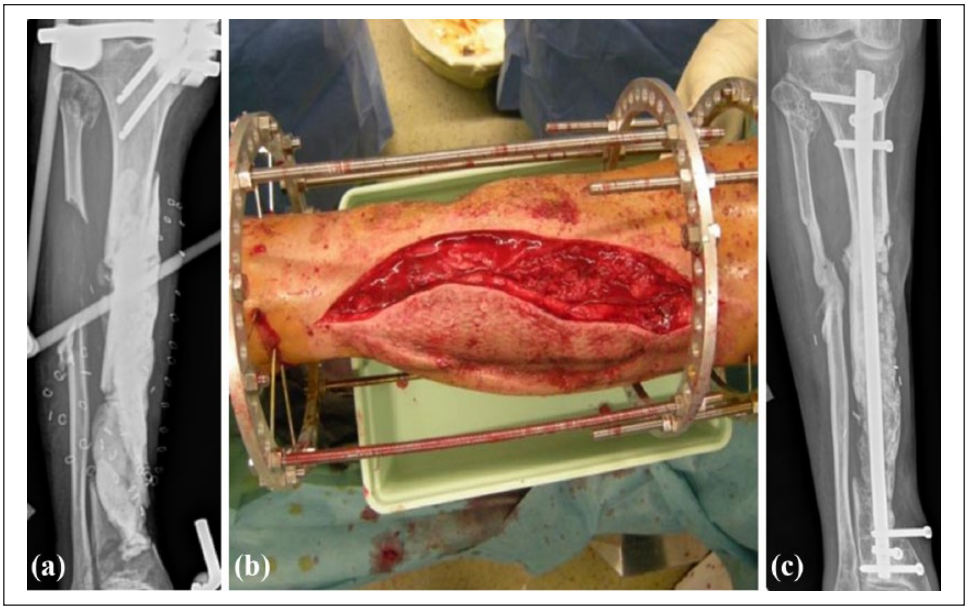

Figure 2. (a) Radiographical view of a right fibula bone loss, after a road traffic accident in a 24year-old woman, with an external fixator. (b) Surgical procedure with the use of allogeneic bone chips. (c) Radiographical view 4months later (courtesy of Dr D. Brinkert).

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]

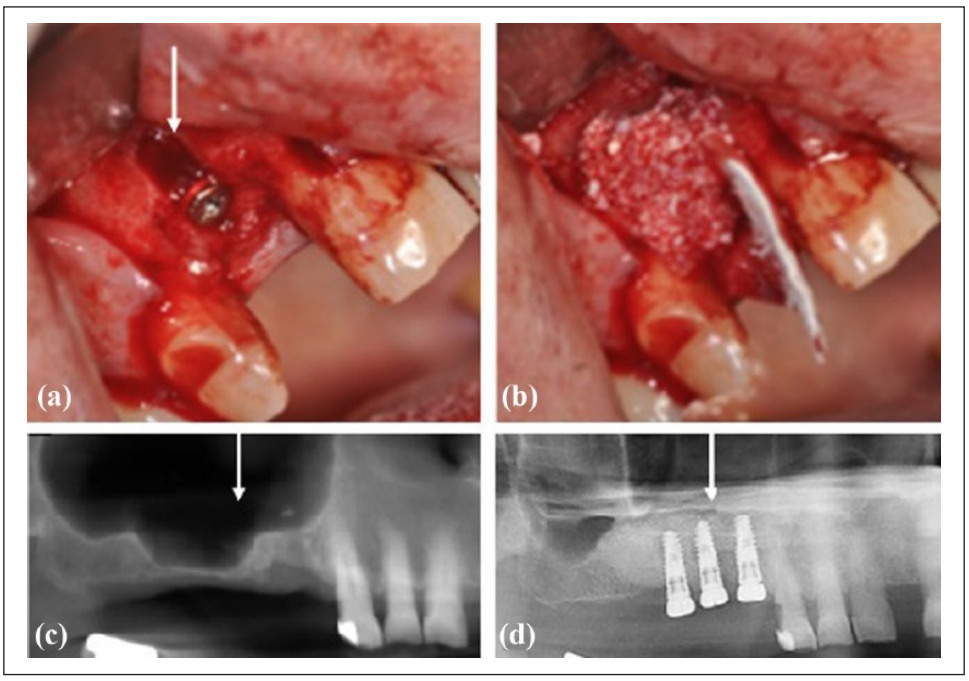

Figure 3. Use of DBM in oral procedures: (a, b) DBM used to fill buccal bone defect (arrow) after implant placement. (c, d) Panoramic X-rays of a maxillary right sinus before (c) and after sinus floor elevation (d) filled with DBM and dental implants placement.

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.

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