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Recent advances in bone graft substitute for oral and maxillofacial applications: a review

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Abstract

Bone grafts are generally used to promote new bone formation and guided tissue regeneration. It's more commonly used in oral and maxillofacial reconstruction. To review and update of the biomedical application and clinical outcomes of most used bone graft substitutes in different procedures: sinus elevation, socket preservation and alveolar bone augmentation. A literature review was conducted using MEDLINE, MEDPILOT and SYSTEMATIC REVIEWS. It concentrated on manuscripts and overviews published in the last seventeen years (2000-2017). The key terms employed were names of natural and synthetics different recants bone graft scaffold substitutes, growths factors, stem cell and their combinations. The results of clinical studies and animal trials were emphasized. Clinical evidence of BMPs application and dosage remains limited and controversial results on osteconductivity of Ca-P bone substitute's application are present. The alveolar ride preservation and implant position after extraction depend on the attentive surgery procedure and the properties of using materials which capable to maintain the prior space and be helpful in implant support and bone tissue regeneration. Novel materials will likely to build up on innovative polymeric platforms with controlled biophysical and biological properties that enable the targeted delivery of growth factors and cells.

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Introduction

The alveolar bone process is a specialised part of the jaw that supports teeth. It undergoes significant structural changes at the tooth extraction site, which considered a significant clinical problem in implant and conventional restorative dentistry as well. Within the first 24 - 48 hr after exodontia, a clot blood cells fill the entire socket and followed by vasodilation, cystic migration, and fibrin layer formation. During 4 – 5 days, this clot is replaced by granulation tissues, representing a scaffold that aid in angiogenesis and cell migration. Osteoclasts take active alveolar bone crest resorption place. The clot becomes organised into a microvascular network and fibroplasia by the 2nd week of the extraction. Then, within the 3rd week, the new woven bone island from the periphery of the wound has filled the socket (Araújo *et al.*, 2015). Within 4 – 5 weeks, the wound will re-epithelialized with slight or no scar tissue formation. Radiographic sign of ossification become apparent at 6 – 8 weeks. Finally, at 16 weeks, the socket's bone fill is complete with little identification of osteogenesis. After 6 – 8 month of remodelling, the extraction site becomes less distinct. Even though bone filling of the extraction socket will last for several months, it won't reach the level of bone height of the adjacent teeth (Farina and Trombelli, 2011).

The remodelling process postextraction results in a significant ridge morphology reduced in vertical and horizontal dimension and the collapse of the surrounding tissue. In the bone level, 2/3 of this change occurred in the first three months postextraction with a buccal wall vertical reduction of 1.2 mm and about 5 – 7 mm of horizontal bone reduction. Over a 6 – 12 month period, about 50% of the initial ridge width changes that corresponded by 2.0 – 4.5 mm reduction of vertical height (Iasella *et al.*, 2003). As a consequence, the bone filling of the socket won't reach the bone level of the adjacent teeth(Farina and Trombelli, 2011).

The alveolar ridge resorption remains all through at a slower rate and resulting in loss of the variable amount of jaw bone structure.

Clinical studies reported, in first few months following tooth extraction, 3-5 mm in ridge width and 1-3 mm in alveolar ridge height may be resorbed. Unfortunately, the bone loss is permanent and has severe consequences regarding aesthetic and dental implant placement, as sufficient alveolar ridges are essential to successful rehabilitation (Iasella *et al.*, 2003). Subsequently, after teeth extractions, and Orofacial myology can address problems. In addition to, the adjacent teeth shift causing chewing problem, muscular collapse causing facial wrinkles and loss of soft tissue volume which is essential in providing camouflage of restorative components. Various regenerative procedures using bone grafts and multiple substitutes together with the use of barrier membranes have been suggested. The bone graft and its substitutes recommended include autogenic, allogeneic and xenogeneic bone and alloplast. Although some of these were able to preserve a certain degree of dimensional bone tissue alterations following tooth extraction, the quality and the quantity of the newly formed bone have been different, and their existence often obstructs the normal healing process (Heberer *et al.*, 2011).

The regeneration depends on the availability of diverse characteristics such as osteogenesis via stem cells(Yamada *et al.*, 2004), osteoconduction using grafting material as a scaffold(Fickl *et al.*, 2008) osteoinduction using growth factors (Calixto *et al.*, 2007), and osteointegration in case of implant (Rani *et al.*, 2012). Unlikely, not all bone substitutes are suitable for every clinical use or provide all those four characteristic features.

In the interest of updating clinicians' knowledge on the bone graft and bone graft substitutes available for bone preservation, this review discusses some commonly used bone and bone graft substitutes and its biomedical application, advantages, disadvantages and clinical outcomes. This review would potentially help the clinician and researcher to know which is the most widely bone graft material used and studied and to assist them to decide which type is more suitable than another indefinite site.

Method

Search strategy

An electronic search of MEDLINE, MEDPILOT, and SYSTEMATIC REVIEWS were undertaken. It concentrated on manuscripts and overviews published in the last seventeen years (2000-2017). The search strategy was of Mesh keywords and text word of names of natural and synthetics different recants bone graft scaffold substitutes, growths factors, stem cell and their combinations. Abstracts of the resulting articles were reviewed against the inclusion criteria. Full-text copies of promising abstracts were obtained for further scrutiny, and an initial list of eligible papers was generated. A hand search was performed from the reference lists of the included studies and reviews to identify potentially available studies. The results of 48 studies were included in this review and emphasised.

Inclusion criteria: Full-text, English language, clinical studies, animal trials (preclinical studies) articles in the scope of bone regeneration in Oral and Maxillofacial sites, and the that focused on assessment of type bone graft in bone regeneration quantity and quality as the primary aim of research.

Exclusive criteria: Studies with neither goal nor research question described or complete data, opinion or conference reports, abstracts, in vitro studies, review papers, studies that were not to assess or compare the bone grafts materials, and studies that had not a clear description of the context, the research question, sampling, study design, data collection, data analysis, and findings.

Bone grafts materials

Bone grafts are transplantable materials that can be placed in a bony defect to aid in the reconstruction and healing of the bone. Bone graft was first established in the 1800s (Meeder and Eggers, 1994). Orthopaedic, neuro, craniofacial surgeons and periodontists use them to provide support, fill defects, and enhance normal biologic healing of skeletal tissue defects. Several types of bone grafts have been studied over the years, and the search of the ideal bone graft replacement is still continued. Summarization of most commonly used bone grafts together with its advantages, disadvantages and biomedical application a is showed in Table 1. In general, there are four types of bone grafts which are;

Autograft bone

Autograft bone is referred to bone which is harvested from one site and transplanted to another part of the recipient's body. It provides the three essential components that are necessary to generate and maintain bone: scaffolding for growth factors for osteoinduction, osteoconduction, and progenitor cells for osteogenesis (KUBO *et al.*, 2004). It can be provided in different chaps such as matchsticks, chips, morsels, paste, strips, segments and blocks.

Depending on the harvested site, it may be cortical or cancellous. The revascularisation of the cancellous grafts occurs in approximately 2 weeks, while cortical might take two months or more to revascularize. Cancellous bone has a higher percentage of cells; thereby has more osteogenic potential. Conversely, cortical bone has fewer cells. However, it has higher levels of Bone morphogenic proteins (BMP's), and is useful when immediate framework or 3D augmentation is needed (Zipfel *et al.*, 2003).

The most versatile bone graft reserve is the iliac crest. It is subcutaneous and easy to harvest in prone, lateral, supine or other positions. It is expendable and has a vast reserve of cancellous and cortical bone. Other sites commonly used for autograft are tibia and fibula. The most common sites harvested intra-orally are around the surgical site, ascending ramus, chin, and tuberosity (Darby *et al.*, 2008). Garg (2001) demonstrated that intraoral bone harvested from the ramus and coronoid process of the mandible could serve as a good source of autogenous bone(Garg *et al.*, 2015). Nevertheless, intraoral sites do not provide sufficient quantities of bone for a grafting medium on large alveolar defects (Nkenke *et al.*, 2002). In quantified and compared the amount of bone that could be harvested, the symphysis had the highest average thickness, whereas the ramus had the highest

average cortical bone area and volume harvested(Yates *et al.*, 2013). However, the coronoid process of the mandible can provide adequate quantity and quality of the bone for selected oral and maxillofacial reconstructions, such as the reconstruction of deformities due to alveolar atrophy, trauma, or temporomandibular joint ankyloses (Sabhlok *et al.*, 2014).

Autogenous bone remains the standard graft for stimulating bone healing and for filling bone defects. Superior osteogenic capacity, rapid incorporation, lack of disease transmission and union with a lack of immunologic deliberations makes autograft ideal. Nevertheless, amount of bone tissue that can be harvested from autograft are restricted, weakening of donor bone, donor site morbidity, increased blood. Del Fabbro *et al.* in their systematic review (2004) reported that the survival rate of implants placed in the grafted sinus utilizing 100% autogenous bone was an 88% and, they stated that 418 implants failed due to graft resorption from 3,398 implants placed (Del Fabbro *et al.*, 2005). Besides, they found increased morbidities such as increased risk of infection, pain and postoperative neurosensory deficit. Thus, there is an obvious need for a bone graft alternative to serving as an off the shelf substitute to autograft. Therefore, many types of bone-graft substitutes have been searched and developed to eliminate and drawbacks of the autogenous graft.

Allograft bone substitutes

Allograft bone is bone harvested from genetically non-identical members of the same species. Allograft is osteoconductive and osteointegrative and may exhibit an osteoinductive characteristic. However, it has not osteogenic potential because it does not contain an osteogenic cell. Virtually any size or shape of graft needed may be supplied by contemporary bone banks.

Allograft bone can be processed as mineralised or demineralised, fresh-frozen or freeze-dried bone forms. The advantages of allograft bone upon the autograft are that it avoids the morbidity associated with donor-site complications of autograft transplantation and is readily available in the desired quantity and configuration. Furthermore, the use of the allograft bone affords considerable time saving during Surgery. Fresh-frozen allograft is harvested and banked at least six months aseptically under 80°C to be available for human recipients(Simpson *et al.*, 2007). It provides osteoinductive and osteoconductive properties whereas freeze-dried bone forms are just giving osteoconductive properties. It is supplied in various forms such as cortico-cancellous, cancellous or cortical with different configurations such as powder, cortical chips, cancellous cubes and cortical struts. The processing procedure is the principal factor in determining the biological and physical properties of the material. Guidelines on donor selection, tissue processing, bone antigenicity diminishing and record-keeping procedures have been developed by bone banks to supply of safe bone. However, the allograft processing makes allograft loss its osteogenesis and osteoinductive potential and reduces the mechanical strength of the graft. Furthermore, freeze-drying retard the graft incorporation(Giannoudis *et al.*, 2005). However, diminishing immune response caused by freezing is more important than the negative effects of freezing on graft incorporation.

Many studies found that fresh-frozen bone is effective and reliable as an inlay and onlay grafting material in restoring atrophic alveolar bone in humans (Contar *et al.*, 2009; Contar *et al.*, 2011). Use of fresh-frozen tibia bone chips in the reconstruction of maxillary alveolar bone ridges has been evaluated clinically and histologically in patients who had atrophic bone ridge and need bone grafts before implant placement. This study showed that this material is a suitable alternative to autografts as it can be successful as graft material for the maxillary ridge preservation and before implant insertion (Contar *et al.*, 2011).

However, Allografting introduces the risk of post-operative infections (such as HIV infection, and hepatitis (C) and invoke the host immune response(Bauer and Muschler, 2000). Many

processing techniques have been used to reduce the risk of the allograft. Liquid nitrogen-treated allogeneic dentine grafts were found to accelerate bone healing in femurs rabbited effects. It showed to be biocompatible, non-toxic, non-antigenic and space-maintaining (Al-Namnam *et al.,* 2010).

Table 1. Properties of recent bone and bone graft substitutes used for oral and maxillofacial surgical applications.

Bone and bone substitute	Chemical composition structure	Biological behaviour	Disadvantages	RS	OG	OI	OC	P
		1-	Biological					
		i.	a- Human source					
Autogenous bone	A dense organic matrix, an inorganic and mineral	Scaffold/Carrier/cells/growth factor/signals	Need to obtain the graft from another surgical site, increase operation time	+	+	+	+	+
Demineralized freeze-dried bone allograft	Contains collagen, GFs, and proteins that are extracted from the allograft bone	Scaffold/Carrier/Extender	Slight risk of immunogenicity and pathogenicity	+	+/-	+	+	+
Freeze-dried bone allograft	Consists of organic and an inorganic matrix	Scaffold/Carrier/Extender	Regenerated bone at 8 months is softer than that made of the other materials (Fugazzotto, 2009).Slight risk of immunogenicity and pathogenicity	+	+/-	+	+	+
INFUSE® Bone Graft	Contains recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) placed on an absorbable collagen sponge (ACS) (Labres *et al.*, 2014)	Scaffold/Carrier/ growth factor	Hypersensitivity, elicit antibodies that are capable of crossing the placenta. Women of childbearing potential should be advised to not become pregnant for one year following treatment with it	+	-	+	+	-
DynaBlast	A combination of mineralized and demineralized allogenic bone	Scaffold/expander	Slight risk of immunogenicity and pathogenicity (Berberi *et al.*, 2014)	+	-	-	+	+
		b-	Xenogeneic source					
Deproteinised Bovine-derived bone mineral	Bovine hydroxyapatite	Scaffold/ carrier	May take more than 12 months to reinsert appropriately (Fugazzotto, 2009)	+	-	+	+	+
Coral- derived hydroxyapatite	Consists of calcium phosphate (hydrothermal conversion of the calcium carbonate skeleton of coral)	Scaffold/carrier /extender	structural density prevents rapid resorption. Inherent mechanical weakness (Damien & Revell, 2003)	+/-	-	+	+	+
Biocoral	Calcium carbonate (97-98%) in the form of aragonite, sodium, fluoride, magnesium, strontium and potassium	Scaffold/carrier /extender	Very porous and week	+	-	-	+	+
		2-	Alloplast					
Unsaturated polyester PPF	PPF, Benzoyl peroxide, HA, Sodium bicarbonate, Citric acid, vinyl-2-pyrollidone, N-N-dimethyl ptoluidine and water	Scaffold /expander	Occasional inflammatory foreign body reaction	+	-	-	+	+
Sintered synthetic hydroxyapatites	$Ca_{10}(PO_4)_6(OH)_2$	Scaffold/expander/carrier	It is relatively insoluble at neutral ph. Slow rate of dissolution (Tampieri *et al.*, 2005)	+/-	-	-	+	+
TCP (tricalcium phosphate)	$Ca_3(PO_4)_2$	Scaffold/expander/carrier	Unpredictable rate of bioresorption. Has not significant compressive strength by itself (Bauer & Muschler, 2000)	+	-	-	-	+

Vitoss	Ultraporous beta-tricalcium phosphate	Scaffold/expander/carrier	Does not have significant compressive strength (Bauer & Muschler, 2000)	+	-	+	-	+
Straumann Bone Ceramic	$Ca_{10}(PO4)_6(OH)_2$+B-$Ca_3(PO4)_2$	Chemotactic & scaffold	Lacks mechanical bone characteristics	+	-	+	-	+
Calcium Sulfat	$CaSo_{4\cdot1}/2H_2O$, POP	Scaffold/ carrier	Is less desirable for weight bearing applications due to loss of mechanical properties during degradation	+	-	-	-	+
Bioactive glass polymers	Silicate-based glass	Extender	Shaping, and they may fracture in the process. As a consequence they are difficult to fix to the skeleton	+	-	-	-	+
Hard-tissue replacement Polymer (Bioplant)	Combining PMMA and PHEMA and very thin layer of barium sulfate and calcium hydroxide or carbonate.	Scaffold/ carrier	No degradable, may cause bone resorption due to stress shielding, can cause necrosis to the surrounding tissue (Peter *et al.*, 2000; Temenoff and Mikos, 2000)	-	-	-	-	+/-
Nanobone®	Nanocrystalline hydroxyapatite and silica (76-24% weight percent)	Scaffold/ carrier		+	-	-	-	+
IngeniOs HA	Hydroxyapatite ceramic with a putty phase of ≥ 95%	Scaffold	Minimal resorption over time(Berberi *et al.*, 2014)	+	-	-	+	+
		3-	Composite graft					
Collagraft®	HA-TCP granules + bovine collagen	Scaffold/carrier/extender	Poor mechanical strength, risks of adverse reaction in patients allergic to bovine collagen.	+	-	+	-	+
B-TCP/Clg	Beta-tricalcium phosphate + type I collagen	Scaffold/carrier/extender	Poor mechanical strength	+	-	+	+	+

Kao *et al.* (2009) reviewed that the Federal Drug Administration (FDA) restricts incorporation of growth factors with demineralised freeze-dried bone or freeze-dried bone allografts. Thus, they are not commercially offered(Kao *et al.*, 2009). However, off-label use of this combination is common both in the oral surgical procedures and orthopaedic. On the other hand, diversity of xenograft bone and alloplastic materials are offered as bone tissue engineering.

Xenograft Bone substitute

Xenograft is a tissue harvested from one species and transplanted into a different species. Bovine, coralline and porcine are the three familiar sources of xenografts that are osteoconductive and readily available (Rodella *et al.*, 2011).

Bovine hydroxyapatite (Bio-Oss®) is the most commonly researched and used xenogeneic graft. Bio-Oss has been used in dentistry for more than 20 years for implant encouragement. It exhibited good osteoconductive potential in several studies and reports (Cordaro *et al.*, 2008), as it has a high degree of porosity and shows a large inner surface area that makes it serve as a scaffold for more penetration and ingrowth of capillaries, perivascular tissue and osteoblastic proliferation by which new bone generation attained (Chiappelli, 2010). It could be supplied in block and granular that is available in different particle sizes. It subjected to a detailed biochemical, histochemical and biophysical analysis and considered safe and poses no risk of disease transmission as it contains no detectable amount of proteins. Bio-Oss® is often used in combination with Bio-Gide®, a thin resorbable guided bone regeneration (GBR) membrane consist of natural fiber material that is not indicated for patients who has an allergic response to porcine or collagen derived products. In a study by Owczarek *et al.*, 2003, this combination showed a reduction of the periodontal pockets depth and the reconstruction of the attachment (Owczarek *et al.*, 2003). On another hand, Bio-Oss® collagen acted as a scaffold for tissue modelling in the fresh extraction socket but did not enhance bone regeneration.

Table 2. Summary of recent studies on bone grafts used for Oral and Maxillofacial surgical applications.

Author	Year	Sample size	Purpose of the study	Experimental site (Bone graft substitute)	Methods	F/U (m)	Results
Preclinical studies							
Stavropoulos *et al.*	2001	30 rats	Examine the influences of Bio-Oss with GBA in bone formation	Mandibular ramus (Bio-Oss vs empty capsules (control))	Teflon capsule with Bio-Oss placed in the lateral surface of the ramus	4	Bio-Oss interferes with bone formation
Kawata *et al.*	2004	Male and female C57BL mice	Explore AB transplantation into craniofacial bone defects	Alveolar bone defects (Hyaline cartilage with chondroid bone)	A critical size defect was formed in the premaxillary and distraction osteogenesis was done using an external fixation device and filled by the graft	1	Bone adhesion was better in chondroid bone grafting site than in fibula bone grafting
Feng *et al.*	2018	Thirsty-six New Zealand rabbits	Particulate decellularised cartilage matrix (PDCM), chondrogenically primed bone mesenchymal stem cell (BMSC) bricks (CB), and enriched platelet-rich plasma gel.	Rabbit tibia bone defects around implants	In rabbit tibia bone defects around implants PDCM + BMSC bricks (CB) + and enriched platelet-rich plasma gel were implanted aroungd thre implant	3	CBs transformed into bone tissue rapidly, significantly promoted bone remodelling and replacement of PDCM, thus realising osseointegration of dental implants within 3 months
Clinical studies							
Barone & Covani[	2007	56 patients	Evaluate the success of bone reconstruction of atrophic maxilla	Maxillary atrophy (AB harvested from iliac crest)	The onlay grafts in the atrophic area of the maxilla	5	Iliac bone graft is a favourable treatment for maxillary atrophy
Schlegel *et al.*	2007	48 sinuses	Evaluate the possible effects of PRP on AB grafts and on a bovine bone substitute	Sinus augmentation (PRP on AB grafts / on a bovine bone substitute)	A lateral approach with simultaneous insertion of 3 implants in each site. Groups were randomized using AB alone and combined with PRP/ a bovine HA alone in combination with PRP	2	Good result of sinuses augmentation with no significant influence of PRP was found in both graft
Di Stefano *et al.*	2009	5 patients	Evaluation of an equine spongy bone in augmentation of the alveolar ridge	Mandibular defects (Equine spongy bone)	A ridge was augmented by an equine bone and covered by a titanium-reinforced membrane	6	The graft appeared to be biocompatible and associated with neovascularization
Schlee & Esposito	2009	23 patients	Evaluate aesthetic after tooth extraction using Bio-Oss or Bio-Oss Collagen	Dental extracted socket (Bio-Oss or Bio-Oss Collagen)	Grafts were discretely condensed to the crestal edge of the bone	32	Placement of Bio-Oss in well-preserved post-extraction sites, showed good aesthetics
Lee *et al.*	2009	20 patients	Compare the DBBM, ICA, and SDA to preserve extraction sockets	Extracted socket (DBBM, ICA, SDA)	Bone grafting in extraction sockets with ICA (n = 8), DBBM (n = 7), or SDA (n = 5)	--	DBBM showed more of an osteoconductive effect than SDA or ICA
Contar *et al.*	2009	15 patients	Evaluated the fresh-frozen bone in reconstruction of maxillary alveolar ridges and implant support	Atrophic maxillary ridge (Fresh-frozen bone allograft)	Tibia fresh-frozen chips block was grafted prior to implant placement in maxillary alveolar ridge reconstructions	24-35	Bone allograft is suitable alternative to autogenous grafts
Thuaksuban *et al.*	2010	30 patients	compare AB+DBB and AB alone for repairing alveolar cleft	Alveolar clefts (AB and DBB)	The alveolar cleft sites were grafted and closed by the gingival flap	24	Both grafts were comparable in terms of bone remodelling and tooth eruption
Pelegrine *et al.*	2010	30 patients	Potential of an Autologous Bone Marrow (ABM) in preserving the alveolar ridges	Extracted socket (Autologous bone Marrow)	Sockets were grafted with an ABM in the test sites and unfilled in the control sites	6	ABM graft can contribute to alveolar bone repair post extraction
Pagliani & Volpe	2010	2 patients	Evaluate porcine bone mixed with a collagen gel	A bone deficit (Extracted sockets) (Porcine bone + collagen gel)	Sockets were filled with the graft. Implants inserted after 1 month with a healing period of 4 months before the positioning of the abutment	12	Porcine bone graft has strong osteoconductive properties.
Balaji	2011	42 Patients	Present the outcome measures of the use of iliac bone graft,	Alveolar cleft defect closure (Iliac crest	Retrospective analysis of details (Jan. 2008 –Dec.	4	The use of rhBMP-2 evades the need for additional surgery. It

			rhBMP-2 with zygoma shavings	graft/rhBMP-2/rhBMP-2 with zygoma shaving)	2010). RhBMP-2 (n=13), rhBMP-2 with zygoma shavings (n=9) and iliac crest graft (n=20)		showed maximum benefits with zygoma shavings
Kim *et al.*	2011	30 dentals sockets in 9 patients	Test the feasibility of DBM + cancellous bone chips in a reverse-phase medium carrier (DynaBlast) with an extracellular matrix membrane (DynaMatrix)	Extracted sockets (DBM and Cancellous bone chips + extracellulr matrix membrane in dynablast and dynamatrix membrane)	Sockets were grafted with dynablast and dynamatrix.	6	It promoted the preservation of the post-extraction ridges
Yamada *et al.*	2013	Patients	Assesse the injectable tissue-engineered bone (TEB) in bone regeneration in alveolardeficiencies	Severe alveolar ridge atrophy (Mesenchymal stem cells and platelet-rich plasma)	---------	2	Its safely and effectively used as therapeutic agents after cell transplantation for long-lasting improvement
Lorenz *et al.*	2018	61-year-old female patient	Investigate the ability of a well- xenogeneic bone substitute material, together with PRF components without the need of autologous bone	3-D planned titanium mesh combined with platelet-rich fibrin and deproteinized bovine bone	A severe tumor-related bony defect within the mandible of a former head and neck cancer patient	16	Bony defect in the anterior mandible was reconstructed with an 3D titanium mesh. PRF can be considered a reliable source for increasing the capacities of bone substitute materials.

F/U, Follow-up;m, months, GBA, Guided bone augmentation; AB, autogenous bone; CSD, critical-size defect; PRP, platelet-rich plasma; DBBM, deproteinized bovine bone mineral; ICA, irradiated cancellous allograft; FDDMA, freeze-dried allogeneic dura mater membrane; SDA, solvent-dehydrated allograft; DBB, deproteinized bovine bone; DBM, Demineralized bone matrix; RBM, resorbable barrier membrane; PRF, Platelet-rich fibrin.

In spite of this, preservation of the profile of the alveolar ridge process and its dimension as well as the after teeth extraction is better grafted by Bio-Oss rather than to non-grafted. Baldini *et al.*, 2011 concluded that placement of biomaterial in the socket following tooth extraction might prevent marginal ridge contraction that follows tooth removal (Baldini *et al.*, 2011).

Although many studies have proved the osteoconductivity and predictability of Bio-Oss®, some published studies found that the Bio-Oss® interfered with long-term bone generation. Stavropoulos *et al.* (2001) examined whether implantation of Bio-Oss effects bone regeneration when used as a scaffold to guided bone augmentation (GBA) in mandibular ramus of 30 rats (Stavropoulos *et al.*, 2001). Histologically, he found that the mean volume of the newly formed bone in Bio-Oss® defects is less than that in empty capsules (control), which resulted in a more new bone generation at two and four months. Thus, he concluded that Bio-Oss interferes with bone formation. Moreover, there are conflicting views about the Bio-oss resorption. The same author showed that there was no histologic evidence of Bio-Oss® resorption after one, two and four months of being grafted in rat mandibles. Whereas, a significant increase in new bone formation accompanying with Bio-Oss resorption at eight months, two years and ten years when implanted in the maxillary sinus of an old man with simultaneous placement of implants (Sartori *et al.*, 2003).

Coralline HA (CHA) is a coral-derived material. It has the same natural trabecular structure of the bone by the hydrothermal conversion of the calcium carbonate skeleton of coral to Calcium phosphate (hydroxyapatite). It is a highly porous particle consists of very dense hydroxyapatite with high carbonate content. CHA is founded in two forms either natural or synthetic, depending on the technique of the processing of sea coral. The difference between them is that the carbonate component of the coral's mineral is replaced by phosphates in the synthetic form whereas its only cleaned and sterilised in natural form. The synthetic commercially-available types are Pro Osteon®,

Biocoral®, Bio Eye® and Interpore® (Damien and Revell, 2004). The porosity of the Coralline HA enables cell attraction and ingrowth as well as it anchors the prosthesis to the surrounding bone, blood supply, and nutrients to the bone-like vascular canals. However, the density of its structure prevents rapid resorption of the particle (Kim Hae-Won *et al.*, 2003). The advantages of CHA as bone graft; include biocompatibility, safety, and osteoconductivity. As a result, it can be used in many indications clinically as a bone graft substitution(Damien and Revell, 2004).

Coralline hydroxyapatite grafts repaired bone defects during complex acetabular reconstructions in the acceptable form(Wasielewski *et al.*, 2008). While many studies have reported the biocompatibility and osteogenicity results of CHA, as a bone void filler graft and bone substitute, its used may be limited due to reduced biodegradation and its inherent mechanical weakness (Damien and Revell, 2004).

Table 3. Summary of recent studies on bone graft substitutes used in Oral and Maxillofacial surgery.

Preclinical studies							
Author	Year	Sample/sample size	Purpose of the study	Experimental site (Bone graft substitute)	Methods	F/U (m)	Results
Hile *et al.*	2005	24 rats	Evaluate the reconstruction of the alveolar ridge using expander with bone graft substitute	Molar Extraction sockets (Unsaturated polyester PPF as expander + a HA filler + effervescent agents)	Defect sites (4 groups): Treated with PPF + nanometer-sized HA, PPF material + micrometer-sized HA, demineralized freeze-dried bone allograft, left untreated	3	PPF scaffold could function as a graft substitute in an alveolar defect, and defects treated with PPF containing nanometer sized HA healed at a faster rate
Calixto *et al*	2007	Rats	Compare Bioactive glass particles, inorganic bovine bone	Extracted sockets	Socket was filled with either bovine bone or bioactive glass with flexible polyethylene cannula and embolus	2	Both grafts delayed new bone formation
Pieri *et al.*	2009	16 extracted sockets in 8 adult minipigs	Evaluated the synergic effect of MSCs and PRP incorporated into a FHA on bone formation	Alveolar defects (PRP-FHA, FHA alone or MSCs-PRP-FHA)	4 standardized defects were grafted with AB, FHA alone, PRP-FHA, or MSCs + PRP-FHA. RCM was placed over the defect area and the flaps were sutured	3	MSCs-PRP-FHA group resulted in a significantly greater bone formation idefect than other group
Schwarz *et al.*	2010	4 dogs	Assess influence of a guided bone regeneration procedure on the biologic activity of an rhPDGF-BB soak loaded NBM	alveolar ridge (RhPDGF + NBM + CM)	Chronic defects augmented with: NBM + rhPDGF-BB+CM (test) vs. NBM + rhPDGF-BB (control), and lower jaw: NBM + rhPDGF-BB+ CM (test) vs. NBM + CM (control)	Less than 1	RhPDGF-BB soak-loaded on NBM have the potential to support the newly formed bone and CM ensured a stabilization of the graft particle
Yamauchi *et al.*	2010	5 dogs	Compare results of ß-TCP block alone and mixed with PEO	Alveolar ridge (ß –TCP)	Buccal corticotomy was performed. The veneer graft (ß-TCP block), was used on the right side and PEO + ß -TCP block on the left side	2	The ß-TCP block worked as a space-maker under the soft tissue, and acted as a bone graft substitute
Zecha *et al.*	2011	96 rats	Assess the capabilities of eHAC blocks compared with Bio-Oss spongiosa bone blocks and AB in alveolar augmentation	Lateral augmentation of the mandible (eHAC (Equine hydroxyapatite collagen) and Bio-Oss)	They underwent bilateral augmentation of the mandible with eHAC bone block or Bio-Oss or AB was covered with a biogide, the other was left uncovered	3	eHAC and Bio-Oss spongiosa were biocompatible. Bone formation and bone growth into the blockswas significantly higher in eHAC than Bio-Oss spongiosa blocks, but lower than in autologous grafts
Schmidlin *et al.*	2013	12 rabbits	To compare two moldable synthetic calcium phosphate materials	Calvarial bone (An *in situ* hardening polylactide-coated ß-tricalcium phosphate (TCP), an *in situ* hardening	6 mm diameter defects were drilled and the filler materials were randomly applied to 48 defects	4 weeks	BCP was more efficient in centripetal bone formation when compared with TCP

				polylactide-coated biphasic calcium phosphate (BCP))			
Kaya *et al.*	2013	28 Male rats	Evaluate the efficacy of rifampin with allogeneic, alloplastic, and heterogeneous bone graft substitutes on osteogenesis	Two bone defects were created in the left and right tibias (Rifampin with allogeneic, alloplastic)	1st group, the defects were irrigated with rifampin alone/sterile saline alone. 2nd group, with rifampin and allogeneic bone graft/ allogeneic bone graft alone. 3rd group, with rifampin and alloplastic bone graft/alloplastic bone graft alone. 4th group with rifampin and heterogeneous bonegraft/heterogeneous bone graft alone	21 days	Topical rifampin can accelerate the bone repair process, but the combination of rifampin and allogeneic bone grafts can also reduce new bone formation in osseous defects that may resulted from contamination of the bone defects by antibiotic-supplemented bone grafts.
Park, *et al.*	2015	20 Sprague-Dawley rats'	Examine the potential of using demineralized deciduous tooth powde (DDTP) as a bone graft material	Created calvarial defects (DDTP)	DDTP was grafted in calvarial defects and compared with un filled defects	8 weeks	Experiment indicated new bone formation in DDTP-grafted sites and gradual resorption of the grafted particles. Defect closure was significantly higher in the DDTP-grafted group compared with control
Kim *et al.*,	2015	rabbits	Study the effect of adding Silicon (Si) to cuttlefish bone (CB) -derived hydroxyapatite using a natural CB to improve the bioactivity for bone formation.	Calvarial defect model (Si-CB-Hap compared to CB-Hap alone)	The bioactivity of the Si-CB-HAp was evaluated using human mesenchymal stem cells. In addition to, Si-CB-Hap was grafted in calvarial defects and compared with CB-Hap	8 weeks	Si showed to enhance cell proliferation and early cellular attachment of hMSC. It also enhanced osteoblast differentiation. Bone defect healing experiments showedbone formation is higher with Si-CB-HAp than CB-Hap.
Artas *et al.*	2018	32 female Sprague-Dawley rats	Compare the effects of HA, DPB, human-derived allogenic bone (HALG), and CAP graft biomaterials used with titanium barriers for bone augmentation	peri-implant defects in rat calvarium	Four groups: DPB, HALG, HA, and CAP. One titanium barrier was fixed to each rat's calvarium after the titanium implants had been fixed. In total, 32 titanium implants and barriers were used.	3	no statistically significant between-group differences in new bone regeneration or vascular endothelial growth factor (VEGF) expression. None of the grafts used in this study showed superiority with respect to new bone formation.
				Clinical studies			
Knapp *et al.*	2003	12 patients	Feasibility of using a bioactive alloplast and a physical barrier	Alveolar ridge defect (Bioactive glass particulate + TR e-PTFE barrier)	Defects were augmented with a bioactive glass and a titanium-reinforced e-PTFE barrier (TR e-PTFE)	6	The graft did not reliably augment the defects for dental implant placement
Thompson *et al.*	2006	13 extracted sockets in 2 patients	Compare 3 C-Graft 228, Puros, or pepgen P-15 228 flow for bone formation	Sockets (C-Graft 228, Puros®, or PepGen P-15 228 FLOW)	Immediately extraction sockets were grafted with C-Graft 228, Puros, or pepgen P-15 228 flow	4	Pepgen flow putty produced significantly greater bone as compared to others
Kim *et al.*	2008	17 patients	Evaluate the use of osteon (HA + TCP) in sinus augmentation	Maxillary Sinus (Osteon® + Greenplast1(fibrin adhesive) +AB chips + RCM)	The mixed graft and tissue adhesive mixture was grafted as a bolus in the sinus cavity and covered by RCM before primary suturing	6	Osteon is suitable for use in sinus graft application
Cordaro *et al.*	2008	48 sinuses in 37 patients	Compare ABB and a new BCP in sinus augmentation	Maxillary sinus floor (Bio-Oss (ABB) + BCP)	Lateral sinus augmentation using either ABB or BCP	8	Both grafts are suitable for sinus augmentation and dental implants placement

Froum *et al.*	2008	12 patients	Compare formed bone following bilateral sinus grafting with BCP to Bio-Oss	Sinus lift (ABBM to Bio-Oss)	Lateral sinus walls were elevated, and one material was placed in the right and the other in the left sinus	8	There was not significant differ-ent, and both materials are osteoconductive
Friedmann *et al.*	2009	5 patients	Prove the enhancement effect of BCP in defect healing	Sinus grafting (BCP: HA/ TCP (60/40	One-stage lateral augmentation; two-stage lateral augmentation; and two-stage sinus grafting. a degradable collagen membrane	10	BCP comparable to xenogenic and alloplastic graft materials
Horowitz *et al.*	2009	30 patients	Determine the efficacy of ß-TCP in the preservation of ridge volume and implant placement	Extracted dental sockets (ß-TCP + resorbable collagen or dense polytetrafluoroethylene barrier)	Extraction sites were grafted with a pure-phase ß-TCP (Cerasorb) of small particle size, 150 µm to 500 µm and covered with a barrier	6	ß-TCP is ideal for use after tooth extraction in conventional and implant dentistry
Mardas *et al.*	2010	27 patient	Compare the a synthetic bone combined with CMto preserve the alveolar ridgedimensions	Dental extracted sockets (SBC, Bio-Oss, CM)	Sockets were grafted with SBC (experimental group), Bio-Oss (control group). A collagen barrier was used to cover the graft.	8	Results were comparable. Both biomaterials partially preserved the dimensions of the ridge, and supported implant placement
Shapoff & Katta	2010	32 sinus in 27 patients	Evaluate sinus elevation surgeries using PG in combination with AB or FDB	Sinus elevation (Periogla + AB or FDB in a 1:1 ratio)	Implants were placed simultaneously with the subantral elevation	6	PG showed excellent handling characteristics and ability to be used as a extender for sinus elevation surgeries
Kesmas *et al.*	2010	8 patients	Evaluate the ridge preservation technique used with BCP and RCM	Extraction sockets (BCP and a RCM)	Labial sockets defect were sealed with RCM and the defect filled with BCP	12	Graft can be used as an alternative treatment for maintaining ridge dimension before implant placement
Naruse *et al.*	2010	-----	Present a vertical ridge augmentation with composite synthetic bone graft	Atrophied bone (Nonresorbable and resorbable HA and DFDB allograft particles)	HA+DFDB (1:2), and Titaniummicro mesh was used, and implant placement and augmentation were performed.	8	Method has the potential for using in esthetic implant rehabilitation on the highly atrophied alveolar bone
Kumar *et al.*	2011	20 defect in 10 patients	Compare the response of periodontal osseous defects treated by open flap debridement with and without glass-reinforced HA alloplast	Periodontal osseous defects (HA + TCP + bioactive glass)	Defects were treated either with open flap debridement or open flap debridement and bone graft implantation in a split-mouth study design	6	The composite alloplast demonstrated marked improvements in all hard tissue parameters when compared to control group
Gonshor *et al.*	2011	22 patients	Evaluate CPS putty as a bone graft in alveolar sockets healing	Extracted sockets (CPS putty)	All cases in this study were of tooth extractions with immediate socket grafting without membranes	5-6	CPS putty can be a reliable choice for osseous regeneration in cases of crest preservation and around implant.
Lazarou *et al.*	2011	10 patients	Evaluate alveolar cleft grafting with a calcium substitute before primary canine eruption	Alveolar cleft (Calcium substitute paste)	Elevation of nasal, oral, and anterior alveolar mucosal flaps around the cleft, closure of nasal and oral flaps, placement of calcium substitute paste or crystals in the pocket	36-84	Calcium substitutes showed primary alveolar cleft reconstruction that teeth can erupt through this material.
Brkovic *et al.*	2012	20 patient	Investigate the healing of sockets filled with β-TCP/Clg Cones with or without a BM	Extracted socket (B-TCP/Clg, BM)	Eithers sockets were grafted with β-TCP/Clg cones without covered with BM and with a mucoperiosteal flap. Implants were placed after 9 months	9	There was no significant difference between the two groups in the areas occupied by new bone, and dental implant placement was possible
Kattimani *et al.*	2014	8 patients	Evaluate the efficacy of eggshell derived hydroxyapatite (EHA) in	Maxillary cystic bone defects (Eggshell derived hydroxyapatite (EHA)	Maxillary bone defects were grafted after cystic enucleation and/or apicoectomy	3	EHA is biocompatibe and yielded promising results. EHA is very cost-effective, efficient

			the bone regeneration				bone graft substitute
Kim *et al.*	2017	23 patients	assess the healing potential of DDM fixed with rhBMP-2	demineralized dentin matrix (DDM) fixed withrecombinant human bone morphogenetic protein-2 (rhBMP-2)	Human DDM fixed with rhBMP-2 (AutoBT BMP) with implant placements (36 implants; maxilla: 14, mandible: 22)	10.5	AutoBT BMP provides good osteoinductive and osteoconductive potential and clinical efficacy.
Schwarz *et al.*	2018	30 patients	Compare the efficacy of autogenous tooth roots(TR) and autogenous bone blocks (AB)	Lateral alveolar ridge augmentation and two stage implant placement.	Lateral ridge augmentation were allocated to parallel groups receiving either autogenous tooth roots or cortical autogenous bone blocks harvested from the retromolar area.		Soft tissue healing was uneventful in both groups. successful and comparable implant placement in all patients of both TR and AB groups

TR e-PTFE barrier, A titanium reinforced expanded polytetrafluoroethylene; PPF, poly(propylene Glycol-co-fumaric acid); DFDBA, Demineralized freeze dried bone allograft; DBM, Demineralized Bone Matrix; RCM, resorbable Collagen membrane; AdEGFP,; Adenovirus vector encoding Enhanced Green Fluorescent Protein; BMSc, Bone marrow stromal cells; ABB, anorganic bovine bone; BCP, biphasic calcium phosphate; GDF-5, growth/differentiation factor; PDGF, platelet-derived growth factor; 5PTH, parathyroid hormone; BMSc, Bone marrow stromal cells; NBM, Natural bone mineral, PEO, periosteal expansion osteogenesis, SBC, Straumann Bone Ceramics; RCM, resorbable collagen membrane; CPS, calcium phosphosilicate; eHAC, Equine hydroxyapatite collagen, PG, Perioglas; ACS, A cross linked collagen membrane; FHA, fluorohydroxyapatite; rhPDGF-BB, Recombinant human platelet-derived growth factor BB.

Porcine bone graft has osteoconductive properties and is remodelled and replaced with new bone over time. However, particles without bone contact in the deepest areas of the biopsy were evident (Wasielewski *et al.*, 2008).

In general, xenograft bone has been used successfully in grafting procedures. However, the disadvantages with this graft include a host rejection immune response and risk of transmission of disease. To reduce the side-effects, the xenograft is treated rendering them sterile and totally biocompatible. However, bone xenograft still shows slow resorption (Block *et al.*, 2002). Table 2 showed most of the recent studies on bone graft for oral and maxillofacial surgical applications in 2000-2017 years.

To sum up table 2, the allograft is comparable to the autograph (Contar *et al.*, 2009; Thuaksuban *et al.*, 2010). Deproteinized bovine bone mineral showed more of an osteoconductive effect than mineralised bone structure(Lee Dong-Woon *et al.*, 2009). RhBMP-2 in combination with bone graft showed maximum benefits with bone shavings in recipient site(Balaji 2011). Bio-Oss interferes with bone formation in ramus (Stavropoulos *et al.*, 2001), while it showed good aesthetics in extraction site (Schlee and Esposito, 2009). The author suggests because of the muscle movement may cause graft instability and dislodgement at the ramus site. No significant influence of PRP was found in added to bone graft (Schlegel *et al.*, 2007), while it's effectively used as therapeutic agents with stem cell transplantation for long-lasting improvement in alveolar bone atrophy(Feng *et al.*, 2018; Lorenz *et al.*, 2018; Yamada *et al.*, 2013).

Alloplastic Bone Graft Substitutes

Alloplasts are synthetic bone grafting materials that have been used mostly since their unlimited supply. They are biocompatible, osteoconductive and do not carry the risk of disease transmission. Concerning resorption, degradation of alloplasts depends on the physicochemical property, volume, physical environment of the grafted material, patient age, number of adjacent bony walls, and local vascularity for use as bone graft substitutes. The synthetic materials of interest are those that mimic the mineral phase of bone. They afford some structural support and prevent fibrous tissue ingrowth when facilitating creeping substitution by the host bone.

Calcium sulfate: Calcium sulfate (plaster of Paris, Gypsum) is considered the oldest synthetic bone graft

substitute used in bone regeneration. The chemical reaction which occurs during the setting time of calcium sulfate leads to the change in its crystalline structures and thus unstable chemical properties. This inconsistency leads to rapid resorption, within 4-8 week s, that exceeds the capacity of the bone regenerate process, potentially outstripping the rate of newly formed bone and leaving an unhealed bone defect. Because of its poor bioactivity, it cannot osseointegrate with host bone tissue at the early stage of therapy (Middleton and Tipton, 2000).Thus it is not very reliable clinically. However, it may still have a future role as a carrier until superseded with more reliable osteoinductive materials (Feuille *et al.*, 2003).Furthermore, it is not used for socket grafting or implant site development as a stand-alone material because of its resorption rate. Instead, it can be used as a binder to other types of the bone and bone substitutes grafts to achieve better handling and restrict particles migration (Fisher *et al.*, 2002).

Table 4. Biological mediator.

Biological mediator	Chemical composition &structure	Biological behaviour	R	OS
Collagen	Extracellular matrix protein (natural polymer)	Good as delivery vehicle system/ extenders/ porous scaffolds	+	-
DBM	Mainly composed of Type I collagen, various growth factors	Supplies osteoinductive, bone graft extender	+	+
BMPs/OPs	Pleiotropic members of the TGF- β supergene family	Soluble signals for the *de novo* initiation of bone formation, sculpting tissue constructs	+	+
PDGF	Mitogen	Potent mitogen and chemotactic factor	+	-
Enamel matrix derivative	A group of proteins isolated from the tooth germs	A very intriguing biological mediator	+	-
Hyaluronic acid	Polyanionic disaccharide units of glucouronic acid and N-acetyl glucosamine (Ballini *et al.*, 2009)	Facilitate the application of bone graft in the damaged site/ extender	+	+

R, Resorbability; OS, Osteoinductivity.

Calcium phosphate: Calcium phosphate (Ca-P) ceramics have been used in dentistry since the 1980s (Shastri *et al.*, 2004). They have the similar mineral composition of the bone. They consist mainly of hydroxyapatite (HA) or tricalcium phosphate (TCP) or HA/TCP in a different ratio to form a biphasic mixture (BCP). They are available in many different forms such as wedges, granules, blocks, pastes, and cement. They are widely used for bone substitution, repair, and augmentation and have a clinical acceptance in many areas of dentistry. Ca-P ceramics have little tensile strength and offer limited structural integrity. Porosity percentage and size of the pores of Ca-P affect their mechanical properties (Salgado *et al.*, 2012a). Moreover, porosity, pore size and surface area all affect the healing and biological potential. Hossein Fathi *et al.* (2009) suggested that prepared nanocrystalline HA could be more useful and effective for the treatment of oral bone defects than conventional one (Salgado *et al.*, 2012a). Hydroxyapatite Porous hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is the most extensively bone substitute for treating periodontal defects. It has been marketed in different forms; solid or a dense non-resorbable, a porous, nonresorbable and a resorbable form. It is available in a variety of form from paste to rigid blocks. HA shows excellent biocompatibility with the human tissue, however, its applications are limited to coat and non-load-bearing areas due to its low mechanical properties. Its exhibits slow resorbability and brittleness, thus it is often combined with other materials for improved its function and accelerate its resorption. The osteoconductivity of synthetic hydroxyapatite is controversial. While some authors found promising results regarding scaffolding of these materials, others have opposite effects. Okuda and his co-workers (2005) found that HA alone or in combination with PRP offers the potential of bone ingrowth into the micropores that lead to bone regeneration and potentially treats intrabony periodontal defects (Wang *et al.*, 2009). A combination of PRP and HA led to a significantly

more favourable clinical improvement than to HA alone, since the PRP is a rich source of growth factors that stimulate the mitogenic activity of the bone cells. On the other hand, Taylor *et al.* (2002) showed that the synthetic HA materials allowed osteoclast attachment but exhibited limited surface etching, which is consistent with limited osteoclast resorptive activity (Jabbari *et al.*, 2005).

Tricalcium phosphate (TCP) is a porous form of the calcium phosphate. It is partially resorbable and has osteoconductive properties. Moreover, it has gained clinical acceptance; unfortunately, its outcome in bone regeneration is not always predictable (Al-Namnam *et al.*, 2017).The β-tricalcium phosphate is the most commonly used form of TCP; it's another available ceramic material that has been recently used in grafting alveolar ridge defects in the oral and maxillofacial site. The β-tricalcium phosphate is present in two form, the granular wedges, and blocks. Some studies showed that β-tricalcium phosphate is a suitable scaffold (Al-Namnam *et al.*, 2016).Conversely, others found that it is unreliable due to its early resorption during the bone healing process that leads to insufficient bone generation(Coutinho *et al.*, 2010).

Biphasic calcium phosphate (hydroxyapatite with tricalcium phosphate) (BCP) is available in different forms including granule, sticks, and cylinders. HA and β-TCP can be found in blocks with micropores and macropores. They are highly biocompatible, but they differ in the biologic response created at the recipient site. TCP-ceramic is faster resorbed at the implant site than HA which is more permanent. Fujita *et al.* (2003) compared the result of implant BCP in the parietal bone and the cranial periosteum in rats. The quantity of newly formed bone around HA particles was much more than that around β-TCP, and there was no notable change in the amount of remaining of HA. However, that of β-TCP decreased. They concluded that the HA blocks are more suitable for Onlay grafts, because of its stability, than the β-TCP (Leor *et al.*, 2005).Another study found that the BCP was excellent additional bone graft substitutes for autogenous bone graft in filling bone defect after the curettage of benign bone tumours (Burg *et al.*, 2000).

β-TCP has some advantages than HA when used as a filler, in that it is more rapidly reabsorbed since surface layers of TCP-ceramic enhance bonding with an adjacent bone that in turn stimulates the new bone formation and remodelling process within the area of the resorbed implant. Because of the different resorption rate between HA and β-TCP, researchers sometimes combined and modified them with other materials (e.g. HA/TCP combined with autogenous bone) to improve functionality and enhance the resorption process (Shin *et al.*, 2003).An ideal composition of BCP ceramics which consist of HA and ß-TCP in the weight % ratio is approximately 70:30. Nevertheless, another ratio has been proposed. A ratio of 55% HA: 45% β- TCP was used to induce bone in-growth in experimentally created circular defects in dogs' femurs. It produced an excellent biocompatible implant as well as osteoinductive and conductive to fill bone defect (Leclerc *et al.*, 2007).In human, it has been reported that the application of β-TCP/HA graft after anterior cervical discectomy resulted in a high rate of fusion and patient satisfaction (Zagris, 2001).However, there is just a few reliable clinical data describing the resorption rates of BCP for socket grafting.

Bioactive glasses: Bioactive glasses are non-porous and hard materials which consist of phosphorus, calcium, and silicon dioxide. By varying the proportions of its components, a wide range of forms from non-resorbable to resorbable material can be produced. The unique surface of bioactive glasses is the presence of HA bioactive layer that occurs through a biochemical transformation following implantation. It has been thought that this HA layer is responsible for bone cell attraction and bonding (Seong *et al.*, 2010).A novel alloplastic material formed by combining the useful properties of HA, β-TCP and bioactive glass has recently been introduced and widely tested in the maxillofacial region. Kumar *et al.* (2011) have used a liquid phase sintering

process for producing bioactive glass that results in a glass-reinforced HA with α and β forms of TCP as a secondary crystalline phase (Kumar *et al.*, 2011). This system allows the combination of several ions, such as sodium, magnesium, and fluoride, resulting in a bone graft substitute that has the comparable chemical composition to that of the bone mineral phase. Furthermore, its microstructure enhanced bioactivity and improved the mechanical properties when compared to commercial HA. Ceramics with lower density and higher porosity provide a greater surface area for angiogenesis and bone ingrowth.

This new composite resulted in better treatment outcomes, but the literature still lacks data on their predictability and effectiveness in living tissue (Meijer *et al.*, 2007).The commonly used alloplastic ceramics are β-TCP and HA crystals. Table 3 a & b showed recent studies on bone graft substitutes used in maxillofacial surgery.

From Table 3, its conclusion that bioactive glass is not reliable as a bone graft for dental implant placement and delayed socket bone healing (Knapp *et al.*, 2003; Thompson *et al.*, 2006). Bone healing is more accelerated by grafting nanometer HA than micrometre HA (Hile *et al.*, 2005), and it could act better if combined with TCP since it increases its resorbability (Kim Young-Kyun *et al.*, 2008). Bio-Oss and BCP are suitable graft for sinus augmentation and dental implants placement, and both bone grafts substitutes are comparable (Cordaro *et al.*, 2008; Friedmann *et al.*, 2009; Froum *et al.*, 2008; Kumar *et al.*, 2011). Furthermore, BCP showed its superiority in centripetal bone formation than TCP(Schmidlin *et al.*, 2013)and its ability to maintain the ridge dimension in labial sockets defect when sealed with RCM before implant placement (Kesmas *et al.*, 2010). EHA is biocompatible and yielded promising results in bone regeneration. However, it is very cost-effective (Kattimani *et al.*, 2014). Although, eHAC showed bone growth into its blocks form higher than in Bio-Oss spongiosa blocks, it still lower than that founded in autologous bone grafts(Zecha *et al.*, 2011). It founded that ß-TCP is ideal for use after tooth extraction in conventional and implant dentistry and its block form can be worked as a space-maker under the soft tissue(Horowitz *et al.*, 2009; Yamauchi *et al.*, 2010). Further, β-TCP/Clg showed no significant difference in the areas occupied by new bone and dental implant placement when used with or without covered BM(Brkovic *et al.*, 2008). Novel promising tooth dentin bone graft substitute showed the equivalent result to ideal autogenous bone graft, is under clinical trial (Kim *et al.*, 2017; Park *et al.*, 2015, Schwartz *et al.*, 2007).

Composite grafts

Composite grafts offer the advantages of autograft and allograft added to the synthetic materials. Such graft provides osteoinduction and osteoinductive properties for new bone formation. In essence, the demineralized bone matrix affords osteoinductive properties, while the ceramic provides an osteoconductive matrix. Thus mixtures of these materials could be created at the surgical table to achieve similar goals. Both minerals containing synthetic bone and composite grafts appear radiopaque on postoperative x-ray and over time may be incorporated into the host bone (Beaman *et al.*, 2006).

Polymer-based bone graft substitutes: Polymer-based bone graft substitutes offer different physical, mechanical and chemical properties that are not available with other groups. The polymers can be classified into a biodegradable polymer such as copolymers, polycaprolactone, polyanhydrides, polylactic acid and polyglycolic acid and polyphosphazenes, and a non-degradable polymer such as Polymethylmethacrylate (PMMA), and polytetrafluoroethylene (PTFE). According to Middleton and Tipton (2000), an ideal biomaterial for medical applications should be biocompatible *in vivo*, biodegradable or metabolised in the body after the intended corresponding tissue has regenerated (Middleton and Tipton, 2000).

It should be easily sterilized and processed into the final product form, has an acceptable shelf life and is

capable of providing sufficient mechanical strength until the surrounding tissue has restored.

Currently, the most commonly used injectable and flexible bone cement is poly(methyl methacrylate) (PMMA). It is used for cranioplasties, arthroplasties, dentures, and orthopaedic prostheses replacement or repair of hard tissues. Hard tissue replacement (HTR-MFI) is a commercial name of PMMA which can be exhibited as blocks and particulates. Whereas.

The block format is for bone augmentation while particulates format has periodontal applications to restore deficient alveolar bone. However, this bone cement is a permanent implant which is not degradable, and there is a risk of carrying infectious agents. It may cause bone resorption due to requires revision surgery, stress shielding and produces high curing temperatures that can cause necrosis of the surrounding tissue(Peter *et al*., 2000; Temenoff and Mikos, 2000).

Biodegradable materials offer significant advantages when used as a bone scaffold. They do not necessitate a second surgery for removal while slowly degrades in vivo and further provides space for tissue regeneration. Hence, in the oral and maxillofacial application, the biodegradable bone scaffold is engineered to degrade at a rate that matches the bone healing time.

The development of in-situ crosslink materials that are easily implanted in vivo (i.e. with the minimally invasive procedure) provides good contact between the bone scaffold and the native tissue, as well as osteogenic cells carriers, has become a major trend in the research of developing scaffolds for bone tissue engineering. In this context poly(propylene fumarate) chemically-induced cross-linkable polymeric monomers, have been developed as filler materials to repair irregular bone defects(Fisher *et al*., 2002; Shastri *et al*., 2004).

Polymers can be bioabsorbable. Therefore, they can be made to dissolve and be slowly absorbed by the body. The advantage of having a biodegradable scaffold in the body is that the body can heal completely by itself without retaining foreign bodies. However, there may be foreign body reactions present due to the presence of degradation products (Middleton and Tipton, 2000). However, because of the high crystallinity and hydrophobic character of Poly(e-caprolactone) (PCL), the resorption kinetics and degradation are considerably slower than other aliphatic polyesters. Nevertheless, it has gained US FDA approval for some medical and drug delivery devices. PCL modified by crosslinking a functional group such as fumarate, resulting in the synthesis of PCLF(Salgado *et al*., 2012b; Wang *et al*., 2009). In addition to, Jabbari *et al*. (2005) reported the synthesis and biocompatibility of linear polycaprolactone fumarate (PCLF). However, the PCLF semi-crystalline structure needs to be preheated to a high temperature before it can be injected into an osseous defect site which might result in damage/necrosis to the surrounding tissue can occur (Jabbari *et al*., 2005).

In the past decade, an interesting candidate material with reliable properties for using as osteoconductive material for aiding in bone healing and reconstruction have been successfully produced. It has a major advantage in that it can use directly as an injectable material into the bone defect area and solidify in situ at room temperature without any major side effect to the surrounding tissue(Al-Namnam *et al*., 2017). This novel material named as Poly(caprolactone-trifumarate)- Gelatin microparticles (PCLTF-GMPS). The biocompatibility and osteoconductivity of PCLTF-GMPs have been approved through the bone healing and formation of new bone in the PCLTF-GMPs filled critical size cranial defects in a rabbit model(Al-Namnam *et al*., 2016). In future, this scaffold can be implanted with or without osteoblasts cells, growth factors, or PCLTF-based composite scaffolds to enhance its activity.

Tissue engineering

Tissue engineering is rapid evolution in a scientific area that involves engineering and life sciences by

using a combination of cells, biomaterial, and/or biologically active molecules that maintain, restore and improve tissue function (Coutinho *et al.*, 2010). Tissue engineering is based on the knowledge of tissue construction and regeneration. It aims to offer great promise in the context of replacement of damaged organ and restoration of the lost function. Classic tissue engineering strategy in medical applications involved the isolation of specific cells from a patient. These cells are grown on a 3D biomimetic and biodegradable scaffold under specific culture conditions. After that, the tissue construct is sent to the desired site in the host. This allows the tissue construct to organize and develop into a specific functional organ, while the scaffold degrades over time(Leor *et al.*, 2005).

According to Burg *et al.* (2000) and Shin *et al.* (2003), the concept of tissue engineering requires four components that make up the biological tissues. These are signal responsive osteoprogenitor cells, the bone morphogenetic signal that can modulate cellular activities, a suitable scaffold that can deliver it to specific sites which then act as mechanical support for progenitor cells growth and finally, a viable, well-vascularized host bed or implant site (Burg *et al.*, 2000; Shin *et al.*, 2003).

Cells present in the ground substances are responsible for extracellular matrix secretion in the presence of proper signalling systems that trigger differential activation of genes or cascades of genes whose secreted or transcriptional products stimulate and adjust cellular functions such as adhesion, migration, proliferation, differentiation, and morphogenesis (Leclerc *et al.*, 2007; Zagris, 2001). Various stem cells including embryonic stem cells (ESCs), bone adipose tissue-derived stem cells (ADSCs), marrow-derived mesenchymal stem cells (BM-MSCs), umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs), muscle-derived stem cells (MDSCs), and dental pulp stem cells (DPSCs) have received wide attention in the field of bone tissue engineering due to their biological capability to self-renew and differentiate into multiple different cells types (Seong *et al.*, 2010). However, the most used one in bone tissue engineering is MSCs with a successful outcome. There are four factors needed for tissue engineering success: (1) sufficient numbers of osteogenic capacity cells; (2) Recombinant growth/differentiation factors to stimulate osteogenic differentiation in vivo; (3) an appropriate scaffold to seed the cells; and (4) sufficient vascular supply (Meijer *et al.*, 2007).

Meinel and his co-worker (2004) isolated MSCs from human bone marrow and characterised them for the expression of stem cell surface markers and the capability to undergo chondrogenesis and *osteogenesis in vitro*(Meinel *et al.*, 2004). After culturing them for five days, They showed that calcium deposition of MSC grown on collagen scaffolds and films was comparable in static culture, while the MSCs on collagen scaffolds deposited more calcium and had a higher alkaline phosphatase (AP) activity than MSC on the films under medium flow. Based on the time rate of the degradation, the amount of DNA was markedly higher in constructs on slowly degrading modified collagen and silk scaffold than on fast degrading unmodified collagen scaffolds. They concluded that the properties of the scaffold could modulate osteogenesis in cultured MSCs and flow environment.

Growth factors mediate the action of cells and their responses to various environmental signals. These transcription and growth factors are large polypeptides, which are expressed and synthesised in very low physiological concentrations. They act as local regulators of cell behaviour (Porter *et al.*, 2009). They are produced both systemically and locally by bone cells and from other sites, consequently. A very wide range of cell actions could be resulted by specific cellular response triggered by growth factor signalling, including morphogenesis, cell migration from one site to another, cellular proliferation or mitogenesis. These large molecules direct cellular activity by binding to specific receptors on the transmembrane cell that subsequently triggers the intracellular domain and activates transcription of a

gene into mRNA and consequently protein production. The extracellular matrix contains many components to bind and modulate the activity of some growth factors such as Notch signalling molecules, traction-enabling adhesion molecules, adhesive molecules and proteoglycan molecules. The producer cell secretes the growth factor that initiates the signal transmission mechanism. The pathway that transduces the growth factor-binding signal to the cell nucleus involves a complex array of events involving cytoskeleton protein phosphorylation, ion fluxes, changes in metabolism, gene expression, protein synthesis and ultimately an integrated biological response (Cao *et al.*, 2009; Lee Kangwon *et al.*, 2011).

The dosage of cells and growth factors depend upon the particular application and the relative health status of the patient. By way of illustration, in the case of bone repair, a smoker or an older diabetic patient heals differently than a healthy child or young person. Thus each would need different dosing of growth factors and cells.

Popular growth factors in tissue regeneration are angiopoietin (Ang), BMP, basic fibroblast growth factor (bFGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TFG), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF) and nerve growth factor (NGF). PDGFs, BMPs, TGF-bs have been proven in vivo and hold great potential for the future of bone engineering. Of the 20 growth factors discovered, only BMP-2, -4, and 7 that have been able to promote the differentiation of the osteoprogenitor cells into mature osteoblasts *in vitro*.

Several techniques have been employed to control the release of the BMPs, biodegradable polymeric scaffolds or hydrogel is one of the most common method (Porter *et al.*, 2009). Van Hout *et al.* in 2011, compared iliac crest bone grafting with BMP-2-aided bone tissue regeneration. They showed the comparable result in bone quantity in the mixed dentition patients, whereas it was superior in the BMP-2 group in skeletally mature patients. Furthermore, favourable results reported with the BMP-2-aided reconstruction of the alveolar bone cleft (van Hout *et al.*, 2011).

In implant site clinical study by Nevins &and Reynolds in 2011, 0.5 mL of 0.3 mg/mL rhPDGF-BB was delivered by a particulate bone allograft (FDBA or DFDBA) as a scaffold However, controlled clinical trials are still necessary to establish the effectiveness of rhPDGF-BB and different mammalian scaffolds combination for alveolar bone augmentation.

Delivery of more than one GF at mimicking rates of the natural biological process has clinically promising potential in the management of severely diseased tissuesMesenchymal progenitor cells (MPC) and their differentiation to osteoblasts were examined in response to human basic rhbFGF for chemotaxis, rhPDGF-bb, rhTGF-beta1, rhBMP-2, and recombinant BMP-4 of Xenopus laevis (rxBMP-4) from 0.001 to 1.0 ng/ml each. The effect of rhBMP-2, rxBMP-4, and rhPDGF-bb as chemoattractive proteins for primary human MPC, including the variation in response to growth factors (GFs) after differentiation has been suggested as a functional role for recruitment of MPCs during bone fracture healing, as well as bone development and remodelling(Fiedler *et al.* 2002). Table 4 summarizes some of the commonly used Biological mediator in tissue engineering.

In general, the injected GF rapidly diffuses out from the regeneration site within one day. Thus direct injection of the growth factors is ineffective. Thereby, improving the unsatisfactory outcomes in the classical delivery of growth factors and cure the rapid diffusion has been solved by simply encapsulated in a biodegradable (bioabsorbable) scaffold or adding them to the culture media to use as a proper carrier and delivery system over a long time. Tissue engineering frequently involves the construction of 3D scaffolds which meets application-specific criteria, such as biocompatibility, degradability, and stiffness

and allows for cell adhesion in a special environment (Neuss *et al.*, 2011). Polymer matrices for the carrying and delivering of growth factors could be good platforms for the delivery of growth factors (Fischbach and Mooney, 2007). Neuss *et al.*, 2011 analysed two synthetic materials which were long-term bio-absorbable polymers for their effect on MSC-based bone tissue engineering: poly(ε-caprolactone) (PCL) and PLLA-co-TMC (poly(trimethylene carbonate-co-L-lactide) (Resomer® LT706). They showed that both polymers enhanced osteogenic differentiation as compared to tissue culture polystyrene (TCPS)(Neuss *et al.*, 2011). Bioactive factors can be chemically immobilised or physically encapsulated into polymer matrices, which in turn prevent their denaturation and control their release by the degradation of the polymer matrices(Fischbach and Mooney, 2007).

Gelatin is a natural protein extracted from the collagen of bone. It is commonly used for pharmaceutical and medical application because of its enzymatic biocompatibility and biodegradability in physiological environments. Gelatin gel, alone or in combination with other polymers, can act as delivery carriers for various bioactive molecules (Thakur *et al.*, 2013). It has been used for controlled release device for a variety of growth factors known to enhance bone formation. When gelatin microspheres were incorporated in the middle PCL (poly-ε-caprolactone)/PLLA (poly-l-lactic acid) nanofibers and the upper layer from PCL/Gelatin nanofibers to control the delivery of growth, preliminary cell culture showed that the FGF-2 could be actively loaded into the gelatin microspheres and enhanced cell adherence and proliferation (Selcan Gungor-Ozkerim *et al.*, 2014). RhBMP-2/gelatin sponge grafts showed bone regeneration and strong osteogenic effects in a rabbit radial bone defect model (Kim Seong-Gon *et al.*, 2013).

Gelatin is considered cheaper and more available in solutions than collagen. Gelatin has been used as a matrix of porous scaffolds in combination with HA particles as reinforcement (Askarzadeh *et al.*, 2005). A proper mixing ratio of gelatin, chitosan, and HA for developing porous bone scaffold produced appropriate porosity, biodegradability and swelling properties for bone grafting (Wattanutchariya and Changkowchai, 2014). Moreover, spontaneous porosity when using gelatin in the scaffold will eliminate the necessity of using porogens to create porosity (Askarzadeh *et al.*, 2005). Thus the application of composites with one of its component being made of gelatin biomaterials can bring about interesting results.

In this context, hopefully, our review open new windows to choose the favourable bone graft substitute and elements need for tissue bone regeneration depends in the anatomic situations. From our point of view, multicentre clinical studies should be carried out in the future which in turn the bone healing mechanism can be improved, and graft costs decrease. Additionally, improved the pre-existing self-crosslink injectable material to be injected through a gap without the need for open surgery. Thus, produced minimally invasive injectable graft material. Further reviews focusing on the last two years (2018-2019), related to gene therapy and 3-dimensional printing bone graft substitutes that have important future applications in clinical field is strongly recomended.

Conclusion

To select a suitable bone substitute scaffold, should depend on many parameters having in mind the character of the ideal bone graft substitute that depends on the chemical composition, morphology, particle size and porosity of the biomaterial. The incorporation of GFs is a very promising option in bone healing and/or stems cells that capable of reconstructing bone and marrow structures. However, there are controversial results in the supportive role of BMPs in alveolar bone regeneration and the quantity of the MSCs required for optimum bone tissue regeneration after teeth extraction. Further materials will be likely to develop on innovative polymeric platforms with controlled biophysical, biomechanical and biological properties

that target in the delivery of growth factors and cells. From now on, researching is necessary to determine how the bone graft substitutes can be mixed, modified and applied to help the preservation of height and width of the bone wall and reconstruct the bone in closed and open defects.

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