



A REVIEW STUDY ON THE BIOMATERIALS AND BONE GRAFTS FOR BONE DEFECTS APPLICATIONS

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ABSTRACT

The graft of bones were used widely to treat the defects of the bones. Bone defects may occur for several reasons, such as injuries, illnesses, surgical interventions, and accidents, some of which may heal on their own. Bone substitutes have been widely used in plastic surgery, oral, maxillofacial, dental, and orthopaedic surgery, making it one of the most implanted tissues in the medical field. The purpose of this study was to review experimental and clinical experiences about the use of graft materials to treat the defects of the bone. From the database that were published about the experimental techniques to produce this materials and their clinical applications for them, they present the key data about the use of an induced grafts materials to address critical bone size defect of bones. The use of an induced membrane to treat critical sized bone defects of the limbs is a simple, reliable and reproducible technique. Certain technical steps should be pointed out and observed with great caution in order to avoid any pitfalls. This technique will probably be a key step for facilitating bone inclusion of new bone substitutes proposed by recent bioengineering.

KEYWORDS: Bone grafts, bone defect, Bone tissues engineering.

1- INTRODUCTION

Bone is one of the critical and complex tissues in the body. It serves many functions such as a mechanical support for tissues, and is considered to be one of the leading sites to produce blood in the body, it is also one of the central places that provides calcium, magnesium and other ions in the body; an essential factor to protect the vital internal organs.^[1,2]

Bone is composed of two parts, organic and inorganic, the inorganic part possesses a high percentage of hydroxyapatite (40-70%) and water (~10%), and the organic part include collagen (40-70%) as well as minor proteins.^[3] Accordingly, the bone can be classified into two types- compact and cancellous bone. The compact bone forms about 80% of the mass of the skeleton, while the cancellous bone comprises 20% of the skeleton mass in the human body. The function of the cortical bone is to provide protection and mechanical support, and it is located in the outer part for the skeleton, while the trabecular (cancellous) bone which is considered to be more elastic than the cortical has a higher turnover rate.^[4]

The bone is considered as a dynamic tissue that has the possibility of remodelling itself constantly. The remodelling of the bone includes bone synthesis and resorption. The cells in the bone can be classified into

two main groups- osteoclasts and osteoblasts. These two forms play essential roles in the formation of the new and the resorption of bone, respectively.^[5,6]

2- Bone defect

The bone is exposed to many defects such as injury, infection and bone tumor.^[7] Some of these defects are small (i.e. 1\3 inch), and can be self-treated as the bone is a tissue that has the ability to repair itself, but there are some defects that are large (more than 1\3 inch) such as bone fractures, as well as defects that are caused by diseases and shocks and significant bone defects, in such cases the bone cannot repair itself, so it is necessary to conduct orthodontic repairs.^[8,9]

2.1 Bone Healing Process

There are three steps to healing the injured bone- information, repair, and remodelling. Chen et al.^[10], prepared fa-ICMPC filler as a paste treat the defects of bone, which involved three steps, first, after one month of implantation for the filler, tightly and was surrounded by bone tissue. However, the interface between the FA-ICMPC and the host's bone was clearly visible. Secondly, two months later, some new bone tissue was formed and partially grown into ICMPC. The boundary between the host bone and the bones was unclear due to the proper structure of the new bone tissue. Lastly, in the

cultivation of 3 months, P-ICMPC continued to decompose and new bone was formed in many scaffold areas.

The bone remodelling process

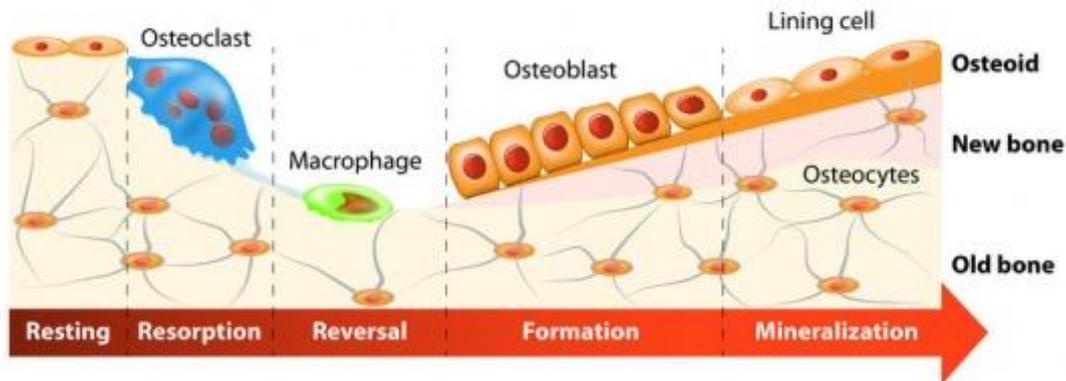


Figure 1: bone healing process.^[42]

2.2 Bone graft materials

The process that includes fixing the problems of the bone using a surgical procedure is a bone graft. Bone grafting of bone tissue is beneficial in fixing bones that are damaged from trauma or problem joints. It is also useful for growing bone around an implanted device, such as a total knee replacement where there is bone loss or a fracture. A bone graft may fill a void where the bone is absent or to help to provide structural stability.^[11,12]

The majority of methods that are used for the purpose of bone grafting have been involved with the use of autografts or allografts. The use of autografts in bone graft has been considered to be limited, due to three reasons, contouring difficulty, donor site morbidity, and limited availability, also its applications are limited because of disease transmission, and the concerns of cased immunoselection.^[13,14]

Autograft and allograft have many disadvantages, and to overcome these negatives, the graft substitutes materials that have been developed as suitable materials for bone graft, these materials are generally classified into four types of metals (Alumina ceramic (Al_2O_3), Tantalum, Magnesium and its alloys, Stainless Steel), ceramics (Calcium-phosphate, Bioglasses, glass-ceramics), polymers (natural: collagen, gelatin, silk fibroin, synthetic: Poly-glycolic acid (PGA0), Poly-lactic acid (PLA)) and composites (HA/chitosan-gelatin, Calcium-phosphate coatings on metals.^[15-17] The graft bone has been used for many years and its materials are formed as granules or porous blocks. Accordingly, the form of bone graft substitutes has been developed to be as self-hardening pastes, which has many advantages such as good adaptability to the site of the bone defect and accessible to shaping.^[18,19]

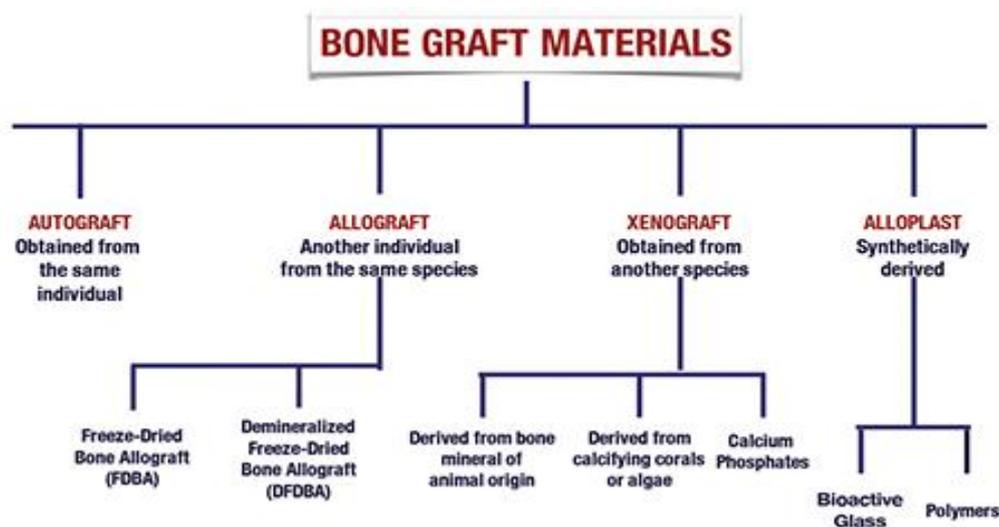


Figure 2: Bone graft materials.

2.3 Ceramics as a bone graft

Initially developed was the self-hardening calcium phosphate cement that was made through a combination of a powder phase with a liquid phase. This procedure was performed by mixing the powder phase with an aqueous solution to get a paste form, where the paste form of the filler was easy to be shaped to the damaged bone and fitted it.^[20]

The powder of CPC (calcium phosphate cement) is composed of one or various phosphate compounds. Tung *et al.*^[21], have been the first to develop the CPC, which contains Tetracalcium phosphate (TTCP), and Dicalcium phosphate anhydrous (DCPA) or with Dicalcium phosphate dehydrate (DCPD). Since then, many different compounds have been proposed from calcium phosphate, which has been investigated as to their use as the calcium phosphate cement powder.^[22]

The formulation of calcium phosphate cement (CPC) depends mainly on the ratio of powder to liquid (P/L). The mechanical properties and the handling of CPC, are influenced by the ratio of (P/L), which has been investigated in the previous study.^[23] The decrease of the P/L ratio leads to a more accessible and better injectability, while the mechanical properties of the body of cement are negatively affected by the low ratio of P/L, due to its high porosity.^{[24][109-114]}

The biological properties for CPC have been investigated in many studies, which was both *in vivo* and *in vitro*.^[25] The *in vivo* has investigated the exceptional

osteoconductivity and biocompatibility of the calcium phosphate cement (CPC), previous studies have also investigated the higher resorption for CPC.^[26-28] The physicochemical properties include density, porosity, crystal structure, and chemical composition; they have a direct effect on the resorption of CPC.^[29,30] The resorption of CPC is influenced by the implantation sites, experimental models and animal species, which are studied experimentally.^[31,104-108]

2.3.1 Tricalcium Phosphate Ceramics (β -TCP)

The forms of TCP are classified into two forms β -TCP and α -TCP.^[32] The most form of TCP which is used widely in the bone grafts files is β -TCP. The TCP has good properties such as faster biodegradation and absorption and the ratio of Ca/P is higher.^[33] Many desirable properties for pure β -TCP such as good osteoconductivity, good resorbability, ease of handling and osteogenic cell adhesion.^[34] It is commonly used to repair marginal periodontal and periapical defects and Molecules as a partially resorbable filler in alveolar bony defects. Nakajima *et al.* found that the bone regenerative potential of β -TCP is comparable to that of freeze-dried bone allograft, deproteinized freeze-dried bone allograft and autograft materials. However, the mechanical properties of this material limit its wider application.^[35,36]

Table 1 shows the techniques that have been used to prepared β -TCP from different sources for wide range applications such as Biocompatibility, Cell proliferation assay and Biomedical implant etc.

Table1: Preparation and application of Tricalcium Phosphate Ceramics (β -TCP)

	Method	Application	Results	Ref
1	Annealing a compact preform	Biocompatibility	The MTT assay showed that there was no difference between viability assay of NCTC L929 cells in the presence of liquid extracts from biphasic α,β -tricalcium phosphate ceramic samples after 24 h cultivation sample and control. The decrease in the cell vitality is not statistically significant in comparison with control.	[43]
2	Wet precipitations	Cell proliferation assay	The results of the <i>in vitro</i> cell experiments confirmed that the ceramics could promote proliferation and angiogenesis of HUVECs by stimulating HFs to secrete angiogenic factors as a paracrine effect, and up-regulating HUVECs to express these angiogenic factors and their receptors as an autocrine effect	[44]
3	Chemical precipitation method	bone tissue regeneration	Excellent cytocompatibility to support the growth of HBMSCs in both powder extract and ceramic disc forms	[45]
4	Mechano-chemical activation synthesis method	Biomedical implant applications and Antibacteria	The applications of the developed material will significantly contribute to fulfill a number of unmet clinical needs in orthopaedic surgery	[46]
5	Wet chemical process.	Regeneration in bone repair.	Results suggest that silicate-containing α -TCP is advantageous for initial skeletal fixation and wound regeneration in bone repair.	[47]
6	The fast microreaction process	bone tissue regeneration	Results showed that the β -TCP nanoparticle crystal shape and size as well as the Ca/P molar ratio could be well controlled using the micro dispersion process	[48]

2.3.2 Bioactive Glass

Bioactive glasses are considered highly reactive surfaces formed by melt or sol–gel techniques. Bioactive glass forms a hydroxy-carbonated apatite layer when immersed in biological fluid, which enhances protein adsorption to the surface of the implant and integration with surrounding bone.^[37,38] Bioactive glasses have been investigated for decades and have shown good results in bone regeneration. In all these years several types of bioactive glasses are developed: the conventional silicate glass (45S5 bioactive glass or Bioglass®), glass ceramics (S53P4 bioactive glass or BonAlive®), and borate-based glasses (19-93B3 bioactive glass).^[39] BGs of varying compositions have been shown to be effective in promoting angiogenesis by affecting the secretion of relevant growth factors or cytokines. It has been shown that the effect could be mainly achieved through the release of therapeutic ions from BGs. Here, it is possible

to control cellular responses by introducing several biologically active ions in specific concentrations.^[40] BG (such as 45S5) has been shown to offer further advances as compared to HA or, more in general, to calcium phosphates. For instance, it was reported that granules of 45S5 BG, implanted in rabbit femurs, promoted bone proliferation more rapidly than synthetic HA. Furthermore, 45S5 glass is considered to be not only osteoconductive (like HA), but also osteoinductive because it supports new bone growth along the bone–implant interface as well as within the implant away from the bone–implant interface.^[41]

The preparation methods that were used to produce bioactive glasses were mentioned in table 2. The bioactive glasses were used in many applications such as biomedical applications, Bone tissues engineering and Bone implant.

Table 2: Preparation and application of bioactive glasses.

	Method	Application	Results	Ref.
1	Sol–gel	Biomedical applications	Nanocomposites resulting from the combination of these materials with chitosan exhibited bioactive character and may be potentially used in a series of orthopaedic applications, including in membranes for tissue guided regeneration	[49]
2	freeze drying	Bone tissues engineering	This bioactive glass ceramic nanoparticle with excellent bioactivity would be a promising filler material for bone tissues engineering.	[50]
3	Sol-gel method	Bone defect repairing.	Excellent apatite-forming activity and high biocompatibility, which demonstrated their potential applications in the field of bone defect repairing.	[51]
4	Simulated body fluid	Bone implant	Possessed good drug release behaviour due to its well-ordered mesoporous structure, and a higher ability to induce hydroxyapatite formation in SBF. Therefore, well-ordered mesoporous bioactive glasses might be used as a bioactive drug release system for preparation of bone implant materials.	[52]
5	Simulated body fluid	Bone tissues engineering	The results show that scaffolds with a wide range of bioactivity and degradation rate can be achieved by replacing varying amounts of SiO ₂ in silicate bioactive glass with B ₂ O ₃	[53]
6	Sol-gel synthesis	Hyperthermia application	The results suggest that hematite nanocrystals' superparamagnetic properties may be explored in multifunctional glass-ceramics applied in bone cancer treatment by hyperthermia allied to bone regeneration.	[54]

2.3.3 Biphasic calcium phosphate (BCP)

Biphasic calcium phosphate (BCP) is another widely used commercial ceramic obtained by mixing hydroxyapatite and tricalcium phosphate in different concentrations for the purpose of combining the advantages of both calcium salts. By adjusting the formulation, the dissolution rate and mechanical properties can be controlled within ranges and subsequently applied in bulk or as implant coatings.^[55,56] Calcium phosphate biomaterials are devoid of local or systemic toxicity, do not elicit inflammatory or foreign body responses, can become functionally integrated with natural bone with no fibrous tissue encapsulation and cause no generation of normal bone mineralization process.^[99-103] Calcium phosphate biomaterial provides a

physical matrix suitable for deposition of new bone and can display growth-guiding properties causing bone to extend its growth into areas that otherwise it would not occupy. It also has the ability to maintain bone bulk in areas where bone resorption formally takes place. HA implants have been used successfully to prevent post-extraction alveolar ridge resorption.^[57-60]

The BCP were used widely in the bone tissue engineering to treat the defects of the bones. The table 3 explain the applications and methods of the synthesis of BCP.

Table 3: Preparation and application of Biphasic calcium phosphate (BCP)

	Method	Application	Results	Ref.
1	cycled freeze-thawing method	Bone tissue engineering	The results suggested that prepared CGB nanocomposites had the potential to be applied in bone tissue engineering.	[61]
2	In situ incorporated	Biomedical applications	The above results manifested the significance of the final AgSeB-NPs for biomedical applications.	[62]
3	Wet chemical synthesis	Bone tissue engineering	The differential thermal analysis (DTA) and thermogravimetric analysis (TG) results show that the as-prepared samples are thermally stable.	[63]
4	Freeze-drying method	Bone regeneration	The bioceramic/biopolymer scaffolds functionalized with signaling biomolecules successfully provided a favorable microenvironment for bone formation and thus serve as potential candidates for use in bone tissue engineering	[64]
5	Freeze-drying method	The segmental bone defects.	These experiments indicate that low-temperature robocasting could potentially be used to fabricate 3D printed BCP/PVA/PRF scaffolds with desired shapes and internal structures and incorporated bioactive factors to enhance the repair of segmental bone defects.	[65]
6	Freeze-drying method	Bone tissue engineering	The results showed excellent osteogenic capacity in the rat model. The SF/BCP scaffold can highly simulate the micro-environment of natural bone formation and can meet the requirements of tissue engineering.	[66]

2.3.4 Hydroxyapatites

Hydroxyapatites (HAp) is a natural occurring mineral form of calcium apatite with the formula of $\text{Ca}_{10}[\text{PO}_4]_6[\text{OH}]_2$ and comprises about 50% of the weight of the bone, which accounts for its excellent osteoconductive and osteointegrative properties.^[67,68] Meanwhile, HAp has a similar initial mechanical property compared to the cancellous bone—brittle and weak under tension and shear but resistant to compressive loads^[69, 96] and may decrease by 30e40% in situ after being implanted for several months.^[70, 95] The macroporosity (pore with diameters > 100 mm) and pore interconnectivity of synthetic HAp allow the adhesion, proliferation, and differentiation of osteoprogenitor cells,

as well as the revascularization, and subsequently ingrowth of new bone, when implanted in vivo^[71,72]

Also from a mechanical point of view, HA shows interesting features in terms of stiffness (Young Modulus $E = 35 - 120 \text{ GPa}$) and compressive strength (CS) (120 – 900 MPa)^[73, 94] and toughness investigated by a number of molecular dynamics (MD) models and confirmed experimentally.^[74-78] For instance, microspheres of HA have been studied by many research teams for bioengineering applications due to their potential as local drug and protein delivery systems. [79-84] On the other hand, few studies have investigated the incorporation of HA microspheres within polymeric matrices produced via AM.^[85-88]

Table4: Preparation and application of Biphasic calcium phosphate (BCP).

	Method	Application	Results	Ref.
1	Microwave-assisted	Adsorbent for the removal	It was concluded that the prepared MNHA nanocomposite is simple, fast, eco-friendly adsorbent for the removal of U(VI) ions from water with excellent adsorption capacity. However, further modifications of hydroxyapatite nanoparticles for its involvement in further applications will be considered in future studies.	[89]
2	Precipitation method	Support of bone healing	The PLLA/Eu3+:HAp composites were obtained as prospective candidates to theranostic applications (therapy and diagnostics) due to support of bone healing by hydroxyapatite and bio-imaging possibility of Eu3+ ions.	[90]
3	Simple mixing method	Heavy metals remediation in aquatic environments	The results showed that hydroxyapatite synthesised from calcite waste represents a low-cost material for the adsorption of hazardous Pb2+ in contaminated waters and a promising alternative for heavy metals remediation in aquatic environments.	[91]
4	Simple mixing method	Bone fillers	The activities of the antimicrobial in the composites were found against Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus). For the cytotoxicity study, the composites showed non-toxic effects on MG-63 human cells at high concentrations.	[92]
5	infiltration method	Bone fillers	The beads morphology demonstrated a homogeneous surface with AgNPs scattered in the matrix.	[93]
6	Co-precipitation and hydrothermal methods	biomedical applications	These studies facilitate the formation of biocompatible HAp–Al ₂ O ₃ composite nanorods for biomedical applications.	[97]

2.4 CONCLUSION

Orthopaedics scenarios such as large segmental bone defect may result in delayed union or even non-union if improperly treated clinically. Hence, surgical interventions together with bone grafting techniques are usually necessitated in the treatment process. Even though the emergence of various synthetic bone substitutes offers diversity options, the treatment outcome is still incomparable to the approach of autologous bone graft in terms of bone healing quality and time. Then, pro-angiogenic factors will be released from the scaffold and promote fast vascularization. Finally, pro-osteogenic cues will also be released from the scaffold to stimulate osteogenic differentiation and bone formation. In cases where osteoblasts recruitment is affected by age and health conditions, the functionalized scaffold can promote fast proliferation and osteogenic differentiation of stem cells to remedy the limited osteoblasts recruitment. Consequently, research efforts with bioinspired functionalized cell-free scaffolds must be sustained to pave their way to successful clinical applications for the benefit of patients.

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