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Basic Concept of Bone Cements

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Abstract: Every year numerous patients in the world undergo bone replacement and reconstruction treatment due to severe trauma, tumor resection, systemic and periodontal diseases, abnormal skeletal development of genetic disorders and bone defects caused by fracture, all represent major causes of disability and a loss of quality of life which urge the need for replacement .

Keywords: : *Bone cment, calcium sulfate cement, calcium phosphate cement*

Every year numerous patients in the world undergo bone replacement and reconstruction treatment due to severe trauma, tumor resection, systemic and periodontal diseases, abnormal skeletal development of genetic disorders and bone defects caused by fracture, all represent major causes of disability and a loss of quality of life which urge the need for replacement (1).

I. Bone Replacement Material:

Currently, autograft is the gold standard for the treatment of bone defects and bone regeneration, where bone tissue harvested from and implanted in the same individual (a patient's own tissue), it can be obtained from intraoral sites from the same individual, such as the mandibular symphysis, mandibular ramus, external oblique ridge due to being good sources of cortical and cancellous bone. However, its main disadvantages include morbidity at the donor site and the need for two operative procedures, donor-site injury, chronic postoperative pain and infection. Allograft is an alternative method, where bone tissues are harvested from a compatible living individual implanted in another one of the same species (from a donor). Allografts exhibit good histocompatibility and are found available in various forms, from whole bone segments, cortico-cancellous, and cortical pieces to chips, powder, and demineralized bone matrix (DBM). It has many postoperative complications such as rejection of the donor tissue by the recipient's immune system and concerns with disease transmission such as HIV and hepatitis. To overcome potential immunogenicity and morbidity at donor sites, artificial synthetic bone substitute materials are generated to closely mimic the biological properties of natural bone and are promising alternative for the repair and replacement of bone defects(1,2).

Bone cements are bone substitute and bone filling materials, can be defined as biomaterials obtained by mixing powder and liquid phases, forming a plastic paste, which can be moulded and implanted as a paste. They have the ability to self-set once have implanted in the body, ensuring perfect fit at the implant site and good bone–material contact as well. The term "cement" is a misnomer since the term cement is used to represent a substance that bonds two things together. However, bone cements have no inherent intrinsic adhesive properties, but instead, they depend on the close mechanical interlock between the irregular bone surface

and the prosthesis. They are widely used in various orthopedic and dental implant fixation and of great significance for filling and repairing the irregular trauma site and bone defects(3).

II. Characteristic of an ideal bone substitute material:

The main function of bone cement is to provide mechanical support and stimulate osteo-regeneration, with the goal of bone replacement. The four fundamental biological properties of osseointegration, osteogenesis, osteoconduction, and osteoinduction, are paramount in performing this role effectively. **Osseointegration** is the ability of a grafting material to chemically bond to the surface of the bone in the absence of an intervening fibrous tissue layer. **Osteoconduction** refers to the ability of a bone grafting material to generate a bioactive scaffold on which host cells can grow. This structure enables vessels, osteoblasts, and host progenitor cells to migrate into the interconnected osteomatrix. **Osteoinduction** is the recruitment and activation of host mesenchymal stem cells into the grafting site, where local proteins (BMPs) and other factors induce the differentiation of stem cells into osteoblasts. **Osteogenesis** is the formation of new bone via osteoblasts or progenitor cells present within the grafting material. These four fundamental properties enable new bone formation which occurs in parallel to direct osseous interconnection. Additionally, various properties influence the success rate as biocompatibility, bioresorbability, sterility, structural integrity, adequate porosity for vascular ingrowth, plasticity, ease of handling, and compressive strength(2).

III. Classification of bone cements:

Bone cements materials currently in clinical use can be classified into: polymethylmethacrylate (PMMA), calcium sulfate-based bone cements (CSCs), calcium phosphate ceramics, the most used in bone tissue engineering are hydroxyapaptite (HA), tricalcium phosphate (TCP) or combination of the two, known as biphasic calcium phosphate (BCP), calcium phosphate cements (CPCs) and organic-inorganic composite bone cements.

To date, the most used biodegradable bone cements mainly include calcium phosphate-based cements (CPCs), calcium sulfate cements and composite bone cements. The biggest advantage of biodegradable bone cements is that they gradually degraded by chemical dissolution and cell absorption after implantation in the bone defect and finally replaced by newly formed bone (1).

1. Acrylic bone cements (ABC):

The term ‘bone cement’ was initially applied to acrylic bone cements (ABCs), widely used since the 1960s for anchorage of implants in orthopaedic surgeries, and bone defect. ABCs are based on polymethylmethacrylate (PMMA) which is an acrylic polymer that is formed by mixing two sterile components a liquid MMA monomer and a powered MMA-styrene co-polymer. When the two components are mixed, the liquid monomer polymerizes around the pre-polymerized powder particles to form hardened PMMA. It is accepted as a biocompatible polymer when cured.

PMMA bone cement has some favorable properties such as ease of handling and application, significant mechanical strength (used for high and medium load-bearing applications), suitable curing time and economical. The major reason for its limited application in the oral environment can be attributed to its very low biodegradability, it is bio-inert and lacks bioactivity, the poor interfacial integration between the host bone tissue and the cement brings a major challenge in the clinical practice and may cause interfacial loosening,

with no functions of bone conduction or induction, tissue necrosis resulting from the exothermic setting reaction, the heat generated during curing may reach up to 110°C which can cause thermal necrosis of surrounding bone cells and extensive bone damage since collagen denatures with prolonged exposure to temperatures in excess of 56°C, as well chemical necrosis can occur due to unreacted monomer release , monomer toxicity, degradation of fragments causes irritation and inflammation at the implanted site(4,5).

2. Calcium Sulfate Cements:

Calcium sulfate also referred to as gypsum, it is the first synthetic scaffold used for bone regeneration. The advantage of calcium sulfate cement is biocompatiblility, low cost, osteoconducitivty, safe as the degradative products even cause no tissue inflammatory reaction when implanted in the body. Major drawback is it lacks bioactivity and the rapid degradation of calcium sulfate which exceeds the rate of new bone formation, (too rapid to be replaced by new bone invivo) , resulting in significant loss of mechanical properties at the defect site, limiting its clinical application. It is reported that calcium sulfate cement generally takes 4–6 weeks to completely degrade under the condition of good blood vessels. However, the degradation time of calcium sulfate was prolonged to 6–10 weeks in the poorly vascularized bone defect(1).

3. Calcium phosphate ceramics:

The synthetic mineral salts, HA and b-TCP are calcium phosphate–based ceramics. Ceramics are inorganic solids, that require high temperature and high-pressure processing to produce dense, highly crystalline, bioinert ceramics. They are produced in a highly thermal process known as “sintering,” where they are heated between 700°C and 1300°C to form their crystalline structure, this allows for improved strength but slower resorption.

3.1. Hydroxyapatite (HA):

The chemical composition of HA closely resembles that of the inorganic component of bone, enables it to be used as a bone grafting material and as a defect filler. It is classified as bioactive, referring to its support towards the formation of hard tissue and osseoconduction and as well osteointegrative. However, synthetic HA do not contain trace amounts of Na^{+}, Mg^{2+}, K^{+} and Sr^{+}, which are found in naturally derived HA and influences various biomechanical reactions. Synthetic HA does not possess a microporous structure, as seen in bovine-derived.

HA has a delayed and low resorption rate due to its relatively high Ca/P ratio, high stability and crystallinity. HA ceramic is a valid alternative to autogenous graft without donor morbidity, it can be used as a structural bone substitute to correct and fill bone defects due to its good mechanical strength.

The application of HA in dentistry is usually coating on surface of metallic implants, to improve osteoblast activity or to increase the contact area of bone implants, improving the biological fixation, biocompatibility, and bioactivity of implants(2,6).

Recent advances have investigated producing nano-sized HA, enhances biomechanical properties that more closely mimics the composition of natural bone, with a much closer resemblance to bone extracellular matrix; enhanced delivery and controlled release of bioactive molecules, such as growth factors, allowing for enhanced osteo-regenerative properties. Nanocrystalline HA exhibits improved biological performance and dissolution compared with its conventional forms of HA, with a larger surface to volume ratio, promoting more effective adhesion, proliferation, and differentiation of osteogenic progenitor cells, resulting in improved fracture toughness and mechanical properties(2).

3.2. Tricalcium Phosphates (TCP)

TCP possesses two crystallographic forms, α-TCP, and β-TCP. The α-TCP only exists at very high temperatures (around 1500 ◦C). TCP are bioactive, biocompatible, osteoinductive, and bioresorbable materials that allow and promote bone tissue regeneration. β-TCP is formed at a temperature of 900–1100 °C. β-TCP has a more stable structure and lower biodegradation rate than α-TCP, therefore, β-TCP preserves the structural stability for a longer time and has more uses in clinical applications comparatively, in bone regeneration and as a bone substitute material, and can also used in developing monophasic/biphasic bioceramics. β-TCP is less stable than HA, exhibits faster biodegradation and higher solubility compared with HA due to its lower Ca/P ratio(2,6).

In dentistry, α-TCP is used primarily as a fine powder to prepare calcium phosphate cements due to its high solubility and reactivity, which makes it ideally used as injectable biodegradable cements. However, the main drawbacks that limit the use of α-TCP in its pure form in biomedical applications are its rapid resorption rate which is faster than the formation of a new bone, and its limited mechanical properties.

Pure phasic β-TCP possesses many desirable properties, such as its ease of handling, radiopacity allowing monitoring of healing, good osteoconductivity due to macroporosity, has excellent cell adhesion and biomineralization promoting fibrovascular ingrowth, proliferation of osteoblasts cells osteogenic, good resorbability, and low immunogenicity and risk of disease transmission. Whilst the interconnected porous structure of β-TCP allows for improved vascularization, it also results in the material's poor mechanical strength under compression. This results in β-TCP being unsuitable as a bone substitute however it is suitable for use as a filler in bony defects and repair at morphological sites. It is commonly used to repair marginal periodontal and periapical defects; it considered useful in supporting the growth of bones after surgery. However, the mechanical properties and brittleness of this material limit its use to non-load bearing applications(7).

3.3 Biphasic Calcium Phosphate Ceramics (HA and β-TCP Ceramic)

Advancements have attempted to develop a material combining two phases, ideally mimicking the extracellular matrix properties of the respective tissues, which are tightly connected to each other without additional adhesive components. Some of the strands of one material are extended into the part of the other material to realize an interlocking of both parts. Phases of incompatible calcium phosphates, such as the more stable HA and the more soluble β -TCP, to harness both the resorbability of β-TCP as well as the osteoconductive potential of HA. This results in more rapid and higher bone regeneration rates seen compared with the use of HA alone, and the greater mechanical properties than β-TCP present the major benefits of using biphasic. Thus, BCP material possesses superior bioactivity, biodegradability, osteoinductivity, and mechanical properties than HAP or β-TCP alone and has greater ability to stimulate osteogenic differentiation of BMSCs(2,6).

Despite the improvements in mechanical strength compared with β-TCP alone, biphasic CP ceramics still possess compressive strengths lower than that of cortical bone. The use of biphasic CP ceramics has been indicated as bone grafts, bone substitute in periapical surgery and has shown predictable clinical outcomes and complete alveolar bone healing over a two-year period. Hence, this material has shown the potential for bone healing via osteoconduction and osteoinduction processes(2).

4- Calcium phosphate cements (CPCs)

CPCs belong to the group of bioactive synthetic materials, they occupy a particular position due to their resemblance to the chemical components and structures of natural bone tissue, they can directly be injected

into the bone defect and allowed to set in situ. When used for in vivo applications, it is prepared by mixing a calcium phosphate salt (powder component commonly containing sintered CP materials such as α-TCP and HA) with water or with an aqueous solution to form a workable paste that reacts at room or body temperature. The calcium phosphate cement dissolves and precipitates into a less soluble calcium phosphate.; and self-set as hydroxyapatite when moistened. During precipitation, the calcium phosphate crystals increase in size, giving rise to a precipitate containing one or more calcium phosphates and gets interlocked, thus the entanglement of the precipitated crystals is responsible for hardening and providing structural rigidity to the cement(8).

These cements are great candidates for various clinical applications. CPCs are considered as the most suitable injectable biomaterials to accommodate narrow and irregular dental bone defects, and used as bone fillers and can be injected to form a bioactive scaffold for tissue engineering, Moreover, since the calcium phosphate cements are fabricated at room or at body temperatures, also they can be used as drug delivery vehicle for antibiotics, antitumor drugs and to deliver bioactive agents.

The major reason for CPCs' wide uses in oral environment are their unique combination of osteoconductivity, bioactivity that favors their combination with growth factors, drugs, polymers, capacity to directly bond to bone, thus establishing a uniquely strong interface, biocompatibility, biodegradability, injectability, moldability, and negligible shrinkage. In addition, CaPs do not cause an antigenic response in the body and can be easily customized to its intended application. Another advantage of calcium phosphate cement is their ability to set at physiological temperature, replicate the structure and composition of bone in a repeatable manner to form hydroxyapatite that resembles biological apatites without the addition of any additives, during the setting reaction only a small amount of heat is released (nonexothermic setting) as compared to polymethylmethacrylate cements and also the volume of calcium phosphate cement remains constant during the setting reaction. As well the porosity and microstructure of CPCs can be altered by adjusting the process parameters, such as the liquid-to-powder ratio and the particle size of the powder phase (5,6).

However, calcium phosphate cements are brittle materials with low mechanical strength and fracture toughness. It cannot be used in load bearing regions of bone due to the possibility of collapse under physiological conditions, and weak mechanical properties that cannot match the strength of human cortical bone (4,9)

According to CPCs end product of reaction, they can be classified into three groups: apatite (HA, $Ca_5(PO_4)_3OH$), brushite (DCPD, $CaHPO_4 \cdot 2H_2O$) and monetite (DCPA, $CaHPO_4$) (1).

4.1. Apatite Cements

There are two different reaction paths for the setting of apatite cements. The first is an acid–base reaction, one acidic and one alkaline calcium phosphate source react to form a neutral product. Tetracalcium phosphate (TTCP) is the most frequently applied alkaline calcium phosphate source. The mixture of TTCP with an acidic calcium phosphate source (DCPA or DCPD) produces the precipitation of HA. Apatite formation occurs at pH > 4.2.

$$2\ CaHPO_4 + 2\ Ca_4(PO_4)_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2$$

The second type of reaction is a simple hydration reaction. Calcium-deficient HA (CDHA) is prepared via the hydrolysis of a single CaP compound such as $\alpha\text{-}Ca_3(PO_4)_2$ (α-TCP), which is applied in most clinical products.

$$3\ \alpha\text{-}Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5(OH)$$

Apatite cements generally degraded through chemical dissolution and active degradation mediated by cellular activity (osteoclast activity) and the active degradation is dominant. Due to the limited degradation of cellular activity, HA is the least soluble and most stable of the different CPCs. Many experiments indicated that apatite cements showed only slight degradation and new bone regeneration after being implanted in vivo for several months or even years. The slow degradation of apatite not only hinders the regeneration of new bone, but also severely limits its clinical application. Apatite cements have better mechanical strength than brushite cements.

4.2. Brushite Cements (dicalcium phosphate dihydrate)

Brushite cements are prepared using an acid–base reaction composed of acidic phosphorus source and basic calcium source. The most applied formulation is monocalcium phosphate monohydrate (MCPM) and β-tricalcium phosphate (β-TCP). It precipitates at more acidic conditions of the paste at pH < 4.2.

$$Ca(H_2PO_4)_2 \cdot H_2O + \beta\text{-}Ca_3(PO_4)_2 + 7\ H_2O \rightarrow 4\ CaHPO_4 \cdot 2\ H_2O$$

Brushite-based biomaterials are characterized by good bioactivity, bioresorbability and biocompatibility. Under physiological conditions, the dissolution rate of brushite cements is almost three times that of HA cements. Ideally, the biodegradation rate of brushite cements should be in line with the newly formed bone to allow the newly formed bone to gradually restore its mechanical properties. However, compared with the regeneration rate of bone, the degradation rate of brushite cements is still slightly slower. There are several methods to improve the degradation rate of brushite cements to be in line with rate of bone formation, while retaining its osteogenic ability and biocompatibility by: (i) reducing the powder-to-liquid ratio of CPCs increases its injectability (ii) improving porosity, by introducing different pore sizes into bone cement to improve the local metabolism and the promote degradation rate of cement, (iii) inhibiting phase conversion by preventing brushite cements from recrystallizing to form apatite (e.g.by incorporation of Mg^{2+} into the brushite cement to prevent phase conversion). Brushite (dicalcium phosphate dihydrate) cement is a promising bone substitute material. It is degraded by simple chemical dissolution; therefore, they are of special interest for applications where replacement of the cement by newly forming bone is desired.

4.3 Monetite Cements

Monetite is the anhydrous form of brushite, can be obtained by adjusting the reaction conditions of brushite cements. For example, setting brushite cements in excessively low pH conditions, in water-deficient environments, or in the presence of metallic ions, favoring monetite formation Another way of fabricating monetite cements is via the thermal dehydration of already-set brushite cements.

$$CaHPO_4 \cdot 2\ H_2O \rightarrow CaHPO_4 + 2\ H_2O$$

Monetite cement is an excellent calcium phosphate cement, its resorption can offer a good balance between implant degradation and new bone regeneration thus, maintaining mechanical stability, an advantage that separated monetite from brushite and HA. Compared with brushite cements, it was found that monetite cements resorb at a faster rate in vivo, as monetite is not transformed, not recrystallize into apatite as readily as brushite.

5- Organic-Inorganic Composites

To further improve the properties of bone cement in various aspects, researchers often add organic components to the inorganic phase. The organic components added in composite bone cement can be divided into natural polymers and synthetic polymers. Natural polymers mainly include gelatin, sodium alginate and chitosan; the synthetic polymer is mainly composed of Polycaprolactone (PCL), Poly (Lactic Acid) (PLA), PLGA. These polymers are often added into bone cement in different ways (polymer chain, microspheres) to regulate the degradation rate to meet the corresponding clinical needs. Poly-lactic acid (PLA) has been defined as a biomaterial with potential clinical applications in many studies due to its slow degradation properties and reliable biocompatibility. However, the drawback of pure polymer scaffolds is the lack of osteogenic inducement, which is also the main reason why researchers were chosen to explore composite materials. The addition of polymers enriches the types of biodegradable bone cement and improves its degradability and provides a good method for the clinical customization of personalized biodegradable bone cement and are suitable for the repair of critical bone defects as they possess sufficient mechanical properties(1).

A promising xenograft material currently being researched is chitosan, a naturally occurring polymer. Chitosan can stimulate bone regeneration by providing a structural scaffold that supports osteoblastic activity, the formation of mineralized bone matrix and inducing differentiation of MSCs into osteoblasts. Due to the poor mechanical properties of chitosan, it is often combined with other materials such as gelatin, calcium phosphates and bioglass to provide more desirable properties, by mixing chitosan with gelatin and hydroxyapatite (HA) produces a porous scaffold with desirable properties, as decreased degradability and an open pore structure conducive to cell attachment and vascularization.Recent studies in dental field reported successful use of chitosan-based materials as a membrane for GBR, guided tissue regeneration, coating implant surfaces, restoring alveolar bone height(2)

Recently the fabrication of high toughness, biocompatible and resorbable organic–inorganic composite bone cements consisting of brushite, gypsum, and polyglactin fibers was investigated. Brushite has fast in vivo resorption rates and tend to transform into the insoluble hydroxyapatite phase after implantation, which impairs their in vivo resorption and limits their clinical application. Adding gypsum and functionalized polyglactin fibers composed of poly (lactic-co-glycolic acid), PLGA, fibers have been used as a reinforcing agent with calcium phosphate cements because of their resorbability and biocompatibility, have great potential for bone regeneration and tensile strength and it further increased the toughness of the material due to the chemical interactions between the functionalized fibers and the cements. Combining brushite and gypsum can prevent hydroxyapatite precipitation, thus increased their in vitro resorbability and produce a biocompatible composite with a resorption rate closely matching the new bone formation (10).

For brushite-gypsum composite, brushite and gypsum initial powders were mixed at 5 different weight ratios (table 1). The control groups were prepared using either pure brushite powders (100/0) or pure gypsum powder (0/ 100), (10).

Table 1
Initial powder compositions and abbreviations for tested groups.

Composition of the initial powder (Wt%)	Calcium phosphate/calcium sulfate
100 wt% calcium phosphates	100/0
80 wt% calcium phosphates and 20 wt% calcium sulfate	80/20
66 wt% calcium phosphates and 34 wt% calcium sulfate	66/34
50 wt% calcium phosphates and 50 wt% calcium sulfate	50/50
34 wt% calcium phosphates and 66 wt% calcium sulfate	34/66
20 wt% calcium phosphates and 80 wt% calcium sulfate	20/80
100 wt% calcium sulfate	0/100

Since fracture toughness of cement materials is inversely correlated to their porosity, the porosity of brushite-gypsum composites was measured using a helium pycnometer. Results revealed that adding gypsum to brushite cements decreased the porosity of the hardened composite and thus increases the fracture toughness of the cement. Composites with a brushite-gypsum ratio of 34/66, showed the highest fracture toughness, had the lowest porosity (20%), which was 41% lower than the porosity of pure brushite cement (100/0) ($P < 0.05$). On the other hand, the cements with higher porosity such as the pure brushite and pure gypsum cements, presented lower fracture toughness (10).

IV. Dental Applications of bone cements (2,8,11,12):

1. Calcium phosphates are used in the form of injectable cements or as coatings on titanium and titanium alloy implants to combine the bioactivity of the calcium phosphates and the strength of the metal.
2. Bone-filling material is of great significance for repairing bone defect site.
3. Bone cement can be used to improve stability of implant, especially in patients with insufficient cortical bone, bone cement can be used as the bone graft material, for dental implant fixations.
4. Calcium phosphate cements can be successfully used in different oral applications, including repair of periodontal defects and periodontal regeneration, alveolar ridge augmentation, sinus lifting graft.
5. the application of HA in dentistry is generally limited to the coating on surface of metallic implants.
6. β-TCP has wide applications in periodontics due to its chemical similarity with the cancellous bone, showing improved integration into the natural bone and quick resorption. It is commonly used to repair periodontal defects, followed by alveolar bone and periapical defects around the dental implant.
7. Synthesis of calcium phosphate scaffolds in tissue engineering for bone or dentin regeneration.
8. Bone cements can carry drugs directly to the bone without causing adverse effects on healthy tissues, since systemic drug delivery to the bone is difficult as human bone has limited perfusion. Growth

factors in addition to anti-inflammatory, anticancer, analgesic, and antibiotic reagents are just a few of the medicinal chemicals that may be added into bone cements for various treatments.

Growth factors (GFs) have been widely utilized in bone repair for their bone remodeling functions. Bone morphogenetic proteins (BMPs), are effective osteogenic proteins that promote bone regeneration and bone formation, have ability to recruit and signal to mesenchymal progenitor cells to differentiate toward a bone-forming cells, regulating bone balance by controlling the differentiation of osteoblasts and osteoclasts. Among them, BMP-2 and BMP-7 are the most effective factors for skeletal development including proliferation and formation of bone and cartilage cells for clinical use.

Mixing of growth factors can alter the osteoinductive properties of CaP materials, hence promoting bone repair and formation. It is widely accepted that in the regeneration of lost bone and periodontal tissues, growth factors play a vital role in the complex cascade of tissue regeneration process (potent osteoinductive activity)(6).

BMP has been incorporated into several scaffold systems to localize the delivery of BMP to the defect area whilst minimizing protein diffusion, to increase effectiveness. Porous β-TCP have a high affinity used as potential carriers and delivery systems for loading of bone morphogenetic protein-2 (BMP-2). Scaffold were briefly etched with citric acid in order to increase surface area and thus protein adsorption and loading, The incorporation of BMP-2 was sufficient to induce bone within the scaffolds pores and resulted in an amount of newly formed bone that was 1.3 times higher than with unloaded scaffolds(13,14).

In a comparative study, some commercial biomaterials, such as β-tricalcium phosphate, calcium phosphate cement, and polylactic/polyglycolic acid, incorporated with BMPs, were assessed. The highest bone regeneration was observed in β-tricalcium phosphate kind. Most of calcium phosphate cement remained because of its low degradability. In the polylactic/polyglycolic acid, although the materials wholly degraded, the remained polymer fragments created inflammatory response besides bone regeneration.

9. Human Demineralized bone matrix can be used to regenerate mineralized bone filling in extraction sockets in an attempt to minimize post-extraction atrophy and help to preserve and restore dimensions of the alveolar ridge(bone height and thickness) following tooth extraction for implant placement. DBM can be as used as a bone repair matrix and a carrier for delivering bioactive agents.

DBM is an allograft derivative, which is acid-treated to remove the mineral mesh. This demineralization process results in exposure, of the underlying inner bone matrix rich in growth factors and bone morphogenetic proteins, collagen (mainly type I and type IV), a small amount of calcium phosphate, and cell debris. DBM is relatively easy to handle with minimal immunological rejection due to the elimination of the antigenic surface structure of the bone during acid-treatment; good bone conduction ability, they also exhibit the conventional benefits of allograft materials and demonstrated to be an osteoconductive and osteoinductive substitute. DBM provides a lack of structural support due to the loss of many inorganic components and thus possesses poor mechanical properties, thus it is not suitable for the repair of bone defects in load-bearing areas. The use of DBM is only limited to filling bone defects and is generally used in combination with other allografts, BMPs or composite bone substitute material(15).

DBM cannot fullfil the role of scaffold owing to lack of calcium/phosphate and causing rapid resorption before new bone formation occurs. To improve DBM's ability for bone-graft material, mixing DBM with calcium phosphate enriched material may be a key. One of the most used forms of calcium phosphate for

synthetic bones is β-tricalcium phosphate (TCP), widely studied in the field of tissue regeneration due to its osteoconductivity, biocompatibility, and bio-resorption. The mixture of DBM and TCP exhibited excellent bone formation by a synergistic effect, since TCP has a suitable rate of degradation, it can promote the release of calcium and phosphorus ions to induce bone formation(15)

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