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Review Article

Recent Advances in Bone Graft Substitutes in Dental Implantology: A Review

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***ABSTRACT*:**
Dental Implant surgery has become popular with the advancement of surgical techniques such as sinus lift, guided bone regeneration, and block bone graft. Alveolar ridge augmentation can be completed with various types of bone augmentation materials (autogenous, allograft, xenograft & alloplast). Currently autogenous bone is available in cancellous, cortical, or bone marrow aspirate form. Autogenous bone graft is labelled as the "gold standard" due to faster healing times and integration between native and foreign bone. However, drawbacks including donor-site morbidity and limited quantity of graft available for harvest make autograft a less-than-ideal option for certain patient populations. Progressive advancements in allograft and bone graft substitutes in the past decade have created viable alternatives that sidestep some of the weak points of autografts. Allograft can be a favourable substitute for its convenience, abundance, and lack of patient morbidity. Preferences encompasses structural, particulate, and demineralized bone matrix form. Most frequently used bone graft substitutes include calcium phosphate and calcium sulphate synthetics—these grafts also provide structural support and availability. Other alternatives for allogenic bone grafting include innumerable isolated or combined substitutes of calcium phosphate, tricalcium phosphate, calcium sulphate and coralline hydroxyapatite. Not all bone grafts will have same properties. Therefore, the necessities of the clinical situation and specific properties of the various types of bone grafts is essential to identify the epitome graft. We present a review of the bone repair process and properties of bone grafts and their substitutes to help guide the clinician in the decision-making process.

Key words: Bone Grafts, Dental Implants, Recent Advances

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BACKGROUND:
Bone loss followed by extraction is a common physiological phenomenon. Nevertheless, this phenomenon takes place with alveolar resorption and subsequent formation of bone within the socket followed by osteoblastic differentiation and osteoprogenitor cells [1]. The restoration of missing teeth with dental implant prosthesis has enormously

increased in clinical practices. For thousands of year reconstructing and regenerating significant skeletal defects have puzzled the mankind. Grafting techniques were employed as early as 2000 BC when Khurits used a piece of animal bone to repair a small skull defect, which proved successful epochs later when anthropologists discovered the remains exhibiting regrowth around the graft [2]. As the eon advanced, the first documented bone graft was done in 1668 by Job van Meekeren, a Dutch surgeon. He also, used a xenograft to repair a skull defect in an injured soldier [3]. A notion of autogenous bone graft came into reality when Von walter described clinical application of an autogenous bone transplant for the first time in Germany. [4] Further Ollier gave prime focus on periosteum for the formation of new bone and represented the view that autogenous bones covered with periosteum can survive when being transplanted. [5] Scrupulous examination of bone grafting criteria and outcomes was preached in the early 1900s with the effort of Vittorio Putti who delineated the principles of grafting. Putti's work provided a groundwork for grafting science in the field of orthopaedic surgery. Ever since, surgeons and researchers have continued to refine the science of bone grafting to allow for the most appropriate surgical intervention with the best outcomes. The experimental work of George Axhausen (1909, 1911) headed to the so-called classical osteoblast doctrine. [6,7] The osteoblast doctrine of George Axhausen faced in the discussion the induction doctrine. Their trailer represented the view, that the surrounding tissue becomes lively for bone new formation by the transplanted bone material (1934). [8] But as of limited amount and exertion in reconstructing large segmental bone defects, allogeneic bone and bone substitutes have been brought into picture for application in many of these circumstances. [9, 10] Bone allografts are harvested tissue from human cadaveric donors. Cancellous allografts offer minimal to no structural strength, mild-to-moderate osteoconductive properties, and mild osteo-inductive properties. Cortical allografts, on the other hand, can provide structural strength but little osteoinduction [11]. The first bone bank for the consumption of allogenic transplants was vindicated in1945, in New York by Bush and Garber. [12] The problem of the antigen reaction caused by the transplanted allogenic material were highlighted for the first time with the publications of Medawar (1944), Chalmers (1959) and Enneking (1962). [13–15] But soon after, H2O2-macerated bone, mentioned as ''Kieler span'', was in 50's and 60's the subject of many experimental and clinical studies. The ''Kieler span'' presented by Maatz (1957), in a distinctive procedure deproteined and degreased, should lose its antigenity by processing, but the ability of bone regeneration should remain preserved [16] . With constant progression in the bone graft field till the recent spell, efforts to attain an ideal bone graft is still going on. This review will address the different bone substitutes as adjuncts and recent advances in implant site preparation, reconstruction and bone regeneration. Bone graft and their substitutes should possess some basic properties to enhance the implant site defect as mentioned below:

PROPERTIES OF BONE GRAFTS

1. **Osteoconduction.** The ability to provide an environment capable of hosting the indigenous mesenchymal stem cells, osteoblasts, and osteoclasts is essential for the function of bone graft. Osteoconduction is the process by which a graft acts as a scaffold, passively hosting the necessary cells. [17]
2. **Osteoinduction.** The concept of osteoinduction was first described by Urist in the discovery of BMP. [18] Osteoinduction has been defined as the process of recruitment, proliferation, and differentiation of host mesenchymal stem cells into chondroblasts and osteoblasts. Extensive research has identified BMPs (specifically BMP-2, -4, -6, -7, -9, and -14), FGF, PDGF, and VEGF as common growth factors involved in the osteoinductive process of new bone formation. [17,19]
3. **Osteogenesis.** Osteogenic bone grafts have all the cellular elements, growth factors and scaffolding required to form new bone. Bone marrow aspirate in combination with allograft has also been employed to deliver osteogenesis while limiting the morbidity of iliac crest bone graft. [17]

BONE GRAFT TERMINOLOGY

Type of graft	Tissue transfer	Remarks
Autograft	From one site to another in the same individual	
Allograft	From two genetically different individuals of the same species	
Xenograft	From one species to a member of different species	
Isograft	From one monozygotic twin to the other	Usually done in laboratory experiments with transfer from inbred genetically identical strains of animal

Table 2: Summary of main advantages and disadvantages of bone graft: [20]

Bone graft	Advantage	Disadvantage
Autologous	• high osteoconductivity • highest degree of biological safety • no risk of immune reaction	Need of an additional surgery
Xenografts	•architecture and geometric structure resemble bone • Well documented • predictable clinical outcome	•slow bio-absorbability preserves augmented bone volume •possible disease transmission and potential unwanted immune reactions •lacks viable cells and biological components • resorption rate is highly Variable
Natural biomaterials	Similarity to native extracellular matrix	Mechanical properties poor - biodegradability Less controllable
Synthetic polymers	• tuneable physicochemical properties • tuneable degradability	• low cell attachment •timing of absorption (alteration of mechanical properties) • release of acidic degradation products
Synthetic bioceramics	• high biocompatibility • osteoinductive properties • chemical similarity with bone • stimulation of osteoblast growth	• high brittleness • low ductility • not predictable absorption
Composite xenohybrid substitutes	• high similarity with human cancellous bone • higher bioactivity • tailored degradation rates	• incorporation of active biomolecules • cleaning and sterilization process partially alter biological performances • limited clinical data

AUTOGENOUS AND ALLOGRAFT BONE

Autograft is considered a golden standard. It was first used (to trace back from the literature) in the early 1800s. After drilling holes to release pressure in the skull, Walther [21] repaired the defect by refilling the hole with the original bone plug. The repair resulted in good healing and informally began the practice of autografting [22]. Since then, more reports on autografting emerged [23]. One of the most primary reasons for the success of autografts is its osteoinductive ability due to the presence of blood, factors, and proteins within the graft that stimulate and facilitate healing [22]. Although autografts provide the best replacement tissue to a defect site, the harvesting procedure requires an additional surgery at the donor site, which can result in complications, most commonly pain and risk of infection. It was reported that the donor site morbidity occurs in approximately 20% of all cases [24,25]. Cadaveric allograft bone is available in either cancellous or cortical forms, or as demineralised bone matrix (DBM). Allografts are primarily osteoconductive, while DBM is processed in such a way as to retain osteoinductive properties. [26] Cortical allografts can also provide structural support. However, allografts do not lead to such complete healing as observed with the use of autogenous graft, and they carry the potential for the transmission of viruses and other infective agents.19,26,27. Advantages and disadvantages of different bone grafts are mentioned in table 2.

BIOCOMPATIBLE BONE GRAFT MATERIAL

Different stoichiometric compositions of calcium phosphate such as hydroxyapatite (HaAP), tricalcium phosphate (TCP), tretacalcium phosphate (TTCP), and other calcium phosphate salts and minerals, have all been employed to match the biocompatibility, structure, and strength of natural bone. The role of pore size and porosity in promoting revascularization, healing, and remodelling of bone has been recognized as a critical property for bone grafting materials. [28]

POROUS CERAMIC COMPOSITE BONE GRAFTS

The porous ceramic composite developed by Smith et al. incorporates biodegradable polymers (polycaprolactone) for use as a bone substitute in the field of orthopaedics and dentistry or as a scaffold for tissue engineering applications. The biodegradable polymer allows for the passage and/or delivery of a variety of agents throughout the porous ceramic matrix and improves mechanical properties of the implant in vivo. [29] The graft, composed of a porous osteoinductive ceramic matrix and a biodegradable polymer, possesses optimum pore size, pore size distribution, porosity, and pore connectivity to promote the rapid in-growth of bone tissue upon implantation.

BIOACTIVE BONE GRAFT SUBSTITUTE – COLLAGEN ENHANCEMENT

Clineff et al. [30] proposed a biocompatible bone graft composed of resorbable calcium phosphate, resorbable collagen, and bioactive glass. The graft replicates the natural osteoactivity of native bone by the addition of a bioactive glass. Bioactive glasses explored in the invention include glass-ceramics, crystalline phase materials, and a combination of acrylic polymerizable species. The purpose of the bioactive glass is to react as it comes in contact with physiologic fluids including, but not limited to, blood and serum.

The reaction of the bioactive glass and the surrounding fluid will lead to bone formation by forming an apatite layer on the surface of the graft. The bioactive glass can have a glass ceramic composition, comprised of heterogeneous particles with an irregular morphology and regions of crystallinity. The inclusion of a bioactive glass as an osteoinductive component is believed to be novel bone technology application.

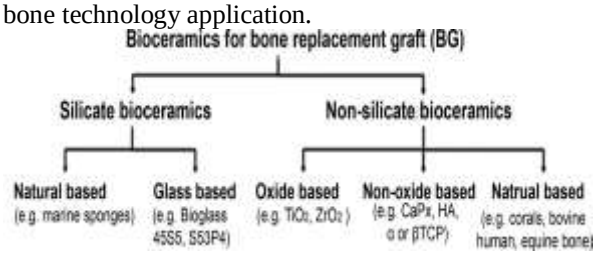

Fig 1: Classification of bioceramic bone grafts divided into silicate and non-silicate ceramics according to their main composition (adapted from Müller 2016) [31]

GROWTH FACTOR ENCAPSULATION SYSTEM FOR ENHANCING BONE FORMATION

Lu et al. [32] developed a bone technology, which enhances bone formation by releasing various growth factors and/or platelet-rich plasma (PRP) from a solid material. PRP is known to contain a number of autologous thrombocyte growth factors that may aid in the acceleration of bone regeneration [33]. These growth factors include platelet-derived growth factor (PDGF) and transforming growth factors 1 (TGF- β 1); both are produced by platelets and released during granulation. PDGF stimulates mitogenesis of osteoblastic precursors while TGF- β 1 stimulates proliferation and collagen synthesis by osteoblasts and osteoblast precursors. PRP gel has most recently been used as an adhesive with cancellous bone particles in oral and maxillofacial surgery bone grafting procedures. Such materials include collagen, Bio-Oss (calcium phosphate-based bone graft substitute), Pepgen P-15 (synthetic P-15 peptide bound to natural form of hydroxylapatite) and AlloGraft (demineralized bone matrix, allograft-based bone graft substitute). Chitosan beads are also explored and mentioned as a possible containment for growth factors/PRP. This novel hydrogel delivery system permits prolonged and modulated release of growth factors relevant to bone regeneration. [34]

IMPLANTABLE BONE GRAFT MATERIALS

Melican et al. [35] provide an implantable bone graft material comprised of a resorbable ceramic and a resorbable polymer, wherein the polymer has a covalently attached growth factor binding peptide. BMP has shown clinical benefit in the treatment of bone defects, injuries, disorders, or diseases. In particular BMP-2 and BMP-7 have shown benefits in implant site.

BONE GRAFT SUBSTITUTES

Long et al. proposed a powder composition process to generate a shaped product comprised of a granulated bone material, such as demineralized bone matrix. Currently clinicians perform bone graft procedures for a variety of reasons, often to fill a bone void created by loss of bone or compaction of cancellous bone. [36]

BONE GRAFT MATERIAL DERIVED FROM EXTRACTED TOOTH

Recently use of extracted tooth, which is considered as biomedical waste and hence disposed, unlocks the simple and readily available bone substituet material. The different and various preparation methods of extracted tooth provide their potential use as bone substitutes. Various previously published studies had shown the possibility of tooth derived bone graft materials. The demineralized dentin matrix is exceedingly biocompatible with the property of both osteoinductive and osteoconductive which have been highlighted in previous studies conducted in vitro as well as in animal models [37,38,39].

STEM CELLS AND TISSUE ENGINEERING

Stem cells have the potential to augment the performance of current bone graft substitutes and are the focus of a great deal of ongoing research. Bone marrow aspirate contains a diluted solution of mesenchymal stem cells and it may be possible to produce a stem cell concentrate from a sample of bone marrow by centrifugation. [40] Tissue engineered bone grafts have been demonstrated to provide all the fundamental properties of an ideal bone graft in vitro; however, it has proven difficult to achieve vascularisation in grafts which are large enough for use in clinical applications. [41]

CURRENT PERSPECTIVE AND FUTURE DIRECTIONS

Despite the decades of biomaterial research, synthetic bone substituting materials are still largely inferior to auto- or allografts as the gold standard in orthopaedics and dental surgery. The clinical success of the current generation of bone substituting materials is disappointingly limited since they lack high functionality of bone tissue in terms of biological and

mechanical properties [42, 43]. Depending on the clinical problem, different types of substitutes or combinations thereof are necessary. Even though the ideal properties of bone graft have already been defined in the literature three decades ago, the market still has no available biomaterials that meet all of these properties. The evolution of new-generation bone grafts continues to evolve with novel biomaterials and processing methods such as additive manufacturing. The ideal bone graft in the future will likely contain a combination of biomaterials with varying features that can control mechanical properties, pore morphology, interconnective pores, surface structure, release of active bone-promoting biomolecules and controlled biodegradability, which ensures resorption during the tissue-remodelling process while maintaining the defect volume for bone ingrowth. These features will improve osteoinduction compared to today's bone graft material. In view of the development in the regenerative strategy, nowadays stem cell treatments have been introduced extensively as well. Stem cells can be defined by two properties: the ability to make identical copies of cells (self-renewal) and the ability to form other cell types of the body (differentiation). For cell-induced tissue regeneration to succeed, it is often necessary to use stem cells. This is because ideally the cells used for tissue engineering should have the capacity to first proliferate and then differentiate. Unfortunately, the renewal capacity decreases by time. Thus, to learn how to control and regulate natural regeneration potential is a long-term goal in the context of tissue engineering.

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