

Effortless Effort in Bone Regeneration: A Review

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Abstract:

Since the beginning of the 20th century, the concept of osteoconduction in bony changes in the oral cavity showed a wide range of biomaterials and their osteoinductive potential that emerged gradually and has to a large extent improved the quality of the bone prior to the placement of an implant. Alveolar bone loss is a major concern after tooth extraction in patients and therefore atraumatic extraction procedures should be followed to avoid further bone loss. To overcome the alveolar bone loss and to augment support for placing dental implants, many bone regenerative substitutes are available such as allografts, autografts, xenografts, synthetic biomaterials and osteoactive agents. In light of the steady progress in bone grafting techniques and graft materials, it has become possible to improve the volume, width, and height of bone in deficient areas of the oral cavity. These advances in regenerative dentistry thus facilitate an easy and convenient placement of an implant in an ideal position and angulations resulting in superior esthetics and function. Bone grafting materials and their substitutes are the alternative filler materials, which facilitate to reduce additional surgical procedures, risks, chances of cross infection involved in placing autografts and allografts into the bony structures. This review literature highlights various biomaterials that are helpful in bone healing and thus create an anatomically favorable base for ideal implant placement.

Key Words: Alveolar bone, bone resorption, grafting, ridge augmentation

Introduction

Bone is a highly complex structure and constantly undergoes tissue changes, which is capable of self-repairing and adapts to new forces. Wolff's law proposes that pushing and pulling stimuli, performed by the presence of dental elements allows the maintenance of bone sharp and density.¹ Bones being highly dynamic in nature illustrates two fundamental concepts of modeling and remodeling. Modeling is a process by which

independent sites of resorption and formation change the form (shape or size or both) of a bone. Remodeling is a process in which specific coupled sequence of bone resorption and formation occurs to replace previously existing bone.

Extraction of teeth follows a three-dimensional resorption pattern. It is apparent that the bone resorption of jaws after the loss of teeth is highest during the first 3 months, even though up to four-fold variations have been reported across individuals over a 14-month period. Bone resorption marked differences can occur between the maxillary bone and the mandible. The resorption rate of mandible averages four times the rate of maxillae. Over a period of 25 years, the alveolar ridge may lose up to 10 mm in height of the mandible. After a tooth loss, the vestibular cortical wall is quickly remodeled when put side by side to the palatine. Bone resorption can be reduced if not completely eliminated by atraumatic extraction, properly compressing the extraction sockets. In implant dentistry, preservation of available bone is very important in implants placement. Deficient existing bone often hampers the success rates of implants creating further complications. As a result, in order to enhance the quality and quantity of the deficient alveolar ridge bone grafting materials and other substitutes are used.

Bone graft materials in dentistry are those implanted material that promote new bone formation through osteogenic, osteoinductive or osteoconductive process.² The term osteoinduction, osteoconduction and osteogenic are used frequently but not always correct. Osteoconduction implies to bone growing on a surface. This occurs when the graft material serves as a scaffold, allowing osteogenic cells to infiltrate from adjacent bone margins, to proliferate and form a bone on the surface of the graft material with subsequent replacement or incorporation of graft material with new bone.³ Osteoinduction suggests that the graft material stimulates undifferentiated mesenchymal stem cells from the surrounding tissue to differentiate into osteogenic cells to form new bone.⁴ Osteogenic means that a graft material contains viable osteoprogenitor cells capable of differentiating into osteoblasts to produce new bone. Four different types of bone grafts have been commonly used they are classified as: Autografts, allografts, xenografts, and alloplasts.

Bone Graft Materials

Autogenous bone grafts

Autogenous bone graft is considered as the gold standard bone graft material and possesses osteogenic, osteoinductive, and osteoconductive properties. Autografts possess osteogenic

properties due to the presence of viable osteogenic cells, osteoinductive properties due to the presence of like bone matrix proteins (BMPs) and osteoconductive properties due to porous mineralized component of bone. Autogenous bone is accessible in the oral cavity itself from edentulous areas such as maxillary tuberosity, mandibular ramus, and mandibular symphysis.⁵ Extraoral autogenous bone is accessible in large quantities from the iliac crest, rib, tibia and calvarium. The benefit of autogenous graft is that it maintains bone structure such as minerals and collagen as well as viable osteoblasts and BMPs. Nevertheless, only a diminutive percentage of cells in reality survive after transplantation. This graft offers returns like it avoids complications like immunologic reaction and possibility of antigenicity. Considering the other side of the coin, it presents other limitation like donor site morbidity, chronic postoperative pain, hypersensitivity, infection. There are other limitations as to how much bone tissue can be harvested and harvesting requires an additional surgery at the donor site.⁶

Allogenic bone grafts

Allogenic bone is a non vital osseous tissue taken from one individual and is transferred to another individual of the same species. Considering its properties, dental surgeons generally opt for these grafting materials as their second alternative after autogenous grafts. These provide Type I collagen which encompass the mainstream of the organic components of bone and ought to be processed carefully to guarantee safety. There are three forms of allogenic bone: Fresh frozen, freeze dried bone allograft (FDDBA) and demineralized freeze dried bone grafts (DFDBA). Fresh frozen bone is seldom used at the present time for the purpose of bone reconstruction in the cranio-maxillofacial skeleton because of concern related to the transmission of viral diseases.⁷ FDDBA works for a good number part through osteoconduction and osteoinduction processes.⁸ Although FDDBA has been recommended in practice, there are few human histological studies to verify normal healing. Therefore, they are placed in conjunction with autografts. DFDBA is assumed to induce bone formation due to the influence of bone inductive proteins called BMPs uncovered during demineralization process. Thirteen proteins have been identified (BMP 1-BMP 13) as osteoinductive compounds and encourage new bone formation.⁹ As a consequence, DFDBA is thought to be osteoinductive and osteoconductive.¹⁰ Recent advances have seen allograft materials incorporated into various carriers such as collagen or selected polymers.^{11,12} These forms are sponge-like, gel or putty-like in consistency or as matrix plugs. The drawback of allografts are that they need processing techniques like freeze drying, irradiation or lyophilization to eliminate most immunogenic factors causing immunogenic reaction. Although processing techniques alters material properties, removal of organic factors with limited osteoinduction, it compromises both mechanical and

biological integrity of the graft.¹³ The processed allografts are well tolerated by the body and seldom these cases allografts are totally rejected.

Xenogenic bone grafts

Xenogenic bone grafts consist of de-protenized cancellous skeletal bone tissue that is harvested from one species and transferred to the recipient site of another species. At present, due to deficiency in availability of human grafts, xenografts are used after sterilization, processing or treatment techniques to the effort to migrate the inadequacies of these grafts. The organic contents of the xenogenic grafts are materials completely removed due to immunological reaction and pathogenic transmission. The remaining inorganic component of the xenograft not only serves as natural structural matrix for new bone formation, but also results in an excellent source of calcium, which is essential for bone formation. Bovine derived xenograft, Bio-oss is a case of xenograft currently used in dental applications after processing. Furthermore, xenografts are used in combination with growth factors and or allografts to simulate the autogenous bone.¹⁴ There are two processes at present used to put in order the bovine cortical bone. One uses a low temperature, chemical extraction process, while the other uses high temperature (>1500°C) to remove residual organics. The procedure of using the high temperature method gives longer hydroxyl-apatite crystal with higher crystalline structure.¹⁵

Alloplastic bone grafts

Major categories are metal, ceramics, polymers and composites. Alloplast are synthetic materials that have been developed to replace human bone. The changeable nature of commercially available graft materials showing variation in porosity, geometries, different solubility's and densities determine the resorption of these calcium phosphate based graft materials. The alloplasts are osteoconductive materials and the three types of alloplastic materials are calcium phosphates; other ceramics hydroxyapatite, biphasic calcium phosphate (BCP), tricalcium calcium phosphate, calcium sulfate, and biocompatible composite polymers.

Osteoinductive Biomaterials

History of osteoinduction

The phenomenon of osteoinduction to begin with was in the beginning of 20th century by Bunting C.H in the year 1906 after observing true bone formation in human aorta. Osteoinduction was first documented by Levander in 1934 when he injected crude alcoholic extracts of bone in the muscles. The first experimental support on osteoinduction was reported in 1952 by Urist and Mclean in 1952 after extra-skeletal implantation of calcified tendon.¹⁶ Urist in 1965 set landmark in the investigation of osteoinduction by observing regular bone formation, after implantation of demineralized bone matrix (DBM) in soft tissues of rabbits, rats, mice and guinea pigs.

Osteoactive agents

An osteoactive agent is a material which has the potential to encourage the deposition of bone. These may be classified in three categories: Osteoinducers, osteopromoters and bioactive peptides.

Bone morphogenetic proteins

Bone morphogenetic proteins are group of proteins, which were acknowledged by Urist in 1965 and they appear under transforming growth factor beta (TGF- β). BMPs take vital part in the differentiation, proliferation, growth inhibition, and arrest of maturation of the wide variety of cells, depending on the cellular micro environment and interactions with other regulatory functions. BMPs are of amazing interest as therapeutic agents for healing bone fracture, preventing osteoporosis, treating periodontal bone defects and enhancing bone responses around alloplastic materials implanted in bone. Recombinant human bone morphogenetic proteins (Rh-BMP-2) delivered with an absorbable collagen sponge has been used for augmentation of maxillary sinus floor in human. BMP-2 regeneration was achieved when Rh-BMP-2 was applied to the defect site with a collagen membrane or collagen gel. At present, there are 20 different BMPs, which have been identified, but only BMP-2, 4, 6, 7 have revealed considerable osteoinductive properties. BMP signal transduction is induced via interaction with the heterodimeric complex of two transmembrane serine/threonine kinase receptors.¹⁷ BMP promote bone production through two pathways. They recruit mesenchymal cells (MSCs) from surrounding tissue and differentiate the cells into either osteoblast that puts together bone directly or cartilage cells, which consequently change to bone cells. BMP-2 regenerates bone in irradiated tissues, providing the clinical potential to treat patients who have undergone radiation therapy and need bone regeneration. BMP acts as an extracellular molecule that can be classified as a morphogen as its action recapitulates embryonic bone formation. One of the challenges of BMP is to bring into play its delivery to a site of action.¹⁸ Handling properties and biologic action activity are improved when BMPs are delivered with carrier materials. Various carrier vehicles have been used to deliver BMP like non-collagenous proteins, DBM, collagen, HA, polylactide and/or polyglycolide combinations, calcium carbonate, calcium sulfate, and fibrin glue. Host age is an additional drawback which affects the biologic potential of many growth factors. The bone inductive ability of BMP-2 is diminished in older organisms and higher doses are mandatory to induce the bone formation effect.^{17,19}

Platelet derived growth factors

Platelets are known to contain a number of different growth factors, which are unrestricted and get hooked on the tissues after injury. These include TGF- β , platelet-derived growth factor, insulin-like growth factor, and fibroblast growth factors which proceed as differential factors on regenerating

periodontal tissues.²⁰ Autologous platelet rich plasma (PRP) was foremost used in cardiac surgery by Ferrari *et al.* in 1987.²¹ PRP is obtained by extracorporeal blood processing techniques from a unit of autologous whole blood. PRP is arranged by standard blood banking techniques or through point of care devices including cell savers/separators or table top devices. Shortcoming of obtaining PRP by blood bank by means of discontinuous plasmapheresis method is avoided, as high costs and delayed availability of PRP. Depending upon the need of surgical procedures and amount of pg looked-for, individual method of using cell savers/separators larger blood volumes (250-500 ml of whole blood) can be obtained which results in PRP volumes of 20-50 ml. Table top on the other side is used for centrifugation of a smaller amount of PRP (50-150 ml).

Method to Obtain Platelet Rich Plasma

After drawing blood from median cubital vein cell savers is used to produce PRP, autologous whole blood is collected into standard donor bags filled by gravity. In table top devices blood is collected by inspiration techniques into syringes with needle having a larger diameter than 17 gauge to avoid trauma to the platelets. Blood is collected in adequate amounts of anticoagulant citrate dextrose-A solution (ACD-A). Maintaining the ratio of 1 ml of ACD-A to 7-8 ml of whole blood. Blood is centrifuged at 5600 rpm and separates the platelet poor plasma. This is taken into another container. Then centrifugation is slowed down to 2400 rpm to obtain leukocytes and PRP. These PRP contains 500,000-1,000,000 platelets, which are mixed with thrombin/calcium chloride (1000 units/10) solution to form gel.²² This gel can be used in combination with bone regeneration material such as HA or DBM as a source of autogenic growth factors.²³

Transforming Growth Factors

Transforming growth factor beta is the name given to a group of proteins with a molecular weight of approximately 25Kd that are involved in formation and development of many tissues.²⁴ These are considered as osteopromoters agents, which boost bone healing. Out of the three subtypes of TGF- β present only TGF- β 1 and TGF- β 2 are of significance with regard to general connective tissue repair and bone regeneration. Mostly found in platelets and some in macrophages in latent form. TGF- β has been shown to contribute in all phases of bone healing. During the initial inflammatory phase, TGF- β is released from platelets and simulates MSCs proliferation. It is ischmotactic for bone forming cells, stimulating angiogenesis and limiting osteoclastic activity at the revascularization phase. Studies done by Dieudonne *et al.* showed some concern about the use of TGF- β . They appreciated that low concentrations have a stimulatory effect on bone cell proliferation and at high concentration proliferation is suppressed. Once bone healing enters osteogenesis, TGF- β increases osteoblast mitosis, regulating osteoblast function and increasing bone matrix synthesis, inhibiting Type II collagen but promoting Type I

collagen. Combinations of BMP and TGF- β enhance the osteoinduction of an implant, while simultaneously make it osteopromotive. BMP carrier vehicles however for its delivery of TGF- β are under development.

Bioactive polypeptides

They act as osteoinducers or osteo-enhancers. P-15 and Obstructive sleep apnea-117 MV are two short amino acids chain peptides, which have revealed bone activity. P-15 has been an aid in the exchange of mechanical signals as well as to promote cell differentiation. Like many other bone augmentation materials, P-15 associated with an organic derived bone matrix, improved the overall osteoinductive effect.

Emdogain

Emdogain (EMD) comprises 90% amelogenin and 10% of non-amelogenin enamel matrix proteins such as enamelin, tuftelin, amelin, enamelin and ameloblastin and other proteins such as albumin. It has been used in periodontal regeneration to mimic the cellular and signaling events that arise during periodontal development by promoting MSCs differentiation into cementoblasts to form acellular cementum, periodontal ligament fibroblasts to form periodontal ligament and osteoblasts to form alveolar bone after exposure to EMD.²⁵ Enamel matrix protein EMD consists of a group of proteins isolated from the tooth germs pigs. Clinical trials have rediscovered some potential in bone regeneration.

Stem cells and gene therapy

Stem cell is an important breakthrough in the field of regenerative dentistry. Human MSCs are multipotent cells capable of differentiating into various mesenchymal tissues and are obtained from bone marrow. Due to their capability to differentiate into osteoblasts or bone forming cells they play a major role in bone regeneration and orthopedics. They can be taken from bone marrow in small volumes and expanded due to their proliferative capacity. MSCs can be used in combinations with porous, BCP ceramics.

Conclusion

Although bone is capable of self-repairing, it needs constant stimulation in order to avoid bone atrophy. Preservation of alveolar bone during extraction should be given more emphasis. One of the most common treatment options nowadays is replacement of missing teeth by dental implants. The successful treatment outcome is dependent on sufficient bone quantity and quality at the surgical site. Newer technologies and materials in regenerative dentistry have allowed dental surgeons to place implants in deficient areas in teeth with questionable prognosis. By using different materials, which are osteoinductive or osteoconductive in nature, which aid in creating a foundation that is essential for both esthetics and function in dental rehabilitation.

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