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Review Article

Bone Grafting and the Materials for Using in Orthopedics

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Abstract

Treatment of delayed nonunion and bone defect is a challenge in orthopedic in medicine and veterinary. This review highlights the bone substitutes that used in bone grafting. An exquisite analysis of these studies reveals the properties of bone substitutes that are designed by the researchers to find an optimal bone graft. In this study we pay attention to four types of bone grafting including: autograft or auto transplantation, allograft or transplantation in one species, xenograft or transplantation between species and Synthetics materials: Ceramic and Polymer. A ceramic is a non-metallic, inorganic solid performed by thermal treatment and subsequent cooling, about calcium phosphates ceramics thermal treatment is sintering. The most important Ceramic that are using in bone grafting including: Gypsum, Plaster of Paris, Calcium carbonate, calcium phosphate, bioactive glass and hydroxyapatite. The polymers used today can be loosely divided into natural polymers and synthetic polymers. Natural polymers, such as alginate, collagen and chitosan present great solutions and their use has been growing. Synthetic bone grafts may obviate the requirement of bone grafting. Must of synthetic bone substitutes are osteoconductive or osteoinductive alone but natural bone substitutes have both osteoconductivity and osteoinductivity prosperities. There is an interest in combining osteoconductive and osteoconductive compounds to facilitate bone formation. Today tissue engineering is generating new bone substitute for repair, regenerate and restore tissue to its functional state.

Keywords: *Bone Healing; Bone Grafting; Autograft; Allograft; Xenografts; Ceramic; Polymer*

Introduction

Delay in bone union, nonunion, disunion, incomplete union, vascular necrosis, shortness, stiffness of the joints, osteomyelitis, ischemic contraction, osteoarthritis Requires surgery because of instability and hematoma [1].

Treatment of delayed nonunion and bone defect is a challenge in orthopaedy in medicine and veterinary. This review highlights the bone substitutes used bone grafting. An exquisite analysis of these studies reveals the properties of bone substitutes that are designed by the researchers to find an optimal bone graft. A bone graft is clarifying as any implanted substance that promotes bone healing, lonely or in combination with the other material [1]. Bone grafting is carrying out to restore bone that has been lost due to tumors, trauma, osteomyelitis etc. That requires replacement. Bone graft is necessary to fill voids, provide support, and improve biologic repair of skeletal defects. Different bone substitutes have been reported for using in bone healing. Biologic bone grafts are dividing into the following subtypes: autografts, allografts, xenografts, and synthetic materials [2]. A good bone graft must possess 3 key properties: osteoinductivity, osteoconductivity and osteogenicity. Osteoconductivity is the ability of bone graft for providing biocompatible scaffolding that subsequent growth and supports new bone formation. Osteoinductive property of a bone graft is simply the capacity to induce arrangement of the

bone-forming cells with differentiation of its stem cells from the surrounding host tissues for production of osteoprogenitor cells followed by growth of osteoblasts [3]. Osteoconductivity prevents the formation of fibrous tissue encapsulation but it brings about a strong bond between the host bone and scaffold. The excellent bone graft functions through all 3 mechanisms by providing a template that directs 3D bone growth induces differentiation of resident bone-forming cells. Osteoconduction is a passive process that described by recipient site derived bone resorption, neovascularization, and new bone formation. These events happen within the framework or scaffold in the form of passive that provided by the bone graft and its structural properties [4].

Autograft

Autogenous bone grafting is preferred because of its effectiveness. It still remains the gold standard of bone graft material in all facets of orthopedic surgery; because it possess all of the previously mentioned characteristics; they are from the host itself, there is not antigenicity and there is less risk of the graft rejection because the graft originated from the patient's own body [5]. Depending on where the transplant site and the size of the graft, an additional blood supply may be required (Hung). Bone autograft is the only graft material that has osteoinductive, osteoconductive and osteogenic, properties, which makes it an ideal graft material and the current standard to which all other grafts should be compared. Surviving cellular elements in the autograft may also contribute to this process. These factors emanate from the matrix of autograft bone in the form of the molecules that termed bone morphogenetic protein (BMP), a low molecular weight, non-collagenous protein that has been extracted from various bone structure [6]. This unification is due to its osteogenic properties, abundance of signals, and large surface area it provides for bone formation to happen. The cells present in the donor graft are capable of responding to local stimuli and releasing growth factors of their own, which accelerate angiogenesis and bone formation. The iliac crest is the most popular donor site; it is cumbersome to prepare a separate operation site. The operations like this cause many complications and postoperative morbidities [7]. Autografts can be cancellous or cortical or a mixture of both. Cancellous grafts can be re-vascularizing because of their spongy architecture. The use of vascularized cortical bone graft can accelerate this process, but it is a significantly more complicated procedure. Before revascularization, the cellular survival in the bone graft actually depends on oxygenation, nutrition and elimination of metabolic waste products with diffusion of plasma. The cells of bone seem to survive if they be within 0.3 mm of a capillary. Cancellous grafts tend to be weak initially because of their open architecture but continually gain in strength [8]. Cortical bones for grafts need too much resorption by osteoclasts before osteoblastic bone formation. This process is called ''creeping substitution''. As a result of the different biology of cancellous and cortical bone, the properties of a graft composed of each type differ [9]. Using autografts diminishes the risk of the transmission of infectious disease, whereas osteoinductive, osteoconductive, and osteogenic properties of the graft are optimal. There isn't immune response after bone implantation, which enhance its ability to incorporate into its new site. In the procedures that need large amounts of graft, there can't be adequate quantities of autogenous bone available. Because of the high shortcomings of autogenous bone grafting, a current understanding of available grafting alternatives is necessary. So other sources of bone graft have been proposed [10] (Figure 1).

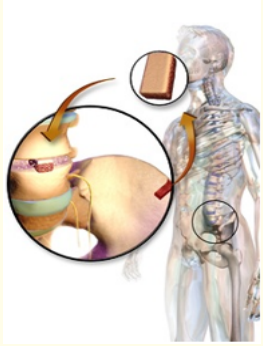

Figure 1: *In most cases, surgeons use ilium to obtain autograft bone.*

Allograft

Allografts are grafts shared between two individual in one species. Allograft has different characteristic depending on its preparation, for example allograft cancellous bone has no osteogenic potential. Allograft is used as a scaffold in which new bone formation and revascularization can occur, providing an osteoconductive material. Bone allografts become unique when the cellular component is typically removed to minimize their rejection because of antigenicity [11]; but allografts are treated of disease transmission. Allografts are osteoinductive, osteoconductive, but not osteogenic, and when they be used; it is recognized to has a high rate of nonunion. This high rate of nonunion may be the result of slow vascular and osseous formation as well as delayed junction between graft and the host site [12].

Demineralized bone matrix (DBM)

Demineralization of bone is considered advantageous because it destroys the antigenic surface structures of bone. There is, however, marked variation in the results of various studies with DBM. Demineralization is evaluated with radiography and calcium analysis. It is hypothesized that the rigid structure of non-decalcified bone does not permit the release of bone-inducing proteins, which become available when bone is demineralized [13]. The decalcification of compact bone exposes these growth factors buried within the bone matrix; thereby increase the bone formation process. Bone consists of two major components: organic proteins and inorganic mineral. Collagen is the main constituent of the organic material that gives bone its toughness and resilience. In addition, there are many growth factor proteins that closely regulate bone formation and remodeling [14]. The mineral part of bone is essentially comprised of calcium phosphate salts. This component of bone dissolves readily in acid medium resulting in demineralized bone matrix. The organic matrix of bone consists of collagen (mainly type I) and approximately 5% (by weight) non-collagenous proteins. The collagen prepares the elasticity to the bone structure that prepares resistance to impact loading, and serves like a template for the oriented deposition of mineral element [15]. DBM is an allograft bone which lost inorganic mineral and left organic matrix. This process perform with acid and results in demineralization of the majority of the bone, and leaving the non-collagenous proteins, collagen type I, and growth factors. The extracellular matrix contains osteoinductive elements that can stimulate new bone formation by enchondral ossification [16]. The advantages of DBM using including availability in large amounts and inherent osteoinductive capacity. A chemically analysis show there are fibroblast stimulating and angiogenic characteristic in DBM to enhance the bone regenerative capability of it. DBM has several disadvantages; it is an allergenic substance, there is the potential to transmit diseases [17]. DBM doesn't provide structural strength, and must use is in a structurally stable condition. It is not suitable for situations that bone support is required. DBM formulations are available as a granules, freeze-dried powder, putty, gel, or strips. Some of the DBMs using in surgery include: Filling contained and uncontained defects, Condylar defects, Non-unions, Long bone fractures, Supracondylar fractures, Impaction grafting, Osteotomies, Osteolytic defects and Segmental defects with fixation [18] (Figure 2).

Figure 2: *Demineralized bone matrix is provided as frozen powders, granules, gels, cements or tapes, etc.*

Xenograft

Xenografts are tissues which shared between different species. In Xenografts usually organic components are removed to avoid immunological reactions. Currently available sources of xenografts are used as bone substitutes is bovine bone. There are several researches about using different animals in xenografting such as canine [15], bovine [13,19-27], porcine [28] and coral graft [29,30]. Bovine bone xenografts have had organic substances extracted; the remaining structure with fine pores is like natural bone, chemical compound or microstructure. It has a non-antigenic, natural porous matrix and is identical to the mineral phase of bone tissue; it has been demonstrated which high osteoconductive property and to show a very low resorption rate [31]. The researches demonstrated that all the materials, with the exception of mineralized bovine bone (Surgibone), were biocompatible for osteoblasts of human. Anorganic bovine bone doesn't have osteoinductive properties, and when it is in the form of granules makes it difficult to hold on surgical sites. Moreover, bovine xenograft is non-resorbable *in vivo* [32] (Figure 3).

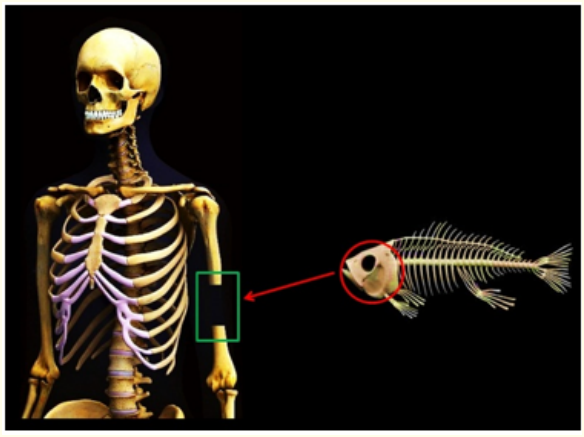

Figure 3: *Xenografts are tissues which shared between different species. Common xenografts are come from canine, bovine, porcine coral and fish*

Synthetics materials and biomaterial

In recent years, synthetic materials for bone grafting have become a viable alternative to autograft, allograft and xenograft devices. Synthetic materials preparations have been the focus of extensive research and have recently reproduced a huge industry. Synthetic materials can be polymers with osteoconductivity property in the form of granules, blocks, pellets or cements and contain osteoinductivity proteins that have been studied previously [29]. Injectable cements have a benefit over blocks, granules, and pellets, in that a custom fill of the defect is possible. Synthetic materials have only osteoconductive properties, and they best function as graft extenders or carriers for osteoinductivity. Some of synthetic materials have been classified as: metals such as Tantalum, Titanium, Iron, or Magnesium; polymers such as polylactides, polyglycolides, polycaprolactones, or polyurethanes; and ceramics such as calcium sulfate hemihydrate, silicate based glasses, and dehydrate and calcium phosphates [33].

It is not surprisingly because of pressing clinical need; the market of biomaterials for orthopedics may build. Researchers have shifted toward the design of bioactive materials such as bioactive glass which mix with biological molecules and cells. About bone, biomaterials should be osteoinductive and osteoconductive and capable of osseointegration. These materials intended to replace the need for allograft or allograft bone have been evaluated resent years. They including biological or synthetic polymers, bioactive glasses, bioactive ceramics and composites of them. It is assumed that these materials are replaced by new bone formation made by the body [31] (Figure 4).

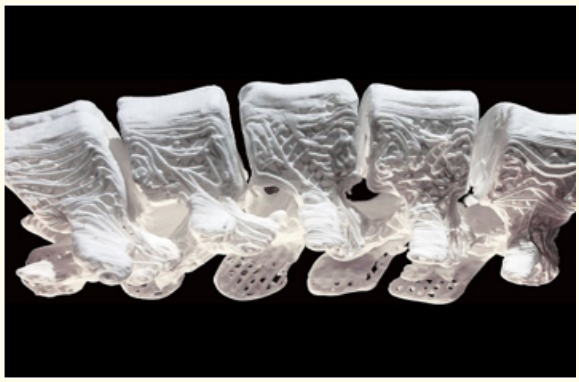

Figure 4: *Artificial vertebra, today artificial bones are produced using synthetic materials.*

Ceramic

A ceramic is a non-metallic, inorganic solid performed by thermal treatment and subsequent cooling, about calcium phosphates ceramics thermal treatment is sintering. In the sintering process volatile chemicals are removes and crystal size is increased, resulting in a porous and solid material. Their structure is entirely distinct from the poorly crystalline formation of normal bone and for this reason they resorb slowly [34]; ceramics have been used in spinal surgery to extend autograft in the long fusion necessary for scoliosis. The poor bioresorbability and difficulties of ceramics handling have stimulated work to develop materials that are similar to mineral phase of bone matrix more closely that led to the development of calcium phosphate Cements. Most of ceramics are hard and porous yet friable. There have been attempts in developing seems bioceramics materials to increase their mechanical and biological characteristics as well as cytocompatibility for use in tissue engineering applications [35].

Calcium phosphate grafts (Gypsum)

Between different ceramic calcium phosphate is the base of ceramics such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP) and bioactive glass; in which are used quite for long time. Calcium phosphate has been used in dentistry since 1970s and in orthopedics since 1980s.The first calcium phosphate used approved in 1998 is the bone repair system. It approved for fractures healing in the distal radius, it's now approved for general orthopedic surgeries specially use in metaphyseal defects [36]. Biphasic calcium phosphates are mixture of different bioceramics. They aim to balance biomechanical properties and resorption rates for developing an ideal bone substitute. Different types of calcium-phosphates are tri-calcium-phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite; available in pastes, putties, solid matrices and granules [37].

Calcium sulfate (Plaster of Paris)

It is most familiar to orthopedic surgeons as plaster of Paris and is the oldest osteoconductive material that use for bone healing. It's resorption is quick which may exceed the capacity of bone regeneration. The family of calcium sulfate component is less latitude than calcium phosphate. Calcium sulfate provides an acidic environment (sulfuric acid and calcium phosphate) that may be toxic for bacterial growth [38], so it has long been used for treatment of osteomyelitis, with or without antibiotic. Calcium sulfate increases the amount of graft material, expedite bone formation, and it is safe in the treatment of non-unions and fractures with bone defects. Calcium sulfate also is biocompatibility and osteoconduction [39].

Calcium carbonate

This materials start to decrease in usage because it's entirely resorbable in short time. Some studies used calcium carbonate and hyaluronan as a bone substitute material. Pro-osteon, a resorbable calcium carbonate with a 2 - 10 μm outer layer of calcium phosphate. It is a bone graft that resorbed slowly. It is seemed that more study is needed to exam a newer formulation with calcium carbonate may allow for faster resorption [40].

Dicalcium phosphate (DCP)

Dicalcium phosphate anhydrate/poly composite nanofiber mimics the mineralized collagen fibrils via biomimetic in situ synthesis and electrospinning for bone healing. Dicalcium phosphate when mixed with water forms a dense paste [41].

Octacalcium phosphate (OCP)

Octacalcium phosphate is shown to be a suitable precursor of biological apatite in hard tissues and has shown better biodegradable and bone regenerative characteristics than other bone substitute materials [42].

β -tricalcium phosphate (β-TCP)

Tricalcium phosphate is resorbed faster than synthetic HA, but is not as strong. It is successfully used in posterolateral spinal fusions, dental procedures, and in combination of bio-resorbable screws. It is derived from inorganic sources. It has three crystalline polymorphs α, α' and β. The α and α' states are formed at high temperatures [11].

Bioactive glass

Bioactive glass or bioglass is a biologically active silicate-based glass, which has high modulus and brittle nature. It is a synthetic, non-toxic biocompatible material. Bioactive glasses have been used traditionally to fill bone defects. Now using bioactive glass in bone healing is an emerging research field in applications of hard tissue engineering. Bioactive glasses have been the subject of considerable research [30]. It has been shown osteoconductivity prosperities in bone healing. 45S5 Bioglass®, a silicate bioactive glass, induce the release and exchange of critical concentrations of soluble Ca, Si, Na and P ions, which cause to extracellular and intracellular responses promoting fast bone formation. Bioactive glasses have used in combination with metal implants as a coating to form a calcium-deficient carbonated calcium-phosphate layer that facilitates the chemical bonding of implants to the host bone [43].

Hydroxyapatite (HA)

Hydroxyapatite is a mineral form of calcium phosphate that comprises up to seventy percent of the dry weight of bone. Synthesized hydroxyapatite is slow resorbing and may stay at the site of implantation for long time. In the calcium phosphate family, hydroxyapatite by formula of Ca10(PO4)6(OH)2 is derived from the sea corals Porites and Goniopora [44]. It's made by a hydrothermal exchange that converts calcium carbonate to crystalline hydroxyapatite. Hydroxyapatite's pore size (200 - 500 μm) is similar to human trabecular bone. Hydroxyapatite is available in granules, blocks, or cement form. Hydroxyapatite has compressive strength but remains fragile, with low tensile strength. Coralline implants are use directly in natural form for the treatment of bone defect. Another process for using hydroxyapatite is Replamineform process. One of hydroxyapatite implantation disadvantages was its very long resorption time [45].

Polymer

Since bone tissue is a combination of organic and inorganic parts, studies attempted to recreate its structure by using scaffolds prepared from a combination of polymers and ceramics as inorganic part. The polymers used today can be loosely divided into natural polymers and synthetic polymers. Natural polymers, such as alginate, collagen and chitosan present great solutions and their use has been

growing [46]. Polymers natural forms, biocompatible and biodegradable which are given more attention in comparison with synthetic biomaterials. There is heterogeneous population of polymers according to both composition and molecular weight that use as a bone graft. Some polymers, such as cellulose and chitosan are used in medicine [47]. Other polymers, for example hyaluronan, fibrin glue and collagen, can be decomposed enzymatically; but all polymers are susceptible to degradation by reactive oxygen species. Polymers usually have high ductility, toughness, favorable formability, processibility and plasticity. Dense type of them can match cancellous bone properties and approach compact bone properties. Polymers are used in research for implantable drug delivery systems, orthopedics, intraluminal grafts, temporary vascular stent-like devices, grafts, and temporary conduits for nerve regeneration [48]. Polymers have some properties that the other bone grafts do not. Polymers also can be divided further into degradable and nondegradable form. Many factors change degradability, for example chemical structure, molecular weight, architecture, copolymer composition, morphology, surface area and medium character [49].

Cellulose

Cellulose is an organic substance in cell wall of algae, green plants, and the oomycetes. It is secreted by some bacteria. Cellulose is the one of the most abundant organic polymer in world. It is used to make absorbent and hydrophilic sponges. It is also benefit in combination with other materials in hart tissue engineering applications. Depending on the monomer grafted onto cellulose, it gains new properties [50].

Fibrin Plasmin

Fibrin is natural wound healing matrix that forms after injury. The precursor of fibrin, fibrinogen, is obtained from blood. Fibrin facilitates the migration of blood cells to the area of injury. This ability of cells which can contract this matrix through which they migrate is modeled in vitro and in vivo (peri-implant site) could possibly cause retraction of the temporary fibrin scaffold away from the bone graft surface [51]. If implants become recovered a few days after implantation, the adhesion of this temporary matrix to some surfaces can be easily visualized. Fibrin just like collagen scaffolds contain locates for cell adhesion and the scaffold characteristic vary depending on the concentration of its fibrin contain [52]. Rapid degradation of fibrin is the most disadvantages in this scaffold. Fibrin scaffold can be covalently modified to further alter its properties. In recent study fibrin scaffold with or without other materials has been used as a biomaterial for stem cells to regenerate adipose tissue, cartilage, cardiac tissue, bone, liver ocular tissue, skin, nervous tissue, tendons, and ligament. Fibrin is a biopolymer that shows a great potential in wound and bone healing [53].

Collagen

Type I collagen is the most profuse protein in ECM of bone. Each Type I collagen fiber is coated with HA and they fabricated and crosslinked into a 3D, and stable final format. Collagen can be used in combination with bone marrow for providing osteogenic and osteoinductive bone graft [54].

Chitosan

It is a natural polysaccharide which is obtained from insect's chitin. Chitosan is a deacetylated form of it. It has biocompatibility, biodegradability and osteoconductivity Properties. Today, it is in focus of many research programs and it has been shown that it has an excellent biological activity. Chitosan have stronger and stiffer structure even after crosslinking of collagen [55].

Albumin

Albumin is a protein that is in excess in blood plasma, almost half of the total volume of the plasma. It is a degradable and water soluble protein [56].

Hyaluronic acid

Hyaluronic acid is one of the glycosaminoglycans, that is linear polysaccharide consisting of glucosamine and glucuronic acid. Because of hyaluronic acid's immunoneutrality and the tissue repair with promoting cell migration, differentiation and enhancing collagen production and angiogenesis hyaluronic acid can be used in irregular shaped defects. It has been shown that hyaluronic acid have promising curative effects on tendon-bone healing in laboratory animals [57]. A direct bond was formed between the tendon and the bone. Several physiochemical properties of hyaluronic acid are beneficial for biomaterial fabrication and application, thereby enhancing tissue formation and playing a crucial role in cell growth and promoting cell differentiation [1].

Alginic acid

Alginic acid is one of polysaccharide. The high functionality of this material makes it a biocompatible substance. In medicine this substance is widely used as cell transplantation vehicles for new bone formation as well as wound healing. The biological behavior of Alginic acid is slow degradation and insufficient mechanical integrity that make it impossible for long term implants. The advantages of this material are availability in abundance, non-toxicity and biocompatibility, biodegradable and bioreabsorbable property. Poor mechanical strength is a disadvantage for this material [58].

Metal

Some meals such as: magnesium (alloy), iron (alloy), tantalum, titanium, and aluminum oxide are used for bone implant [59].

Miscellaneous

Bone marrow

Bone marrow has used for stimulation of bone formation in bone defects and nonunion fractures, by growth factors and cytokines secreted by the transplanted cells. The advantage of this material is that it can be prepared percutaneously, without patient morbidity. Differentiation and Proliferation of stem cells may be enhanced by adding them into growth factors or addition them to collagen. Autogenous bone marrow mixed with DBM has used to fill bone defects successfully. Injection of autogenous bone marrow, with or without carriers, has used to treat nonunion of several bones [60].

Conclusion

Synthetic bone grafts may obviate the requirement of bone grafting. Must of synthetic bone substitutes are osteoconductive or osteoinductive alone but natural bone substitutes (such as autograft, allograft or xenograft) have both osteoconductivity and osteoinductivity prosperities. There is an interest in combining osteoconductive and osteoconductive compounds to facilitate bone formation. Today tissue engineering is generating new bone substitute for repair, regenerate and restore tissue to its functional state.

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