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Current Status and Prospect of Artificial Bone Repair Materials

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Abstract. Artificial bone repair materials play an irreplaceable role in current bone transplant surgery. The investigation novel biomimetic bone repair materials isone of the hottest fields at present which is critical for the development of medical science and clinical needs. Thisarticlereviews the current progresses on materials,mechanicalproperties and biocompatibilities ofbone repair materials, and analyzesexisting problems and future trends in this field. Drug-loaded bone repair materials will display a broader application prospect in orthopedic field.

Keywords: Artificial bone, Repair materials, Biocompatibility, Drug-loaded

1. Introduction

Repairing of damaged bone has been taken as a difficult clinical issue by surgeons for a long time and is usually carried out by bone transplantation. Bone transplantation materials can be divided into three types, namely same body bone, different body bone and artificial bone. Excellent bone substitutes should not only provide fine biological compatibility but also act positively in bone reconstruction in terms of speeding bone repair and achieving better therapeutic effects.

Traditional medicine injection is lacking of efficiency because it releases medicines periodically in the body, which leads to drug concentration fluctuations and can have side effects. Researchers make a development on bone repairing materials to achieve a true bone repairing by loading medicines into bone substitutes.

2. Current Status and Prospect of Artificial Bone Materials

2.1. Metallic materials

Metallic materials are first used biological material and have been applied in medical science for a long time. Au, Ag and Pt are applied to clinical treatment first. They have good stability and processing performance. After then, Cu, Pb, Mg and Fe are used in clinical test. Stainless steel is applied to clinical experience gradually along with metallurgical industry. The shape memory Ni-Ti alloy is proved to have good biocompatibility ,good wear resistance and high corrosion resistance. Porous NI-Ti alloy is a hot research topic. S.J.Simskeet al. have measured the micro-hardness and tissue parameters of newly grown bone and proved that newly grown bone had similar properties asproximate cranium and jaw bones. V.I.Itinet al. have shown that higher porousness and smaller average pore diameter of Ni-Ti alloy lead to higher deformation restore percentage.Although metallic materials have fine biocompatibility, the application is limited because metallic materials are lacking of bioactivity and difficult to bond with bone tissues.

2.2. Inorganic non-metallic materials

2.2.1. Hydroxyl Apatite(HA)

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HA is the main inorganic component of nature bones, counting for about 60 wt%. The basic unit of HA is needlelike apatite crystal which is 200 to 400 nm long and 15 to 30nm thick. HA is an excellent bone repair material[1]. However, HA is fragile and poor in hardness and stiffness, which restrict its clinical applications. Collagen-nanocrystalline HA is similar as natural bones and is characteristic by its layer-structure and nano-size[2].

2.2.2. Coral

Corals are deposited bones of marine invertebrate and mainly consist of calcium carbonate and trace organic matter. Corals have porous structures that are similar as bones and are utilized to repair bone damage for decades. They are of considerable mechanical strength and their 3-D structure is good for bone cell growth and proliferation. The combinational bone made of coral, type I collagen and recombinant bone morphogenetic protein-2 (rhBMP-2) is able to extend the degradation period of coral. In addition, a collagen film covering the coarse micro-pores of coral could be generate during the combination of collagen sol and coral[3], which is good for the adhesion and growth of cells and the formation for new bone issues.

2.3. Polymers

2.3.1. Chitin and chitosan

Chitin is proved to have good biocompatibility and biodegradability. Chitosan and its derivatives are good for cell adhesion and are celling growing factors which is able to control cell growth and proliferation. Klod-Devoid et al. studied the influence of chitin on in vitro osteoblast differentiation and bone formation and have shown that it could facilitate the differentiation of preosteoblasticcells. Lu et al. discovered that chitosan could induce joint cartilage growth in their rat knee joint research . Hidaka et al. studied the histopathology and immunohistology of chitosan membrane and discovered that after implanted into rat skull, chitosan membrane was able to induce bone formation . Chitin can be degraded and absorbed in body by depolymerizing. The intermediate and final products do not accumulate in body and do not have immunogenicity.

2.3.2. Alginate

Alginate is one kind of polysaccharide extracted from seaweed. Under the presence of Ca^{2+}, alginate is able to form 3D hydrogel through ionic crosslink. Calcium alginate can be decomposed by enzymes, generating non-poison products. Therefore, alginate is applied as wound cover, drug carrier, bacterial culturing substrate, etc. Paige et al. implanted calcium alginate hydrogel under rat skin and discovered new cartilage was formed. The disadvantages of calcium alginate lie in that it is hard to degrade in body, the composition is not stable and the purity varies in different products.

2.3.3. Poly-capro- lacktone(PCL)

Although currently applied degradable polyester materials, such as polylactic acid, polyglycolic acid and their copolymers have good biocompatibility, it is discovered that delayed aseptic inflammatory disease exists at the interface of materials and bone tissue. Moreover, this type of materials is expensive and difficult to make. Recently, synthetic PCL is proved to be highly biocompatible, biodegradable, permeable, cheap, malleable and easy to be attached by osteoblast[4]. AiHemaiti Yusubuet al. studied the bone repair ability of PCL by implanting PCL cylinder into New Zealand rabbit's right bone defect[5]. No osteolysis and aseptic fluid were found at the interface of material and bone.

2.3.4. Poly lactic-co-glycolic acid(PLGA)

PLGA is made from the copolymerization of polylactic acid (PLA) and polyglycolic acid (PGA) under a certain ratio. PLA was first used as support material for bone and cartilage tissue engineering and is also a widely used cartilage tissue engineering material at present. PLGA keeps PLA's original advantages and optimizes the degradation rate and mechanical strength. PLGA has been approved for clinical application by FDA, and is already widely applied in bone, cartilage, blood vessel, nerve, skin etc. PLGA degradation in body involves several factors of which biological degradation and chemical degradation are considered as the main reasons. It is generally believed that the degradation period of PLGA is about 6 months, which is the same as bone repairing period. As a result, PLGA only plays a role in bone repairing process and will

degrade completely and excrete outside after bone repairing. During degradation, the strength of PLGA decreases, which gradually transfer stress to fracture and stimulates bone cell growing and healing.

2.4. Composite Materials

2.4.1. Nanometer Hydroxyl apatite/Collagen composite (n-HA/C)

N-HA/C is a bone substitute based on the concept of bionic . It is a composite prepared from modulated mineralization in calcium phosphate solution by using purified and antigen removed type I collagen as the template. Nano artificial bone, namely self-setting calcium phosphate artificial bone, is one kind of biological inorganic material. It sticks to bone directly and reaches the maximum strength in 4 hours. The self-setting artificial bone is composed of white odorless powder and colorless curing liquid. The mechanical strength of hardened material is comparable to cancellous bone and the internal fixation device can be installed according to requirements without damaging its crystal structure and mechanical stability. The strength of hardened material is enough to support restored fracture and the internal fixation will not be lost during internal fixation. Composite don't affect human body even if some leakage into joint gap happens during surgery because it can be absorbed completely, which is suitable for shin bone fracture.

2.4.2. Nanometer Hydroxyl apatite/polyamide 66 composite (n-HA/PA66)

The main mechanisms count for the facilitation of bone healing by n-HA/PA66 include: ①bone transmission: n-HA/PA66 is a type of active porous nano-composite, similar as nature bone, and is able to guide cell growing and cell osteoid generation. ② inducing new bone formation: n-HA can boost function and metabolism of osteoblast more than HA. ③ nanometer particles: the diameter of nanoparticle enlarges its surface area, facilitating the adhesion, crawling and biological mineralization of bone cell at material surface. Previous animal studies confirmed that n-HA/PA66 have good biocompatibility, biological activity and mechanical properties.

2.4.3. Nanometer hydroxyl apatite/Chitosan/Carboxy methyl cellulose (n-HA/CS/CMC)

n-HA/CS/CMC has been well studied and widely applied. Chitosan (CS) is a positively charged degradable natural polymer whose degradation product is non-toxic, non-allergenic and has no carcinogenicity. n-HA/CS/CMC has been widely applied in biological medicine. Bone repair materials composites of HA and chitosan have already been reported. However, their mechanical strength is not satisfied. As a result, the application of cross link agent was applied to improve the mechanical properties of the composite[6]. Carboxymethyl cellulose(CMC) is one kind of chemically modified soluble cellulose ethers derivatives which belongs to anionic polymers and is generally used in its sodium salt form. N-HA/CS/CMC organic composite prepared by solution blending method not only has an improved bioactivity but is also featured by the degradability and non-toxicity.

2.5. Drug-Loaded materials

2.5.1. Drug-Loaded microspheres

Drug loaded microsphere is a hot topic of current researches because of its targeting for specific organs, tissues and the slow release of loaded medicine. Slow release agent refers to the type of agent that is able to release medicine for a relatively long time so as to have a long time effect after medicine uptake. The medicine release is primarily a first-order process. For injected agent, the release of medicine could continue for days to months. When it comes to oral drugs, the release period is dependent on their staying time in gastrointestinal, normally measured by hours. Controllable release agent is defined as the medicine whose release rate and time could be controlled to an expected range so as to keep blood medicine concentration to an effective level for a long time. So the main difference between slow release agent and controllable release agent is that slow release agent releases medicine according to the first order process. On the other hand, controllable release agent can release medicine at a constant rate so as to reach a more stable bold medicine concentration. That is to say, the concentration fluctuation is smaller until complete absorption.

2.5.2. Minocycline of antimicrobial gel/ Nanometer Hydroxyl apatite composite materials (GEL-HA-M)

Artificial bone repairing materials still have problems with biological activity, degradability and anti-infection which to some extent limit their clinical applications [7]. The currently reported biomimetic materials are generally simple in composition and structure. At the other hand, the organic matter of bone is composed of collagen and non-collagen protein and growth which do not have release effect.The organic phase of GEL-HA-M is gel, which has good biocompatibility and bone inductivity, and could be absorbed and degraded by body [8]. Inorganic low-crystalline nano HA is able to be absorbed easily [8]. Minocycline is one type of broad spectrum antibiotics for G+ and G- and anaerobic bacteria that has a strong affinity to bone tissues. It is indicated by in vitro bacterio static tests that the combination of minocycline and GEL-HA-M can keep antimicrobial activity for a long time and can restrain bacteria growing for over 30 days. GEL-HA-M nano compositeis a very promising bone repair material.

2.6. Prospect

Ideal external substrate of bone tissue engineering cells has the following requirements: A. good biocompatibility; B. good biological degradability; C. 3D porous structure; D. plasticity and mechanical strength; E. bone inducing activity; F. disinfection.

Bone repairing material develops from single repairing function to multiple repairing and curing functions. Along with the development of biological material, new drug loaded materials will possess better biological performance, mechanical strength and degradability to promote defect repairing and drug release. Composite combines two or more benefits together. If composite proportioning, combination mode, distribution effect are optimized to improve biocompatibility, mechanical strength, bone conducing and inducing, drug loaded and released capacity, it is easy to imagine that ideal composite would appear.

Along with study deepening and technology mature, drug loaded repairing materials will evolve to controlled release type or smart release type with benefits of multidrug function, drug release accurately and controlled, intelligent, eventually develop to personal curing to solve increasing bacteria drug resistance and mixed infection effectively and to improve curing result and repairing effect with controlling drug adverse reaction at the extreme. Drug loaded repairing materials appear more and more application prospect in bone field for better choice of curing bone defect and bone fracture.

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