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Porous bone tissue scaffold based on shape memory polymer

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Shape memory polymer (SMP) is a class of polymer with properties of non-toxic, environmentally friendly and biocompatibility. It can be activated by an external stimulus to change and subsequently recover its original shape. Duo to its biodegradability, easy forming properties and shape memory effect, shape memory polymer has been widely used in bio-medical applications. This paper details an application of SMP on porous bone tissue scaffold. Compared with traditional bone tissue scaffold, the scaffold based on SMP possesses advantages of low cost, easy assembly and easy adjustment. And most importantly, the bone tissue scaffold based on SMP can adapt to keep the best fixed state. Besides, bone tissue scaffold is designed based on the biological structure, which characteristics of high porosity and high specific surface area will promote the growth of new bone tissue. Combining with 4D printing, it can realize customization. Bone tissue scaffold based on SMP exhibit excellent performance and prove to be a potential application in bone tissue engineering.

Key words: *bone tissue scaffold, shape memory polymer,* 4D printing, customization

1. INTRODUCTION

In recent years, large bone defects caused by trauma have become more and more serious threat to the health of human [1][2]. And how to repair bone defect is a hot topic in clinical research. Autologous and allogeneic bone grafts are usually used to heal bone defects in traditional clinical surgery [3]. However, both treatments have their drawbacks. Immune rejection of autologous bone transplantation is relatively small, which is the best choice in clinical application. However, the transplants are obtained from the patients themselves, which it is easy to cause them additional suffering, new injuries and a series of complications. In addition, diversity of bone defects limits the collection of autologous bone grafts. Allograft is obtained from healthy bone tissue of other individuals. The source of raw materials is relatively broad, but it is easy to cause bacterial infection and immune rejection and low success rate. The increasing demand for surgery has led to the traditional autologous/allogeneic bone grafts cannot meet the practical requirements. Consequently, bone tissue engineering emerged under this background [4][5].

In 1993, Langer and Vacanti [6] first published a paper entitled "Tissue Engineer" in Science and proposed the concept of tissue engineering. In the following decades, the development of tissue engineering gets better and better [7].

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As an important branch of tissue engineering, the development of bone tissue engineering is very quick. Bone tissue engineering is the study and development of biological substitutes that can repair or improve the morphology and function of bone tissue defect by using the basic principles and techniques of cell biology and engineering science [8]. The establishment and development of bone tissue engineering provide a new way to solve the problem of bone defect.

The basic principle of bone tissue engineering is to extract a few seed cells with the differentiative potency of bone formation, such as osteoblasts and mesenchymal stem cells, and then inoculate them and growth factors into bone scaffolds after in vitro amplification and culture. Later, the scaffolds can be cultured in vitro or directly implanted into the bone defects of patients. In vivo, seed cells continue to grow, reproduce and secrete extracellular matrix under the stimulation of growth factors. At the same time, scaffolds are gradually degraded to provide space for new tissues. Eventually, bone scaffolds are replaced by newly generated bone tissues, and the damaged tissue reconstruct and restore to normal physiological function.

The scaffold can replace the bone defect tissue, and it is also the basis of cell growth and cytokine translocation in the early stage of tissue engineering. From a biological point of view, the ideal scaffold for bone tissue engineering should possess characteristics of: (1) excellent biodegradability; (2) excellent cytocompatibility; (3) three dimensional porous structure; (4) operability. And the porous structure is an essential feature of a bone repair scaffold. Studies indicate that the pore sizes required for cell growth are different in different tissues, which should meet the needs of bone units and cell growth. The irregular shape of bone defect also induces more difficulty in the design.

The development of shape memory polymer and 4D printing technology has facilitated the development of bone tissue scaffolds. Shape memory polymer (SMP) is a kind of smart materials, which can retain a temporary shape and recover the initial shape under some external stimuli [9], such as temperature [10], Joule heating [11], light [12], magnetic field [13] and solution [14] etc. Due to the advantages of light weight, large deformation and recovery ability and low cost, SMP has been received increasing attention since the first introduction in 1984 [15]. Besides, many kinds of fillers can be added into the SMP matrix to form shape memory polymer composite (SMPC) to increase the stiffness and strengthen of SMP [16].Nowadays, SMP and SMPC have covered widely application, including deployable space structure [17], morphing structure [18], biomedicine [19], smart textiles [20], and smart mandrel [21], and so on.

Different stiffness can be obtained by changing the temperature of SMP. When the temperature is higher than glass transition temperature, SMP in rubber state is soft and easy to deform to a temporary shape. When the temperature is lower than its transition temperature, SMP in glass state will be stiff, and the deformation can be stored [22][23]. In generally, the stiffness will increase 100 times from high temperature to low temperature.

A typical thermomechanical cycle illustrated shape memory effect of SMP is shown in Figure 1. There are five steps to complete the whole process.

Step 1: the SMP sample is heated above the transition temperature and kept some minutes for fully thermal equilibrium;

Step 2: the temperature is kept in high temperature, and the sample is deformed into a temporary shape by applying outer force;

Step 3: the sample is kept in deformation state, and the temperature is decreased lower than glass transition temperature;

Step 4: the outer force is removed, and shape is preserved;

Step 5: the sample is reheated above the transition temperature, and the sample recover the initial shape.

The high shape fixity (Step 4) and shape recovery (Step 5) ability are the most important properties of SMP.

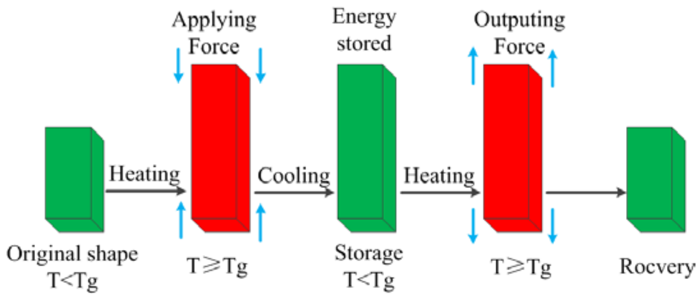

Figure 1 A typical thermomechanical cycle of SMP sample

At present, a series of remarkable achievements of 4D printing based SMP applications have been achieved in tissue engineering [24], medical devices, drug delivery and other biological fields. With the increasing demands for personalized implantable devices with complex structures and high-precision medical devices, the emergence of 4D printing technology is expected to break through the technical bottleneck of intelligent materials and structures in the field of biological medicine. And 4D printing technology is expected to be a new bond for close cooperation between various disciplines in the future.

The bone tissue scaffolds based on SMP have the advantages of easy to shape, low price and degradable, which endow it a broad application prospect in bone tissue engineering. In addition, the shape of the scaffold based on SMP can be modified in advance and implanted into bone tissue in a minimally invasive way. Based on its shape memory effect, it can self-adapt the irregular shape of bone defect and enable the stents to automatically fill the irregular bone defect area, which meets the urgent need for minimally invasive surgery in clinical practice.

2. DESIGN OF POROUS BONE TISSUE SCAFFOLD

Cancellous bone, as a part of bone tissue, is composed of interwoven rod-shaped and plate-shaped trabeculae, and among them is filled with liquid marrow [25]. Generally, cancellous bone has a porosity of 30-90%. In order to adapt to different mechanical environments, bone tissue constantly adjusts its structure and mass, which presents different morphological characteristics in different parts of the body. Cancellous bone, which often bears a small load, produces a relatively low density, open rod-shaped trabecular structure. When the load is large, the trabeculae will thicken and become a closed plate structure with holes. The trabeculae eventually interconnect to form a porous framework. In different anatomical parts of human body, bone trabeculae have different morphological characteristics, such as alignment direction, spacing, quantity, shape and thickness, and their mechanical properties are quite different. In this work, two kinds of porous bone tissue structures are designed by simulating the trabecular structure of bone. As shown in Figure 2, the two bone tissue structures of I and II are obtained by taking the array of the unit cells. The pores in this structure are connected with each other, which are conducive to the exchange of nutrients, the timely discharge of metabolites, maintain of adequate nutrients and keep constant acid-base environment.

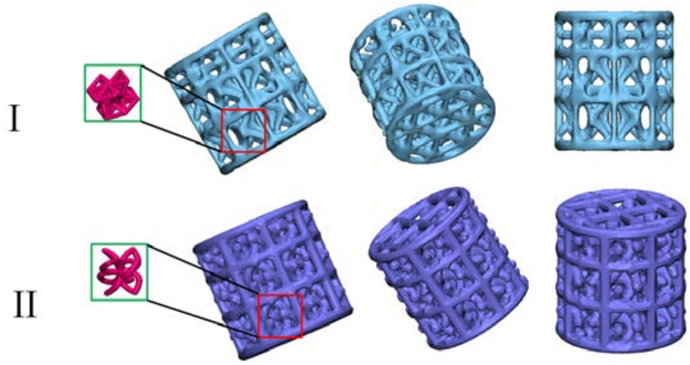

Figure 2 Design models of porous bone tissue scaffolds

3. FABRICATION OF POROUS BONE TISSUE SCAFFOLD

In 2013, Ti-berts [26][27]from MIT proposed the concept of 4D printing technology for the first time at the TED conference, and presented his research results of 4D printing. Combine SMP with 3D printing technology, the 4D printing technology can be realized by utilizing intelligent materials with shape memory property. Due to SMP can sense the external stimulus, the structure printed by 4D printing can change its shape under corresponding stimulus [28][29]. Since the 4D printing technology is proposed, more and more researchers have engaged in the research. With the continuous development and gradual maturity of 4D printing technology, the advantages of 4D printing based SMP structures are more obvious [30-36]. Research indicates that structures fabricated by 4D printing based SMP not only can carry out simple shape changes, but also can achieve self-deformation, self-assembly, self-repair and other functions by pre-setting its deformation plan (including target shape, properties, functions, etc.)[37-42]. In this work, the bone tissue scaffolds based on SMP are prepared by 4D printing technology. The two structures are shown in Figure 3.

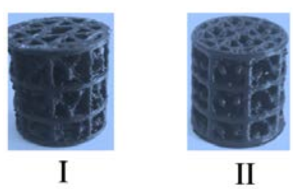

Figure 3 SMP based bone tissue scaffolds fabricated by 4D printing

4. PREDICTION OF EQUIVALENT MECHANICAL PROPERTIES

In order to obtain the equivalent elastic moduli of the designed scaffold, the structures are assumed to be porous foam structure. The open cell foam model developed by Gibson and Ashby is introduced to describe its mechanical behavior. According to this theory, the relative densities of structure play an important role in calculating the effective elastic modulus [43]. In order to simulate the compression behavior of the shape memory scaffold, its parameters need to be adjusted. Its expression is as follows:

$$E^{*}=\left(\frac{\rho^{*}}{\rho_{s}}\right)^{2}E_{s} \tag{1}$$

Where, E^* represents the effective elastic modulus of the scaffold; E_s is the elastic modulus of SMP; $\frac{\rho^*}{\rho_s}$ is the relative density of bone tissue scaffold. And this equation indicates that the effective elastic modulus of the SMP based scaffold is related to its relative density and the elastic modulus of the matrix material.

Based on this theory, the scaffold is simplified as a cubic arrangement structure with an edge length of *l* and a side length *t* of the edge square interface. The second moment of the relative density of pores and the area of the edge is established, as well as the relationship of the size of the simplified model:

$$\frac{\rho_F}{\rho_p} \propto \left(\frac{t}{l}\right)^2 \tag{2}$$

and

$$I \propto (t)^4 \tag{3}$$

The effective modulus of the bone tissue scaffold can be calculated by the liner elastic defection of beam. Based on the beam theory, the defection is proportional to $Fl^3 / E_s I$. Where, E_s is the elastic modulus of material, and the relation between load and compression stress is $F \propto \sigma l^4$. The relationship between strain and displacement can be expressed as $\varepsilon \propto \delta / l$. Therefore, the effective modulus of bone tissue scaffold can be calculated by:

$$E^* = \frac{\sigma}{\varepsilon} = \frac{C_1 E_s I}{l^4} \tag{4}$$

Where,

E^* -----Effective elastic modulus of SMP based bone tissue scaffold

C_1 -----Material parameter

Substitute the above equation into equations (3) and (4):

$$\frac{E^*}{E_s} = C_1 \left(\frac{\rho_F}{\rho_s}\right)^2 \tag{5}$$

The relationship between equivalent elastic modulus and porosity of bone tissue scaffold can be obtained by using the above formula. The corresponding change rule is shown in Figure 4.

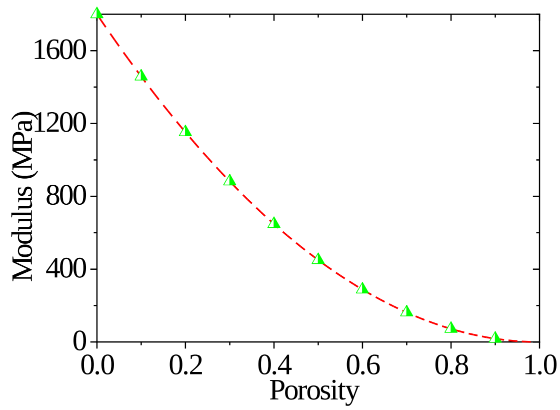

Figure 4 Prediction of effective elastic modulus of bone tissue scaffolds changing with porosities

5. CONCLUSION

Bone tissue scaffold is the precondition for the construction of artificial activated bone. Its structure and physiological function determine the osteogenic performance of large bionic artificial bone. Therefore, the scaffold should not only match the skeleton shape of the replaced part, but also have a three-dimensional microstructure to provide channels for tissue growth, regeneration, nutrient transport and metabolism. At the same time, it must have sufficient strength to withstand the pressure and provide temporary mechanical support for the new growth of tissue. In this work, by using the shape memory effect of SMP, the biomimetic bone tissue scaffold can be highly shrunk into a suitable shape before being implanted into the bone defect site and then implanted into the body through minimally invasive surgery to reduce unnecessary trauma. The two scaffolds are fabricated by 4D printing, and their effective elastic moduli are predicted by micro-mechanical model.

6. ACKNOWLEDGEMENT

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