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NEW MATERIALS FOR BONE REGENERATION

BY

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Abstract. Tissue engineering applications are being developed with the aim to regenerate, remodel, replace or support damaged tissues and organs. Many types of biomaterials have been studied for this purpose. The need for development of new biomimetic materials was the answer for many researchers. Scaffolds utilized in diverse applications of medicine, particularly, for bone tissue engineering must include mechanical properties, integration with host, osteoinductive (actively induce bone formation), osteoconductive (guide and support bone regeneration) properties and material biocompatibility. Also they can act as three-dimensional vehicles to deliver cells.to the human body. The best selections for bone defect repair were considered autografts (from the patient) and allografts (from the donor). Wheter or not multiple complications and risks were connected to the use of both types of grafts (Logeart *et al*., 2005), these remain the principal options for the doctors and patients. Bone is always colonized by osteoblasts and osteoclast cells, so it must be considered as a living tissue.

Keywords: biomaterials; bone formation; scaffolds**;** tissue engineering.

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1. Introduction

Polymer biomaterials are a very important part of the category of materials that are in permanent development and innovation in the last half of the century. The main source of these biomaterials is the renewable resources in nature in various forms. Current modern technologies allow biomaterials to be obtained in different forms such as films, gels and hydrogels, tablets or injectable solutions, microspheres, scaffolds, etc. They can be used successfully in various applications in the field of tissue engineering due to their properties in different medical fields. The structure of polymeric biomaterials presents various types of physiological functions, and they are also biocompatible due to the biological properties supporting the proliferation. The objectives of tissue engineering can be achieved in the presence of essential elements such as:

– Matrices that support cell growth to regenerate tissues;

– Cells that lead to tissue regeneration;

– Bioactive factors involved in cell proliferation.

Nanotechnology wants to develop the next generation of scaffolds to support cell proliferation and efficient delivery systems (Messina *et al*., 2017).

The approach of nanotechnology in biomedical engineering has been proposed for a wide range of biomedical applications.

In recent years, researchers' considerable efforts have been focused to develop scaffolds in tissue engineering using biocompatible and biologically natural or synthetic polymers.

The scaffold design must mimic the biological function and structure of native extracellular matrix (ECM) proteins that regulate cellular activities and provide mechanical support.

2. The Importance of Scaffolds in Bone Tissue Engineering

Worldwide, millions of patients, each year suffer significant bone loss due to congenital ailments, various illnesses, or trauma. Most of these have led to a reduction in the quality of life, but also to premature disabilities (Rahaman *et al.*, 2014). Every year, over 2.5 million bone grafting surgery is performed to repair defects in cranio-maxillo-facial surgery, neurosurgery and orthopedics, of which only 500,000 are in the United States (Giannoudis *et al*., 2005). It is expected that these figures will grow exponentially over the next 15 years due to the fact that the US population aged over 65 will double (Pleis *et al*., 2006).

The tissue-engineering application is a research section that deals with the production, design and development of biomaterials that can be implanted in the interior of the body as artificial organs or/and to help in healing processes of a wounded organ.

Bone tissue engineering focuses on natural tissue regeneration processes, being an interdisciplinary field based on the combination of three

main components: the cells, the signalling molecules and the macroporous artificial structure (scaffold) that acts as a temporary construction of support, growth and proliferation easy.

Scaffolds mimic the extracellular matrix (ECM) and have to provide adequate mechanical properties and adequate porosity to enable growth and tissue vascularization (Hutmacher *et al*., 2000). Ideally, the material created must possess bioactivity, biocompatibility, biodegradability, interconnected porosity, osteoconductivity, osteoinductivity and permeability:

– Bioactivity is the tendency of the material to form a chemical bond with the host bone;

– Biocompatibilty is the ability of the material "to perform its intended function, including an appropriate degradation profile, without eliciting any undesirable local or systemic effects in the host" (Blitterswijk and Thomsen 2008);

– Biodegradability describes the ability of the scaffold material to degrade in vivo;

– Interconnected porosity is required for bone growth, nutrient and waste transport;

– Osteoconductivity of a scaffold concern to the ability to induce bone formation without osteoinductive agents;

– Osteoinductivity is the ability of the scaffold to serve as a template for bone formation. The cells must to adhere to the surface, to proliferate and then produce bone;

– Permeability depends on the pore size which is dependent upon the scaffold pore architecture.

The macroscopic structure is obtained from porous biodegradable materials that can provide the necessary mechanical support during repair and regeneration of affected bone. Thus, the scaffolds were designed and developed for their use in bone tissue engineering in order to support and promote physiological tissue regeneration (Bose *et al*., 2012).

The fabrication of new biomaterials using biomimetic approaches gives the possibility to manipulate the architecture/structure and the chemistry/the composition of developed biomaterials.

Mostly all of the human tissues and organs are in nanofibrous forms or structures like bones, dentin, collagen, cartilage, and skin. All of them are characterized by well-organized fibrous structures realigning on the nanometer scale (Punjabi *et al*., 2015).

Interaction between cell and biomaterial is done at nano level (<100 nm) (Hajiali *et al*., 2010). At nanoscale, the specific surface, porosity, hydrophilicity and wettability, properties that determine cell-biomaterial interactions and influence cell adhesion and provide fusion with host tissue are fundamentally different from micrometric scale (Wei and Ma, 2008).

In the body, cells and tissues are organized in the form of a three-dimensional architecture. To achieve these functional tissues and organs, scaffolds have to be manufactured using different methodologies to facilitate cellular distribution and to guide their growth into three-dimensional space. Techniques for obtaining scaffolds are very important for their applications, having different advantages and disadvantages depending on the scope for which they were made.

These types of new biomaterials should give very specific cellular responses that lead to the formation of new tissue mediated by biomolecular recognition signals.

As biomaterials, scaffolds are in direct contact with muscle and blood. One of the most important problems in clinical use is clot formation, which greatly affects the development of biomaterials.

Thus, the problem of improving the hemocompatibility, in particular, of the anticoagulant property of the scaffold, is very important, and two methods are currently known: endothelization and sulphation.

Bone can be regenerated by repairing defects up to a certain size and can form a new tissue. Bone is always colonized by osteoblasts and osteoclast cells, so it must be considered as a living tissue.

At this time, there are several possibilities to correct bone defects by grafting based on scaffolds.

The scaffolds materials used in bone grafting can be divided into allografts, autografts and xenografts.

– Allograft is a piece of bone from a human donor, available from the bone bank of the hospital or also can be buy from a commercial supplier. These scaffolds can be obtained in different ways for long-term preservation (Aspenberg and Astrand, 2002).

– Autograft uses autogenous bone, which is taken preferably from the iliac crest of the patient and has the most important biological properties to fill up the defects of bone (Gross *et al*., 1991). In the most of the cases, the amount of autograft is limited and it is need also for another sources of bone grafts that should be involved.

– Xenograft utilise untreated animal bone. There are a lot of disadvantage for use of xenogenic transplants like the risk of the transmission of pathogens, strong immunological reactions of the human recipient (Helm *et al*., 2001).

The mechanical properties of the scaffolds are also important in its realization and depend directly on its architectural geometry. Sometimes multiple tests such as creep test, stress test strain, bending strength and dynamic test are also required to ensure the scaffold's predicted function.

The regeneration of specific tissues helped by synthetic materials has been demonstrated to be addicted on the porosity and pore size of the three-dimensional structure (Cima *et al*., 1991). For cell attachment and growth is

necessary a large surface area. Also, a large pore volume is wanted to help and led to deliver a cell mass sufficient for tissue repair. Highly porous biomaterials are required for the easy diffusion of nutrients to and waste products from the implant and for vascularization, which are very important criteria for the regeneration (Klawitter and Hulbert, 1971). The surface area/volume ratio of porous materials depends on the density and average diameter of the pores. Even so, the diameter of cells in suspension managed the minimum pore size, which can be different from one cell type to another. For the most of the applications, pore size must be controlled.

A lot of experiments have been focused to demonstrate optimum pore size and the result of implant pore size on tissue regeneration. In Table 1 we can observe different studies which have defined the optimal pore size for bone regeneration.

Table 1

Bone Regeneration-Optimal Pore Size

Scaffold pore size	Porosity	Reference
2-6 μm Type I	33	Klawitter and Hulbert, 1971
≤ 100 μm	35.3	Wang *et al*., 2010
15-40 μm Type II	46.2	Klawitter and Hulbert, 1971
≤ 200 μm	51	Wang *et al*., 2010
30-100 μm Type III	46.9	Klawitter and Hulbert, 1971
≤ 350 μm	73.9	Wang *et al*., 2010

Researchers have demonstrated optimum pore size of 5 μm for neovascularization, 5-15 μm for fiberblast ingrowth, close to 20 μm for the ingrowth of hepatocytes, 40-100 μm for osteoid ingrowth (Wang *et al*., 2010) and 100-350 μm for regeneration of bone (Klawitter and Hulbert, 1971).

3. Conclusions

In conclusion, scaffolds provide mechanical support and clues to control the structure and function of the newly formed tissue, deliver molecules or inductive cells to the site of repair. At the same time, there is a need for a balance between highly porous scaffolds that allow rapid embedding of tissues and minimization of diffusion limitations and less porous materials that retain both the constructive shape and the ability to withstand mechanical loads in a biochemical and mechanical environment.

In the preparation of scaffolds an important factor is the inclusion of bioactive molecules such as growth factors, enzymes, extracellular matrix proteins and DNA. Thus, the most important challenge in developing scaffolds is primarily to select a suitable blend of biomaterials with a particular set of properties. This area is still open to new ideas and attempts to create the best

configuration that encompasses the full range of features required for an effective tissue replacement in vivo.

Even though science has made many improvements in the medical field over the last few years, offering various biomaterials that are capable of mimicking body tissues, there are still many challenges to be overcome.

Even if a lot of new biomaterials have been studied, the translation of engineered tissues to clinical applications has been limited.

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NOI BIOMATERIALE PENTRU REGENERAREA OSOASĂ

(Rezumat)

Aplicațiile din ingineria tisulară sunt dezvoltate în scopul regenerării, remodelării, înlocuirii sau susținerii țesuturilor și organelor deteriorate. În acest scop au fost studiate multe tipuri de biomateriale. Nevoia de dezvoltare a unor noi materiale biomimetice a fost răspunsul pentru mulți cercetători. Scaffold-urile utilizate în diverse aplicații ale medicinei, în special pentru ingineria țesutului osos, trebuie să includă proprietăți mecanice, integrarea cu matricea gazdă, osteoinductivitatea (inducerea activă a formării osoase), proprietățile osteoconductive și biocompatibilitatea materială. De asemenea, ele pot acționa ca transportori tridimensionali pentru a livra celule către corpul uman. Cele mai bune selecții pentru repararea defectelor osoase au fost considerate autografele (de la pacient) și alografele (de la donator). Chiar dacă au fost legate multiple complicații și riscuri de utilizarea ambelor tipuri de grefe (Logeart *et al*., 2005), acestea rămân principalele opțiuni pentru medici și pacienți. Oasele sunt întotdeauna colonizate de osteoblaste și celule osteoclaste, deci trebuie considerate ca un țesut viu.