Biomimetics in Orthopedic Surgery and Traumatology

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Abstract Biomimetics is considered producing materials in manner that imitate natural tissues and their properties. There is increased need for artificial tissue replacement as autografts that are routinely used have limited resources. There are few different types of tissues in orthopedic surgery and traumatology that frequently need substitution for restoring satisfactory function of locomotory system, thus different kind of biomimetics are developed to fulfill this gap. There are many materials used for this purpose, none of them completely fulfill expected criteria. Basically all biomimetics can be classified as elastic, soft and hard. Elastic are designed for replacing menisci, tendons, ligaments. Soft biomimetics are used as a replacement for skin, muscles and cartilage tissue. Hard biomimetics are replacement for bone tissue. There are some completely synthetic biomimetics but modern approaches tend to combine them with natural materials tending to get best of both worlds. Hybrid materials are expected to combine properties of its ingredients and successfully mimic natural tissues.

Keywords Biomimetics · Orthopedics · Tissue engineering

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1 Introduction

Biomimetics or **biomimicry** is the emulation of the models, systems, and elements of nature for the purpose of solving complex human problems [1]. The terms "biomimetics" and "biomimicry" are derived from Ancient Greek: βίος (*bios*), life, and μίμησις (*mīmēsis*), imitation, from μιμεῖσθαι (*mīmeisthai*), to imitate, from μῖμος (*mimos*), actor.

Living beings have adapted to a constantly changing environment during evolution through mutation, recombination, and selection [2]. The core idea of the biomimetic philosophy is that nature's inhabitants including animals, plants, and microbes have the most experience in solving problems and have already found the most appropriate ways to last on planet Earth [3].

1.1 Biomimetics in Orthopedic

During routine orthopedic work, there are many indications for replacements of soft and hard tissues. Majority of those are due to trauma, malignant diseases and congenital defects. As human body itself has many regenerative potentials its possible, for minor to medium size defects, to be managed by natural healing or combination of reconstructive surgery and natural healing, while huge defects always need additional material for management. At this moment medicine relies on biological scaffolds for managing these problems. Biological scaffold is provided when part of tissue has been harvested with specific technique and transferred on a host patient in order to replace missing tissue and serve as a scaffold for hosts regenerative processes. The term routinely used for this kind of substitute is graft. According to graft origin we are talking about autografts, allografts and xenografts.

Table 1 shows advantages and disadvantages of different graft types.

Autografts are harvested from a patient and used on his organism to manage the tissue defect (tissue transplanted from one part of the body to another).

Allografts are harvested from another patient and transferred to a host patient (same species but different genotype - human to human transplantation).

Xenografts are parts of a tissues harvested from one species and transferred to other species (animals to human). Typically are used porcine dermis and small intestine or bovine pericardium and dermis, sometimes equine tissue.

The key to as good imitation of biological tissues as possible is to achieve physical and chemical properties of target tissue. Therefore, available biomimetics used in musculoskeletal pathology can be roughly divided in educational purposes as elastic, soft and hard.

Elastic Biomimetics Those are ment to substitute tissues that are naturally elastic such as tendons, ligaments and menisci in the knee as well as glenoid labrum in the shoulder.

Table 1 Advantages and disadvantages of different graft types

Graft type	Autograft	Allograft	Xenograft
Advantages	• Provides cells and healing factors that are significant for tissue regeneration • No risk of transmissive diseases • No risk of graft rejection due to immune reaction of the host	• No need for additional surgery • Structural support is provided from the positioning of the graft • In case of bony grafts there is osteoconductivity (but poor osteoinductivity) • No donor site morbidity	• Available in greater amount • Available in larger sizes
Disadvantages	• Availability is limited (especially when in need for substantial graft size) • Donor site pain and morbidity • Need for additional surgery	• Can cause host immunological response • Slower integration compared to autografts • Limited availability • Risk of transferable disease • While restructuring in organism mechanical strength is significantly decreased	• Risk of contamination with animal microorganisms • Can cause host immunological response • Slower integration compared to autografts

Those tissues consist of different kind of cells and extracellular matrix (ECM). ECM is composed of nonfibrous part (glycosaminoglycans) and fibrous part (elastin and collagen). Elastin has huge half life so there is a need for it in organism only when there is trauma to elastic tissue and reparation process demands elastin. Although, it is necessary to know that newly formed tissue have much poorer performance due to inadequate organization of fibers in freshly produced reparatory elastin and limited production of elastin in adult cells. Therefore, elasticity must be incorporated in synthetic scaffold itself.

There are few methods for acquiring elastin in laboratory. Animal derived elastin is challenging for production. By producing elastin with recombinant techniques, mostly on bacteria, it is possible to achieve good results in protein synthesis but the crosslinks and topography of such elastin fibers will produce elastin with lower mechanical quality compared to native one. Purely synthetic elastomers have advantage of possible producing in variety of dimensions and forms. Additionally they can be modified by changing a part of their structure or way they are crosslinked. Polyglycerol co-sebacate (PGS), poly-1,8-octanediol co-citrate (POC), polyurethanes (PU), polyhydroalkanoate (PHA) are frequently used in research. In order to achieve desired biocompatible and mechanical properties it is often necessary to combine different materials and produce hybrid tissue replacements. There is vast number of combinations with some authors grouping it as: synthetic polymer-polymer hybrid, protein-protein hybrid and synthetic polymer-protein hybrid [4].

Menisci are notorious for its almost nonexisting healing potential due to low vascularization in majority of meniscal body. Situation is somewhat better with tendons and ligaments. Using of allografts and meniscal transplantation are pretty demanding procedure mostly for problems with providing sufficient amounts of allografts. For obtaining good functional results with this procedure proper patient selection should be performed as well as good preoperative planning and especially templating of meniscal size which implies need for considerable stock of allografts for successful surgery. Some papers show high rate of complications and need for revision surgery [5]. Those are reasons for conducting research towards bioengineered materials for those purposes. Materials with most promising properties for use as elastic biomimetics in meniscal pathology are collagen, native elastin, elastin-like polypeptides, synthetic elastomers and elastic hybrid materials [4].

Soft Biomimetics Primary idea of developing those materials is to make substitutes for skin, muscles and cartilage tissue. AT this moment majority of techniques for soft tissue reconstruction rely on tissue grafts. Application of synthetic implants are limited by few factors and most noticeable are implant tearing or deformation and tissue resorption. Natural biomaterials can be used as synthetic replacement for soft tissues separately or combined with synthetic materials that reinforce them. Most widely used in this manner are collagen, hyaluron, fibrin, cryopreserved amniotic membrane, chitosan, acellular dermal matrix etc. In commercially available products they are often combined with stem cells or differentiated cells (fibroblasts and keratinocytes mostly). Natural polymers are very demanding for manipulation so there are attempts of using synthetic polymers as base for constructing scaffolds of different mechanical and chemical properties. Unfortunately there are some problems associated with this concept, typical for almost every synthetic materials in vivo: over time there is deterioration of materials and subsequent emission of degradational products of material as well as issues with biocompatibility [6].

Cartilage tissue is specific for its minor self-repair capacity. It is an avascular tissue and oxygen and nutritive substances necessary for its normal functioning are provided by direct diffusion from synovial fluid and repetitive moving of the joints enhances this process. This means that any degree of injury may cause significant degenerative changes in joint due to repetitive stresses, especially on bear loading joints. When in need for managing chondral defect, nowadays surgeon will routinely use one of the following techniques, depending on the defect size:

- Microfracture: usually used for managing of smaller defects or eventually moderate size when patient expect lower activity level. It is performed by creating few minor holes that reaches subchondral bone marrow expecting to form fibrous clot that will cover defect and afterwards be transformed in fibrocartilage tissue.
- Autologous chondral transplantation for moderate size defects. Donor area can be non weight bearing part of the joint cartilage tissue and graft can be harvested as a solitary one or as few minor grafts when using a mosaicplasty technique.
- When defects exceed 2.5–3 cm^2 osteochondral allografts or autologous chondrocyte implantation are used.

For few decades it is well known there is possibility for engineering cartilage tissue using autologous adult chondrocytes. This method has limitations in everyday surgical work so there are many attempts of using different progenitor cell sources [7]. It was shown there are significant potentials of cells from adipose and other tissues as well as use progenitors from embryonic stem cells. A beginning of 1990 is period of uprising of biomaterials with nowadays present concept of commercially available materials based on hybrid natural-synthetic platforms. Due to specific histological organization of hyaline cartilage tissue it becomes stiffer as the rate of loading increases [8].

Aiming to imitate this characteristic, researchers found materials for hyaline cartilage substitution have to be designed with nonlinear, inhomogeneous and viscoelastic properties [9]. Ideal scaffold should have adequate architecture and mechanical properties, as mentioned, biodegradability, biocompatibility, to enable cell adhesion, porosity and permeability. At this moment in commercial use are the scaffolds that serves as a temporary matrix for implanted cells, giving mechanical support for new tissue formation. Those scaffolds are made from type I/III collagen and hydroxyapatite based materials [10]. Natural material based scaffolds have advantages being similar to local tissue (biocompatibility, bioactivity, biodegradability), but their principle disadvantages are: mechanical weakness (especially in moist environment) and nonresistance to many processing conditions (high pressure and temperature). Next instance are hydrogels that have similar nonresistance to aquatic environment as natural scaffolds. Thus research are going toward synthetic scaffolds that can provide mechanical strength alongside with biocompatibility and biodegradability by virtue of hardiness to physical and chemical challenges of surrounding tissue. Synthetic materials currently most frequently used are: polyethylene glycol (PEG), polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA) and copolymers as polylactic coglycolic acid (PLGA). They have very promising results, but still remains huge disadvantage of releasing acid products during biodegradation, with possibility of consequential inflammatory reaction in organism. Analyzing current literature, hybrid scaffolds seems to be most promising one, with combining synthetic polymers (mostly PLGA and PLA) with natural materials (collagen and chitosan).

Hard Biomimetics They are designed as an attempt to substitute bone when necessary. Bone itself is highly specialized form of connective tissue with multiple functions: provide hard framework for the body, protects internal organs, enables motion serving as attachment for muscles, enabling lever mechanism for tendons and maintenance of mineral homeostasis. Another property of bone of paramount importance is possibility of constant remodeling. In this process parts of old bone are resorbed by bone resorbing cells (osteoclasts) and gradually replaced with new bone produced by bone forming cells (osteoblasts). This constant remodeling enables bone to adapt to mechanical loads. This is defined as Wolf‘s law, developed by German surgeon Julius Wolf in nineteenth century. According to it, bone in healthy person will adapt to the loads under which it is placed. When loading on bone or part of bone increases it will be remodeled and become stronger to resist load. The same stands for reverse process: if load is decreased, the bone becomes less dense and weaker due to lower stimulus needed for remodeling process. Whole remodeling process is performed through mechanism called mechanotransduction when mechanical signals are converted in biochemical signals and cellular signaling. When reduction in bone structure occurs it is named osteopenia. Sometimes it is consequence of generally lower activity (older people), treating of fractured bone, when load is not permitted while fracture is healed. Special form of osteopenia is stress shielding, phenomenon known in hip arthroplasty with some endoprosthesis design. It occurs in situation when implant take overload instead of bone, so parts of bone around implant underwent process of osteolysis that ultimately can produce implant loosening.

Bone is natural composite consisting of organic, inorganic part and water. Organic component of bone consists of more than 30 proteins with collagen type 1 making more than 90% and rest are noncollagenous proteins. Those different proteins have various functions, although not completely cleared. Majority of them have significant roles in mineralization of bone matrix. They also take part in regulation of osteoclasts and osteoblasts function and differentiation of bone cell by supporting their attachments to bone. Inorganic component is primarily crystalline hydroxyapatite. Organic component makes approximately 30% and organic 60% of weight while 10% is water weight. As about volume, inorganic component occupy40%, organic 35% and water 25%.

It is also important to have basic knowledge of macroscopic bone architecture.

Long bones are composed of cortical and cancellous bone tissue. Those are differently presented in various areas of bone. Diaphysis or the bone shaft is the central part of long bones and it has walls made of cortical bone. Metaphyses are widening of the bone at its ends and these areas are mostly made from cancellous bone with cortical bone forms the outer shell. Cortical bone is very resistant to a one way directioned loads while cancellous bone and its trabecular structure are capable for withstand loads in different directions.

Due to increased incidence of traumatism in last decades, there is great need for bone graft materials. There is also huge increase in number of implanted artificial joints in degenerative and rheumatic diseases, so there is always search for new materials that would enable longer survival of implants. In adequate functioning of musculoskeletal system there is huge role of soft tissues (muscles, ligaments, tendons, menisci, etc.) that are very frequently injured and very often there is need for artificial replacements of those tissues.

In routine work in majority of health facilities, when substitution for host bone is needed, surgeons use bone autografts (bone harvested from patient) or bone allografts (bone that is harvested from other patient, controlled for infective agents and frozen on −60 to −80 °C). The most important advantage of using those bone grafts is mechanical similarity to a host bone. Principle disadvantages are: possibility of transmission of infective agents (when using allografts) from host and limited amounts of auto- and allografts. Those leaded to investigations for engineering biomaterials with properties and structure similar to those in live organism. Biomaterials are used in orthopedic surgery for more than 50 years but still there is none that has mechanical properties of natural bone and such resistance and adaptation to repetitive stresses. There are many reasons for biomaterial implant failure but majority of them are due to artificial materials acting as a passive scaffold without possibility of remodeling and adapt to biomechanical circumstances in organism. At this moment most widely used substitutes for auto- and allografts are demineralized bone matrix (DBM) and synthetic bone graft substitutes (calcium sulfate and phosphate in majority of cases with addition of collagen, or polymers).

Calcium phosphates are minerals consisting of calcium cations and phosphate anions. Its existence in bones is discovered in 1769 and from beginning of twentieth century it is studied as material for clinical use having a wide range of potential utilization. There is spectrum of features making them excellent biomaterials: acting as bioactive scaffold that enables attachment of bone cells, their stimulation to grow, multiply and form a new bone. It also forms excellent bond with bone tissue without interposition of fibrous layer and facilitate growth of bone tissue and rapid early fixation. Thus the increase in use of CaP as biocompatible and bioactive material in orthopedic surgery. During research in this area many variants of calcium phosphates are considered for orthopedic use in different forms such as: coatings, cement and scaffold based on this material. There are also attempts to improve performance of calcium phosphates in combination with different agents.

Degradation and releasing of ions are crucial for good bioactive properties of calcium phosphate. Increasing of concentration of Ca and P ions stimulates formation of bone minerals on the surface of CaP and also influence expression of various osteoblast differentiation markers. Calcium ions influence many cascades important in bone healing process. They cause bone formation and ripening through calcification, stimulates mature bone cells forming nitric oxide and inducing bone growth precursors cells for bone regeneration [11]. Phosphate ions also influence processes of bone growth in many ways. They regulate proliferation and differentiation of osteoblasts and promotes expression of bone morphogenetic protein [12]. Calcium phosphates have rough surface enabling attachment of proteins and cells on it. Porosity of CaP enables contact with body fluid on larger area and promotes ingrowth of blood vessels.

Types of Calcium Phosphates

Nanodimensional Calcium Phosphates Nanometer size of particles provide maximum strength, better interaction with cells and can be considered as a storage for minerals needed for bone remodelation process. It is found that nano structure decreases percentage of mechanical failure, improves friction and wear characteristics and increases density [13]. As there is significant increase in surface area, there is also improvement in biological and cellular reaction. Due to mentioned properties of nano sized CaP applications are mostly in hybrid biocomposites for enhancing bioactivity and manufacturing of scaffolds. This type of calcium phosphates is also used as a career for drugs providing them safety from degradation, promoting local delivery and control their release [14]. Nano sized calcium phosphates have large surface compared to volume and are able to be loaded with much higher quantity of drugs.

Cements Calcium phosphate cements (CPC) are used for bone augmentation and substitution for a long time. Since 1980 there is increased interest for their improvement which resulted in many commercially available products at this moment. All of them are produced as a result of interaction between liquid and solid phase. Mixing of those produces paste that gradually hardens and become solid mass. Solid phase is made from different calcium phosphate compounds while liquid part are different aqueous solutions (sodium orthophosphate, H3PO4 or citric acid). Mixing liquid and solid phase produces viscous paste that can be manipulated very well manually or injected into a bone and form desired shape. It hardens on body temperature but has an excellent property of hardening with slightly exothermic reaction. For example PMMA (polymethylmethacrylate bone cement) has similar physical properties but hardens with highly exotermic reaction that can cause local tissue necrosis. Although there are numerous available formulations of CaP cement components there are only two possible final products: brushite (dicalcium phosphate dehydrate) or apatite (hydroxyapatite). In vivo settings brushite can transform to apatite.

Calcium phosphates cement seems like very promising material for bone substitution, regeneration and other mentioned applications, still there are some issues that limits application. Pure CPC, without additives is prone to liquid–solid components separation. Without additives it also have low strength, high brittleness, low impact resistance and low tensile strength, so the application is limited mostly to non weight bearing indications in orthopedic surgery [15]. In majority of clinical applications CaP cements are injected in trabecular bone to avoid failures. Once when hardened CaP cement resembles to trabecular bone mostly. In order to enhance mechanical properties of CaP cement various types of fibers, fillers and additives are used: bioactive glass, collagen fibers, carbon nanotube etc. It is preferable to use biodegradable fillers and additives that does not impact porosity of CaP cement thus keeping best properties of CaP unaffected.

Majority of clinical applications of CaP cements are for bone augmentation and bone defect management in appropriate indications. They are used for augmentation of osteoporotic vertebral bodies augmentation and also for treatment of vertebral fractures. They are used for bone defect healing in surgeries that doesn't demand high pressure resistance of implants (maxillofacial, oral surgery). CaP cements are also used as drug delivery systems providing incorporation of drugs as well as gradual emission. There are multiple ongoing research with CaP as delivery agent for antibiotics, anticancer drugs and anti-inflammatory agents with promising results.

Coatings Metallic materials are widely used in orthopedic surgery for different purposes. Biocompatible metals have good mechanical properties in terms of mechanical strength and torque resistance but don't fulfill criteria regarding bioactivity. Surface of orthopedical implants is crucial while trying to achieve stable osteointegration performing joint arthroplasties. Surface optimization with adequate coating is found to be the best way to optimize implant for specific orthopedic application. Calcium phosphate showed good results when applied as a biomaterial in human organism so there are various attempts of using it as a coating on different metallic implants used in joint arthroplasties. Different types of CaP are used as coating materials with good osteoconductive properties enabling stable and rapid osteointegration of implant compared to non coated implants. Osteoconductive properties of different CaP's vary depending on surface porosity, pore size, geometry. There are several CaP coatings methods, commercially most widely used is plasma spray. Beside physical deposition techniques some other techniques are used: wet chemical techniques (sol-gel method, biomimetic precipitation, cathodic electrodeposition etc.). Deposition method hugely depends on metal that is used as an implant main part.

Basic Constituents of Bone Tissue Engineering Basic constituents for bone tissue engineering (Fig. 1) are scaffolds, cells and signals [16].

Scaffolds serves as replacements/reinforcements in order to provide favorable conditions for production of native tissue. Scaffolds used in bone surgery are expected to be bioactive, biodegradable and porous. Bioactivity means promotion of interaction of cells and biomaterial, enhancing adhesion of cells and later proliferation, migration and differentiation. Biodegradability is the feature enabling replacement of scaffold with native tissue during desirable time period, without emitting toxic products during that process. Additionally scaffolds in orthopedic surgery and traumatology of musculoskeletal system are expected to be durable and capable of withstanding significant mechanical loads. Principle problem is not only to achieve desired mechanical sustainability but to preserve it through process of biodegradation, at least sufficiently long for tissue to recover. Some materials (ceramics) can withstand great amount of compressive loads, they are prone to failure on tensile forces and such facts should be considered while choosing ideal material for scaffold.

Based on materials used for fabrication, scaffolds can be: Metals, ceramics and polymers. They also can be observed as naturally derived or synthetically manufactured; resorbable and nonresorbable; with or without osteoconductivity and osteoinductivity. None of those are ideal and choice hugely depends on anticipated use. For example naturally derived scaffolds have excellent biomechanical properties but are in lack of mechanical strength and have high degradation rate. Scaffolds with low

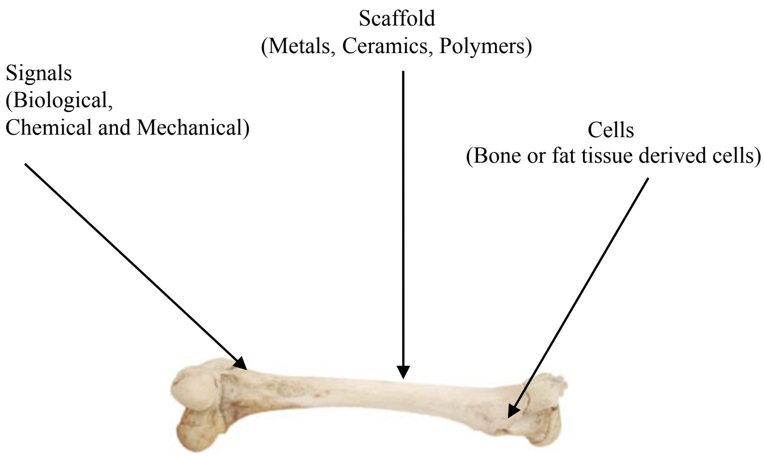

Fig. 1 Basic constituents of bone tissue engineering [16]

degradation rate may not integrate properly into a tissue and start to act as foreign body.

Cells are necessary for tissue origination as well for integration with host organism. Cells are integrated in implied scaffold in different manners and most frequently used in orthopedic regenerative surgery are mesenchymal stem cells (MSC). They are very convenient for this purpose as have ability to differentiate into various types of cells (osteoblasts, myoblasts, chondroblasts, tenocytes) [17]. Another huge advantage of MSC is simple process of harvesting. MSC from bone marrow aspirate are considered gold standard at this moment but MSC derived from adipose tissue are gaining in popularity, primarily for increased availability and easier harvesting. Other sources of MSC are periosteum, skin, umbilical cord blood and amniotic fluid. It is shown that MSC harvested from different tissues have various differentiation potentials [17]. Implanted MSC doesn't have only structural effect in host organism. When implanted they also make modulation of immune response, making less possible tissue rejection by host organism [18].

By signals we consider intrinsic or extrinsic factors that may affect tissue regeneration process. Those signals can be biological (growth factors and platelets rich plasma), chemical (statins, biphosphonates), mechanical (pressure or distraction).

Indications for Using Biomimetics in Orthopedic Surgery and Traumatology As already mentioned all research dealing with bioengineering of hard, soft and elastic tissues are more frequent because there is increased need for substitution of those tissues in routine work. Most frequent indications for using these materials are:

- Acute fractures of long bones
- Delayed unions and nonunions of long bones
- Osteonecrosis (avascular necrosis)
- Osteochondral defects

Majority of acute fractures doesn't require any additional treatment beside surgical stabilization. Many factors influence bone healing process. Age of patient is one of the most important as cell and signal activity decreases rapidly with aging. Comorbidity, as diabetes and osteoporosis, can notably jeopardize bone healing. Life habits as smoking and chronic alcoholism are also risk factors known for decades. There are some other conditions that can influence formation of satisfactory callus at fracture site: nutritional status of patient (intake of proteins and calcium), hypovitaminosis (especially D and C). And last, but not least, fracture related factors are of huge importance while estimating need for additional means of enhancing bone healing (open or closed fracture, degree of comminution, segmental fractures with double impaired vascularization of bone, large devitalized bone fragments). Decision for applying proper enhancement method demands excellent knowledge of bone histophysiology, methods of surgical stabilization and knowledge of characteristics of available bone substitutes materials.

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