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**Review article**

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# *Biocompatible implants in orthopedics: bone tissue engineering*

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***Abstract***

**Introduction** Technological advances in bone tissue engineering have improved orthopaedic implants and surgical techniques for bone reconstruction. This approach allows overcoming inconvenience of the paucity of autologous materials available and donor site morbidity. **Aim** To demonstrate advances of the past 30 years in the development of bioimplants providing alternatives to bone grafting in reconstructive orthopaedics. **Methods** Preparing the review, the scientific platforms such as PubMed, Scopus, ResearchGate, RSCI were used for information searching. Search words or word combinations were bioactive osteoinductive implants, bone grafting, bone reconstruction, hydroxyapatite, bone scaffolds. **Results** This review presents and discusses the experimental and clinical application of biotolerant, bioinert and bioactive materials for reconstructive bone surgery. **Discussion** Future generations of biomaterials are designed to be osteoconductive and osteoinductive. Properties of polycaprolactone (PCL) filled with hydroxyapatite (from 10 to 50 wt %) make this hybrid material with controllable absorption a promising strategy for reconstructive surgery in comparison to other materials. **Conclusion** The main trends in tissue engineering in the field of orthopaedics are represented by construction of three-dimensional structure implants guiding cell migration, proliferation and differentiation as well as mechanical support. Association with bone morphogenetic proteins, growth factors enables proliferation and differentiation of cell types of the targeted bone tissue. A promising advancement should be biodegradability with a controllable degradation rate to compliment cell/tissue in-growth and maturation in limb reconstruction.

**Keywords**: bone tissue engineering, reconstructive orthopedics, clinical translation

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## INTRODUCTION

Methods for surgical treatment of fractures and bone diseases with the use of osteosynthesis technologies have spread globally over the past century. A great number of internal (intraosseous and extraosseous) and external (wire- and half-pin-based) fixators have been proposed to ensure the most reliable osteosynthesis of a broken bone and to provide favorable conditions for reparative bone tissue regeneration: accurate reduction of bone fragments, their stable fixation, sparing attitude to osteogenic tissues, optimal rate of elongation, good blood supply to the involved limb, and early functioning in the postoperative period [1, 2]. Most orthopedic surgeons believe that the Ilizarov method is one of the best methods to provide the above-mentioned conditions. Nevertheless, clinical practice shows that the duration of osteosynthesis with the Ilizarov frame lasts at least four months for closed long bone fractures. In conventional limb lengthening, the excellent external fixation index is about 30 days/cm, the good one is 45 days/cm, the fair one is 60 days/cm [3-9]. In 2004, Eralp et al. reported an index of 1.65 months/cm for lengthening of the tibia with the Ilizarov fixator [10]. It is obvious that long-lasting treatment cannot satisfy either the patient and his relatives or the health care institutions. Therefore, there is a necessity to reduce the period of external frame wearing and to stimulate osteogenesis, both with conservative and invasive methods [11, 12].

Autologous bone grafting and various bioactive products from the decalcified bone, biocomposite matrices, recombinant bone morphogenetic proteins, and biomaterials from ceramics were offered for this purpose. Alongside, experimental studies on cell technologies have intensified [11, 13]. Bioengineering in orthopedics aims at creating biomaterials that are suitable to replace the damaged ones such as skin, muscle tissue, blood vessels, nerve fibers, and bone tissue. Biomaterials are the materials designed to serve as interfaces with biological systems in order to augment or replace host tissue, organ, or body function [14].

This publication aimed to reveal the trends in experimental development and clinical application of advanced bioactive implants in limb reconstruction dedicated to replace bone grafts.

## MATERIALS AND METHODS

We summarized the recently published studies on definition, classification, production, indications and clinical application outcomes for implants with osteoinductive and osteoconductive properties used in limb reconstruction. To prepare the review, we searched for information sources

at the scientific platforms such as PubMed, Scopus, ResearchGate, RSCI, as well as other published products (Elsevier, Springer) using search words or word constructions: bone tissue engineering, reconstructive orthopaedics, clinical translation, scaffolds, hydroxyapatite.

## RESULTS AND DISCUSSION

This area of materials science in orthopedics is also called bioceramics. The name emphasizes the leading role of the ceramic component in implants for joint replacement, filling materials for dentistry, implants for maxillofacial surgery, and medical cosmetic products [15, 16]. Biomaterials must possess certain chemical properties (absence of undesirable chemical reactions with tissues and interstitial fluids, resistance to corrosion), mechanical characteristics (strength, resistance to breakdown, long-lasting mechanical support), biological properties (absence of reactions from the immune system, consolidation with bone tissue, stimulation of osteogenesis).

Biomaterials used as implants that replace a bone part or as temporary fixators for fractures are also classified by their biological activity on bone tissue regeneration:

• Biotolerant materials (stainless steel and cobalt-chromium alloys); a layer of fibrous tissue develops between the surface of those implants and the host bone; reparative regeneration of the injured bone occurs within conventional time and at some distance from the implant (distant osteogenesis);

• Bioinert materials (titanium and aluminum oxides) do not cause the formation of fibrous layer on the implant surface; reparative osteogenesis proceeds in direct contact with the implant surface (contact osteogenesis), but bone union occurs within usual terms;

• Bioactive materials (calcium phosphate ceramics and silicon-based bioglasses) are characterized by the formation of a chemical bond with the bone (bonding osteogenesis), enhance bone formation starting from the implant surface and induce the formation of a continuous bond from the tissue to its surface.

Metal implants occupy a large place in traumatology. Alloy steel is most frequently used to restore the integrity of a fractured bone (screws, locking intramedullary nails or bone plates). Internal fixation implants are made from materials that must primarily meet the objectives of providing reliable fixation of the fracture for functional treatment within a certain period, sometimes for 12-18 months. This is a rather long period of time. Therefore, materials must be chosen to resist fatiguing failure after fixation on the surface of bone fragments in order to maintain them in an anatomical position under loading until biological bone union.

All metals can be classified according to the effect on reparative osteogenesis into biotolerant materials (stainless steel and cobalt-chromium alloys) or bio-inert materials (titanium and aluminum oxides). There are no bioactive metals that would stimulate reparative osteogenesis. Chromium-nickel and chromium-nickel-molybdenum corrosion-resistant steels, alloys of cobalt, tantalum, titanium, and pure metals such as nickel, silver, and titanium are the most frequently used materials for production of surgical implants applied in current medicine. Thus, in dentistry, dental implants are made from titanium and its alloys, since titanium is a biocompatible and corrosion-resistant material. In fact, all metals corrode under the influence of human body fluids. And without exception, all metal implants get protected from corrosion by a passive layer consisting of insoluble products of their oxidation. Corrosion increases by about 100 times if the passive protective layer of a metal implant, which consists of insoluble products of their oxidation, is damaged eventually by friction [17]. Under these conditions, the implant will not be able to provide stable fixation for a long time period required for bone fracture union.

Undoubtedly, titanium is one of the most promising materials for the manufacture of surgical implants widely used in traumatology. Numerous experiments and clinical practice have confirmed that titanium and its alloys is the most optimal metal for implantation [18].

Typical bioactive materials include bioglasses. The most common composition is 24.5 % $Na_2O$, 24.5 % CaO, 45.0 % $SiO_2$, 6 % $P_2O_5$. By varying the composition, one can change their bioactivity and resorbability. Other materials are based on hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$ (dense and porous ceramics) [15, 19].

Hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, is one of the few known bioactive materials. It enables bone ingrowth and osseointegration of an orthopedic, dental, and maxillofacial implant due to its high biocompatibility. In recent years, a special term has appeared in the literature, biocompatible nanoceramics (where HA grains vary in size from one to several hundreds of nanometers), or nanostructured bioceramics, which defines a nanostructured ceramic material used in medicine to regenerate lost bone tissue [20].

The phenomenon of bioactivity is determined mainly by chemical factors, such as the crystalline phase and the molecular structure of the material, and by physical factors such as roughness and porosity of the material surface. Back in 1973, Hulbert et al. [21] proposed a new concept of the so-called biological fixation of skeletal implants by active bone growth (osteoconduction) on their surface. The materials were oxide ceramic and carbon compounds, as well as metals coated with stable oxide layers. Later, the concept of bioactivity of materials was defined as their ability to interact with the surrounding host bone tissue and to form a chemical bond with it [15, 22-24]. The ion-exchange reaction between the bioactive implant and the surrounding body fluids leads to the formation of a layer of carbonate apatite on it, which is chemically and crystallographically equivalent to the mineral composition of the bone. This ability of the implant to initiate the formation of calcium phosphate under *in vitro* conditions is interpreted as the first sign of possible bioactivity *in vivo*.

Multiple complex and interrelated processes take place on the surface of a bioactive implant. First, ions and proteins are adsorbed there, forming a biofilm on the surface of the implant. This process strongly depends on the physical and chemical characteristics of the surface topography (roughness, porosity, morphology), chemical composition, energy and charge. As a result, both the amount and functionality of adsorbed proteins are largely controlled by the surface of the biomaterial. The adsorbed biofilm promotes the adhesion of cells facilitated by specific transmembrane receptors, integrins [16, 25]. The surface of the material, its biocompatibility determines the degree of adhesion of osteogenic and mesenchymal stem cells on their surface [26-28]. The degree of adhesion and disposition of these cells determine their ability to proliferate and differentiate into osteoblasts upon contact with the implant. The latter is crucial in the development of a mechanically strong interface of complete fusion between the implant surface and bone tissue without a layer of fibrous tissue [29-33].

The traumatology science currently develops two fundamentally different approaches to address injuries and bone loss: 1) simple replacement of a damaged area of the bone with a massive implant, with or without bioengineered structure, that replaces the bone and adjacent joints, or 2) creating conditions for regeneration of the bone in the injured area with an osteoinductive (absorbable or non-absorbable) implant. An analysis of literature reveals that both directions are increasingly associated with bioceramics, the use of which in medicine has been expanding as the developments in the field of chemistry progress and technologies for production of materials with the properties that are close to bone tissue improve [34-36].

Among the synthetic materials that can be used for implantation, calcium phosphate-based ceramics are the most promising. Hydroxyapatite is not only biocompatible, but also the most bioactive. However, the main shortcoming of ceramics is its fragility. Therefore, bioinert metals and alloys with a calcium phosphate coating can be used for fabrication of orthopedic devices for the musculoskeletal system, which experiences significant mechanical loads [37-40]. The coating provides biological compatibility and expressed biological activity in the formation of bone tissue around the metal. There are two research trends:

1. Development of joint prosthetic devices, the bearing metal part of which is covered with ceramics for the purpose of osteoinduction and formation of an extensive bone coupling that ensures reliable contact of the metal with the bone tissue over the maximum area, thus eliminating the failure of fixing the elements of the joint on the bone for many years [37, 40].

2. Development of intramedullary implants that do not experience significant load, but their hydroxyapatite coating contributes to the filling of extensive bone defects after trauma or surgical bone resections [41, 42].

Such a coating is designed to induce reparative osteogenesis around the implant, thereby contributing to the filling of extensive bone defects. The coupling created in this way around the implant provides optimal conditions for consolidation of bone fractures or nonunion, the formation of a distraction regenerate [40].

The main biological advantage of HA coatings is enhanced bone formation, accelerated bonding between the implant surface and surrounding tissue, and a reduced release of potentially harmful metal ions [30].

Methods for applying a bioactive coating to implants are numerous. The basic technologies for the deposition of hydroxyapatite are microarc oxidation, magnetron sputtering, formation of composite polymer coatings, vacuum arc deposition under the conditions of short-pulse high-frequency plasma immersion ion implantation. The technology of coating determines mechanical properties of the coating and physicochemical characteristics of the implant surface [18, 28, 29, 43-47].

The inconvenience of metal implants with a bioactive coating includes the second surgery to remove them. A solution to this problem is found in using of an implant fabricated from a strong composite material which will gradually undergo resorption while the defect is filled with regenerating bone tissue.

The first fixation devices for osteosynthesis made from biodegradable materials have been available since the early 1980s [48, 49]. However, their use for fracture treatment has not been widely accepted yet due to a number of reasons. A few types of biodegradable orthopedic implants available are either not intended for management of fractures, or do not meet the requirements of the AO/ASIF principles in terms of their properties and application methods [50-52].

Nowadays, it has become possible not only to obtain biodegradable materials with strong mechanical properties and an optimal degradation profile for fracture management, but also to produce structures close to classical metal fixators in sizes, what enables to consider biodegradable fixators of the latest generations as their full alternative [53, 54]. However, most of the researches are still devoted to either products or materials of early generations not related to osteosynthesis of limb bone fractures. Very few publications describe practical aspects of their use [55, 56].

Materials that undergo degradation due to the physiological effects of body tissues can be conditionally designated as biodegradable, including bioabsorbable and bioresorbable. Biodegradable materials is a wide group and is defined as a community of materials that undergo decay due to the physiological effects of body tissues on them (*in vivo*), regardless of the removal of degradation products from the body [56, 57]

In 1966, Kulkarni et al. [58] reported the results of a study on the biocompatibility of polylactic acid (PLA) and its stereoisomer (Poly-L-Lactic Acid, PLLA). In 1971, the first result of a medical evaluation of the polymers in suture, rod, and film form was also presented [59]. The requirements for orthopedic fixators made of biodegradable materials were formulated

later: adequate fixation of bone fragments and/or soft tissues to the bone implant must retain mechanical properties within the estimated consolidation period; degradation period should not be too long to avoid the problems typical for metal fixators; implant must be made of materials that are completely safe for humans: non-toxic, non-antigenic, non-pyrogenic and non-carcinogenic [60-65].

The group of polymeric biodegradable materials for osteosynthesis includes polyesters based on lactic and glycolic acids, polycaprolactone, as well as their co-polymers, which can be characterized as bioinert bioresorbable. The degradation of these compounds proceeds mainly along the hydrolytic path. However, it also partly occurs enzymatically, mainly after the hydrolytic decomposition of the molecule into relatively small fragments due to the enzymes of phagocytes, macrophages and neutrophils, while the end products of decomposition are $CO_2$ and water [66-72]. As a material for the manufacture of orthopedic fixators, PLLA is of main interest. It has a high crystallinity, hydrophobicity and retains its properties for a long time, sometimes even too long (up to 5 years or more), is non-toxic and does not elicit an immune response [73].

The PLLA strength for compression is 80-500 MPa, the tensile strength is 45-70 MPa, the elastic modulus is 2.7 GPa, that are close to the values of the human bone tissue, which for the cortical bone are 131-224 MPa, 35-283 MPa and 17-20 GPa, respectively, and for spongy bone 5-10 MPa, 1.5-38 MPa and 0.05-0.1 GPa, relatively. PLLA products retain their original mechanical resistance for at least 3 months after implantation; degrade within 24 months. In some cases, after 4 years of implantation in the tibia, only initial surface signs of screw erosion were noted, what makes us consider that products made from pure PLLA are conditionally biodegradable [48, 71-74]. PLLA of high crystallinity degrades very slowly, while being inferior in strength to both polyglycolic acid (PGA) and biostable materials (metals). By combining PLLA and PGA, it was possible to solve the issue of relatively insufficient strength of the promising copolymer containing polylactic and glycolic acids [55, 56, 74-81].

Polylactic acid screws and pins are used in the clinical practice for fixation of small bone fragments in intra-articular fractures, fractures of the ankles and tibiofibular syndesmosis, bones of the wrist joint [75, 77]. In most fractures of the upper and lower extremities, it is not possible to ensure the stability of bone fragments only with such degradable implants. The economic effect of the use of biodegradable materials in fractures of various locations, including ankle fractures, was estimated by Böstman et al. and ranged from 410 to 903 US dollars due to minimization of repeated surgical activity needed for the removal of metal implants [81, 82]. The terms of fracture union remain standard [83, 84].

To obtain a real opportunity to stimulate osteogenic processes, a number of researchers propose to add special inductors (fillers) to the composite material as matrix for transplantation of stromal progenitor cells, native bone marrow cells [85, 86].

Several biocomposite materials containing bone collagen and bone sulfated glycosaminoglycans of animals and humans have been developed in Russia in order to restore bone defects: *Biomatrix* – bone xenocollagen and bone sulfated glycosaminoglycans; *Allomatrix-implant* – bone allocollagen and bone allosulfated glycosaminoglycans; *Osteomatrix* – biocomposition based on natural bone components xeno- or allocollagen, sulfated glycosaminoglycans and hydroxyapatite; *CollapAn* – a calcium-phosphate biocomposite material based on synthetic hydroxyapatite, collagen and an antibiotic [86-92].

These materials have porous and cellular structure corresponding to the architectonics of native cancellous bone. Such a structure provides not only volume maintenance in the defect due to elastic properties, but also an optimal opportunity for penetration and ingrowth of connective tissue cells, blood vessels and bone formation into the implant [88, 89, 92]. However, for all their advantages, they do not have the necessary mechanical characteristic of native bone tissue.

*Osteomatrix* is used in dentistry to replace bone defects formed after the removal of cysts and teeth. It was shown that 3 months after surgery the bone defects were actively filled with young bone tissue [91]. Good clinical results were also demonstrated for the *CollapAn*. In the area of the defects filled with *CollapAn*, the cortical layer and the medullary canal gradually formed by the 4-5$^{th}$ month, along with an increase in the intensity and uniformity of the callus. It was well tolerated; there were no cases of rejection and allergic reactions. In fracture treatment, an endosteal callus with a small periosteal component occurred by the end of the 4$^{th}$ week after the operation. The use of *CollapAn* in delayed fracture union and nonunion contributed to the formation of callus, mainly in its periosteal part, by the end of the 6-8$^{th}$ week after the operation. On average, by the end of the 8-9$^{th}$ month, bone consolidation was confirmed [92, 93].

Western European and American firms have developed a whole series of calcium-phosphate-collagen composites for filling bone defects or synostosis of vertebrae in order to replace autologous bone material in surgical practice. Thus, *Collagraft*®, a composite of collagen and biphasic calcium phosphate ceramic, contains highly purified type I collagen and biphasic calcium phosphate, which consists of 65 % hydroxyapatite and 35 % tricalcium phosphate ceramic [94].

Hydroxyapatite-poly-L-lactide (u-HA-PLLA) composites contain poly-L-lactide (PLLA). When u-HA-PLLA-composite rods were implanted into the subcutaneous layer, their bending strength retained 85 % of the original value after 8 weeks and 80 % after 25 weeks, while after 25 weeks the molecular weight of the rods decreased to approximately 20 % of original [95]. It was reported [96] that complete degradation of u-HA-PLLA composite rods for bone fixation happens approximately 4.5-5 years after implantation.

Beneficial properties of u-HA-PLLA composites enable to use bioresorbable devices made from them for internal fixation in bone fractures, orthopedic reconstructive and restorative operations. However, all degradable products based on PLLA have a significant drawback. In the course of degradation, the acidity of the environment of surrounding tissues increases, which negatively affects the processes of reparative regeneration of bone tissue and, consequently, the terms of fracture consolidation increase [97].

In order to eliminate this issue of implant degradation, the researchers at Tomsk Polytechnic University (Russia) together with researchers from the Ilizarov center (Russia) proposed to use polycaprolactone (PCL) as an implant matrix. Products from PCL with the inclusion of hydroxyapatite (from 10 to 50 wt %) were studied in the treatment of fractures of long bones in animals, treatment of bone defects and experimental limb lengthening. Experimental studies revealed a high biological activity of this new type of intraosseous implants: pH of the environment remained at the level of 6-7, bone union of tibial fractures occurred within 1 month, external fixation index for limb lengthening did not exceed 20 days/cm in monofocal procedures [98].

## CONCLUSION

Thus, ceramic polymer composites are commercially available nowadays for treatment purposes. The combination of inorganic and organic components seems reasonable for designing in bone reconstruction surgery. Although autografts and allografts are still widely used due to the lack of artificial materials, some hydroxyapatite-polymer composites are attractive due to their similarity to the structure and properties of the bone tissue and osteoinductive activity. The use of materials depends both on medical and biological characteristics of a bone defect and particularities of underlying pathology. Variability of clinical problems requires a large range of biomaterials and implants on their basis.

The main objective of tissue engineering in the field of orthopaedics should be construction of implants serving as three-dimensional structures to guide cell migration, proliferation and differentiation along with mechanical support. Association with bone morphogenetic proteins, growth factors enables proliferation and differentiation of cell types of the targeted bone tissue. Tissue-engineered implants must be biodegradable with a controllable degradation rate to compliment cell/tissue in-growth and maturation.

The manufacture of implants should easily and efficiently reproduce various shapes and sizes. They have to ensure bone union in non-complicated fractures within three to four weeks and stimulate bone healing in lengthening procedure after two to three weeks of fixation phase. Osteoiductive implants should accelerate mineralization of newly formed organic matrix of a lengthened bone.

***Conflict of interest*** *The authors do not have conflicts of interest.*

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**Contribution of the authors:**

Popkov A.V. developed the concepts of the review. Popkov A.V. and Popkov D.A. collected and analyzed the data. All authors discussed the results and contributed to the final manuscript.