BONE TISSUE AS AN OSTEOPLASTIC SCAFFOLD FOR BONE REGENERATION*

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Present review covers definitions of reparative regeneration, investigation of properties of materials used for bone grafting, and analysis of bone regeneration mechanisms. It was shown that the regeneration of bone tissues could not be implemented without allowance for implant properties. Bone tissue transplantation could be one of the methods for biological stimulation of reparative regeneration.
Key Words: bone tissue, bone grafting materials, bone regeneration mechanisms.

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Introduction

Bone tissue is a specialized type of connective tissue that consists of bone cells and the intercellular substance. The term "bone tissue" strictly refers to the bone formation elements: bone forming and resorbing cells, intercellular substance, and also periosteum and endosteum in a bone growth state [13].

Bone as an organ is a complex structure that includes specific bone cells, periosteum, bone marrow, blood and lymph vessels, nerves and in some cases cartilage tissue [2, 13, 25].

Types and structure of bone tissue

In adults there are two morphofunctional bone types [2, 11, 13, 25].

1. Cortical (compact) bone comprises the outer layer of all bones (Fig. 1). An osteon, which resembles concentric bone sheets of cylindrical shape, is the main structural unit of the cortical bone. There is a Haversian canal in the middle of each cylinder. Blood vessels residing in the Haversian canals originate from larger vessels that are coming into the bone via Volkmann's canals. Lamellae are located in the space between osteons. Up to 80 % of the skeletal bone mass consists of cortical bones.

2. Trabecular (cancellous or spongy) bone tissue is located in the attachment sites of tendons to long bones, in the vertebral bodies, epiphyses of tubular bones, pelvic bones, and large flat bones. Trabecular bone tissue is composed of a rather dense network of rod- and plate-like elements of various forms and thickness, which are interconnected with each other and have a branched structure. These elements limit the irregular gap cavities that are interconnected as if in a sponge and are filled with bone marrow. The ground substance of trabecular bone contains less inorganic material (60–65 %) compared to that of the cortical bone. Collagen fibers are the main organic material of bones. Trabecular bone can carry the mechanical support function, as it is observed in the spine. It is metabolically more active as compared to the cortical bone and can provide the initial supply of minerals in the case of their acute shortage.

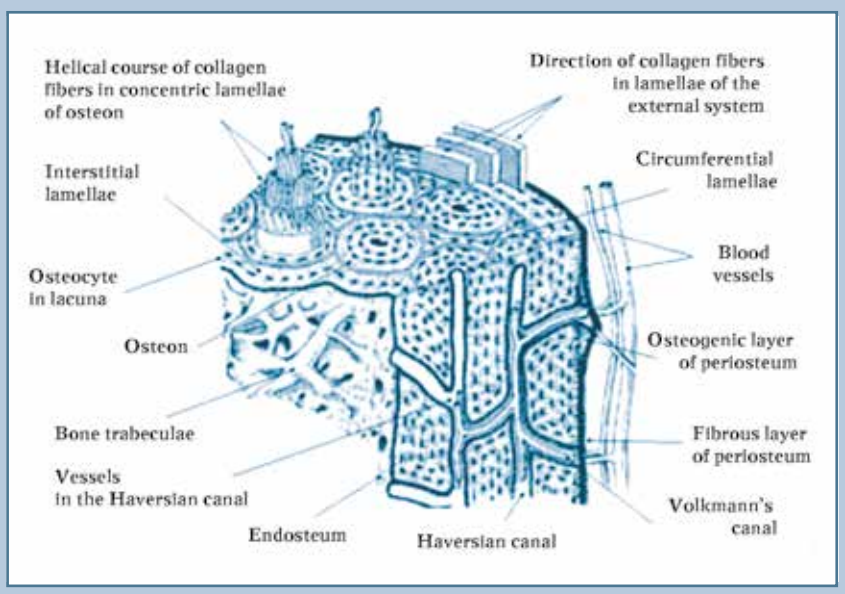

Fig. 1
Bone anatomy [2]

Bone composition

Bone tissue is a nature made composite material that consists of: organic component (collagen) – about 25 % of bone mass; mineral component (inorganic salts) – about 60–70 %; and cell elements – cells of osteoblastic (preosteoblasts, osteoblasts, osteocytes) and monocytic (osteoclasts) origin [2, 13, 19, 21, 25].

Bone tissue is the main structural component of the musculoskeletal system.

The peculiar and highly specialized association of organic and inorganic bone components, proper orientation of collagen fibers along the bone axis, ordered arrangement of crystals in the bone mineral matter have created a perfect structure exhibiting specific mechanical and physiological properties [11, 25].

Bone tissue is a dynamic polymorphic system, in which there are two correlated processes of bone remodeling cycle taking place during the life of a human: resorption (degradation of the old bone) and osteogenesis (formation of a new bone) [11–13].

Bone tissue and its reparative regeneration are always under close attention of traumatologists, orthopedists, and maxillofacial surgeons.

Reparative regeneration

Reparative regeneration is remodeling of tissue after any kind of damage. The mechanisms of physiological and reparative regeneration are qualitatively similar and are based on the same regularities [20]. Reparative regeneration can be considered as an enhanced physiological regeneration [10].

According to the data obtained by G.I. Lavrisheva [13], the bone has a high reparative potential. The normal reparative regeneration processes can be accelerated only to a little extent by enhancing the metabolism rate (several days or weeks). However, it can be easily slowed down by changing favorable conditions for regeneration, which often happens due to inadequate estimation of bone physiology condition.

S.S. Tkachenko and V.V. Rutscky [21, 22] believed that reparative regeneration is a complex process, which is caused by degradation of bone structures to a greater extent than the physiological regeneration limits; and which aims at restoring the anatomical integrity and providing bone functions.

A.A. Korzh and N.V. Dedukh [11] envision regenerative processes of the bone as a complex interconnection of general influences at a systematic level and as local changes in tissue metabolism including changes at a molecular level.

Unlike the physiological regeneration, which is essentially adaptive, the reparative regeneration is a negative feedback process that results in restoration of the disturbed homeostasis after the destruction of a part or the entire organ [13, 15].

Reparative regeneration of each type of tissues has its own features; however, it always includes decay of damaged cells and intercellular components, proliferation and differentiation of viable cells, establishment of intercellular communications (such as integration and adaptive reconstruction of the regenerated tissue). Reparative regeneration can be either complete or incomplete. Complete regeneration (restitution) is characterized by replacement of the defect with tissues identical to the lost ones. Incomplete reparative regeneration (substitution) results in replacement of the defect with the dense connective scar tissue [12].

Bone tissue is a unique tissue, in which even large sized defects can be completely healed [9, 11–13].

Reparative osteogenesis is a multicomponent process that mainly consists of cell differentiation, proliferation, resorption of the dead bone and the formation of a new one during remodeling process, formation of organic extracellular matrix and its mineralization. All of these processes occur simultaneously, but one of them can be prevalent at different stages of reparative osteogenesis [11, 16].

Osteoplastic materials are currently used to treat severe bone defects; their properties are essential for reparative regeneration and restoration of the bone [1, 3, 4, 8, 9, 15–17, 19, 27, 28].

Osteoplastic materials can be subdivided into three groups: biological (auto- and allografts, xenografts, biologically active molecules of protein and non-protein nature, which have growth factors properties); artificial (synthetic) ones that are based on the β-tricalcium phosphate, hydroxyapatite, various ceramics, calcium sulfate, etc.; composite materials (composites) is a combination (composition) of several synthetic and/or biological materials to impart synergistic properties [1].

A wide variety of these materials indicates the necessity of the development of new materials that will serve as a scaffold for formation of the regenerated tissue of organotypic bone structure. The developed material should lead to the formation of osteonic bone and cancellous bone structures when grafted into the cortical and trabecular bone, respectively. Therefore, materials should have a specific set of characteristics and should meet the following requirements:

- identical chemical and architecture of those of the bone (at the grafting site);
- modeling properties;
- resorption properties prolonged from 3 to 12 month;
- osteoconductivity;
- osteoinductivity;
- substitution by the organotypic bone tissue;
- targeted delivery and prolonged release of drugs in the defect zone (antibacterial and analgesic effects).

These requirements could be addressed only by osteoplastic materials based on the allograft bone treated using various technological procedures.

Depending on the type of chemical treatment of the bone tissues, the allograft could be one of three types:

1) natural, with the bone structure and the organic-to-mineral components ratio retained;

2) demineralized, the bone matrix without the mineral component;

3) deproteinized, without organic component, or crystal structure of biological.

In addition to chemical treatment, the bone allograft fragments vary in size and shape (which are imparted to the

material during the modeling process). Thus, the cortical bone fragments can resemble diaphysis fragments of fibula (ulna, tibia, etc.); cortical fragments may resemble the plates from the tibia of various dimensions (e.g., 10.0 × 2.0 or 3.0 × 2.0 cm) and thickness of 0.2 to 0.5 cm, depending on the donors' cortical bone thickness; bone straws – longitudinal cuts of cortical bone fragments of various lengths, usually 10.0–12.0 cm long, 0.1–0.3 cm wide, and 0.2–0.5 cm thick.

Chemical pretreatment of bone tissues and methods of sterilization and preservation can affect physicochemical, osteoconductive, and osteoinductive properties of bone allografts.

Thus, native bone fragments will retain both the organic-to-mineral composition ratio, and the strength properties that are typical of similar skeletal parts [7].

Fragments of deproteinized allografts are less immunogenic compared to those of native bone due to the treatment that removes the organic component of the bone. Besides that, the deproteinization process increases viral and bacterial safety of the allograft, which is constantly referenced by manufacturers of synthetic bone grafting materials [3, 27, 28]. In fact, the bone material obtained this way is a carbonate hydroxyapatite of allogeneic origin with retained architectonic and microelements composition [18].

Demineralized bone allografts do not possess good strength properties due to the removal of the mineral component. The whole group of bone morphogenetic proteins (BMPs) located in the demineralized bone tissue will stimulate proliferation and differentiation of osteodifferon ancestors and angiogenesis [5, 14, 19, 26].

According to the current knowledge, there are four types of the impact of osteoplastic materials (OPM) on the bone regeneration process [4, 6, 8].

1. Osteoblast osteogenesis stimulated by transplantation of the so-called differentiated osteogenic progenitor cells (DOPC) that demonstrate the potential of bone formation induction. This principle takes place in the transplantation of the trabecular bone autograft [23].

2. Osteoconductive osteogenesis (osteoconduction) as a method of passive stimulation of DOPC using synthetic or partially synthetic bone substitutes and bone allografts [3, 29]. The direct osteoblast osteogenesis cannot be employed during this process (as opposed to the implantation of living grafts), since non-vital material that cannot promote this effect is used in this case. Non-vital biological and synthetic implants serve as scaffolds for blood vessel ingrowth. Cell ingrowth from the original bone into the graft occurs subsequently. This mechanism includes resorption and formation of a new bone starting from the defect borders. The cellular mechanism of graft resorption and new bone formation are similar to those that take place in fracture consolidation during osteosynthesis [30, 34]. Axhausen [24] proposed to use the term "creeping substitution", by which he meant the initial resorption of the graft followed by secondary ingrowth of a new bone from the original bone. Apparently, in the original bone with a high DOPC content, these cells are activated under the influence of the graft. The graft is connected to the original bone by the granulation tissue and is gradually resorbed and replaced with the new bone [25].

3. Osteoinductive osteogenesis (osteoinduction) by means of phenotypic transitions of nonspecific pluripotent stem cells [25] under the influence of specific substances, such as BMPs. According to Reddi, Anderson [33], cellular and molecular processes occur via a specific cascade mechanism.

4. Stimulated osteogenesis (osteostimulation) is the effect of certain factors that accelerate and stimulate the existing osteogenesis processes (e.g., growth factors).

Considering the relationship between OPM and regeneration mechanisms, one can state that all the mechanisms occur only during implantation of the cancellous bone autografts (Fig. 2), since the autobone contains cellular elements inducing osteoblast osteogenesis, the ground substance of the graft (the osteoconductive matrix), OPM exhibiting osteoinductive properties, and biologi-

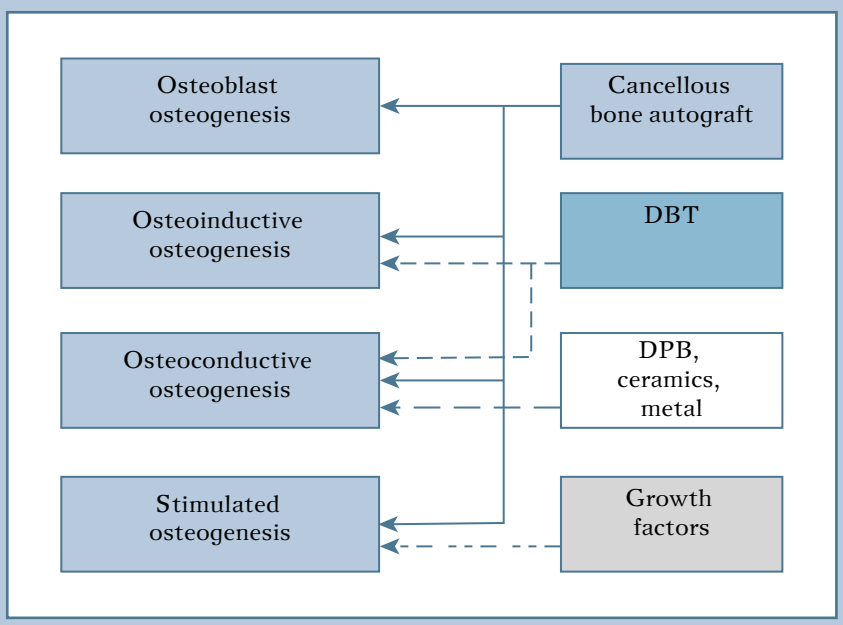

Fig. 2
Bone regeneration mechanisms; DBT – demineralized bone tissue, DPB – deproteinized bone

cally active molecules that are released during bone dissolution and promote osteogenesis.

Mechanisms 2 and 3 are implemented during the implantation of allograft bone; the use for synthetic materials is associated with the mechanism 3 only; and the use of composite materials is associated with mechanisms 2–4.

In order to increase the number of regeneration mechanisms involved, tissue engineered constructs based on the materials loaded with growth factor and and/or cellular components are used in each single case [15–17, 27, 28, 31, 32, 35]. The maximum number of mechanisms utilized should hypothetically result in the formation of organotypic regenerate at the procedure site. However, this assumption works only for OPMs that are degradable over time. Most of the synthetic materials are non-degradable or partially degradable and therefore the formation of organotypic regenerate upon their implantation is unlikely. In this case one can speculate about osseointegration or formation of adhesion of the material with the native bone.

The use of materials with different properties and characteristics is available only in conditions where these characteristics are demanded the most.

OPMs are the most commonly used grafts for treatment of tumor and tumor-like diseases [1, 15]. However, several types of bone grafting can be used even to manage the same disease. This could be varied based on the lesion size, and localization in the skeleton segments, with allowance for the biomechanical load experienced by a particular region of the musculoskeletal system. Summarizing the above information, we determined two main types of bone grafting materials: voluminous or supporting ones (Fig. 3).

Voluminous bone graft is a graft designed to cover the shortage of bone material in the region not exposed to biomechanical loading in the musculoskeletal system.

Supporting bone graft is a graft focused on the fixation of the supporting bone structures (spine, lower limbs) that experience significant biomechanical stress.

Based on this criterion, we divided the entire range of OPM requirements (criteria) into mandatory and desirable ones. In turn, the mandatory criteria were subdivided into common and differential ones. The mandatory criteria are the ones required for any type of successful bone grafting procedures.

A mandatory differential criterion is the one that allows one to adequately implement selection of the OPM for each specific clinical case. The graft supporting ability was selected as such a criterion.

Desirable criteria are the ones that are not essential but their use could lead to a decrease in the further drug loads in the postoperative period.

In addition, there are unconditional criteria declared by the sanitary standards and GOST (State Standards). The unconditional criteria for materials grafted inside the human body inclde infection safety (negative tests for syphilis, hepatitis B and C, HIV), sterility, non-toxicity, integrity and tightness of packaging, unaltered color, absence of foreign matters in the package.

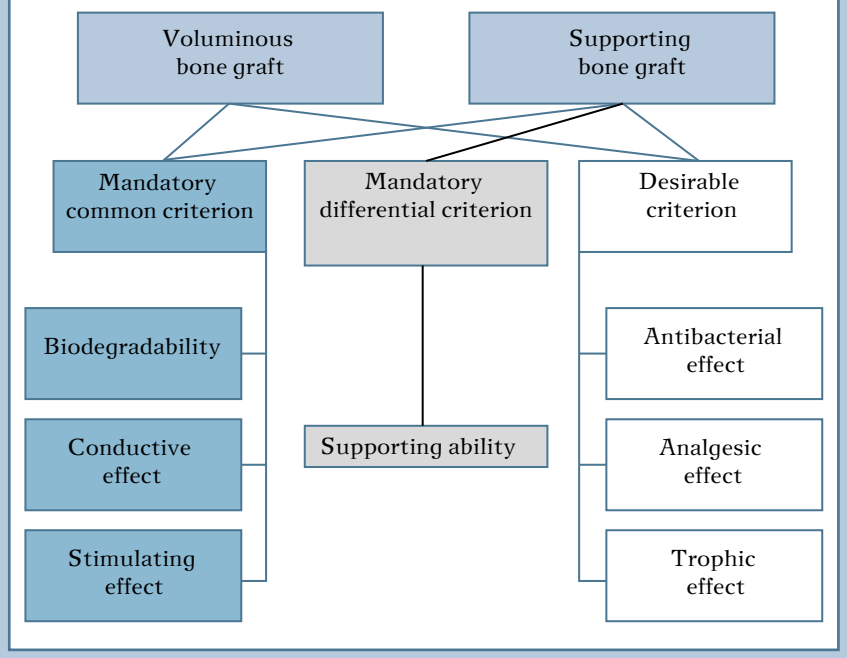

Fig. 3
Types of bone grafting and criteria for selection of osteoplastic materials

Conclusion

Several types of technological processing and variation in size of allografts allow producing materials that induce several mechanisms of reparative regeneration: osteogenesis, osteoconductivity, osteoinductivity, osteostimulation.

Material inducing the ability of the bone for complete regeneration needs to have the chemical composition and architectonic properties identical to those of the bone (at the grafting site), to be easily modeled, resorbable, osteoconductive, osteoinductive, capable of being substituted by organotypic bones, should be loaded with drugs for delivery to the defect zone (antibacterial and analgesic effect).

The criteria for selection of osteoplastic materials, depending on the bone grafting type, allow one to use the differentiated approach to application of these materials in traumatology and orthopedics.

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