




DENTISTRY СТОМАТОЛОГИЯ

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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Modern osteoplastic materials

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Abstract. Relevance. Bone tissue regeneration and the development of methods for directed influence on the processes of bone healing are of the most urgent problems of modern medicine. Defects in the jaw bones are widespread, which in turn leads to the search for modern bone — replacing materials that meet the basic characteristics of the bone. Information was searched based on the PubMed and E-library databases, using the keywords: “bone tissue” AND “bone regeneration” AND “osteoplastic materials” AND “osteoiduction” AND “osteoconduction”. Autologous bone is considered the clinical gold standard and the most effective method of bone regeneration. It is the autograft that has three main characteristics: osteogenicity, osteoinductive and osteoconductive. The autograft has limitations due to the limited amount of bone tissue and the soreness of the donor site. A viable alternative to autologous bone is an allograft. The most widely used allograft is demineralized freeze — dried bone allograft (FDBA). The freeze — drying process promotes damage to osteoblasts, which limits its osteoinductive potential, but it is a profitable alternative in terms of convenience, abundance of choice and absence of pain due to the absence of additional surgical intervention. The main component of xenogeneic materials is collagen, which has the ability to resorb in tissues and stimulate regenerative processes. The material has osteoconductive properties and is capable of bone ingrowth, with the formation of a new bone directly from the xenomaterial bed with the deposition of bone cells on its surface. Subsequently, the xenomaterial undergoes resorption with complete replacement with new bone tissue. Alloplastic materials are fully synthetic materials synthesized from inorganic sources. Alloplastic materials have the property of osteoconduction, and when various growth factors are added to

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their composition, the property of osteoinduction is added to osteoconductive. The clinical use of bone substitutes is limited by their fragility as well as their unpredictable rate of resorption, which render these materials generally less favorable in clinical outcomes. *Conclusion*. Until now, a scientific search for various materials capable of replacing an autogenous transplant is being carried out. At the moment, none of the currently available materials has all the desired characteristics and the choice of materials directly depends on the specific clinical situation in the oral cavity.

Key words: bone tissue, bone regeneration, osteoplastic materials, osteoinduction, osteoconduction

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Introduction

Bone tissue is one of the few body tissues capable of restitution, to complete regeneration with the restoration of the original structure [1]. Bone remodeling entails a genetically determined process in which bone ages or is then lost, replaced by osteoclasts, and replaced by new bone formed by osteoblasts. There is a close relationship between bone formation and resorption to ensure that bones are resistant to changes in bone mass or quality after each remodeling [2].

The problem of bone tissue regeneration and the development of methods for directed influence on the processes of bone healing are one of the most urgent problems of modern medicine [3,4]. Defects of the jaw bones are widespread and can be caused by trauma resulting from the growth of odontogenic cysts, benign tumors, the consequence of osteomyelitis processes, congenital malformations, infections and surgical interventions. Even though bone has a great capacity for self — healing, some defects or

fractures are too large to regenerate. To initiate bone regeneration, bone growth must be induced by a range of bioactive implantable materials, cell types, and intracellular and extracellular molecular signaling pathways. Because mesenchymal stem cells (MSC) and their differentiation during remodeling processes play an important role in bone regeneration, understanding the involved molecular signaling pathways is believed to be critical for the development of bone replacement materials and cell — based scaffolds for bone regeneration [5–7].

The need to create new osteoplastic materials for maxillofacial surgery and surgical dentistry is due to the fact that about 4 million operations are performed annually in the world [8]. Based on this, the choice of osteoplastic materials that satisfy the basic properties of bone tissue becomes relevant.

The modern range of osteoplastic materials for surgical dentistry and maxillofacial surgery is divided into several groups presented by figure1.



Fig.1. Osteoplastic materials used in dentistry

Autogenous materials

An ideal bone graft has three characteristics: osteoinduction — the ability to provide a scaffold for bone regeneration, osteoconduction — the content of growth and regulation factors that produce bone formation, and osteogenic — have cells that promote bone formation [9,10].

Autologous bone or autograft with its inherent osteogenic, osteoinductive and osteoconductive properties is still considered clinically the “gold standard” in bone regeneration, in comparison with other groups of osteoplastic materials. Only autologous bone contains viable osteoblasts and stem cells. Autogenous bone does not contain antigens, which leads to the absence of an immune response. The use of an autograft at the defect site promotes the creation of a bone matrix with the differentiation of local stem cells into bone tissue cells — all this demonstrates the manifestation of a combination of osteoinductive and osteoconductive properties [11–14].

The site of autograft sampling can be both from intraoral sites — maxillary tubercle, retromolar area, oblique branch of the lower jaw, and extraoral sites — rib and iliac crest [15].

However, the limited amount of bone and tenderness of the donor site are the most important dis-

advantages of autotransplantation. In view of these shortcomings, improved biomaterials are needed to match the characteristics of the autograft, as it continues to outperform other groups of bone materials [16, 17].

Allogeneic materials

Advances in allografts over the past decades have contributed to the creation of viable alternatives that allow them to be equated with autografts. The most widely used allograft is the demineralized freeze — dried bone allograft (FDBA), which is freeze — dried during manufacture to reduce its antigenicity. Lyophilization is a stabilizing process in which the substance is first frozen and then the amount of solvent is reduced first by sublimation (primary drying) and then by desorption (secondary drying) [18].

However, osteoblasts are damaged during this process, which limits its osteoinductive capacity and participation in the process of osteogenesis. Due to the inevitable immune response associated with FDBA, the period of integration with surrounding tissues is longer than that of autologous bone material [19].

Bone allograft is a beneficial alternative to autograft in terms of convenience, abundance, and absence of pain in patients associated with additional surgery at the donor site. Variants of allografts include structural shape, particle shape, and demineralized bone matrix. Commonly used allografts include synthetic calcium sulfate/phosphate materials — these grafts provide their osteoconductive properties. In addition, various growth factors, including bone morphogenetic proteins released during the demineralization process, can accelerate the healing process of bone defects [20–23].

Xenogeneic materials

Another area of research is the search for xenogeneic materials that satisfy the basic properties of bone tissue. As previously described, autografts and allografts have inherent limitations despite their excellent success rates in bone grafting practice. Therefore, natural bone substitutes have been developed to stimulate the improvement of osteogenic, osteoconductive

and osteoinductive potentials by creating a favorable microenvironment for bone growth. Xenografts are materials obtained from a genetically unrelated species, in particular, deproteinized bovine bone is a common source of materials for xenografts in dentistry [24].

One of the groups of xenogeneic materials is the materials whose main basis is collagen. Collagen is synthesized by fibroplastic cells. Of all the types of collagens, it is type 1 collagen that is used to interact with the bone. Collagen materials have the ability to be resorbed in tissues and stimulate regeneration processes.

Materials based on collagen have been successfully used in medical practice since the second half of the 20th century [25].

Collagen materials have the ability to be resorbed in tissues and stimulate regenerative processes, including bone. In the process of deep cleaning of the matrix, natural collagen is preserved, which is a supporting protein that provides physiological bone regeneration. However, the negative property of collagen materials is their immunogenicity, which, as already emphasized earlier, increases the period of integration with surrounding tissues.

Another group of xenogeneic osteoplastic materials is deproteinized materials, which are the mineral component of the bone, completely purified from all organic elements. Most often, xenogeneic materials from bovine bone are used, which have undergone special processing, as a result of which there is a decrease in immunogenicity and the likelihood of rejection of the material in the body. The material has osteoconductive properties and is capable of bone ingrowth, with the formation of a new bone directly from the xenomaterial bed with the deposition of bone cells on its surface. Subsequently, the xenomaterial undergoes resorption with complete replacement by new bone tissue [26–30].

Alloplastic materials

Alloplastic materials belong to the group of fully synthetic materials synthesized from inorganic sources. Materials that include calcium or phosphate, or a combination of them, are the main synthetic materials,

because they are the chemical constituents of natural bone and are known to promote bone regeneration, although they do not necessarily resemble its natural structure. Alloplastic materials are osteoconductors and differ in the degree of dissociation.

Since the regenerative abilities of alloplastic materials are weak, they are often used with vascular endothelial growth factors that have the ability to induce human endothelial cells and neoangiogenesis, as well as with ions of micro — and macroelements that affect the regenerative potential, as a result of which an osteoinductive property is added to the property of osteoconductive [31–34].

Synthetic alloplastic materials have varying degrees of dissociation and resorption, which are inextricably linked with the formation of interstitial fluid and osteoclast activity. Materials having low dissociation and resorption include some preparations of synthetic hydroxyapatite. Highly dissociated materials include TCP and sulfates; studies indicate a high degree of metabolic activity of these substances [35].

The general advantages of alloplastic bone materials are the standardized quality of the product, the absence of the risk of infectious diseases compared to allogeneic and xenogeneic bone grafts. Also, the advantages of alloplastic materials lie in their biological stability and volume maintenance, which ensures bone remodeling. Synthetic alloplastic materials based on calcium sulfate, calcium phosphate, bioactive glass, and combinations thereof are the most common synthetic bone substitutes currently available. They are of particular interest because they are similar in composition to native bone. The use of calcium phosphate — based materials has received little attention for bone applications due to its biocompatibility, biodegradability, and similarity in structure to the inorganic composition of bone minerals. Materials based on hydroxyapatite, beta — tricalcium phosphate and their combinations have demonstrated the ability to partially integrate into natural bone tissue. Based on the fact that hydroxyapatite is the main mineral of bone tissue, it exhibits osteoconductive ability when implanted into a bone defect, stimulates osteoblast differentiation, osteoblast growth, and inorganic matrix deposition.

However, the clinical use of bone substitutes is limited by their fragility compared to bone, as well as their unpredictable rate of absorption and the inability to maintain defect volume, making these materials generally less favorable clinical outcomes. Thus, new bone tissue cannot withstand the mechanical load compared to natural bone, and such biomaterials are mainly used and used to fill bone cavities with low load [36–38].

Combined materials with growth factors and morphogens

Among the bone graft materials that are not part of the general classification, numerous studies have developed combined materials with the addition of growth factors and various substances that enhance osteoinductive properties. Due to the fact that autograft remains the gold standard and other materials have their own advantages and disadvantages, and mostly possess osteoconductive properties, the search for the most effective bone graft material remains a relevant problem.

One direction in bone engineering is the creation of various carriers for placing factors that promote bone tissue induction. In particular, the use of VEGF and BMPs is a promising direction.

VEGF — vascular endothelial growth factor regenerates bone tissue by influencing osteogenesis processes, stimulating angiogenesis. BMPs — bone morphogenetic proteins regulate the growth and differentiation of cells, particularly osteoblasts. So, let's examine each of the factors in more detail.

BMPs are extracellular multifunctional signaling cytokines and members of the TGF- β superfamily, which are powerful growth factors that influence bone formation. These pleiotropic growth factors play a crucial role in bone formation and remodeling. The use of BMPs has become clinically accessible for enhanced bone regeneration and predictable results in complex cases. They are one of the potential growth factors inducing osteogenic differentiation and bone formation. Based on studies of osteogenic mechanisms in fracture models, it has been proven

that growth factors and cytokines interact with BMPs to participate in its recovery. All of this serves as the basis for incorporating BMPs into synthetic bone graft materials, which serve as a delivery platform for BMPs to the site of bone defects, ensuring prolonged release of target molecules throughout the remodeling period [39, 40].

VEGF plays a key role in the early stages of osteogenesis and a significant role in the mechanisms underlying skeletal growth and recovery. The pro-angiogenic activity of VEGF affects endothelial cells, promoting increased vessel permeability and cell migration. The interaction of VEGF with BMPs initiates the mechanism of bone tissue repair by stimulating osteogenic processes, increasing cell migration, and inducing angiogenesis [41–44].

In a study by Senatov F. et al. (2022), scaffolds were recreated with the inclusion of recombinant BMP-2 and erythropoietin, followed by studying their properties *in vivo* on a model of critical-sized cranial defects in mice. The study demonstrated that the introduction of BMP-2 leads to the induction of new bone formation. The introduction of erythropoietin leads to enhanced angiogenesis in the implantation area of the scaffold. Thus, scaffolds with recombinant proteins can be used as bone implants for the reconstruction of bone defects [45].

In another study by Vasyliiev A.M. et al. (2019), the biocompatibility and osteoinductive properties of a hydrogel based on highly purified collagen and fibronectin, impregnated with BMP-2, were demonstrated. *In vitro* cultures of human mesenchymal stem cells (MSC) using PCR and *in vivo* ectopic osteogenesis models in male Wistar rats showed that the minimum effective dose of BMP-2 is 10 $\mu\text{g/ml}$. Analysis of cytotoxicity on MSC cell cultures showed high cytocompatibility of the material *in vitro*. The absence of inflammation on subcutaneous injection of the material to rats also indicated high biocompatible properties of the material *in vivo*. The collagen-fibronectin hydrogel containing BMP-2 showed pronounced osteogenic properties and by the end of 28 days was replaced by newly formed bone tissue by $8 \pm 4\%$ of its volume when subcutaneously implanted in the area of the

withers, by 17 ± 10 % when intramuscularly implanted in the triceps muscle of the thigh, and by 26 ± 11 % when intracortically implanted in the area of critical defects of the temporal bones. The optimal combination of biocompatibility and osteogenic properties of the collagen-fibronectin hydrogel impregnated with BMP-2 allows considering this material as a promising basis for creating new generation bone graft materials in dentistry [46].

Regarding VEGF, Zha Y. et al. (2021) developed a cell-free tissue engineering system using functional exosomes. Gene-activated engineered exosomes were used to encapsulate the VEGF gene. The results of this study showed that the constructed exosomes play a dual role as an osteogenic matrix inducing osteogenic differentiation of MSC and as a gene vector for controlled release of the VEGF gene for remodeling the vascular system. Under natural conditions, evaluation also confirmed that constructed bone scaffolds mediated by exosomes can effectively induce a large part of vascularized bone regeneration. The authors demonstrated a new bone restoration technology using exosomes that provide vascularized bone restoration for segmental bone defects [47].

Equally promising is the development of materials based on various biocomposites for creating advanced bone graft materials. Creating biocomposite bone graft materials in dentistry is one of the most promising areas in the development of modern medicine. Biocomposites have high biocompatibility, which helps to avoid the risk of allergic reactions and other complications.

In an article by Profeta A.C. et al. (2016), the use of bioactive glass in maxillofacial surgery is discussed. The potential benefits of using bioactive glass in bone regeneration, wound healing, and implant coatings are emphasized. The authors suggest that bioactive glass could become a valuable alternative to traditional materials in this field [48].

In another article, Apanasevich V. et al. (2020) investigated the potential of a synthetic biocomposite CaSiO₃/HAp, made from calcium silicate and hydroxyapatite powder, for bone regeneration. The authors conducted a study to assess the morphological characteristics of the biocomposite and its ability to

support osteoplastic activity. The results showed that the biocomposite has a porous structure, which is favorable for bone regeneration as it provides cellular infiltration and vascularization. Additionally, the biocomposite demonstrated good osteoconductivity, meaning it supports the growth of new bone tissue.

The authors concluded that the synthetic powder biocomposite CaSiO₃/HAp has potential for use in maxillofacial surgery, especially in cases where traditional materials may not be suitable [49].

In another study by Dunaev M.V. et al. (2014), a comparative analysis and clinical experience of using osteoplastic materials based on non-demineralized bone collagen and artificial hydroxyapatite for closing bone defects was described.

The study revealed that the use of both types of materials allows for effective closure of bone defects. However, the use of materials based on non-demineralized bone collagen showed higher effectiveness in bone tissue regeneration. It was also noted that the use of osteoplastic materials based on non-demineralized bone collagen does not cause negative reactions from the body, making it more preferable for surgical interventions.

Thus, the use of osteoplastic materials based on non-demineralized bone collagen is an effective method for bone tissue regeneration when closing bone defects [50].

The saturation of bone grafting materials with VEGF in combination with BMPs, as well as the creation of composite bone grafting biocomposite materials, can significantly modulate the processes of reparative bone tissue regeneration, allowing for the development of tissue engineering in recreating and using combined bone grafting materials.

Conclusion

Tissue engineering of bone continues to develop steadily. A vast number of materials have shown excellent results in the restoration of bone defects, but each material group has its own advantages and disadvantages, as presented in Table.

Comparative characteristics of osteoplastic materials

Material	Definition	Advantages	Disadvantages	Examples	References
Autogenous bone	Patient's own bone	Excellent biocompatibility, contains live osteoblasts and bone stem cells. There are no antigenic proteins	An additional operation is required, causing pain in the postoperative period. There may be complications	Cortical or cancellous bone	[12, 13, 17]
Allogeneic bone	A transplant taken from a genetically different member of the same species	Presence of growth factors, including bone morphogenetic proteins. No additional operation	Immune response. Long period of integration with surrounding tissues	Cortical or spongy bone of a corpse. FDBA	[19, 20, 22]
Xenogeneic bone	Transplants derived from animals (particularly cattle)	Large volume of material, bone conduction	High antigenicity	Bio – Oss	[24, 27, 29]
Alloplastic (synthetic) bone	Synthetic materials from inorganic sources	Wide choice, similar in composition to native bone. biological stability	Brittleness, unpredictable absorption rate	Calcium sulfate, calcium phosphate, TCP, synthetic hydroxyapatite, etc.	[32, 33, 36]

Currently, there is an active direction in the recreation of completely new bone graft materials that include growth factors and morphogens in their composition, which promote bone tissue induction. Additionally, the creation of biocomposite materials is also a promising direction in bone engineering. At present, there is no perfect option for bone graft material, and its selection depends directly on specific conditions, factors, and clinical situations in the oral cavity.

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Современные костнопластические материалы

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Аннотация. Регенерация костной ткани и разработка методов направленного воздействия на процессы заживления костей являются актуальными проблемами современной медицины. Дефекты челюстных костей широко распространены, что, в свою очередь, обуславливает поиск современных костнозамещающих материалов, отвечающих основным характеристикам кости. Поиск информации проводили на основе баз данных PubMed и E-library по ключевым словам: «bone tissue» AND «bone regeneration» AND «osteoplastic materials» AND «osteoinduction» AND «osteoconduction». Анализ литературных данных показал, что аутологичная кость считается клинически золотым стандартом и наиболее эффективным методом костной регенерации. Именно аутотрансплантату присущи три основных характеристики: остеогенность, остеоиндуктивность и остеокондуктивность. Аутотрансплантат имеет недостатки в связи с ограниченным количеством костной ткани и болезненностью донорского участка. Жизнеспособной альтернативой аутологичной кости является аллотрансплантат. Наиболее широко используемым аллотрансплантатом является деминерализованный лиофилизированный костный аллотрансплантат (ДЛКА). Процесс лиофилизации способствует повреждению остеобластов, что ограничивает его остеоиндуктивный потенциал, однако именно он является выгодной альтернативой по удобству, обилию выбора и отсутствия болезненности после дополнительного оперативного вмешательства. Основной составляющей ксеногенных материалов является коллаген, обладающий способностью резорбироваться в тканях и стимулировать регенеративные процессы. Материал обладает остеокондуктивными свойствами, и способен к костному прорастанию, с образованием новой кости непосредственно от ложа ксеноматериала с отложением на его поверхности костных клеток. В дальнейшем ксеноматериал подвергается рассасыванию с полным замещением новой костной тканью. Аллопластические материалы полностью синтетические материалы, синтезируемые из неорганических источников. Аллопластические материалы обладают свойством остеокондукции, а при внесении в их состав различных факторов роста к остеокондуктивности присоединяется свойство остеиндукции. Клиническое применение костных заменителей ограничено их хрупкостью, а также их непредсказуемой скоростью резорбции, что наделяет эти материалы в целом менее благоприятными клиническими результатами. **Выводы.** До сих пор проводится научный поиск различных материалов, способных по своим характеристикам заменить аутогенный трансплантат. На данный момент ни один из доступных в настоящее время материалов не обладает всеми желательными характеристиками, и выбор материала напрямую зависит от конкретной клинической ситуации в полости рта.

Ключевые слова: костная ткань, костная регенерация, костнопластические материалы, остеиндукция, остеокондукция

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