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HYDROXYAPATITE AS A MATERIAL FOR TRANSPLANTOLOGY: CLINICAL EXPERIENCE AND PROSPECTS OF APPLICATION

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The centrepiece of this analytical review is the metabolism of hydroxyapatite in its natural, bone, and synthetic forms, where the mitochondria-mediated mechanism may serve as the leading mechanism. The possibility that osteoblast mitochondria play an important role in the initial stages of bone mineralisation is discussed. Furthermore, the paper highlights the key role of mitochondria in the metabolism of synthetic hydroxyapatite. Differences between the results of *in vivo* and *in vitro* studies using synthetic hydroxyapatite of different morphologies are also detailed. It is noted that long-term infiltration with immune cells and *in vivo* studies are necessary to adequately evaluate hydroxyapatite as a bone-plastic material. Particular attention is given to the interaction of hydroxyapatite with immune cells and its ability to affect the ribosomes and mitochondria of cells. Due to its mechanical properties, scalability, and potential use for the treatment of extensive bone defects of tumor origin, hydroxyapatite is a promising material. This study also highlights the importance of further development of *in vitro* research methods in the context of their biomimeticity. Overall, this work offers a theoretical direction for future studies of hydroxyapatite as a bone grafting material and emphasises the value of *in vivo* studies.

Keywords: hydroxyapatite, bone grafting, nanoparticles, immune response, mitochondria.

INTRODUCTION

The basis of modern medical technologies aimed at bone tissue regeneration is the widespread use of grafts, the main component of which is hydroxyapatite. The diversity of grafts and their constituent materials used is an equal reflection of the extremely large variety of pathological conditions of bone tissue requiring the application of regenerative medicine technologies.

At the same time, the use of any grafts requires preliminary detailed analysis of the immune response in response to the introduction of this or that material. In this context, the unique properties of such materials as hydroxyapatites and their compositions [1, 2], including exceptional phenomena in the context of immune response [3–5], become extremely important. In this regard, there is a need for a more detailed presentation of hydroxyapatites and their compositions as the main components for the fabrication of grafts to restore structural and functional pathologies of bone tissue.

NATIVE FORM OF HYDROXYAPATITE: DESCRIPTION OF STRUCTURE AND FUNCTIONS IN THE BODY

First of all, it is necessary to note the fact that hydroxyapatite is the native form of bone tissue calcium and occupies 70–90% of the bone tissue matrix volume. In bone tissue, hydroxyapatite is represented in the form of crystals of small size and is characterized by the stoichiometric formula $Ca_{10}(PO_4)_6(OH)_2$ [6]. According to the age of a person, three main ranges of their average size are distinguished: up to 6 six years of age, 188–215 nanometers; between 6–19 years of age, 232–252 nanometers; and in adulthood, 252–283 nanometers [7]. Together with collagen I, which occupies up to 90% of the organic phase of bone, it forms the spectrum of the main structural and functional features of bone tissue [8].

The initial onset of mineral component formation in bone tissue is ensured by the energy-dependent transport of Ca^{2+} ions and PO_4^{3-} anions into the mitochondria of osteoblasts (Fig.). Upon reaching the solubility threshold, micropackages of amorphous calcium phosphate or Posner clusters with the proposed formula $Ca_9(PO_4)_6$ are precipitated; these are thought to be stabilized by an organic component represented by acidic non-collagenous proteins, including osteocalcin, osteopontin, and bone sialoprotein. Further release of amorphous calcium phosphate may occur via two pathways: direct transport across the mitochondrial membrane or reverse phagocytosis [9].

At the initial stage, the vesicular contents form shapeless accumulations of calcium phosphate in close association with collagen fibers. During subsequent ion diffusion, nascent hydroxyapatite platelets are formed, which, upon contact with one another, lead to a marked increase in the degree of crystallinity [10]. As a result, partially under the influence of non-collagenous proteins [11–13], lamellar structures 2–4 nm in thickness are formed, with their longitudinal axis oriented parallel to the axis of collagen fibrils (Fig.) [6].

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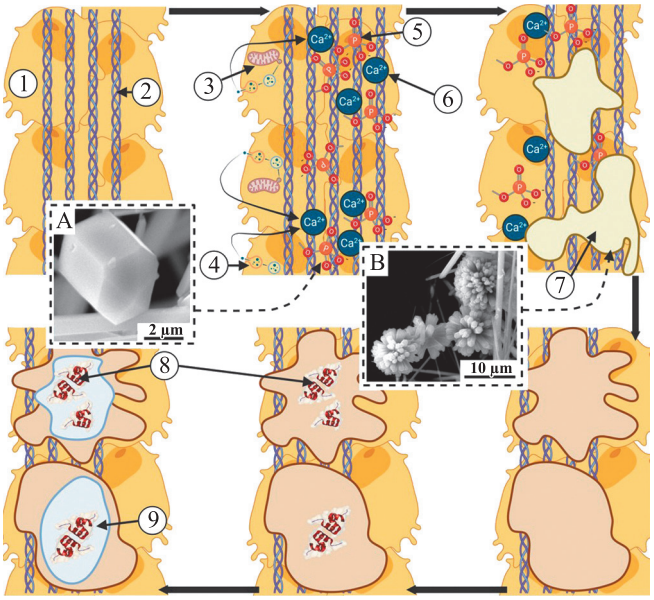


Fig. Scheme of the stages of collagen fibril calcification

Collagen fibrils act as an organizing component in the formation of growth centers of hydroxyapatite crystals [9, 15]. The initiation of hydroxyapatite crystals formation depends on amino acid patterns, in particular, the triplet of amino acids glycine-proline-hydroxyproline, which is the dominant motif of tropocollagen. This process is caused by the formation of ionic bonds between calcium atoms, oxygen atoms of carbonyl groups of the polypeptide backbone, and side chains of proline and hydroxyproline [16]. If we consider a quasi-hexagonal model, lysine at position 108, glutamic acid at positions 110, 116, 582, and 815, and arginine at positions 350, 581, and 816 form a stereochemical pocket for optimal binding of calcium ions and phosphate ions [9]. The functionality of non-collagen proteins is largely due to the effect of osteocalcin. This protein plays a guiding role in the process of intrafibrillar appearance of hydroxyapatite crystals in type I collagen fibrils [17, 18].

As a rule, bone tissue hydroxyapatite is carbonated with carbonate to some extent. The normal range of carbonate substitution is 2–9% [19]. Substitution by carbonate ions occurs at the positions of phosphate ions $(PO_4)^{3-}$ (major B-type substitution) and hydroxyl groups OH^- (minor A-type substitution), thereby provoking a change in crystal structure and molar Ca/P ratio [19, 20]. In the case of hydroxyl ion substitution, which is characteristic of bone apatite, a state of hydroxyl deficiency is formed, which has different degrees of severity depending on the type of bone tissue [21]. Subsequently, it increases the solubility of bone material [22].

As a consequence of this substitution, the mineral component of bone plays the role of the main depot of calcium, phosphorus, magnesium and a number of other mineral elements; this process has a high regulatory potential for the metabolism of these elements in the whole organism [23, 19]. It is quite obvious that substitution by the mentioned elements affects numerous parameters of the crystal lattice. Iron and strontium have a positive effect on the dimensional characteristics of its individual elements, while zinc and magnesium have the opposite effect. For magnesium, zinc, and iron, a negative effect on the crystallinity of hydroxyapatite was revealed, for strontium – positive [23]. It is also noteworthy that the indicated effect of changing the crystalline microstructure of the mineral component demonstrates a striking heterogeneity in the composition of a single bone [24]. Relatively high strontium content is characteristic of regions with high metabolic activity and newly formed bone structures [25].

The most regular pattern of heterogeneity is the difference of surface and inner layers of hydroxyapatite. The surface layer is in the form of hydrated amorphous calcium phosphate 0.8 [19] or 1–2 nanometers thick [26] and a more crystallized core [19]. Hydroxyapatite is characterized by an extremely flexible microcrystalline structure, suggesting an extremely broad list of elements suitable as substituents. This may account for a wider and more localized range of possible biological properties of native bone hydroxyapatite.

The fundamental reason for the structural strength and high resistance to ionic substituents is the hexagonal organization of hydroxyapatite [19]. However, in some cases, the loss of hexagonal structure and formation of monoclinic organization of the crystal lattice is possible [19], which largely depends on the degree of substitution of chlorine anion Cl^- [27]. Changes in the organization of the crystal lattice of hydroxyapatite are also possible as a result of age-related changes [28]. The observed liability has prompted a search for other constituents of the inorganic phase, such as tricalcium phosphate, dicalcium phosphate dihydrate [19] and octacalcium phosphate [29]. For the latter, no direct evidence has been shown for its presence in bone structure [19], except in pathological conditions [27] under relatively low pH conditions. However, there are studies that confirm the presence of a fixable amount of octacalcium phosphate in bone tissue under normal conditions [10].

As for the higher-level organization of the mineral component of bone tissue, the formation of lamellar structures of hydroxyapatite is generally accepted [19]. Spirally twisted needle-like crystals of apatite, located within and between collagen fibrils [30, 10], merge laterally and are organized in the form of spiral subplates along the loading axis. The defined chiral structure of the latter is the basis for tertiary helical plates. The further formation of the mineral base ordered in time and space with the formation of collagen structures results in a multilevel architecture of the inorganic component of bone [30]. The results of modern studies of the dimen-

sional parameters of each level of organization of the inorganic component of bone are presented in Table.

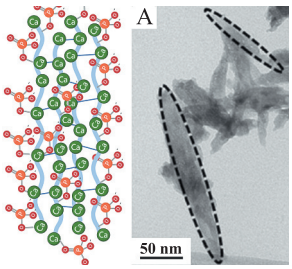
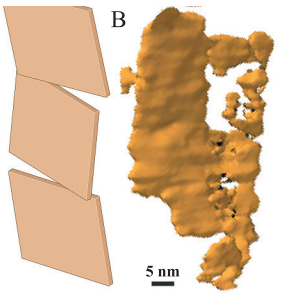
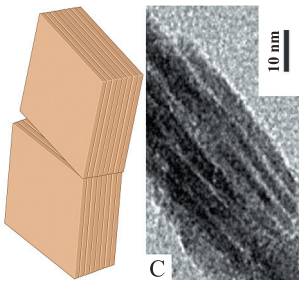
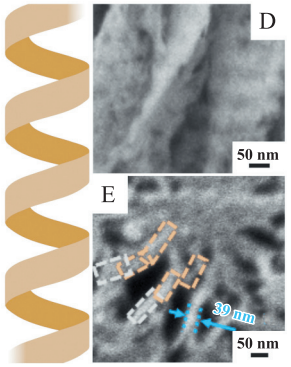
Having analyzed a number of scientific studies of structural, physicochemical and physiological properties of the mineral component of bone tissue, we aim to emphasize the fundamental role of native hydroxyapatite on the scale of the whole organism, defining it as the most valuable and convenient material in bone grafting. The spectrum of features of native hydroxyapatite presented in this section, beginning with the stoichiometric flexibility of the crystal lattice and ending with the complex process of its formation in the living organism, dictates completely new requirements for synthetic analogs of bone hydroxyapatite as a transplantation material. Among them, the multilevel character of the organization, formed in close interaction with the organic component, including the cellular environment, stands out.

HYDROXYAPATITE AS A BONE GRAFTING MATERIAL

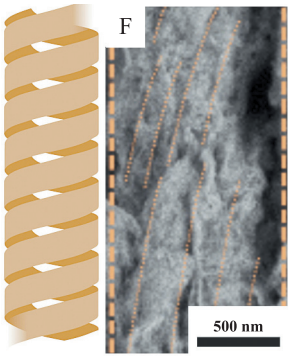
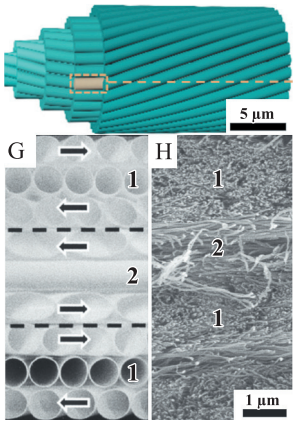
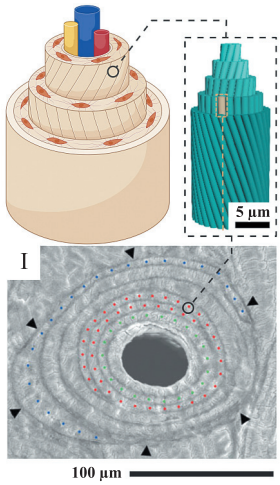
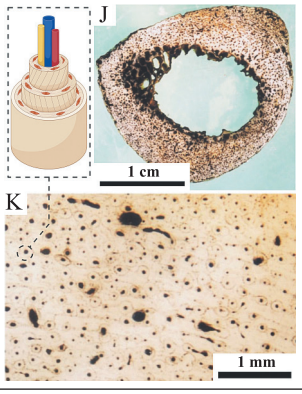
The generally recognized «gold standard» in bone grafting is the use of autologous bone material. Autologous bone grafting has been successfully used in clinical practice for a century [35, 36]. This necessitates a comprehensive analysis of the main advantages of using this method in order to form a kind of reference heuristic model in the development and improvement of alternative sources of material for bone grafting.

Table

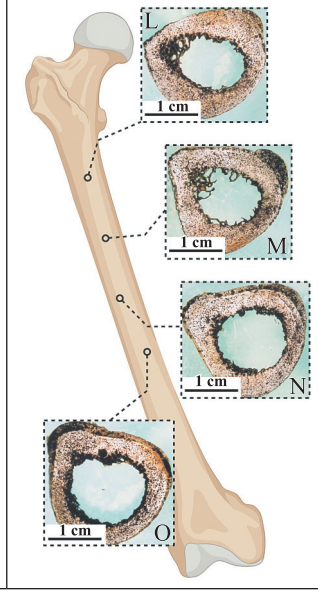
Hierarchy of bone tissue mineral component organization

Hierarchy		Morphology	Size	Step length and chirality
Needle crystal		Thin, twisted long ribbon	Thickness ~5 nm Width 5 to 10 nm Length 50–100 nm	~1.5 μm right-handed
Subplate		Needle-shaped crystal merging laterally at an angle	Thickness 5 nm Width 20 to 60 nm Length 50–100 nm	~4.7 μm left-handed
Plate		Twisted mineral laminae composed of subplates	Thickness 20–40 nm Width 60–150 nm Length 50–100 nm	~4.6 μm left-handed
Mineral fibrils		Mineral plates spirally merge at an angle	Width 60–150 nm Length: Micron level	~2.9 μm right-hand side

Continuation of Table

Hierarchy		Morphology	Size	Step length and chirality
Bundles of mineral fibrils		Mineral fibrils spirally merge at an angle	Diameter 1–2 microns Length: Micron level	Coils: 4.2–6.5 μm right-handed
Lamellar units		The fibril bundles are rotationally stacked layer by layer	Diameter 6–12 microns	Coils: 48–653 μm, left/right; Stacking: ~47.6 μm, right-handed
Haver's canals		Lamellar units are spirally twisted around the blood vessel in the form of coaxial cylinders	Diameter 100–300 microns	Coils: 617–5,167 μm, right/left-handed; Stacking: ~184 μm, right-handed
Compact bone		The haversack channels are laid in layers in a circular pattern	Thickness ~3 mm	Coils: 13.5–119.4 cm, right/left-handed; Stacking: ~9.7 mm, left-handed

End of Table

Hierarchy		Morphology	Size	Step length and chirality
Solid bone		Anatomical shape with curve	Diameter ~3 cm	Left-handed

Notes. A – transmission electron micrograph of Mg^{2+}-doped needle microcrystal (adapted from [31]); B – model of a crowded mineral subplate formed by lateral fusion of needle microcrystals; C – transmission electron micrograph of twisted mineral plates, showing the stacking of subplates; D – scanning electron micrograph of spiral mineral fibrils, cross section; E – scanning electron micrograph of spiral mineral fibrils from a lateral perspective; F – scanning electron micrograph of spiral bundles of mineral fibrils from a side view (model and micrographs adapted from [30]); G – model of twisted plywood showing the ratio of transverse and longitudinal lamellae; H – scanning electron micrograph showing the alternation of transverse lamellae (1) and longitudinal lamellae (2) (model image and micrograph adapted from [32]); I – scanning electron micrograph showing the structure of the lamellar system: red dots display a closed ring structure; green dots display a spiral organization and overlap after a 360⁰ turn; blue dots form a sickle moon structure and display an incomplete ring (adapted from [33]). J and K – cross section of the right femur at a distance of 14 centimeters from the proximal end; L – cross section of a horse femur stained with mercury sulfide, showing the arrangement of osteons in the repeat sheets of the capillary network; M – cross section of the right femur at a distance of 19 centimeters from the proximal end; N – cross section of the right femur at a distance of 23 centimeters from the proximal end; O – cross section of the right femur at a distance of 25 centimeters from the proximal end (photographs and microphotographs adapted from [34]).

There is also a clear need to analyze the main problems of using autografts in order to use them in the formation of alternative solutions.

Starting from the reference value of bone autografts, we should define the attributes of an «ideal graft». First, it should possess the properties of autogenous bone, which include biocompatibility, osteoconductivity, and osteoinductivity. Second, the graft material should be easy to use, safe, and cost-effective [35].

The key conditions for successful bone tissue regeneration formulated in the «diamond concept» are worth mentioning from the generally accepted positions. Its essence is that successful healing of bone defects requires the presence of viable osteogenic cells or their precursors, a suitable connective tissue matrix, adequate vascularization, and a time- and space-specific profile of growth factors [37].

In this context, it is necessary to emphasize the main properties and the distribution spectrum of their values for bone grafts used in clinical practice:

1. The range of values of the structural parameter of the bone implant. Bone grafts have different ability to withstand mechanical loading. For unmodified grafts based on cortical bone, a relatively high resistance to mechanical loads is shown in comparison with grafts based on cancellous bone. Thus, the mechanical properties of bone grafts without additional modification directly depend on the properties of the donor site [38].
2. Spectrum of osteogenic properties. The ability of the graft to initiate neoosteogenesis [39] due to the preserved pool of graft cells including osteoblast precursors [40] is extremely important. Due to the presence of cellular elements, necessary growth factors and matrix framework, such a graft is able to modulate angiogenesis, adequate perfusion [41, 42] and activity of progenitor cells [43].
3. Osteoinductive properties. Autologous graft is characterized by the presence of an exhaustive set of growth factors necessary for regeneration, providing proliferative and differentiative potential of progenitor cells [44–46].

4. Osteoconductive properties. Ability to provide an optimal environment for normal metabolism, proliferation and differentiation of cell populations [47].

The material for autologous bone graft can be spongy or cortical bone. The advantage of the former is relatively high osteoconductive properties due to a significant concentration of osteogenic cells and growth factors. The main disadvantage of this type of graft is its low ability to provide structural support at the early stages of graft integration [35].

It should also be noted that despite all its undeniable advantages over alternative bone grafting strategies, the methodology of graft isolation continues to improve. A prime example of this is the use of femoral medullary bone chips obtained using the Reamer Irrigator Aspirator System (RIA – Synthes®, Inc. West Chester, USA) [48]. With equivalent rates of graft integration compared to traditional iliac crest harvesting, this method demonstrates a lower risk of chronic pain, infection, and excludes damage to the lateral cutaneous nerve of the femur as a result of compression or contusion [49]. However, the risk of complications such as cortical bone perforation and subsequent bleeding is still high [50].

Against this background, it should be emphasized that the autogenous cortical bone graft is also characterized to a greater extent by osteoconductive properties under the condition of lower biological activity compared to the spongy autologous graft. The next problem is the high duration of revascularization [51, 35]. For this reason, vascularized cortical grafting material that provides osteogenic and osteoconductive properties can be used [35]. In this direction, there is also a continuous development of strategies for the allocation of transplant material that ensure a reduction in the risks of donor site pathologies while maintaining the necessary integrative parameters [52]. However, the development of technologies takes place not only within the framework of improving the techniques of obtaining one or another type of autologous grafts separately. Of particular importance are the works in the direction of optimal combination of the presented types of transplant materials, which allows obtaining positive results, including in their clinical use [53, 54].

Despite the benchmarks of autologous bone grafting material in the context of its osteogenic, osteoconductive, and osteoinductive properties, the number and variety of studies aimed at finding alternative strategies for graft preparation continue to grow. This is due to the fundamental disadvantages of all methods of obtaining autologous graft material: firstly, the limited volume of potential graft material [55, 56]; secondly, the possibility of developing complications of the donor bone site [49, 50]. Moreover, when taking autologous grafting material, the risk of bleeding increases, which still remains one of the main problems, including when using the latest methods of bone implant obtaining [50]. Thus, there are studies that confirm a significant incidence of complications both after traditional grafting from the anterior and posterior iliac crest (19.37%) and after using the Reamer Irrigator Aspirator system (6%). The general list of complications included the development of infection, hematoma, seroma, chronic pain, fracture, as well as vascular and nerve damage [50]. In a study conducted by A.J. Suda et al. it was shown that the volume of the removed transplant material has a great influence on the risk of serious complications [57]. Thus, we can say that the main limitation of autologous bone transplantation is the small volume of potential grafting material.

In this context, the development of a number of alternative methods for obtaining transplantation material is extremely important. This series includes obtaining allogenic [58–60] and xenogenic transplantation material of natural origin [61, 59], as well as the creation of new biomimetic transplantation materials of artificial and bioengineered origin [59, 62, 63].

NATIVE SUBSTITUTES FOR AUTOLOGOUS BONE GRAFTING MATERIAL: ALLOGENEIC AND XENOGENEIC BONE GRAFTS

Functionally, the closest of all the listed alternative methods is allogeneic grafting material. The main advantage of this material is its relatively high availability [64]. Therefore, it has been used in clinical practice for reconstruction of extensive bone injuries for many years. Like autogenous graft, allogeneic graft material has a high degree of similarity to the structure of native bone: it has similar mechanical properties, is biocompatible to a certain extent, and ultimately has osteoinductive and osteoconductive properties [60], which are limited [65], probably due to the need for decellularization of the graft material [60]. As noted by some authors, the key problems of this method are the lack of unified decellularization protocols and the potential risk of infectious disease transmission [65].

In addition, the choice of a specific decellularization and delipidization strategy represents a critical factor determining both the biological and clinical performance of allogeneic bone grafts. The use of chemical reagents required for effective removal of cellular and lipid components may be associated with cytotoxicity, thereby necessitating rigorous control and complete elimination of residual agents from the graft structure [60, 65]. Moreover, aggressive processing procedures inevitably result in partial loss or degradation of biologically active matrix components, which may contribute to the reduced osteoinductive and osteogenic properties of decellularized allogeneic materials observed in clinical practice [65].

Conventionally, allogeneic bone grafts can be divided into two main groups. The first group includes various variations of allogeneic bone graft proper – decellularized bone graft of donor origin of one type. The second

group includes demineralized bone matrices obtained by acid treatment of allogeneic bone graft in order to isolate bone collagen matrix [66]. It is important to note that there is an extremely wide range of methodological solutions to obtain allogeneic [67–69]. This, on the one hand, creates the problem of forming a unified protocol for wide implementation in clinical practice. On the other hand, it gives grounds for a personalized approach, which is actively used in clinical practice.

At the same time, demineralized bone matrix is an allogeneic bone material that was modified in accordance with the general provisions of the Marshall Urist technique [66]. It should be noted that this method, which has already become traditional, has undergone a significant number of modifications since its first use [70]. For example, the preparation of commercial demineralized bone matrix has wide limits of variability among different manufacturers, including the use of different acid solutions, changes in the duration of demineralization, different temperature regimes and methods of decontamination [71, 70].

In comparison with autologous grafts, allogeneic transplant material demonstrates some characteristic features. The common property, which directly depends on the main stage of obtaining all allogeneic grafts – decellularization, is the absence of pronounced osteogenic properties [66, 72]. Nevertheless, according to the «diamond concept» [37], allogeneic bone grafting material has high osteoconductive and osteoinductive properties.

A certain degree of bone allograft effectiveness in clinical practice is largely due to its osteoconductive properties and high value of mechanical support [66] in bone injuries requiring a large volume of grafting material [73, 74]. As in autologous transplantation, the most pronounced osteoconductive properties are characteristic of the allograft of carcellous bone [35]. The variability of the content of osteoconductive agents in the final graft material is largely due to the duration of storage and preparation conditions [38, 75]. Alongside storage duration and preparation conditions, the decellularization process represents an important source of variability in the content of osteoconductive agents. The choice of decellularization methodology directly affects the degree of preservation of extracellular matrix components, including those responsible for osteoconductive properties. Consequently, differences in decellularization protocols may lead to partial loss of biologically active matrix constituents, further contributing to the heterogeneity of functional properties observed in allogeneic bone grafts [60, 65].

Taking into account the facts stated in the conclusion of the previous section, we need to focus our attention on clinical practice. As it has already been mentioned, the main indication for the use of allogeneic grafting material is extensive bone tissue damage requiring a significant volume of grafting material [75–78]. The time interval of allografting is of particular importance in this context. Since this type of transplant material, despite decellularization [79], has a relatively high frequency of immunogenic rejection [80]. At the same time, in case of extensive bone injuries, including those caused by infectious agents [81], there may be an immune hypersensitivity reaction to an allogeneic graft due to already existing inflammation [66]. Therefore, in clinical practice, the strategy of delayed bone grafting (after 6–8 weeks after the primary surgery) is often used [81, 82].

The current trend in the use of allogeneic bone grafting material is the use of cellular bone matrices. The essence of this method is the implantation of allogeneic mesenchymal stem cells into the structure of the osteoconductive and osteoinductive base. The cellular component is obtained by isolating multipotent stromal cells from cadaveric bone marrow, adipose tissue, and chorion tissue [83]. However, some authors speak about the controversial efficiency of their use [84].

A combination of allogeneic and xenogenic bone grafting materials can also be used, where the former performs the role of an osteoinductive agent and the latter performs a mechanical role [85]. The category of xenogenic bone grafts should be noted separately: bovine bone material is often used for their production [86–88]. There are data confirming high osteoconductive properties of xenogenic bovine bone material [89], while the independent use of xenogenic bone grafting material, despite the positive postoperative outcome in individual cases [90], demonstrates poor quality of clinical outcome [91, 92]. The main negative results of xenotransplantation are fibrous encapsulation of the graft [93] and improper fusion, which is manifested by pain syndrome [94]. Moreover, due to the extremely high duration of xenograft integration (57 weeks) compared to allograft (16 weeks), many researchers have decided that xenografts should not be used independently [91].

Summarizing the data presented in this section, it is worth noting that, on the one hand, the direction of allogeneic transplantation material use is constantly replenished with original methods, including the use of additional categories of transplantation materials. However, on the other hand, in this area there is a noticeable problem with the standardization of the existing methodological base [95]. In clinical practice, this leads to the need to use strategies of personalized medicine, limiting the prevalence of application.

USE OF HYDROXYAPATITE-BASED MATERIALS FOR BONE GRAFTING IN THE RUSSIAN FEDERATION

In the Russian Federation, hydroxyapatite (HA)-based materials represent one of the most widely used classes of synthetic bone graft substitutes in traumatology, orthopedics, maxillofacial surgery, and dentistry.

Their extensive clinical implementation is associated with high biocompatibility, pronounced osteoconductive properties, chemical stability, and the possibility of reproducible large-scale manufacturing, which is especially relevant under conditions of limited availability of autologous bone grafts and the need to reduce donor-site morbidity [96–98].

The development of hydroxyapatite-based biomaterials in Russia has traditionally relied on fundamental studies in inorganic chemistry, crystallography, and materials science. Significant contributions have been made by Russian research groups focused on calcium phosphate ceramics, composite systems, and bioactive coatings for load-bearing implants [96–100]. As a result, a broad range of HA-containing materials – dense and porous ceramics, granules, composite scaffolds, and plasma-sprayed or biomimetic coatings – has been introduced into experimental and clinical practice.

From a functional perspective, hydroxyapatite-based materials used in Russian clinical settings are primarily regarded as osteoconductive matrices providing mechanical support and spatial guidance for bone regeneration [97, 101]. These materials facilitate the adhesion, migration, and differentiation of osteogenic cells but generally lack intrinsic osteogenic potential. Consequently, they are frequently applied in combination with autologous cancellous bone, bone marrow aspirate, platelet-rich plasma, or growth factor-containing formulations, in agreement with the principles of the «diamond concept» of bone regeneration [102, 103].

A key advantage of synthetic hydroxyapatite materials over allogeneic and xenogeneic grafts is their extremely low immunogenicity and absence of risks associated with pathogen transmission. This property is of particular importance in reconstructive procedures performed under conditions of chronic inflammation, post-traumatic bone defects, and infectious complications, where immune hypersensitivity reactions to biological grafts may compromise clinical outcomes [104, 105].

An actively developing research direction in Russia involves the modification of hydroxyapatite through ionic substitution and the creation of composite materials. Substitution of calcium and phosphate ions with magnesium, zinc, strontium, silicon, or carbonate groups is considered an effective approach to regulate crystallinity, solubility, resorption rate, and biological activity of HA-based grafts [96, 106–108]. These strategies aim to reproduce the stoichiometric flexibility and structural heterogeneity characteristic of native bone hydroxyapatite, thereby improving the integration and functional performance of synthetic implants.

Thus, hydroxyapatite – based materials used in the Russian Federation occupy an intermediate but strategically important position between biological grafts and fully inert synthetic implants. Their application reflects a broader trend toward standardized, controllable, and biologically rational approaches to bone regeneration. Further progress in this field is closely associated with the integration of fundamental knowledge on native bone mineral organization and advanced material engineering solutions.

DEVELOPMENT OF SYNTHETIC HYDROXYAPATITE-BASED MATERIALS FOR BONE REGENERATION

The accumulated knowledge on the multilevel organization, stoichiometric flexibility, and biological functionality of native bone hydroxyapatite has formed the conceptual basis for the development of synthetic hydroxyapatite-based materials intended for bone grafting and tissue regeneration. Unlike biological grafts, synthetic materials offer the advantages of controlled composition, reproducible physicochemical properties, unlimited availability, and reduced risks of immunogenic reactions and disease transmission [24]. These characteristics have positioned synthetic hydroxyapatite as one of the key components in modern strategies for bone defect reconstruction.

The earliest generations of synthetic hydroxyapatite materials were primarily designed to reproduce the chemical composition of bone mineral, focusing on stoichiometric $Ca_{10}(PO_4)_6(OH)_2$ with high crystallinity and structural stability. However, subsequent studies demonstrated that highly crystalline stoichiometric hydroxyapatite differs significantly from native bone apatite in terms of solubility, surface reactivity, and biological performance [109]. This discrepancy prompted a shift toward biomimetic approaches, aiming to approximate not only the chemical composition but also the structural hierarchy and dynamic behavior of natural bone mineral.

One of the central directions in the development of synthetic hydroxyapatite-based materials is the regulation of their micro- and nanostructure. The creation of porous ceramics and scaffolds with controlled pore size, interconnectivity, and surface roughness has been shown to be critical for promoting vascularization, cell migration, and osteointegration [110, 111]. Macroporosity facilitates tissue ingrowth and nutrient transport, while microporosity and nanoscale surface features enhance protein adsorption and osteoblast adhesion, thereby improving osteoconductive performance [112].

Another important strategy involves chemical modification of hydroxyapatite through ionic substitution. Incorporation of biologically relevant ions such as magnesium, zinc, strontium, silicon, and carbonate groups into the crystal lattice allows modulation of crystallinity, dissolution kinetics, and biological activity of synthetic materials [106, 113]. These substitutions are intended to mimic the non-stoichiometric nature of native bone apatite and to impart additional functional properties,

including stimulation of osteogenic differentiation, angiogenesis, and antimicrobial activity [114].

In addition to monophase hydroxyapatite systems, composite materials combining hydroxyapatite with biodegradable polymers, collagen, bioactive glasses, or other calcium phosphate phases have been actively developed. Such composites aim to overcome the intrinsic brittleness of ceramic materials and to provide improved mechanical performance, especially in load-bearing applications [115]. Furthermore, hybrid systems enable a closer integration between inorganic and organic components, reflecting the natural organization of bone tissue and facilitating gradual material resorption synchronized with new bone formation.

From a biological perspective, synthetic hydroxyapatite-based materials are predominantly classified as osteoconductive scaffolds. Their limited intrinsic osteoinductive potential has stimulated the incorporation of biologically active molecules, including growth factors, peptides, and cellular components, into hydroxyapatite matrices [116]. These approaches are consistent with the principles of the «diamond concept» of bone regeneration, emphasizing the synergistic interaction between scaffold architecture, cellular elements, biochemical signals, and vascular supply [101].

Overall, the development of synthetic hydroxyapatite-based materials represents a transition from chemically inert bone substitutes toward multifunctional, biomimetic systems with tunable structural and biological properties. The ongoing integration of insights from bone biology, materials science, and regenerative medicine is expected to further enhance the clinical efficacy of hydroxyapatite-based grafts and to expand their application spectrum in the treatment of complex bone defects.

The authors declare no conflict of interest.

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