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Materials based on tricalcium phosphate as bone defects substitute (literature review)

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The objective of the study is to determine the current tendencies in the use of osteoplastic materials based on tricalcium phosphate (TCP) in orthopaedics and traumatology. Methods. The search of the scientific information for the analysis was carried out in the PubMed, Google Scholar, World Digital Library, ScienceDirect. Results. The development of biomaterials for reconstructive surgery on the skeleton remains an urgent issue of biomaterial engineering, biology and current traumatology and orthopaedics. Calcium-phosphate ceramics have the excellent properties of biocompatibility, affinity with bone tissue, biodegradability as well as perfect osteoconductive and osteointegrative properties. They are used in orthopaedics and traumatology as a coating for endoprosthesis components in order to achieve a strong bond with the bone as well as a filling material for bone defects in the form of blocks, granules or powder. The optimal structure of ceramic materials in order to achieve the necessary hardness and control of the dissolution rate is still undetermined. The interest of researchers in the creation of osteoplastic materials containing TCP is explained by the advanced osteoinductive properties and the ability to quickly degrade with the formation of bone tissue. Due to different configurations and sizes of the bone defects, the creation of a material with osteoinductive and osteoconductive properties that could be inserted into the cavity in a liquid state and which would quickly harden and acquire the properties similar to those of the bone has been of great current interest. The material should be biodegradable while having sufficient time for bone formation at the implantation site. In view of the above, the creation of cements based on calcium phosphates has become more attractive. Unfortunately, this material is limited in use due to its brittleness and insufficient hardness. Certain reinforcing additives are expected to significantly improve the mechanical properties of the cement. It is desirable that these particles should have bioactive properties analogous to those of cement. A slight modification of the material can significantly change its properties, which makes it imperative to investigate experimentally the biological properties of the investigated material. Key words. Bioceramics, β -tricalcium phosphate, calcium phosphate cement, orthopedic surgeries, bone regeneration.

Мета. Визначити сучасні тенденції щодо використання в ортопедії та травматології остеопластичних матеріалів на основі трикальційфосфату (ТКФ). Методи. Відбір наукової інформації для аналізу проведено в пошукових системах PubMed, Google Scholar, World Digital Library, ScienceDirect. Результати. Розроблення біоматеріалів для використання в реконструктивно-відновних операціях на скелеті залишається актуальним питанням біоматеріалознавства, біології та сучасної травматології й ортопедії. Кальцій-фосфатні кераміки мають чудові характеристики біосумісності, спорідненості з кістковою тканиною, здатності до біодеградації, високі остеокондуктивні й остеointегративні властивості. В ортопедії та травматології їх використовують як покриття для компонентів ендопротезів для досягнення міцного з'єднання з кісткою та як матеріал для заповнення дефектів кісток у вигляді блоків, гранул, порошку. Нез'ясованим залишається питання оптимального складу керамічних матеріалів для досягнення необхідної міцності та контролю над швидкістю розчинення. Зацікавленість дослідників у створенні остеопластичних матеріалів із ТКФ пояснюється доведеними остеоіндуктивними властивостями та здатністю до швидкої дегградації з утворенням кісткової тканини. Через різну конфігурацію та розміри дефектів кістки актуальним стало створення матеріалу з остеоіндуктивними й остеокондуктивними властивостями, який можна було б вводити в порожнину в рідкому стані та який швидко твердів би і набував показників міцності, наближених до кістки. Бажано, щоб такий матеріал був біорозчинним, проте залишався в місці імплантації достатній час для утворення кісткової тканини. Із огляду на зазначене, привабливим стало створення цементів на основі фосфатів кальцію. Та на жаль крихкість і незадовільна міцність цього матеріалу обмежує його використання. Очікується, що додавання певних армуючих домішок значно покращить механічні властивості цементу. Бажано, щоб такі частинки мали біоактивні властивості, аналогічні якості цементу. Незначна модифікація матеріалу може значно змінити його властивості, що робить обов'язковим дослідження експериментально біологічних властивостей досліджуваного матеріалу.

Key words. Bioceramics, β -tricalcium phosphate, calcium phosphate cement, orthopedic surgeries, bone regeneration

Introduction

Given the development of bone defects due to degenerative diseases, injuries, resection of tumors and tumor-like masses, metastatic lesions, foci of osteomyelitis, as well as aseptic instability after primary arthroplasty, replacement of defects with various biomaterials is considered to be an expedient surgical approach [1–3].

Autogenous bone material remains the «gold standard» for transplantation, as it meets the necessary requirements, namely: it contains osteoinductive growth factors and osteogenic stem cells, and plays the role of osteoconductive matrix. Unfortunately, its use is complicated by the limited amount of material, additional trauma and pain at the donor site, reduced bone quality in the presence of osteoporotic changes, etc. [4, 5].

These shortcomings have been partially eliminated due to the appearance of allografts in the surgeon's arsenal, which is no less successful. But antigenic properties, the risk of infection (viral diseases, including HIV), ethical issues limit the use of this material. Also, alloimplants partially lose osteoconductive and osteoinductive qualities in the process of manufacture, sterilization and storage [4], and due to immunological conflict, they can be resorbed and fragmented [5]. Xenografts, in addition to these shortcomings, are rebuilt very slowly compared to other bone materials for implantation, and carry the risk of infection with diseases of viral origin (Creutzfeldt-Jakob, etc.) [6, 7]. Bone grafts are an alternative to synthetic materials, in particular calcium phosphate bioceramics, such as hydroxylapatite (HA; $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and tricalcium phosphate (TCP; $\text{Ca}_3(\text{PO}_4)_2$). They have high biocompatible, osteoconductive and osteointegrative qualities, and their composition is close to the inorganic component of the bone matrix, which causes gradual resorption with replacement by bone tissue [8, 9]. In addition, bioceramics can be made in the form of powder, granules, blocks with different porosity, which expands their use in different parts of the skeleton and in the presence of defects of incorrect configuration. The main focus of this literature review is to identify current trends in the use of orthopedics and traumatology of osteoplastic materials based on TCP.

Material and methods

The search for scientific information for the assessment was carried out in search engines PubMed,

Google Scholar, World Digital Library, ScienceDirect by keywords «filling bone defects», «bone cement», «calcium phosphate ceramics», «tricalcium phosphate», «calcium phosphate cement».

Results and their discussion

General properties of calcium-phosphate ceramics

Back in 1989, C. Huggins published conclusions on the main requirements for synthetic material, namely: it should have reliable osteoconductive action, resorbability, low weight, minimal antigenic properties, appropriate geometric shape for clinical use, be easy to sterilize, well modeled and can be stored for a long time. Today, the range of requirements for synthetic materials is even more expanded. They must be inert to biological tissues, non-carcinogenic, strong enough, resistant to the internal environment of the human body.

Bioactive ceramics based on HA and TCP are widely used in orthopedics, maxillofacial surgery, dentistry due to their chemical similarity to the mineral composition of bones [8, 10–12]. In the late 20th–early 21st centuries, many studies have been conducted on the feasibility and rationality of the use of calcium-phosphate ceramics for reconstructive surgery on the skeleton, studying their advantages over other biomaterials. In particular, complex experimental and clinical studies performed at Professor M. I. Sytenko Institute, made it possible to introduce into clinical practice varieties of bioceramics manufactured by domestic manufacturers [10, 13, 14]. To date, it has been proven that the positive properties of calcium-phosphate bioceramics include biocompatibility, affinity for bone tissue, osteoconduction, osteointegration. Osteoinduction, i. e. the ability to stimulate the differentiation of poorly differentiated cells in the osteogenic direction, is inherent only in some calcium phosphate materials, for example: β -TCP [15, 16] or biphasic ceramics with it in the composition (in particular, in the ratio HA/ β -TCP-20/80 [17]). This makes β -TCP particularly promising for the reconstruction of bone defects. It has been established that osteoinduction depends on physicochemical properties, but the mechanism of its implementation is not clear. It is probably associated with the absorption of proteins on the surface of the material [15] or the ability to modulate the functional state of macrophages with a reduced duration of inflammation and the formation of a phenotype of cells that initiate bone formation [16].

In clinical conditions, β -TCP has been shown to be no less effective than autografts for the reconstruction of bone defects (size about 10 cm³) caused by surgical interventions — osteotomy of the tibia with an open wedge and treatment of osteonecrosis. Implantation involved employment of β -TCP granules with a diameter of 1 mm, which combined macroporosity (400 μ m) with microporosity ($2.73 \pm 1.0 \mu$ m). One year after surgery, the authors obtained identical radiological (new bone formation in the defect site) and functional results in groups, and naturally, patients who were administered β -TCP did not experience pain associated with the donor site [18].

The key mechanism that determines the bioactivity of calcium phosphate ceramics is their ability to dissolve with the release of calcium and phosphate ions and the subsequent formation of a layer of apatite on the surface, to which bone cells are subsequently attached. However, it is quite difficult to achieve the prolongation of degradation of bioceramics, which occurs due to chemical dissolution in combination with cellular resorption and depends on the physicochemical structure of the material [19, 20]. HA is the least soluble, and more than other types of calcium-phosphate ceramics, it is resorbed by TCP [12]. The first report on the creation of biosoluble porous matrices with β -TCP dates back to 1971 [21], and implantation to 1973 (according to [12]). Since 1975, TCP has been used in dentistry, although the authors did not note its advantages over HA [22]. In rabbit experiments, α -TCP degradation began earlier than that of β -TCP and occurred more rapidly: histomorphometry showed that the residual area of an α -TCP implant was significantly smaller 4 and 8 days after implantation in the parietal and frontal bones. α -TCP particles surrounded by newly formed bone were resorbed by multinucleated osteoclast-type cells [23].

The main reason that limits the clinical use of calcium phosphate ceramics is their fragility and reduced compressive strength compared to the cortical bone [24], low mechanical reliability due to the small modulus of Weibull [25]. Therefore, the search for substances in composite materials based on calcium-phosphate ceramics that would allow to achieve the required strength, without changing the favorable biological properties.

Thus, calcium phosphate ceramics is a promising material for the replacement of bone defects due to biocompatibility, affinity with bone tissue, biodegradability, high osteoconductive and osteointegrative properties. Their use in clinical practice is limited by lower mechanical properties compared to living bone. The question of the optimal composition of ceramic

materials to achieve the required strength of control over the dissolution rate remains unclear. The interest of researchers in the creation of osteoplastic materials with TCP is explained by the proven osteoinductive properties and the ability to rapidly degrade with the formation of bone tissue.

Calcium phosphate cements

In orthopedics and traumatology, calcium phosphate ceramics are used not only as a coating for endoprosthesis components to achieve a strong connection with bone [26], but also as a material for filling bone defects [10, 11]. Given the different configuration and size of the latter, it became important to create a material with osteoinductive and osteoconductive properties, which could be introduced into the cavity in a liquid state and which would quickly harden and acquire strength values close to bone. It is desirable that such material be biosoluble, but remain at the site of implantation long enough for bone formation. Given the above, it was expedient to create cements based on calcium phosphates with the ideal biocompatibility, solubility, affinity for bone tissue. They, like any cement, are a powder and a liquid phase (usually water or aqueous solution), which after mixing turn into a homogeneous paste-like mass, which is convenient to fill the cavity in the bone, and harden quickly [27, 28]. Due to the content of calcium-phosphate ceramics, such cements have the potential to be replaced over time by bone tissue, depending on the properties of the mineral component used. Calcium-phosphate cements (CPCs) are classified according to the number of solid phase elements (one or more), type of setting reaction (hydrolysis or acid-base reaction), setting mechanism, evolution of microstructure and type of final product [29, 30]. Different formulations are used for manufacturing, but as a result two types of CPCs are obtained according to the final product: brushitic (dicalcium phosphate dihydrate, DCPD) and apatite [8, 29, 30]. Apatite compounds, in particular, include metastable α -Ca₃(PO₄)₂ [8].

Compression strength and setting time are the main parameters that characterize the quality of cement. In particular, the cement should harden relatively slowly so that the surgeon has enough time for implantation, but at the same time fast enough to prevent prolongation of the surgery [31]. The setting time of many CPCs in their primary composition is from 15 to 22 minutes, natural phosphates are added to reduce it to 5–8 minutes [27]. Another important characteristic is the viscosity according to the method of cement administration, by injection in the form of a paste or by the surgeon himself. The most commonly used vari-

ant for a long time was the injection form, the viscoelastic values of which were equal to 100–2,000 Pa [27].

Literature review [27] for the period 1980–2003, included English-language sources for the keywords «calcium-phosphate cement», «HA-cement», «HA-cement and HA», and the prospects of these materials for clinical use were shown. In particular, the value of the modulus of elasticity of CPC is 180 MPa, i. e. similar to human spongy bone tissue, which is important given its protection against overload and, accordingly, the development of secondary fractures. This cement is gradually replaced by bone: its formation with normal bone marrow in the pores of the material is observed in 2 weeks after implantation. CPCs are easy to use, but their mechanical properties and ability to resorb with the formation of bone tissue were imperfect, which led to continued research in this area.

One of the ways to improve the mechanical properties of CPC for use in orthopedics was the combination of α - or β -TCP with polymethyl methacrylate (PMMA). For example, some authors describe CPC, which consists of α -TCP in the form of an aqueous dispersion with an admixture of PMMA. The material is plastic and due to the presence of PMMA it forms a solid cellular matrix with open pores of about 100 μm , containing clusters of α -TCP, which provides osteoconductive properties [32]. A material with similar properties has also been developed, which includes β -TCP and PMMA [33, 34]. Indications for their use are mainly fractures of long skeletal bones, but there are also recommendations for the use of such cements during revision interventions to fill bone defects. Assessment of the results of treatment of 22 patients with injuries, their consequences and benign bone neoplasms, who used β -TCP-PMMA cement to replace bone defects, showed no postoperative complications, the possibility of early exercise, complete recovery of the operated segment [35].

However, the fact that PMMA is the main component, on the one hand, improves the strength characteristics and allows to preserve the amount of material already integrated into the bone over time, and, on the other hand, can have serious side effects. In particular, the modulus of elasticity of PMMA is much higher compared to human cancellous bone (2,700 MPa vs. 50–500 MPa), as a result, the mechanical strength of skeletal areas, such as vertebral bodies after percutaneous kyphoplasty, with its addition is much greater than adjacent, which creates prerequisites for their fractures. In addition, this component is not resorbable, and during its hardening there is an exothermic reaction (temperature can reach

96 °C), which can cause thermal necrosis of adjacent tissues [12].

Therefore, research aimed at improving the physical properties of CPCs remains relevant and is conducted in two directions: 1) increasing the viscosity of the liquid phase; 2) modification of ceramic powder to increase strength characteristics and create conditions for increasing macro- and microporosity [28, 36]. The first task is realized by adding viscous components, such as chitosan, gelatin, hyaluronic acid, etc. [36, 37]. In experiments on sheep, it was shown that the use of sodium citrate-stabilized blood as a liquid phase compared to water led to an increase in the CPC setting period, improved viscoelastic properties and faster degradation with bone replacement (α -TCP granules 12 μm (78% by volume) were the main ceramic component) [38].

Technical solutions to optimize the actual CPC powder are associated with variations in particle size and shape, their interaction, increasing macroporosity, etc. [37]. Admixtures of fillers are also used, which are divided into biocompatible and biotolerant (silver, corundum particles, rust-resistant steel, titanium, etc.). To provide macroporosity, for instance, microparticles of poly-(d, l)-lactic glycolic acid (PLGA) are added. Experiments on rabbits showed that it promotes the germination of bone tissue not only on the periphery of the implant, but also in its central part with a final volume of CPC of 55 % 26 weeks after implantation into the femur [39]. The porosity can also be increased by the use of foaming agents [40], acidic calcium phosphate solution [41], glucose [42] and the like. However, impurities can affect the physicochemical characteristics of the CPC, changing the setting period, viscosity, compressive strength, as well as the properties of biodegradation, osteointegration, osteoinduction. For example, the addition of pathogens (20 wt. % glucose microparticles of two size ranges (100–150 μm and 150–300 μm) or a copolymer of lactic and glycolic acids) to α -TCP powder resulted in faster degradation of CPC 8 weeks after surgery, implanted in the intercostal defects of the femur of rats. A solution of 24 wt. % Na_2HPO_4 , saturated with glucose was used as the liquid phase. Histologically, no adverse bone response to their introduction was detected. However, the rate of bone formation depended on the composition of the cement: only in the case of the use of smaller glucose microparticles, an increase in the amount of bone was recorded 2 weeks after surgery compared with pure α -TCP [42]. Some authors consider HA crystals, which are the basis of bioapatite, to be the most successful for combining the ability to biodegrade and

reinforce the material. In particular, the addition of 60 μm HA fibers with a volume of 1/10 to 4/10 to tetracalcium phosphate and dicalcium phosphate powder significantly increased the fracture toughness and compressive strength compared to cement without the addition of hardeners [8]. However, *in vivo* studies of this material are needed to determine its behavior in living bone.

It is determined that the use of gelatinized starches improves the mechanical properties of CPC, namely: increases the compressive strength and Young's modulus, without having a negative effect on osteoblast proliferation [43]. The combination of 60 wt. % calcium phosphate powder (90 wt. % α -TCP) with 20 wt. % starch and 20 wt. % barium sulfate. 0.25 moles of sodium hydrogen phosphate were used as the liquid phase [44]. In recent years, CPCs with the addition of magnesium and strontium have shown fast setting, improved mechanical strength and good resorption rate. However, in cell culture, different degrees of toxicity of cement were detected depending on the content of Sr^{2+} and to a lesser extent Mg^{2+} [45], the behavior of these materials in *in vivo* experiments was not determined.

Biological properties of CPC are improved by the use of proteins, mesenchymal stromal cells (MSCs), biologically active factors and the like. Addition of type I collagen to CPCs was shown to increase the adhesion and alkaline phosphatase activity in MSC culture, promoted better osseointegration and faster resorption of material with the formation of new bone after performing spondylodesis in rabbits [46]. In the MSC culture of rabbit bone marrow after admixture in the solid phase of CPC, which consisted of α -TCP, calcium monohydrophosphate, calcium carbonate and HA in the ratio of 6.0: 3.0: 0.5: 0.5, allogeneic bone powder (1.0: 0.4) and bone morphogenetic protein (BMP) compared with conventional cement increased alkaline phosphatase activity, levels of expression of aggrecan, collagen types I and II, which the authors regarded as an increase in osteoinductive properties [47]. Saturation of CPC with recombinant BMP-2 or recombinant BMP-2 with MSC contributed to ectopic bone formation in mice when injected subcutaneously and the formation of a larger volume of bone tissue when implanted in the upper jaw after removal of incisors [48].

Thus, CPC is a promising material for filling bone cavities of various configurations and sizes. They can be used alone or as bioengineered structures containing MSCs and biologically active factors to improve osteogenic properties. However, the search for their optimal

composition to achieve the required strength, controlled biosolubility, osteoinductive properties continues.

Conclusions

The development of biomaterials for use in reconstructive and restorative operations on the skeleton remains a topical issue in biomaterials, biology and modern traumatology and orthopedics. Calcium-phosphate ceramics have excellent characteristics of biocompatibility, affinity with bone tissue, ability to biodegrade, high osteoconductive and osteointegrative properties. In orthopedics and traumatology, they are used as a coating for components of endoprostheses in order to achieve a strong connection with the bone and as a material for filling bone defects in the form of blocks, granules, powder. The question of the optimal composition of ceramic materials to achieve the required strength and control over the dissolution rate remains unclear. The interest of researchers in the creation of osteoplastic materials with TCP is explained by the proven osteoinductive properties and the ability to rapidly degrade with the formation of bone tissue. Due to the different configuration and size of bone defects, it has become important to create a material with osteoinductive and osteoconductive properties, which could be introduced into the cavity in a liquid state and which would quickly harden and acquire strength values close to bone. It is desirable that such material be biosoluble, but would remain at the site of implantation sufficient time for bone formation. In view of the above, the creation of cements based on calcium phosphates with the ideal biocompatibility, solubility, and affinity for bone tissue has become attractive. Unfortunately, the fragility and unsatisfactory strength of this material limits its use. It is expected that the addition of certain reinforcing impurities will significantly improve the mechanical properties of cement. It is desirable that such particles have bioactive properties similar to the qualities of cement. A minor modification of the material can significantly change its properties, which makes it necessary to study experimentally the biological properties of the material under study.

Conflict of interest. The authors declare no conflict of interest.

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MATERIALS BASED ON TRICALCIUM PHOSPHATE AS BONE DEFECTS SUBSTITUTE (LITERATURE REVIEW)

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