PROSPECTS OF USING TITANIUM IMPLANTS WITH PREDETERMINED OSTEOGENIC PROPERTIES

A.A. Vishnevsky, V.V. Kazbanov, M.S. Batalov
St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russia

The paper discusses the benefits and drawbacks of using titanium implants in spine surgery. Improved fixation of titanium implants in bone tissue is achieved by applying a variety of textured and nano-based coatings on their surfaces. Coatings made of osteotropic hydroxyapatite (HA)- and tricalciumphosphate (TCP)-based materials prevail over allogenic materials in many features. This permits to achieve positive results in bone defect osteoplasty. However, HA and TCP do not completely meet the needs of clinicians due to the lack of apparent osteoinductive properties. The guided bone regeneration requires creation of initial conditions for the ordered proliferation of osteogenic cells and capillaries in a predetermined space. A prerequisite for this is the presence of biologically active substances providing osteoinduction of osteoplastic material to form a matrix on which the bone tissue will develop. Candidate substances are various fractions of bone morphogenetic protein (BMP) which induce bone regeneration. The advantages of various physicochemical treatments of titanium implants (plasma, ion, sandblasting, ablative, etc.) are still debated, but their clinical use requires further research.
Key Words: titanium, implants, osseointegration, textured coating, nano-based coating.

Please cite this paper as: *Vishnevsky AA, Kazbanov VV, Batalov MS. Prospects of using titanium implants with predetermined osteogenic properties. Hir. Pozvonoc. 2016;13(1):50–58. In Russian.*
DOI: http://dx.doi.org/10.14531/ss2016.1.50-58.

A surgeon dealing with surgical treatment of diseases and injuries of the spine has an arsenal of different plastic materials for reconstruction phase of the surgery. In addition to auto- and xenografts, the list also includes biodegradable and non-biodegradable non-biological implants [67]. While biodegradable implants are used primarily for replacement of bone cavities, the non-biodegradable ones, made from titanium and its alloys, bioceramics, composite carbon and other biocomposite materials are used for stabilizing and radical reconstructive surgery on the spine.

Autobone is still regarded as the gold standard of implants in vertebrology, since it combines osteoinductive (bone morphogenetic proteins and other growth factors), osteogenetic (osteogenic cells) and osteoconductive (building matrix for bone formation) properties. However, traditional isolated use of bone grafts for anterior fusion in radical reconstructive surgeries for patients with diseases and injuries of the spine is subjected to critical re-evaluation due to high incidence of fractures or resorption [4, 17]. Given great durability of titanium and its alloys, combination implants (metal in combination with a bone) are used in vertebrology, bringing together strength and osteotropic characteristics in one implant [4, 48, 56].

Titanium implants are most common in traumatology and orthopedics, since, in addition to low cost, they have almost all the features of an ideal implant: sufficient mechanical strength (6 times stronger than aluminum and 2 times lighter than iron), bioinert, wear-resistant, with low coefficient of thermal expansion. However, titanium and its alloy also have certain drawbacks common for metallic implants: they are susceptible to corrosion, have low reactivity and weak adhesive capacity. These factors contribute to bone resorption around implants [70] and force researchers to look for new ways of neutralizing these negative properties.

The biocompatibility of titanium implants is due to the formation of thin oxide film on their surface. Titanium dioxide film has a thickness of 4 nm. When the oxide film, rather than the metal itself, is brought into contact with a tissue, tissue reaction occurs immediately after the implantation. Thanks to negatively charged oxygen, the titanium oxide compounds on the surface promote fixation of morphogenetic proteins, blood proteins and free calcium (TiO possess ion-exchange properties and may bind calcium ions in tissue fluid), which are involved in the building and rebuilding of bone tissue. However, self-organizing “bone-implant” interface may not be fully represented by organ-specific tissue and this fact may result in osteolysis and loosening of the implant in case of spinal instability [36, 62, 71].

Therefore, the key factor in integration of a vertebral implant is a number and functional activity of a patient’s stem cells, which depend on numerous factors, both general somatic ones (heredity, internal diseases, osteoporosis, age, immunity) and local ones (scope of intervention, biomechanical characteristics of “implant – bone” system, infections, etc.) conditions. Thus, one of the most urgent tasks is to create optimal conditions for osseointegration of the implant, which in some cases can be achieved by special treatment of the implant surface or application of osteoproductive materials.

The development of bone and tissue engineering, which allows studies of the use of bioactive materials with anti-inflammatory and regenerative properties, is the most promising direction. The materials that promote osseointegration of the implant are currently used in clinical practice [16]. A variety of organic and inorganic coatings are being developed to optimize the chemical composition of the implant's surface. Osteoproducing materials may be used at the interface of its contact with the bone to improve the integration of the implant [10, 12, 22, 26, 32, 42, 61, 64]. Materials which improve cellular proliferation, cell chemotaxis and angiogenesis can also be applied to structured metal surfaces. In addition to clinically used bone morphogenetic protein (BMP), osteotropic properties of platelet growth factor, transforming growth factor β, insulin-like growth factor-1, vascular endothelial growth factor and fibroblast growth factor are studied *in vitro* and *in vivo*. However, the results of the research are contradictory and require further study.

The purpose of this study is to classify the materials used in vertebrology for stimulation of osteogenic and osteoconductive properties of titanium implants.

Biocompatibility and osseointegration of titanium implants. Osseointegration was first reported in Sweden in 1950–60ies [5]. Ingrowth of titanium structures into living bone tissue was discovered during experiments in using implants. This phenomenon was called osseointegration. Successful integration of implants and grafts into the tissue environment is a basic requirement for reconstructive surgeries on the spine. Synthetic materials, cell and tissue technologies which are deemed appropriate for this purpose are used where biological integration and functioning of body's own tissues and foreign materials integrated with them occur. By now the prevailing opinion is that bone formation involves two types of bone forming processes on the implant surface: contact osteogenesis (on the implant surface) and distant one (from the parental bone) [18]. These mechanisms have their own specific features, but they share common cellular processes, consisting of proliferation and osteogenic differentiation of body's own mesenchymal stem cells, formation of cells of osteoblastic line, which create the bone that undergoes subsequent restructuring. The healing of cancellous bone includes three overlapping phases: 1) osteoconduction; 2) formation of new bone; 3) remodeling [43].

Osteoconduction, attraction osteogenic stem cells to the implant surface, is the most important stage of intraosseous healing [59]. The surface of the implant adsorbs fibrinogen that acts as an adapter for platelet adhesion [35]. For its part, platelets on the implant surface are activated and produce various osteogenic growth factors. Fibrinogen is proteolytically cleaved to fibrin, which forms temporary three-dimensional networks around the implant. As a result of activation of factors expressed by platelets, the osteogenic stem cells travel through the fibrin frame to the implant surface. This migration causes a retraction of the temporary fibrin matrix [66].

The next phase of bone formation is characterized by progressive degradation of the organic bone matrix due to osteogenic cells, which appear on the implant surface and move toward the periphery. Then the matrix is mineralized as a result of the accumulation of calcium phosphate.

The biological connection between the implant and the bone tissue is fully formed after the first two phases of bone healing; osseointegration has occurred. The subsequent remodeling phase involves organization of periimplant bone tissue due to resorption processes [44].

The main prerequisite for adaptation of non-biodegradable implants in the bone is the formation of regenerate with organotypic beam structure at its periphery. Autobone chips, allogenic bone or synthetic ceramic materials are used for this purpose. Their biological properties are different, but overall they have weaker osteoinductive properties, since the donor material has been subjected to additional processing (devitalization with irradiation, treatment with sonication or freezing). Modern biomedical technology involve the use of osteoinductors, such as recombinant proteins (rhBMP), fixed on various carriers (synthetic, biological, inorganic or biocomposite polymers) [9, 24].

The most promising way to increase osteoinductivity of bone implants and to enhance regeneration of connective tissue is to develop biocomposite materials, containing main components of tissues and active protein substances, various growth factors. In 1965, Urist [72] made a fundamental discovery, proving that the demineralised bone matrix is capable of inducing the formation of new bone as a result of biochemical activation of bone proteins.

The ideal biodegradable implant is expected to gradually dissolve in the body environment while fulfilling its supporting function and the new bone tissue should be formed in its place. Obviously, resorptive function of biological material, along with its support function, is crucial for successful integration of the material into the body. The rate of bone regeneration depends on several factors: porosity, chemical composition, solubility and presence of some of elements that are released during the resorption process of ceramic material, facilitating bone regeneration carried out by osteoblasts.

Search for technologies to improve osseointegration of titanium implants. The long-term stability of the implant depends primarily on osseointegration processes prompting numerous studies of surface modification of titanium implants and the roughness (R) of their surface by a variety of methods. Sandblasting, ion, laser ablation and additive treatment of metal surfaces are the most studied among the physical and chemical technologies. Sa, the average depth of roughness, is the most important surface topographic parameter in implantology. According to Wennerberg and Albrektsson [75], the implant surfaces can be divided into four groups based on their degree of roughness: 1) smooth ($Sa < 0.5$ μm); 2) slightly rough ($Sa = 0.5–1$

μm); 3) moderately rough (Sa = 1–2 μm); 4) rough (Sa > 2 μm) surfaces.

The impact of the implant surface roughness on osseointegration and osteoconduction had been thoroughly investigated. Some authors suggest that metabolic activity of osteoblast-like cells on the titanium surface, which is controlled by the level of osteocalcin, prostaglandin E2, and transforming growth factor-β1 (TGF-β1), and alkaline phosphatase activity, significantly increases after sandblast treatment or plasma spraying [60]. The surface of the implant increases with the increase in the surface roughness, which leads to a further increase in the adsorption of fibrinogen and platelet activation rate. In addition, fibrin frame more firmly attaches to rough surfaces [65]. In experiments on rabbits Larsson et al. [57] have demonstrated that the surface roughness and thickness of the oxide layer affect the adhesion rate of bone in the early stages of implantation (1–7 weeks).

There is general agreement that the implants with smooth (Sa < 0.5 μm) and slightly rough (Sa = 0.5–1 μm) surfaces have worse osseointegrative properties than the implants with moderately rough (Sa = 1–2 μm) and rough (Sa > 2 μm) surfaces. In addition, experiments demonstrated better contact between the bone and the implant with moderately rough surface than with the rough one [75].

Improved fixation of implants in bone tissue is achieved by applying various textured (porous globulous, coral-like) coatings and nano-coatings (nanocrystalline hydroxyapatite, fluoride, metaphosphate or calcium octaphosphate) to their surfaces [1, 6, 10, 12, 28, 34, 55].

Bio-ceramic coating. Spraying bioactive materials based on synthetic calcium phosphates, hydroxyapatite (HA) and tricalcium phosphate (TCP), is one of the promising directions in surgery of the spinal column. HA is an inorganic matrix of mineralized tissues of human and animal body, accounting for 65 % of the weight of a cortical bone. It is characterized by biocompatibility with the human body and does not trigger rejection reaction, it increases proliferative activity of the osteoblasts and stimulates the reparative osteogenesis at the injection site, however, this material is completely devoid of osteoinductive properties [15]. It has been shown that in a biological system the crystals of synthetic HA and TCP are susceptible to the influence of body cells metabolism and are degraded into calcium and phosphate ions, which are later incorporated into regenerating bone structure [31]. Implants coated with a thin layer of calcium phosphate were designed to increase bone mineralization in the bone formation phase [45]. The drug also delays the development of inflammatory response in the bone tissue. Currently, synthetic HA preparations have been successfully used in clinical practice in Russia and in the leading foreign countries.

Despite such a pronounced current interest in HA, the indications for its medical use are quite limited. The drug is used either as a porous (reserved) ceramics intended to serve as a support frame for tissue grafts, gradually dissolving during substitution with newly formed bone tissue, or as a solid (non-resorbing) ceramics intended for coating of metal or synthetic surfaces. Since HA cannot be used in surgery of the spine as a supporting frame, it is interesting to consider the currently available experimental and clinical results of the surface treatment of titanium implants.

An experiment studied the specific effect of the drug based on nanocrystalline “Hydroxyapatite gel” [15]. Several studies have investigated the effect of different surface treatments of titanium implants on the formation of mineralized osteoblastic culture [30, 63]. Cooper et al. [41] cultivated osteoblast culture on various titanium surfaces (after mechanical treatment, plasma spraying, and sandblasting of titanium oxide) and reported no significant differences in cell growth. Later D.A. Dimitrovich [8] has shown that the area of cell material attachment after ion-plasma etching was 50% larger and after shot-blasting was 35 % larger than after microplasma treatment.

One promising area is development of composite materials based on biphasic ceramics using different binders, biologically active substances, stem cells. In reconstructive surgery it is important to take into account the rate of biodegradation of the implant material. Very fast resorption may outstrip the processes of bone formation. In this case, there are extensive fibrous tissue sections in the area of the implant. Ceramics based on HA biodegrade slower than those based on TCP. The advantage of this type of material is a possibility to combine the hardness of HA and the formation of calcium depot (due to biodegradation of TCP). When choosing intraosseous implants with textured coatings it is better to give preference to those that are characterized by a porosity of 10–40 % and pore sizes of 0.1 to 10 μm and have additional hydroxyapatite or hydroxyapatite and calcium phosphate bioceramic layer. Durable dense nanoceramics allow production of new generation of endoprostheses and implants for use in orthopedics, dentistry, arthroplasty, especially in heavily loaded segments of the skeleton (spine, joints, etc.).

Titanium implants with hydroxyapatite coating have been used in vertebrology [2, 11]. Application of nanostructured hydroxyapatite coating on titanium allows creation of meshes with the necessary strength and improved osseointegration properties of the implants. A.B. Makarov et al. [20, 21] have shown that these implants promote formation of bone-metal block within 2–2.5 months, which is considerably faster than for conventional metallic implants.

“HumanTech Germany GmbH” company (Germany) manufactures bioceramic-based cages “TRISTAN®” for cervical spine and “ADONIS®” for lumbar spine which have elasticity modulus close to the bone material. Stability during the installation of the system is ensured by the presence of titanium plasma coating on the bearing surfaces of the cage. Ceramics based on zirconium oxide and aluminum are promising for applications in orthopedics and traumatology due to good strength (from 800 to 1800 MPa), better biocompatibility and chemical stability in the human body than any other material [13, 14, 19]. According to studies by the European Association of Osseointegration, the adaptation of an implant can be expected to improve by covering its surfaces with peptides that stimulate osteoconduction [53]. Bioceramics may serve as a carrier system for osteogenic drugs based on transforming growth factor β (TGF-β) or BMP.

BMP and other cell growth factors. Out of the fifteen known mammal bone morphogenetic proteins of BMP family, rhBMP-2, 4, and 7 are the most often used in clinical practice [9, 40]. A number of experimental and clinical studies in the early XXI century demonstrated safety and effectiveness of using rhBMP-2 and rhBMP-7 as inducers for regeneration of bone graft substitutes. They induce mitogenesis of mesenchymal stem cells and their differentiation from osteoblasts [23]. Animal experiments have demonstrated that fusion begins a few weeks earlier in rhBMP-treated implants than in those without it [33, 58]. Experiments with rhBMP-2-coating of titanium surfaces have shown promising results [27]. Side effects of rhBMP are rare and occur in the form of local erythema and slight edema at the site of introduction of the osteoinductor.

Several BMP materials, particularly ACS “Infuse” (Medtronic, USA) and “OP-1, BMP-7” (Stryker Biotech, USA) are currently approved for use in medical practice. The use of rhBMP-2 in a collagen sponge resulted in higher frequency of bone fusion of the vertebral bodies in comparison with the use of autologous graft from the iliac crest [37, 49]. Some companies combine the osteoinductive properties of BMP with osteoconductive and osteogenic agents. For example, “Cerapedics, Inc.” (USA) created an implant for bone tissue regeneration “i-Factor^{TM}” which combines unique natural calcium phosphate matrix and short synthetic peptide P-15 which stimulates osteogenic cells to release growth factors and natural biologically active molecules.

The effectiveness of rhBMP-7 in achieving bone fusion in vertebral pathology was comparable or even superior to that of autologous bone material [52, 73, 74]. A randomized study included 36 patients who underwent surgical treatment for degenerative lumbar spondylolysis [54]. One group of the patients received autograft from the iliac crest with “Ossigraft” paste containing rhBMP-7 (study group), while the other one received only the graft from the iliac crest (control group). After 1 year of observation the rate of coossification was 86 % in the study group, and 73 % in the control group, after 4 years, the rate was 69 % and 50 %, respectively. [54]. In another series of studies Kanayama et al. [54] compared the efficacy of “Ossigraft” paste containing rhBMP-7 mixed with ceramic pellets (9 patients of the main group) and grafts from the iliac crest (10 patients in the control group) in patients with degenerative spondylolysis in lumbar spine. Coossification was observed in 78 % (7 of 9) of patients in the study group and 90 % (9 of 10) patients in the control group. Histological examination revealed complete coossification in 57 % (4 of 7) patients of the study group and 78 % (7 of 9) patients in the control group. Viable bone formation was observed in 6 of the 7 cases of rhBMP-7 and in all cases of autografts.

Nevertheless, despite such impressive results, some researchers have expressed skepticism about the use of rhBMP-2 in vertebrology, believing that such coating causes a loss of bone mass, and even reduces the degree of osseointegration [53].

In addition to BMP, other growth factors involved in bone regeneration and cell proliferation are used in clinical trials, including platelet-derived growth factor, transforming growth factor β, insulin-like growth factor-1, vascular endothelial growth factor and fibroblast growth factor. Modern technologies allow to cover cages with cell growth factor (“LMP-1” technique, Sofamor Danek), rhBMP-2 (Medtronic, USA), or a combination of recombinant “MP52” bone protein and a bone growth factor (“HEALOS” method, jointly developed by “Orquest” and “Sulzer Spine-Tech” companies, Germany, DePuy Spine Inc, USA) [58].

Creating a nanostructured surface. A promising new way to improve the physical and mechanical properties of titanium and its alloys is the creation of nanostructural implant surface by laser irradiation or different types of treatment (sandblasting, severe plastic deformation). Another interesting trend in implantology is treatment of titanium surface with various types of carbon: fullerenes, DLC (diamond-like carbon) and other materials.

The treatment of the surface with femtosecond laser pulses [7, 50] produce nanostructured surface, which has a well-defined one-dimensional lattice with a characteristic step of 70–600 nm. For example, a series of 500 pulses with the density of laser radiation of 17 mJ/s2 produces a sequence of narrow grooves (thickness of about 100 nm) on the surface of a titanium target which are on average 400 nm apart.

Severe plastic deformation results in structured grains and depressions less than 0.1 mm in size on the titanium surface [29]. Carbon nanotube antennas, which can significantly speed up the process osteoreparation, are then grown in these cavities [3]. Bone tissue grew twice as fast as on the surface with carbon nanotubes than on the unmodified titanium surface [69]. Acceleration of bone regeneration process is particularly noticeable when carbon nanotubes are used together with rhBMP, commonly employed to improve bone growth [68]. However, in vivo application require studies of their biocompatibility and potential toxicity. Due to the uncertainty about biocompatibility and cytotoxicity of carbon nanotubes, the feasibility of their clinical use is unclear [25].

Creating diamond films on the surface of the titanium implants by pulsed cathodic arc deposition of carbon plasma is promising way to improve osseointegration [39]. Their use for the corrosion protection of the implants has been first proposed in the early 1990s [38, 51]. In certain cases the controlled interaction of the implant with the biological medium produce positive results, for example, in order to stimulate growth of bone cells on the implant. For example, Grill et al. [46, 47] used diamond-like coating for potentiation of osteoblastic activity on the implant surface. There are also literature data pointing to the antibacterial properties of diamond-like carbon [39]. However, these properties are not yet sufficiently understood.

Conclusion

Titanium and its alloys are the most widely used materials in vertebrology because of their high strength and biocompatibility. However, self-organizing "bone-implant" interface may not be fully represented by organ-specific tissue which leads to osteolysis and implant instability.

Coatings made of osteotropic HA and TCP prevail over allogenic materials in many features. This permits to achieve positive results in bone defect osteoplasty. However, HA and TCP do not completely meet the needs of clinicians due to the lack of apparent osteoinductive properties. The guided bone regeneration requires creation of initial conditions for the ordered proliferation of osteogenic cells on the implant surface. A prerequisite for this is the presence of biologically active substances providing osteoinduction of osteoplastic material to form a matrix on which the bone tissue will develop. BMPs, inducers of bone regeneration, are potential candidates for this role. For example, bioceramic coating of the titanium implants can serve as a carrier system for osteogenic drugs based on transforming growth factor-β or BMP. The advantages of various physicochemical treatments of titanium implants (plasma, ion, sandblasting, ablative, etc.) are still debated, but their clinical use requires further research.

References

1. **Anfimov PE, Zimin YV, Denisov VM, Bushuev YuI, Pylaeva SI, Krasnova NS.** Effect of xenogenic immobilized bone matrix on the course of wound process. Bull Exp Biol Med. 2006; 141;(4):462–464. In Russian.
2. **Barinov SM, Komlev VS.** Calcium Phosphate Based Bioceramics. Moscow, 2005. In Russian.
3. **Bobrinetskiy II, Morozov RA, Seleznev AS, Podcherniaeva RI, Lopatina OA.** The perspectives of carbon nanotube usage as scaffold material in biological tissues. Cellular Transplantation and Tissue Engineering. 2011;(1):85–90. In Russian.
4. **Burlakov SV, Oleynik VV, Vishnevsky AA, Gordeyev SK.** Experimental validation and clinical application of combined bone-carbon implants and bone autografts for anterior spinal fusion in tuberculous spondylitis. Hir. Pozvonoc. 2012;(4):59–64. In Russian. DOI: http://dx.doi.org/10.14531/ss2012.4.59-64.
5. **Vasin SL, Nemets EA, Perova NV, Rozanova IB, Sevastianov VI, Shekhter AB.** Biocompatibility. Moscow, 1999. In Russian.
6. **Gnedovets AG, Fominski VYu, Romanov RI, Matsnev NP.** Computer modeling of thin film coatings growth during pulsed laser deposition at various pressures of inert gas. Strengthening Technologies and Coatings. 2007;(9):3–9. In Russian.
7. **Golosov EV, Emelyanov VI, Ionin AA, Kolobov YuR, Kudryashov SI, Ligachev AE, Novoselov YuN, Seleznev LV, Sinitsyn DV.** Femtosecond laser writing of subwave one-dimensional quasiperiodic nanostructures on a titanium surface. Journal of Experimental and Theoretical Physics Letters. 2009;(2):107–110. In Russian. DOI: 10.1134/S0021364009140057.
8. **Dimitrovich DA.** Comparative evaluation of surface treatment of intraosseous dental implants (experimental study): MD/PhD Thesis. Moscow, 2009. In Russian.
9. **Zaytstev VV, Karyagina AS, Lunin VG.** Bone morphogenetic proteins (BMP): total characteristics, perspectives of clinical using in traumatology and orthopaedics. Journal of Traumatology and Orthopedics. Priorov. 2009;(4):79–84. In Russian.
10. **Kalita VI, Malanin DA, Mamaeva VA, Mamaev AI, Komlev DA, Derevyanko IV, Novochadov VV, Lantsov YuA, Suchilin IA.** Modification of intrabone implants surfaces: modern research and nanotechnologies. Journal of Volgograd State Medical University. 2009;(4):17–22. In Russian.
11. **Kamenchuk YaA, Zelichenko EA, Guzeev VV, Shashkin AB, Khlusov IA, Zaitsev KV.** Determination of the physicochemical characteristics and biological activity in vitro of the composite Ca-P/chitosan coating obtained by means of electrochemical deposition. Chemistry for Sustainable Development. 2010; 18(5): 577–582. In Russian.
12. **Karlov AV, Saprina TV, Kirillova NA, Fedorov MA, Khlusov IA.** Some clinical and pathophysiological problems and prospects of osteopenia surgical correction in patients with osteogenesis imperfecta. Genij Ortopedii. 2008;(4):84–88. In Russian.
13. **Kirilova IA, Sadovoy MA, Podorozhnaya VT, Buyakova SP, Kulkov SN.** Ceramic and osteoceramic implants: upcoming trends. Hir. Pozvonoc. 2013;(4):52–62. In Russian. DOI: http://dx.doi.org/10.14531/ss2013.4.52-62.
14. **Kirilova IA, Taranov OS, Podorozhnaya VT.** Osseointegration of composite bone-ceramic implants in experimental study. Hir. Pozvonoc. 2014;(4):80–87. In Russian.
15. **Kovalenko AYu, Kezlya OP.** The experimentalstudy of specific effect of nanocrystalline hydroxyapatite gel-based drug preparation for long bone fractures. Medical Journal (Belarusian State Medical University). 2010;(4):109–114. In Russian.
16. **Korzh NA, Kladchenko LA, Malyshkina SV.** Implant materials and osteogenesis. Role of biological fixation and osseointegration in bone reconstruction. Orthopaedics, Traumatology and Prosthetics. 2005;(4):118–127. In Russian.
17. **Kuklin DV, Baulin IA, Belyakov MV, Dorofeev LA, Mushkin AYu.** Efficacy of surgical treatment for generalized spinal tuberculosis using anterior fusion with titanium mesh. Hir. Pozvonoc. 2013;(3):62–67. In Russian. DOI: http://dx.doi.org/10.14531/ss2013.3.62-67.
18. **Kulakov AA, Grygoryan AS.** Problems of integration in dental implantology. Stomatologiia. 2007;(3):4–7. In Russian.
19. **Kulakov OB, Doktorov AA, Diakova SV, Denisov-Nikolskiy YuI, Grotz KA.** Experimental study of osseointegration of zirconium and titanium dental implants. Morphology. 2005;(1):52–55. In English.
20. **Makarov AB, Sergeev KS.** Comparative characteristics of the anterior fusion techniques and implants used for comminuted fractures of the thoracic and lumbar vertebrae. In: Mistakes and Complications in Traumatology and Orthopaedics: Materials of All-Russian Scientific and Practical Conference with international participation, dedicated to the memory of prof. A.N. Goryachev. Omsk, 2011:162–173. In Russian.
21. **Makarov AB, Sergeev KS.** Experimental ground of an innovated fixator application for anterior spondylodesis in low thoracic and lumbar vertebrae comminuted fractures. Medical science and education of Ural. 2011;(3):35–37. In Russian.
22. **Malanin DA, Kalita VI, Mamaeva VA, Derevyanno IV, Krainev EA, Snigur GL.** Formation of the interface between bone tissue and titanium implants with bioactive ceramic coating. In: Abstracts of the 8th Congress of traumatologists and orthopedists of Russia. Samara, 2006: 257–258. In Russian.
23. **Mironov SP, Gintsburg AL, Eskin NA, Lunin VG, Gavryushenko NS, Karyagina AS, Zaytsev VV.** Experimental evaluation of osteoinduction of recombinant bone morphogenic protein (rhBMP-2) of native production fixative on biocomposite or bone matrix. Reporter of Traumatology and Orthopedics named Priorov. 2010;(4):27–31. In Russian.

24. **Mironov SP, Eskin NA, Andreeva TM.** Specialized traumatologic and orthopaedic care for outpatients with injuries and bone-muscular diseases. Reporter of Traumatology and Orthopedics named Priorov. 2010;(1):3–8. In Russian.
25. **Mitrofanova IV, Milto IV, Suhodolo IV, Vasyukov GYu.** Opportunities of biomedical use of carbon nanotubes. Bulletin of Siberian Medicine. 2014;(1):135–144. In Russian.
26. **Novochadov VV, Malanin DA, Pisarev VB, Kalita VI, Mamaev AI, Krainov EA.** Interaction of calcium phosphate bioceramic coatings of titanium implants at the interface with the bone tissue. Bulletin of Volgograd Research Centre of RAMS and Volgograd Region Administration. 2004;(3):20–24. In Russian.
27. **Pavlova LA, Pavlova TV, Nesterov AV, Kolesnikov DA, Goncharov IYu, Zhernovoi MG.** Morphological analysis of bone defect at use of nanostructural titanium implant with various composite coverings in dynamics during the first month of regeneration. Scientific Bulletin of the Belgorod State University. Series: Medicine. Pharmacy. 2010;(9):58–63. In Russian.
28. **Plyusnin MYu, Shtraube GI.** The use of dental implants with fluoride coating: immediate and long-term results of implantation. Aspirant I Soiskatel. 2011;(6):118–120. In Russian.
29. **Salimgareeva GKh.** Formation of a structure and properties of titanium rods manufactured using combined SPD-technology: PhD Thesis in Technics. Ufa, 2009. In Russian.
30. **Sidelnikov AI.** Comparative characteristics of the titanium-group materials used for manufacturing modern dental implants. Infodent. 2000;(5):10–12. In Russian.
31. **Tatarenko-Kozmina TYu, Denisov-Nikolski YuI, Volozhin AI, Doktorov AA, Malginov NN, Krasnov AP.** Effect of hydroxyapatite as a component of biostable composites on population and proliferation of mesenchymal stem cells. Bull Exp Biol Med. 2007;143:519–523. In English.
32. **Shashkina GA.** Microarc calcium phosphate coatings. Structure and properties of titanium biocomposite with calcium phosphate coatings: Abstract of PhD Thesis in Technics. Tomsk, 2006. In Russian.
33. **Boden SD, Hair G, Titus L, Rachine M, McCuaig K, Wozney JM, Nanes MS.** Glucocorticoid-induced differentiation of fetal rat calvarial osteoblasts is mediated by bone morphogenetic protein-6. Endocrinology. 1997;138:2820–2828.
34. **Borsari V, Fini M, Giavaresi G, Tschon M, Chiesa R, Chiusoli L, Salito A, Rimondini L, Giardino R.** Comparative in vivo evaluation of porous and dense duplex titanium and hydroxyapatite coating with high roughnesses in different implantation environments. J Biomed Mater Res A. 2009;89:550–560. DOI: 10.1002/jbm.a.31995.
35. **Broberg M, Eriksson C, Nygren H.** GpIIb/IIIa is the main receptor for initial platelet adhesion to glass and titanium surfaces in contact with whole blood. J Lab Clin Med. 2002;139:163–172. DOI: http://dx.doi.org/10.1067/mlc.2002.121604.
36. **Brun P, Dickinson SC, Zavanet B, Cortivo R, Hollander AP, Abatangelo G.** Characteristics of repair tissue in second-look and third-look biopsies from patients treated with engineered cartilage: relationship to symptomatology and time after implantation. Arthritis Res Ther. 2008;10:R132. DOI: 10.1186/ar2549.
37. **Burkus JK, Sandhu HS, Gornet MF, Longley MC.** Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005; 87:1205–1212. DOI: 10.2106/JBJS.D.02532.
38. **Butter RS, Lettington AH.** Applications of Diamond Films and Related Materials, Third International Conference; NIST Special Publication, Vol. 885, 1995.
39. **Checan NM, Beliauski NM, Akulich VV, Pozdniak LV, Sergeeva EK, Chernov AN, Kazbanov VV, Kulchitsky VA.** Biological activity of silver-doped DLC films. Diam Relat Mater. 2009;18:1006–1009.
40. **Cheng H, Jiang W, Phillips FM, Haydon RC, Peng Y, Zhou L, Luu HH, An N, Breyer B, Vanichakarn P, Szatkowski JP, Park JY, He TC.** Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). J Bone Joint Surg Am. 2003;85:1544–1552.
41. **Cooper LF, Masuda T, Whitson SW, Yliheikkila P, Felton DA.** Formation of mineralizing osteoblast cultures on machined, titanium oxide grit-blasted, and plasma-sprayed titanium surfaces. Int J Oral Maxillofac Implants. 1999;14:37–47.
42. **Dalton JE, Cook SD.** In vivo mechanical and histological characteristics of HA-coated implants vary with coating vendor. J Biomed Mater Res. 1995;29:239–245. DOI: 10.1002/jbm.820290215.
43. **Davies JE.** Understanding peri-implant endosseous healing. J Dent Educ. 2003;67:932–949.
44. **Depprich R, Zipprich H, Ommerborn M, Naujoks C, Wiesmann HP, Kiattavorncharoen S, Lauer HC, Meyer U, K bler NR, Handschel J.** Osseointegration of zirconia implants compared with titanium: an in vivo study. Head Face Med. 2008;4:30. DOI: 10.1186/1746-160X-4-30.
45. **Esposito M, Murray-Curtis L, Grusovin MG, Coulthard P, Worthington HV.** Interventions for replacing missing teeth: different types of dental implants. Cochrane Database Syst Rev. 2007;(4):CD003815.
46. **Grill A.** Diamond-like carbon coatings as biocompatible materials – an overview. Diam Relat Mater. 2003;12:166–170.
47. **Grill A, Meyerson BS.** Development and status of diamond-like carbon. In: Synthetic Diamond: Emerging CVD Science and Technology, Spear KE, Dismukes JP, eds. New York: John Wiley & Sons, 1994:91–141.
48. **Grob D, Daehn S, Mannion AF.** Titanium mesh cages (TMC) in spine surgery. Eur Spine J. 2005;14:211–221. DOI: 10.1007/s00586-004-0748-7.
49. **Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK.** Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J. 2004;4:527–538. DOI: 10.1016/j.spinee.2004.03.025.
50. **Ionin AA, Kudryashov SI, Makarov SV, Rudenko AA, Seleznev LV, Sinitsyn DV, Golosov EV, Kolobov YR, Ligachev AE.** Beam spatial profile effect on femtosecond laser surface structuring of titanium in scanning regime. Appl Surf Sci. 2013;284:634–637. DOI: 10.1016/j.apsusc.2013.07.144.
51. **Jacobs TL, Spence JH, Wagal SS, Oien HJ.** Applications of diamond films and related materials. Third International Conference; NIST Special Publication, Vol. 885, 1995.
52. **Johnsson R, Stromqvist B, Aspenberg P.** Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion: 2002 Volvo Award in clinical studies. Spine. 2002;27:2654-2661.
53. **Junker R, Dimakis A, Thoneick M, Jansen JA.** Effects of implant surface coatings and composition on bone integration: a systematic review. Clin Oral Implants Res. 2009; 20 Suppl 4:185–206. DOI: 10.1111/j.1600-0501.2009.01777.x.
54. **Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D.** A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine. 2006;31:1067–1074.
55. **Kim K, Fisher JP.** Nanoparticle technology in bone tissue engineering. J Drug Target. 2007;15:241–252. DOI: 10.1080/10611860701289818.
56. **Koptan W, Elmiligui Y, Elsharkawi M.** Single stage anterior reconstruction using titanium mesh cages in neglected kyphotic tuberculous spondylodiscitis of the cervical spine. Eur Spine J. 2011;20:308–313. DOI: 10.1007/s00586-010-1537-0.
57. **Larsson C, Thomsen P, Aronsson BO, Rodahl M, Lausmaa J, Kasemo B, Ericson LE.** Bone response to surface-modified titanium implants: studies on the early tissue response to machined and electropolished implants with different oxide thicknesses. Biomaterials. 1996;17:605–616. DOI: 10.1155/2013/412482.
58. **Magit DP, Maak T, Trioano N, Raphael B, Hamouria Q, Polzhofer G, Drespe I, Albert TJ, Grauer JN.** Healos/recombinant human growth and differentiation fac-

tor-5 induces posterolateral lumbar fusion in a New Zealand white rabbit model. Spine. 2006;31:2180–2188.

59. **Mavrogenis AF, Dimitriou R, Parvizi J, Babis GC.** Biology of implant osseointegration. J Musculoskelet Neuronal Interact. 2009;9:61–71.
60. **Meyle J, Gultig K, Rascher G, Wolburg H.** Transepithelial electrical resistance and tight junctions of human gingival keratinocytes. J Periodontal Res. 1999;34:214–222.
61. **Moroni L, Hamann D, Paoluzzi L, Pieper J, de Wijn JR, van Blitterswijk CA.** Regenerating articular tissue by converging technologies. PLoS ONE. 2008;3:e3032. DOI: 10.1371/journal.pone.0003032.
62. **Motomiya M, Ito M, Takahata M, Kadoya K, Irie K, Abumi K, Minami A.** Effect of hydroxyapatite porous characteristics on healing outcomes in rabbit posterolateral spinal fusion model. Eur Spine J. 2007;16:2215–2224. DOI: 10.1007/s00586-007-0501-0.
63. **Novaes AB Jr, Souza SL, de Oliveria PT, Souza AM.** Histomorphometric analysis of the bone-implant contact obtained with 4 different implant surface treatments placed side by side in the dog mandible. Int J Oral Maxillofac Implants. 2002;17:377–383.
64. **Nuss KM, von Rechenberg B.** Biocompatibility issues with modern implants in bone – a review for clinical orthopedics. Open Orthop J. 2008;2:66–78. DOI: 10.2174/1874325000802010066.
65. **Park JY, Gemmell CH, Davies JE.** Platelet interactions with titanium: modulation of platelet activity by surface topography. Biomaterials. 2001;22:2671–2682. DOI: 10.1016/S0142-9612(01)00009-6.
66. **Pedersen SF, Hoffmann EK, Mills JW.** The cytoskeleton and cell volume regulation. Comp Biochem Physiol A Mol Integr Physiol. 2001;130:385–399.
67. **Rihn JA, Kirkpatrick K, Albert TJ.** Graft options in the posterolateral and posterior interbody lumbar fusion. Spine. 2010;35:1629–1639. DOI: 10.1097/BRS.0b013e3181d25803.
68. **Shokuhfar T, Titus E, Cabral G, Sousa AC, Gracio J, Ahmed W, Okapalugo T, Makradi A, Ahzi S.** Modelling on the mechanical properties of nanocomposite hydroxyapatite/PMMA/carbon nanotube coatings. Int J Nano and Biomaterial.s 2007;1:107–115. DOI: 10.1504/IJNBM.2007.016555.
69. **Sirivisoot S, Yao C, Xiao X, Sheldon BW, Webster T.** Greater osteoblast functions on multiwalled carbon nanotubes grown from anodized nanotubular titanium for orthopedic applications. Nanotechnology. 2007;18:365102. DOI: 10.1088/0957-4484/18/36/365102.
70. **Stankiewicz JA, Vaidy AM, Chow JM, Petruzzelli G.** Complications of hydroxyapatite use for transnasal closure of cerebrospinal fluid leaks. Am J Rhinol. 2002;16:337–341.
71. **Steinert AF, Ghivizzani SC, Rethwilm A, Tuan RS, Evans CH, Noth U.** Major biological obstacles for persistent cell-based regeneration of articular cartilage. Arthritis Res Ther. 2007;9:213. DOI: 10.1186/ar2195.
72. **Urist MR.** Bone: formation by autoinduction. Science. 1965;150:893–899. DOI: 10.1126/science.150.3698.893.
73. **Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, Phillips F, Hilibrand A, Albert TJ.** A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2003;12:495–500. DOI: 10.1007/s00586-003-0561-8.
74. **Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, Phillips F, Hilibrand A, Albert TJ.** A 2-year follow-up pilot study evaluating the safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2005;14:623–662. DOI: 10.1007/s00586-004-0845-7.
75. **Wennerberg A, Albrektsson T.** Effects of titanium surface topography on bone integration: a systematic review. Clin Oral Implants Res. 2009;20 Suppl 4:172–184. DOI: 10.1111/j.1600-0501.2009.01775.x.

Address correspondence to:
Vishnevsky Arkady Anatolyevich
Planernaya str., 67/3, ap. 33, St. Petersburg, 197373, Russia,
vichnevsky@mail.ru

Received 17.03.2015

Arkady Anatolyevich Vishnevsky, MD, DMSc, head of the department of phthisio-vertebrology, St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russia;
Vladimir Vladimirovich Kazbanov, MD fellow in the department of phthisio-vertebrology, St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russia;
Murad Sultanovich Batalov, MD fellow in the department of phthisio-vertebrology, St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russia.