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ANTIMICROBIAL PROPERTIES OF METAL/METAL OXIDE NANOPARTICLES AND THEIR POSSIBILITIES IN DENTAL IMPLANTOLOGY

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One of the branches of dentistry that is most interested in nanotechnology is dental implantology. Although the survival rate of dental implants exceeds 90%, infection can impair these results. To prevent peri-implant infection, it is necessary to create dental implants with antimicrobial activity.

The objective is to analyze the current state of application of metal and metal oxide nanoparticles to provide antimicrobial properties to titanium dental implants.

The literature source search was conducted in the PubMed database. Selection criteria included: publication in English; involvement in implantology; 2014-2024 year of publication; original article or review, availability of microbiological research data.

An analysis of the literature showed that peri-implant diseases are caused by dysbiotic bacterial communities that differ between individuals and include both known periodontopathogens and less specific types of microorganisms. To develop implants with antimicrobial properties, they are modified with nanoparticles of silver, gold, copper, zirconium, zinc oxide, and titanium dioxide. Modified materials are characterized by a wide spectrum of antimicrobial action, reduction of microorganisms adhesion, inhibition of biofilm formation in a combination with improvement of osseointegration.

Therefore, dental implants with metal/metal oxide nanoparticles have prospects from the standpoint of preventing peri-implantitis, but their clinical use is complicated by the need to optimize manufacturing processes, achieve long-term release of biologically active nanoparticles or ions, desired corrosion resistance, and guarantee patient safety.

Key words: *dental implantation, peri-implantitis, microflora, nanoparticle, metal, metal oxide, antimicrobial effect.*

Connection of the publication with planned research works.

The presented review is a part of research work of the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Poltava State Medical University «Pharmacological research of biologically active substances and medicines for the development and optimization of indications for their use in medical practice (state registration number 0120U103921). It also relates to the research work theme of the Department of Orthopedic Dentistry with Implantology of Poltava State Medical University «Application of the latest technologies for the diagnosis and treatment of functional pathology of the dental and jaw system» (state registration number 0121U11381).

Introduction.

Nanodentistry is a new branch of dentistry that involves the use of nanomaterials, nanorobots, and nanotechnology for the diagnosis, treatment, and prevention of dental diseases [1]. It finds use in orthodontics, preventive dentistry, prosthetics, restorative dentistry, periodontology, dental surgery, and tooth restoration technologies, although it faces such limitations for the use of dental nanoproducts as cost-effectiveness and availability. One of the fields of dentistry most interested in nanotechnology is dental implantology.

Now, even in the developed countries of the world, a large number of patients are missing one or more teeth and every fourth resident of the United States over the age of 74 has lost all his natural teeth [2]. There are many options for replacing missing teeth, but dental implants have become one of the most popular ways to restore dental defects [3]. Dental implants are an integral part of clinical dentistry, and their global market will reach $13 billion in 2023 [4].

Although the survival rate of dental implants exceeds 90%, there are conditions and risks that compromise these high success rates. These include old age, diabetes, osteoporosis, obesity, and the use of medications that can interfere with the healing of tissues around dental implants [4]. Risk factors for dental implantation also include socioeconomic status, smoking, substance abuse, diet and dietary supplements, mental health disorders, poor oral hygiene, and rare visits to dental clinic [5].

Implantation failure is most often a consequence of plaque biofilm formation in the oral cavity at an early stage of healing after implantation and can be in the form of peri-implant mucositis or peri-implantitis [6, 7]. Peri-implantitis is a biofilm-related condition that affects the soft and hard tissues around implants and causes bleeding, suppuration, and bone loss. Peri-implantitis and mucositis are often detected in patients with low standards of oral hygiene, and especially in patients with prosthetic structures consisting of 3 or more units [8].

It is known that the dental plaque biofilm is a complex community of microorganisms that cause infection, protecting pathogens from the effects of drugs and protective mechanisms of the host organism [9]. Therefore, it is important to provide dental implants with antimicrobial properties, in particular anti-biofilm action. In this regard, antimicrobial nanoparticles (NPs) are a promising strategy to prevent infections associated with dental implants [10].

The aim of the study.

To analyze the current state of use of metal and metal oxide NP to provide antimicrobial properties to dental titanium implants.

Object and research methods.

The literature search for the main part of the review was conducted in the PubMed database. To search for articles, the following terms were used: «antimicrobial metal/metal oxide NPs», «metal/metal oxide NPs and dental implants» as well as these phrases specifying the nature of NPs and their oxides: silver (Ag), zinc (Zn), zirconium (Zr), copper (Cu), titanium (Ti). Selection criteria included: publication in English; involvement in implantology; 2014-2024 year of publication; original article or review. The exclusion criteria were: a case from practice, a report at a conference; lack of involvement in dental implants; lack of microbiological research data.

Main part.

Analysis of the literature confirmed that titanium implants are widely used in dentistry, due to their high strength, durability, and biocompatibility [11]. If their use was complicated by infection, among its causative agents the main bacterial strains were *Staphylococcus aureus* (*S. aureus*), *Streptococcus mutans* (*S. mutans*) and *Escherichia coli* (*E. coli*) [12, 13, 14]. Pathogenic bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*) [15] or *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) [16] and fungi *Candida albicans* (*C. albicans*) [17] have also caused implant infections. Studies focusing on peri-implantitis have found that gram-negative pathogens *P. gingivalis*, *Tannerella forsythia* and *Treponema denticola* proliferate in anoxic niches formed by the accumulation of microbes [18]. Peri-implant disease has been shown to be determined by dysbiotic bacterial communities that differ between individuals and include known periodontal pathogens such as *P. gingivalis* and species less associated with periodontal disease such as *Filifactor alocis* [19]. Study of peri-implant microbiota using 16S rRNA sequencing reveals differences between periodontal and peri-implant microbiota under normal and pathological conditions in terms of its diversity and composition. Peri-implant microbiota has specificity both in the presence of bacteria characteristic of peri-implantitis and in the proportion of microorganisms [20].

Inflammation and infection around implants with peri-implantitis and loss of supporting bone can eventually lead to implant rejection. The only way to get rid of this infection is the disinfection of dental implants, which is performed by mechanical cleaning, laser treatment, photodynamic therapy, air polishing, anodization, radiation, ultrasound, thermal, chemical and electrochemical treatment, the use of antimicrobial drugs and probiotics [21, 22]. Although most of these decontamination methods have been effective in preventing the formation of biofilm on dental implants, one of the most promising approaches is to provide antimicrobial action to the implants themselves.

These facts show that it is important to have materials for implants with antimicrobial properties to reduce the risk of their loss caused by microorganisms [11]. The wide supply of such materials even allowed Zhang et al. to classify these modifications according to their predominant effect on the phases of the infectious process into anti-adhesive, anti-colonization, anti-biofilm, and anti-proliferation ones [23].

In order to create the next generation of antimicrobial dental implants, modern research is focused on NPs of metals and their oxides. Various antimicrobial NPs have been developed for this purpose, such as Ag [17, 24, 25, 26], Cu [27], zinc oxide (ZnO) [28, 29], titanium dioxide (TiO_2) [30, 31], etc.

Silver NPs are most widely used to modify the surface of dental implants. They showed significant activity against gram-negative and gram-positive bacteria [32, 33]. These NPs are synthesized by chemical and physical methods, as well as by «green synthesis» methods [34]. They can be applied to the surface of the titanium implant by using the NP surface coating component [35, 36, 37, 38]. Another way of introducing Ag NPs into the titanium surface is to cover it with sodium-lime glass, in which these NPs are embedded [16, 39]. Another method is the introduction of nanosilver into micro – or nanostructures of titanium, for example, into titanium nanotubes [40, 41, 42, 43]. Plasma immersion was also used to add metal NPs, including Ag NPs, to the implant surface to achieve antibacterial activity [44]. In other *in vitro* studies, such methods of Ag NPs applying to titanium surfaces as electrodeposition, electroplating, and sputtering were used [45, 46].

It is described that nanosilver has a wide spectrum of antibacterial action, which is realized due to disruption of the permeability of the cell wall of bacteria, damage to DNA and inactivation of proteins; and also demonstrates an anti-biofilm effect [47] and is able to reduce microbial seeding of wounds [48]. Silver NPs have antifungal properties, inhibiting the development of pathogenic and conditionally pathogenic fungi, in particular *C. albicans* [49].

The Ti surface conteining of 0.05 ppm of Ag NPs was sufficient to inhibit the growth of gram-positive and, especially, gram-negative bacteria, which are more sensitive to the action of nanosilver [24]. The Ti surface with plasma application of Ag NPs showed a greater inhibitory effect on *Fusobacterium nucleatum* compared to the effect on *S. aureus* [50].

Silver NPs were combined with iron oxide and such nanostructure was magnetically managed and had antibacterial activity similar to pure Ag NPs. Coating with these NPs can maintain antibacterial activity and prevent adhesion of bacteria to the implant, which significantly reduced the number of *S. mutans* colonies [51].

The use of Ag NPs in implantology is limited by the problem of their toxicity [52]. However, most of the reviewed studies showed that Ag NPs on the surface of dental implants do not increase the cytotoxicity of the material, but provide a long-lasting antibacterial effect [53]. Cytotoxicity and antibacterial effects are closely related to how Ag NPs are released from titanium surfaces, with slower release increasing the viability and proliferation of macroorganism cells.

The combination of Ti with hydroxyapatite [54], Ag NPs with chitosan [55], as well as annealed Ag-doped TiO_2 nanotubes [56, 57] demonstrated high antibacterial activity and biocompatibility. In particular, Ti surface with NPs containing Ag, lysozyme, hyaluronic acid, and chitosan provided total inhibition of *S. aureus* in the first four days. It was maintained after two weeks, but decreased to 65–90% [55]. This study confirmed that Ti modified with nanocoatings can maintain strong and stable antibacterial activity for a long time.

In addition to nanosilver, it is suggested to use titanium dioxide NPs for the modification of titanium dental implants. Titanium modified with a TiO_2 layer was able to improve the interaction of this material with human periodontal ligament stem cells and increased their osteogenic differentiation [58]. At the same time, TiO_2 nanorods exhibited strong antifungal and antibacterial properties. These NPs had significantly higher antifungal (against *C. albicans*) and antibacterial (against *A. actinomycetemcomitansand* and *P. gingivalis*) effects compared to pure Ti, which was related to the effect on planktonic and biofilm forms of microorganisms [59].

Modification of the surface of titanium dental implants was carried out with gold (Au) NPs, which contributed to the acceleration of osseointegration [60]. Wang et al. used NPs of this noble metal to load inside titanium nanotubes by magnetron sputtering and obtained antibacterial efficiency against *S. aureus* based on the extracellular electron transfer between bacteria and nanostructure [61].

To create implants with the function of self-protection against infection, it is proposed to use Cu NPs. Plasma electrolytic oxidation has been investigated as a biofunctionalization process of the implant to incorporate nanocopper into the titanium surface. In this case, 93% of surfaces containing Cu led to the decrease in bacterial load by 50% or more [62]. It has also been described that Cu-Ti-O nanotubes with different Cu content had good contact antibacterial activity and at a Cu concentration of 1 atom% demonstrated sufficient cytocompatibility, that means they could potentially be used in dentistry and other biomedical fields [63].

The use of Cu NPs on TiO_2 surfaces to create antibacterial and osteoconductive biomaterials using plasma electrolytic oxidation was investigated. This surface modification ensured the long-term release of Cu ions. When Ag and Cu NP were applayed simultaneously, the authors observed a synergistic bactericidal effect between them, that made it possible to decrease the concentration of Ag by 10 times without the reducing of antibacterial activity [64]. In this study, implants with 75% Ag and 25% Cu NPs completely killed all bacteria in an *ex vivo* model, but did not cause any cytotoxicity.

Zinc oxide was used to create a pH-sensitive Ti implant coating with ZnO-folic acid NPs, by which vancomycin was loaded inside titanium nanotubes [65]. In response to a decrease in pH (simulating the onset of bacterial infection), the antibacterial efficiency of such material increased from 60.8% to 98.8%, demonstrating the ability to achieve initiated drug release. In another study, the loading of Ag and Zn NPs into titanium nanotubes using the magnetron sputtering technique showed antimicrobial efficacy against *C. albicans*, *Candida parapsilosis*, and *S. mutans*, killing microorganisms within 3 hours (*S. mutans*) or 24 hours of contact (yeast strains) [66]. In addition, hydrothermally treated titanium nanotubes with Zn have also been reported to achieve antibacterial effects against *S. aureus* and enhance osteogenic differentiation of stem cells [67].

Zr nanoparticles are of interest for dental implantology because they provide structures with unparalleled strength and flexibility, and also have good biocompatibility when used in dental implants [68]. Nanoparticles synthesized from a combination of garlic, ginger and Zr nitride showed a powerful antibacterial effect against *S. aureus* and anti-biofilm activity, and also improved the formation of material biointegration and cell survival, which allowed the authors to assume the possibility of their use in dental implants [69].

Dental implants with Ti modified with metal/metal oxide NPs have exceptional prospects in terms of prevention of microbial biofilm formation and peri-implantitis caused by it, but important questions arise regarding bridging the gap between experiment and practice. Clinical translation of dental implants made of nanoengineered Ti is complicated by the need to optimize their manufacturing processes, achieve long-term release of biologically active NPs or ions, ensure desired corrosion resistance and electrochemical stability, guarantee patient's safety, and choose the best sterilization and packaging process [70].

Most of the manufacturing of nanotechnical Ti implants described in the literature is based on planar Ti samples, which are far from the complex geometry of clinically used implants, therefore the development of a standardized technology for NPs applying specifically to clinical implants is relevant. Studies are being conducted to evaluate cellular uptake and toxicity of released bioactive substances and ions, to achieve sustained and delayed release *in vivo* when the surface is coated with proteins and cells [71].

The effectiveness and safety of dental implants are evaluated in *in vivo* models, but their limitations slow down the clinical implementation of nanoengineered implants [72]. The researchers point out that these models are not adapted to assess the outcome in the long term and under stress conditions. In addition, animal infection models and quantification of NP release at the site of dental implantation are lacking.

Therefore, the possibilities of modifying titanium dental implants with the help of metal/metal oxide NPs, which give them antimicrobial properties, are widely presented in the literature, but the majority of solutions are still far from clinical practice and require further improvement of technology, efficiency and safety.

Conclusions.

Titanium dental implants have gained recognition as a reliable method of restoring dentition defects, however, infectious complications can lead to impaired osseointegration and loss of implants. This focuses the attention of researchers on the development of implants with their own antimicrobial activity. The main efforts are focused on the functionalization of titanium implants with NPs of metals and their oxides, which are synthesized in various ways and added to the implant material or applied to its surface. All described metal/metal oxide NPs share the ability to be released from the nanomodified material and show the prolonged antimicrobial effect against oral pathogens of bacterial and fungal nature, preventing biofilm formation. The process of clinical translation of these scientific developments has unconditional advantages and can be accelerated by optimizing the manufacturing technology of nanoengineered implants and guaranteeing their safety through further biological and toxicological studies.

Prospects for further research.

The next stage of our work will be an analysis of the literature regarding studies of nanoengineered dental implants in animal models from the point of view of antimicrobial activity and osseointegration.

References

1. Malik S, Waheed Y. Emerging applications of nanotechnology in dentistry. Dent J (Basel). 2023 Nov 15;11(11):266. DOI: 10.3390/dj11110266.
2. Guillaume B. Dental implants: a review. Morphologie. 2016 Dec;100(331):189-98. DOI: 10.1016/j.morpho.2016.02.002.
3. Yefimenko AS, Korol' DM, Odzhubeyskaya OD, Korol' MD. Issledovaniye makro- i mikrostruktury poverkhnosti implantatov. Vestnik problem biologii i meditsiny. 2018;144(2):274-7. DOI: 10.29254/2077-4214-2018-2-144-274-277.
4. Alghamdi HS, Jansen JA. The development and future of dental implants. Dent Mater J. 2020 Mar 31;39(2):167-72. DOI: 10.4012/dmj.2019-140.
5. Darby I. Risk factors for periodontitis and peri-implantitis. Periodontol 2000. 2022 Oct;90(1):9-12. DOI: 10.1111/prd.12447.
6. Wiedmer D, Petersen FC. Antibacterial effect of hydrogen peroxide-titanium dioxide suspensions in the decontamination of rough titanium surfaces. Biofouling. 2017 Jul;33:451-9. DOI: 10.1080/08927014.2017.1322585.
7. Zandim-Barcelos DL, Carvalho GG, Sapata VM, Villar CC, Hämmerle C, Romito GA. Implant-based factor as possible risk for peri-implantitis. Braz Oral Res. 2019;33:e067. DOI: 10.1590/1807-3107bor-2019.vol33.0067.
8. Charyeva O, Altynbekov K, Zhartybaev R, Sabdanaliev A. Long-term dental implant success and survival – a clinical study after an observation period up to 6 years. Swed Dent J. 2012;36(1):1-6.
9. Faustova MO, Ananieva MM, Basarab YO, Dobrobolska OV, Vovk IM, Loban' GA. Bacterial factors of cariogenicity (literature review). Wiad Lek. 2018;71(2 pt 2):378-82.
10. Song W, Ge S. Application of antimicrobial nanoparticles in dentistry. Molecules. 2019 Mar;24(6):1033. DOI: 10.3390/molecules24061033.
11. Li P, Tong Z, Huo L, Yang F, Su W. Antibacterial and biological properties of biofunctionalized nanocomposites on titanium for implant application. J Biomater Appl. 2016 Aug;31(2):205-14. DOI: 10.1177/0885328216645951.
12. Yang Y, Ren S, Zhang X, Yu Y, Liu C, Yang J, et al. Safety and efficacy of PLGA(Ag-Fe3O4)-coated dental implants in inhibiting bacteria adherence and osteogenic inducement under a magnetic field. Int J Nanomedicine. 2018 Jun 28;13:3751-62. DOI: 10.2147/IJN.S159860.
13. Rosenbaum J, Versace DL, Abbad-Andallousi S, Pires R, Azevedo C, Cénédese P, et al. Antibacterial properties of nanostructured Cu-TiO2 surfaces for dental implants. Biomater Sci. 2017 Feb 28;5(3):455-62. DOI: 10.1039/c6bm00868b.
14. Shen XT, Zhang YZ, Xiao F, Zhu J, Zheng XD. Effects on cytotoxicity and antibacterial properties of the incorporations of silver nanoparticles into the surface coating of dental alloys. J Zhejiang Univ Sci B. 2017 Jul;18(7):615-25. DOI: 10.1631/jzus.B1600555.
15. Divakar DD, Jastaniyah NT, Altamimi HG, Alnakhli YO, Muzaheed, Alkheraif AA, et al. Enhanced antimicrobial activity of naturally derived bioactive molecule chitosan conjugated silver nanoparticle against dental implant pathogens. Int J Biol Macromol. 2018 Mar;108:790-97. DOI: 10.1016/j.ijbiomac.2017.10.166.
16. Massa MA, Covarrubias C, Bittner M, Fuentevilla IA, Capetillo P, Von Marttens A, et al. Synthesis of new antibacterial composite coating for titanium based on highly ordered nanoporous silica and silver nanoparticles. Mater Sci Eng C Mater Biol Appl. 2014 Dec;45:146-53. DOI: 10.1016/j.msec.2014.08.057.
17. Matsubara VH, Igai F, Tamaki R, Tortamano Neto P, Nakamae AE, Mori M. Use of silver nanoparticles reduces internal contamination of external hexagon implants by Candida albicans. Braz Dent J. 2015 Oct;26(5):458-62. DOI: 10.1590/0103-644020130087.
18. Maruyama N, Maruyama F, Takeuchi Y, Aikawa C, Izumi Y, Nakagawa I. Intraindividual variation in core microbiota in peri-implantitis and periodontitis. Sci Rep. 2014 Oct 13;4:6602. DOI: 10.1038/srep06602.
19. Gazil V, Bandiaky ON, Renard E, Idiri K, Struillou X, Soueidan A. Current data on oral peri-implant and periodontal microbiota and its pathological changes: a systematic review. Microorganisms. 2022 Dec 14;10(12):2466. DOI: 10.3390/microorganisms10122466.
20. Kim H-J, Ahn D-H, Yu Y, Han H, Kim SY, Joo J-Y, et al. Microbial profiling of peri-implantitis compared to the periodontal microbiota in health and disease using 16S rRNA sequencing. J Periodontal Implant Sci. 2023 Feb;53(1):69-84. DOI: 10.5051/jpis.2202080104.
21. Dhaliwal JS, Abd Rahman NA, Ming LC, Dhaliwal SKS, Knights J, Albuquerque Junior RF. Microbial biofilm decontamination on dental implant surfaces: a mini review. Front Cell Infect Microbiol. 2021 Oct 8;11:736186. DOI: 10.3389/fcimb.2021.736186.
22. Faustova MO, Chumak YV, Loban' GA, Ananieva MM, Havryliev VM. Decamethoxin and chlorhexidine bigluconate effect on the adhesive and biofilm-forming properties of Streptococcus mitis. Front Oral Health. 2023 Nov 7;4:1268676. DOI: 10.3389/froh.2023.1268676.
23. Zhang E, Zhao X, Hu J, Wang R, Fu S, Qin G. Antibacterial metals and alloys for potential biomedical implants. Bioact Mater. 2021 Feb 8;6(8):2569-612. DOI: 10.1016/j.bioactmat.2021.01.030.
24. Weng S, Zhao X. Synthesis, characterization, antibacterial activity in dark and in vitro cytocompatibility of Ag-incorporated TiO2 microspheres with high specific surface area. J Mater Sci Mater Med. 2018;29:50. DOI: 10.1007/s10856-018-6042-8.
25. Pokrowiecki R, Zareba T. In vitro studies of nanosilver-doped titanium implants for oral and maxillofacial surgery. Int J Nanomed. 2017;12:4285-97. DOI: 10.2147/IJN.S131163.
26. Chen P, Wu Z, Leung A, Chen X, Landao-Bassonga E, Gao J, et al. Fabrication of a silver nanoparticle-coated collagen membrane with anti-bacterial and anti-inflammatory activities for guided bone regeneration. Biomed Mater. 2018 Oct 2;13(6):065014. DOI: 10.1088/1748-605X/aae15b.
27. Vilarrasa J, Delgado LM, Galofré M, Àlvarez G, Violant D, Manero JM, et al. In vitro evaluation of a multispecies oral biofilm over antibacterial coated titanium surfaces. J Mater Sci Mater Med. 2018 Nov 3;29(11):164. DOI: 10.1007/s10856-018-6168-8.
28. Memarzadeh K, Sharili AS, Huang J, Rawlinson SC, Allaker RP. Nanoparticulate zinc oxide as a coating material for orthopedic and dental implants. J Biomed Mater Res A. 2015 Mar;103(3):981-9. DOI: 10.1002/jbm.a.35241.
29. Abdulkareem EH, Memarzadeh K, Allaker RP, Huang J, Pratten J, Spratt D. Anti-biofilm activity of zinc oxide and hydroxyapatite nanoparticles as dental implant coating materials. J Dent 2015 Dec;43(12):1462-9. DOI: 10.1016/j.jdent.2015.10.010.
30. Westas E, Hayashi M, Cecchinato F, Wennerberg A, Andersson M, Jimbo R, et al. Bactericidal effect of photocatalytically-active nanostructured TiO2 surfaces on biofilms of the early oral colonizer, Streptococcus oralis. J Biomed Mater Res A. 2017;105(8):2321-28. DOI: 10.1002/jbm.a.36086.
31. Yeniyol S, Mutlu I, He Z, Yüksel B, Boylan RJ, Ürgen M, et al. Photocatalytical antibacterial activity of mixed-phase TiO2 nanocomposite thin films against Aggregatibacter actinomycetemcomitans. Biomed Res Int. 2015;2015:705871. DOI: 10.1155/2015/705871.
32. Jin J, Zhang L, Shi M, Zhang Y, Wang Q. Ti-GO-Ag nanocomposite: the effect of content level on the antimicrobial activity and cytotoxicity. Int J Nanomedicine. 2017 Jun 7;12:4209-24. DOI: 10.2147/IJN.S134843.
33. Besinis A, Hadi SD, Le HR, Tredwin C, Handy RD. Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings. Nanotoxicology. 2017 Apr;11(3):327-38. DOI: 10.1080/17435390.2017.1299890.
34. Shanmuganathan R, Karuppusamy I, Saravanan M, Muthukumar H, Ponnuchamy K, Ramkumar VS, et al. Synthesis of silver nanoparticles and their biomedical applications - a comprehensive review. Curr Pharm Des. 2019;25(24):2650-60. DOI: 10.2174/1381612825666190708185506.
35. Zhou W, Jia Z, Xiong P, Yan J, Li Y, Li M, et al. Bioinspired and biomimetic AgNPs/gentamicin-embedded silk fibroin coatings for robust antibacterial and osteogenetic applications. ACS Appl. Mater. Interfaces. 2017;9:25830-46. DOI: 10.1021/acsami.7b06757.
36. Choi SH, Jang YS, Jang JH, Bae TS, Lee SJ, Lee MH. Enhanced antibacterial activity of titanium by surface modification with polydopamine and silver for dental implant application. J Appl Biomater Funct Mater. 2019 Jul-Sep;17(3):2280800019847067. DOI: 10.1177/2280800019847067.
37. Guo C, Cui W, Wang X, Lu X, Zhang L, Li X, et al. Poly-l-lysine/sodium alginate coating loading nanosilver for improving the antibacterial effect and inducing mineralization of dental implants. ACS Omega. 2020 May 4;5:10562-71. DOI: 10.1021/acsomega.0c00986.
38. Li W, Yang Y, Zhang H, Xu Z, Zhao L, Wang J, et al. Improvements on biological and antimicrobial properties of titanium modified by AgNPs-loaded chitosan-heparin polyelectrolyte multilayers. J. Mater. Sci. Mater. Med. 2019 Apr 23;30(5):52. DOI: 10.1007/s10856-019-6250-x.

39. Martinez A, Guitián F, López-Píriz R, Bartolomé JF, Cabal B, Esteban-Tejeda L, et al. Bone loss at implant with titanium abutments coated by soda lime glass containing silver nanoparticles: A histological study in the dog. PLoS ONE. 2014 Jan 22;9(1):e86926. DOI: 10.1371/journal.pone.0086926.
40. Albashari AA, He Y, Albaadani MA, Xiang Y, Ali J, Hu F, et al. Titanium nanotube modified with silver cross-linked basic fibroblast growth factor improves osteoblastic activities of dental pulp stem cells and antibacterial effect. Front Cell Dev Biol. 2021 Apr 1;9:654654. DOI: 10.3389/fcell.2021.654654.
41. Cheng H, Xiong W, Fang Z, Guan H, Wu W, Li Y, et al. Strontium (Sr) and silver (Ag) loaded nanotubular structures with combined osteoinductive and antimicrobial activities. Acta Biomater. 2016 Feb;31:388-400. DOI: 10.1016/j.actbio.2015.11.046.
42. Ren X, van der Mei HC, Ren Y, Busscher HJ, Peterson BW. Antimicrobial loading of nanotubular titanium surfaces favoring surface coverage by mammalian cells over bacterial colonization. Mater Sci Eng C Mater Biol Appl. 2021 Apr;123:112021. DOI: 10.1016/j.msec.2021.112021.
43. Gunputh UF, Le H, Lawton K, Besinis A, Tredwin C, Handy RD. Antibacterial properties of silver nanoparticles grown in situ and anchored to titanium dioxide nanotubes on titanium implant against Staphylococcus aureus. Nanotoxicology. 2020 Feb;14(1):97-110. DOI: 10.1080/17435390. 2019.1665727.
44. Jin G, Qin H, Cao H, Qiao Y, Zhao Y, Peng X, et al. Zn/Ag micro-galvanic couples formed on titanium and osseointegration effects in the presence of S. aureus. Biomaterials. 2015 Oct;65:22-31. DOI: 10.1016/j.biomaterials.2015. 06.040.
45. Kheur S, Singh N, Bodas D, Rauch JY, Jambhekar S, Kheur M, et al. Nanoscale silver depositions inhibit microbial colonization and improve biocompatibility of titanium abutments. Colloids Surf B Biointerfaces. 2017 Nov 1;159:151-8. DOI: 10.1016/j.colsurfb.2017.07.079.
46. Lampe I, Beke D, Biri S, Csarnovics I, Csik A, Dombradi Z, et al. Investigation of silver nanoparticles on titanium surface created by ion implantation technology. Int J Nanomed. 2019 Jul 1;14:4709-21. DOI: 10.2147/IJN.S197782.
47. Yin IX, Zhang J, Zhao IS, Mei ML, Li Q, Chu CH. The antibacterial mechanism of silver nanoparticles and its application in dentistry. Int J Nanomed. 2020 Apr 17;15:2555-62. DOI: 10.2147/IJN.S246764.
48. Lyakhovs'kii VI, Loban' HA, Hancho OV, Vazhnycha OM, Kolomiyets' SV, Dzhaber VKO. Dynamika bakteriolohichnykh ta planimetrychnykh pokaznykiv rany pid vplyvom nanochastynok sribla, stabilizovanykh meksydolom ta polivinilpirolidonom. Klinichna khirurhiya. 2016;4:67-9. [in Ukrainian].
49. Meran Z, Besinis A, De Peralta T, Handy RD. Antifungal properties and biocompatibility of silver nanoparticle coatings on silicone maxillofacial prostheses in vitro. J Biomed Mater Res B Appl Biomater. 2018 Apr;106(3):1038-51. DOI: 10.1002/jbm.b.33917.
50. Zhu Y, Cao H, Qiao S, Wang M, Gu Y, Luo H, et al. Hierarchical micro/nanostructured titanium with balanced actions to bacterial and mammalian cells for dental implants. Int J Nanomedicine. 2015 Oct 27;10:6659-74. DOI: 10.2147/IJN.S92110.
51. Yang Y, Ren S, Zhang X, Yu Y, Liu C, Yang J, et al. Safety and efficacy of PLGA(Ag-Fe3O4)-coated dental implants in inhibiting bacteria adherence and osteogenic inducement under a magnetic field. Int J Nanomedicine. 2018 Jun 28;13:3751-62. DOI: 10.2147/IJN.S159860.
52. Akter M, Sikder MT, Rahman MM, Ullah AA, Hossain KFB, Banik S, et al. A systematic review on silver nanoparticles-induced cytotoxicity: physicochemical properties and perspectives. J Adv Res. 2017 Nov 2;9:1-16. DOI: 10.1016/j.jare.2017.10.008.
53. Haugen HJ, Makhtari S, Ahmadi S, Hussain B. The antibacterial and cytotoxic effects of silver nanoparticles coated titanium implants: a narrative review. Materials (Basel). 2022;15(14):5025. DOI: 10.3390/ma15145025.
54. Besinis A, Hadi SD, Le HR, Tredwin C, Handy RD. Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings. Nanotoxicology. 2017 Apr;11(3):327-38. DOI: 10.1080/ 17435390.2017.1299890.
55. Zhong X, Song Y, Yang P, Wang Y, Jiang S, Zhang X, et al. Titanium surface priming with phase-transited lysozyme to establish a silver nanoparticle-loaded chitosan/hyaluronic acid antibacterial multilayer via layer-by-layer self-assembly. PLoS One. 2016 Jan 19;11(1):e0146957. DOI: 10.1371/journal.pone.0146957.
56. Yeniyol S, He Z, Yüksel B, Boylan RJ, Urgen M, Ozdemir T, et al. Antibacterial activity of as-annealed TiO2 nanotubes doped with Ag nanoparticles against periodontal pathogens. Bioinorg Chem Appl. 2014;2014:829496. DOI: 10.1155/2014/829496.
57. Gao A, Hang R, Huang X, Zhao L, Zhang X, Wang L, et al. The effects of titania nanotubes with embedded silver oxide nanoparticles on bacteria and osteoblasts. Biomaterials. 2014 Apr;35(13):4223-35. DOI: 10.1016/j. biomaterials.2014.01.058.
58. Li Z, Qiu J, Du LQ, Jia L, Liu H, Ge S. TiO2 nanorod arrays modified Ti substrates promote the adhesion, proliferation and osteogenic differentiation of human periodontal ligament stem cells. Mater Sci Eng C Mater Biol Appl. 2017 Jul 1;76:684-91. DOI: 10.1016/j.msec.2017.03.148.
59. Jia L, Qiu J, Du L, Li Z, Liu H, Ge S. TiO2 nanorod arrays as a photocatalytic coating enhanced antifungal and antibacterial efficiency of Ti substrates. Nanomedicine (Lond). 2017;12(7):761-76. DOI: 10.2217/nnm-2016-0398.
60. Heo DN, Ko WK, Lee HR, Lee SJ, Lee D, Um SH, et al. Titanium dental implants surface-immobilized with gold nanoparticles as osteoinductive agents for rapid osseointegration. J Colloid Interface Sci. 2016 May 1;469:129-37. DOI: 10.1016/j.jcis.2016.02.022.
61. Wang G, Feng H, Gao A, Hao Q, Jin W, Peng X, et al. Extracellular electron transfer from aerobic bacteria to au-loaded TiO2 semiconductor without light: a new bacteria-killing mechanism other than localized surface plasmon resonance or microbial fuel cells. ACS Appl Mater Interfaces. 2016 Sep 21;8(37):24509-16. DOI: 10.1021/acsami.6b10052.
62. van Hengel IAJ, Tierolf MWAM, Fratila-Apachitei LE, Apachitei I, Zadpoor AA. Antibacterial titanium implants biofunctionalized by plasma electrolytic oxidation with silver, zinc, and copper: a systematic review. Int J Mol Sci. 2021 Apr 6;22(7):3800. DOI: 10.3390/ijms22073800.
63. Hang R, Gao A, Huang X, Wang X, Zhang X, Qin L, et al. Antibacterial activity and cytocompatibility of Cu-Ti-O nanotubes. J Biomed Mater Res A. 2014 Jun;102(6):1850-8. DOI: 10.1002/jbm.a.34847.
64. van Hengel IAJ, Tierolf MWAM, Valerio VPM, Minneboo M, Fluit AC, Fratila-Apachitei LE, et al. Self-defending additively manufactured bone implants bearing silver and copper nanoparticles. J Mater Chem B. 2020 Feb 26;8(8):1589-602. DOI: 10.1039/c9tb02434d.
65. Xiang Y, Liu X, Mao C, Liu X, Cui Z, Yang X, et al. Infection-prevention on Ti implants by controlled drug release from folic acid/ZnO quantum dots sealed titania nanotubes. Mater Sci Eng C Mater Biol Appl. 2018 Apr 1;85:214-24. DOI: 10.1016/j.msec.2017.12.034.
66. Roguska A, Belcarz A, Zalewska J, Hołdyński M, Andrzejczuk M, Pisarek M, et al. Metal TiO2 nanotube layers for the treatment of dental implant infections. ACS Appl Mater Interfaces. 2018 May 23;10(20):17089-99. DOI: 10.1021/acsami.8b04045.
67. Huo K, Zhang X, Wang H, Zhao L, Liu X, Chu PK. Osteogenic activity and antibacterial effects on titanium surfaces modified with Zn-incorporated nanotube arrays. Biomaterials. 2013 Apr;34(13):3467-78. DOI: 10.1016/j.biomaterials.2013.01.071.
68. Hossain N, Mobarak MH, Hossain A, Khan F, Mim JJ, Chowdhury MA. Advances of plant and biomass extracted zirconium nanoparticles in dental implant application. Heliyon. 2023 May 6;9(5):e15973. DOI: 10.1016/j. heliyon.2023.e15973.
69. Chowdhury MA, Hossain N, Mostofa MG, Mia MR, Tushar M, Rana MM, et al. Green synthesis and characterization of zirconium nanoparticlefor dental implant applications. Heliyon. 2022 Dec 30;9(1):e12711. DOI: 10.1016/j.heliyon.2022.e12711.
70. Gulati K, Chopra D, Kocak-Oztug NA, Verron E. Fit and forget: The future of dental implant therapy via nanotechnology. Adv Drug Deliv Rev. 2023 Aug;199:114900. DOI: 10.1016/j.addr.2023.114900.
71. Barrak FN, Li S, Muntane AM, Jones JR. Particle release from implantoplasty of dental implants and impact on cells. Int J Implant Dent. 2020 Dec;6:50. DOI: 10.1186/s40729-020-00247-1.
72. Blanc-Sylvestre N, Bouchard P, Chaussain C, Bardet C. Pre-Clinical Models in Implant Dentistry: Past, Present, Future. Biomedicines. 2021 Oct 26;9(11):1538. DOI: 10.3390/biomedicines9111538.

ПРОТИМІКРОБНІ ВЛАСТИВОСТІ МЕТАЛ/МЕТАЛОКСИДНИХ НАНОЧАСТИНОК ТА ЇХ МОЖЛИВОСТІ В ДЕНТАЛЬНІЙ ІМПЛАНТОЛОГІЇ

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Резюме. Зубні імплантати стали одним із найбільш використовуваних шляхів відновлення дефектів зубних рядів і мають високу успішність. Невдача імплантації може бути наслідком утворення біоплівки зубного нальоту в ротовій порожнині після проведеної імплантації і розвитку мукозиту або периімплантиту, тому актуальним є надання зубним імплантатам протимікробних властивостей, зокрема за допомогою наночастинок.

Мета роботи – проаналізувати сучасний стан застосування наночастинок металів та їх оксидів для надання протимікробних властивостей зубним титановим імплантатам.

Пошук джерел літератури було проведено в базі даних PubMed з вибором публікацій за останні 10 років, які одночасно причетні до імплантології та мікробіологічного дослідження.

Аналіз літератури підтвердив, що, коли використання дентальних імплантатів ускладнювалося інфекцією, серед її збудників основними були *Staphylococcus aureus, Streptococcus mutans* і *Escherichia coli*. Патогенні бактерії *Porphyromonas gingivalis* або *Aggregatibacter actinomycetemcomitans* і гриби *Candida albicans* також викликали інфекції імплантату. Периімплантатна мікробіота мала специфічність як у присутності бактерій, так і в пропорції мікроорганізмів. Для розробки протимікробних зубних імплантатів дослідження зосереджені на їх нанорозмірних модифікаціях за допомогою наночастинок металів та їх оксидів: срібла, золота, міді, цирконію, оксиду цинку, диоксиду титану. Додавання цих наночастинок до матеріалу дентальних імплантатів надає йому тривалої протимікробної дії проти оральних патогенів, зменшує адгезію мікроорганізмів та утворення біоплівки, що в багатьох випадках поєднується з достатньою цитосумісністю. Зубні імплантати з титану, модифікованого метал/металоксидними наночастинками, мають виняткові перспективи з позицій профілактики утворення біоплівки та зумовленого нею периімплантиту, однак існує проблема їх практичного впровадження.

Отже, зусилля дослідників зосереджені на функціоналізації титанових імплантатів метал\/металоксидними наночастинками, які в різний спосіб синтезуються і додаються до матеріалу імплантату, здатні вивільнятися з нього і справляти протимікробну дію. Процес клінічної трансляції зазначених наукових розробок може бути прискорений оптимізацією технології і подальшими біологічними та токсикологічними дослідженнями.

Ключові слова: дентальна імплантація, периімплантит, мікрофлора, наночастинка, метал, оксид металу, протимікробна дія.

ANTIMICROBIAL PROPERTIES OF METAL/METAL OXIDE NANOPARTICLES AND THEIR POSSIBILITIES IN DENTAL IMPLANTOLOGY

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Abstract. Dental implants have become one of the most used ways of restoring dental defects and have a high success rate. Implantation failure can be a consequence of plaque biofilm formation in the oral cavity after implantation and the development of mucositis or peri-implantitis, therefore it is important to provide dental implants with antimicrobial properties, in particular with the help of nanoparticles.

The objective is to analyze the current state of application of metal nanoparticles and their oxides to provide antimicrobial properties to dental titanium implants.

Literature sources were searched in the PubMed database with a selection of publications over the past 10 years that are simultaneously involved in implantology and microbiological research.

Analysis of the literature confirmed that when the use of dental implants was complicated by infection, *Staphylococcus aureus, Streptococcus mutans* and *Escherichia coli* were the main causative agents. Pathogenic bacteria *Porphyromonas gingivalis* or *Aggregatibacter actinomycetemcomitans* and fungi *Candida albicans* have also caused implant infections. The peri-implant microbiota had specificity both in the presence of bacteria and in the proportion of microorganisms. For the development of antimicrobial dental implants, research is focused on their nanoscale modifications using nanoparticles of metals and their oxides: silver, gold, copper, zirconium, zinc oxide, titanium dioxide. The addition of these nanoparticles to the material of dental implants gives it a long-lasting antimicrobial effect against oral pathogens, reduces the adhesion of microorganisms and the biofilm formation, which in many cases is combined with sufficient cytocompatibility. Dental implants made of titanium modified with metal/metal oxide nanoparticles have exceptional prospects for the prevention of biofilm formation and peri-implantitis caused by it, but there is a problem of their practical implementation.

Therefore, researchers' efforts are focused on the functionalization of titanium implants with metal\/metal oxide nanoparticles, which are synthesized in different ways and added to the implant material, capable of being released from it and exerting an antimicrobial effect. The process of clinical translation of these scientific developments can be accelerated by technology optimization and further biological and toxicological studies.

Key words: dental implantation, peri-implantitis, microflora, nanoparticle, metal, metal oxide, antimicrobial action.

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MONITORING OF MODERN VIEWS ON THE CAUSES AND MECHANISMS OF PERIODONTAL DISEASE DEVELOPMENT

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Periodontal diseases are accompanied by a complex of morphological and functional changes in the dentoalveolar system and the body as a whole and are an urgent problem of modern dentistry.

The purpose is to monitor current views on the aetiology and pathogenesis of periodontal diseases based on the results of the analysis of medical and scientific literature based on the databases Scopus, Web of Science, MedLine, PubMed, and NCBI over the past ten years.

According to the study's results, a number of etiological factors and links of pathogenesis were identified from the standpoint of modern science. The key factors are disorders of the immune system, namely its homeostasis, metabolic disorders, genetic factors, and the state of individual oral hygiene. The study indicates a significant role of systemic immunological changes, which result in a cytokine attack of the body as a whole and periodontal tissues in particular. However, only a few studies in the scientific literature outline the role of immunological changes at the local level, namely, from the side of the components that ensure oral homeostasis. The study of the latter will enable the development and implementation of a system for preventing inflammatory diseases of periodontal tissues in young patients without concomitant somatic pathology.

The above gives a clear understanding of the cause-and-effect relationship between the etiological factors of periodontal diseases and the links of pathogenesis, which in turn creates the prerequisites for the development of more effective ways to prevent and treat this group of diseases.

Key words: *periodontium, periodontal disease, dentistry, inflammatory process, antigens.*

Connection of the publication with planned research works.

The work is a fragment of the planned research work of the Department of Therapeutic Dentistry of the I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine on the topic «Development and implementation of differentiated approaches to the diagnosis, treatment and prevention of periodontal and oral mucosa diseases», state registration number 0123U100071.

Introduction.

Periodontal diseases are an important and urgent problem of modern dentistry, as they are accompanied by a whole complex of severe morphological and functional disorders of the dentoalveolar system and a cascade of metabolic disorders in the body [1].

The prevalence of periodontal diseases in different countries of the world is relatively high. It should be noted that there are different taxonomies and clinical and morphological forms of nosologies depending on the aetiology, type of underlying pathological process, clinical course and immune response. Polymorphic clinical manifestations of periodontal diseases are associated with different compositions of subgingival microflora. The role of factors that implement the antimicrobial response and regulate the new metabolic status of the organism remains important [2].

The problem of early diagnosis of generalised periodontitis (GP), as well as the development of effective measures for its prevention and treatment aimed at achieving positive long-term results, is one of the lead-