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The Possibility of the Development of Antibacterial Properties on the Metallic Constructions for the Treatment and Rehabilitation of Patients with Bone Pathology

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ABSTRACT

Treatment and rehabilitation of patients have always been the most important goals of medicine, and nowadays implantology becomes one of the most important aspects of medical science. Various materials and methods are used in the traumatology and orthopedics among which metals take significant place. And one of the main problems of the modern medicine is the complication of implants application by the growth of infectious diseases that can progress on the surface of the implant. To prevent these complications various nanocoatings and methods of prevention of the infection are used over the surface of implants and surrounding organs and different antibacterial properties are being applied during the development of metallic constructions. The goal of this work was to analyze the results of various studies related to the use of nano-coatings as well as the application of antibiotics in bone pathology and subsequently make conclusions on the topic of the best material for use in medical practice for the treatment of infectious complications on the basis of examined studies.

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BACKGROUND

The treatment and rehabilitation of pathologies of the human body has been one of the imperious necessities from the earliest foundations of human civilization. That fact led to the usage of different materials including metals for the making and the development of biomedical technologies in general and implants in particular.[1] And nowadays the theoretical possibility of complete restoration of organic and body functions had lead to the accelerated pace of the development of implantology.

Implant materials are used for numerous purposes: for example, pacemakers and artificial heart valves are used for the sustenance of a patient's normal life activity with heart defects and also implants are used for the mobility of artificial joints.[2] Biomaterials can be divided into three general types including metals, polymers, and ceramics. Herewith metals are used more widely in biomedicine, the development of implants including.[3]

Also combined implants are used more often, with the base of a strong metal like bio inert titanium, zirconium or tantalum coated with a bio ceramic material representing a specially formed metal oxide layer.[25]

Metals are highly preferable in the production of implants during loads of dynamic and cyclical nature because of the combination of their density and plasticity. But modifications of metal coating are necessary from time to time because of their incompatibility with the blood and biological activity of the organism.[4] As such the nosocomial infection that can lead to the defect of the implant itself with the decline of its functionality can be detected in the post-operational period on the surface of implants.[5] This problem is especially manifested during the implantation of orthopedical prosthetics due to the necessity of two or three surgical involvements during several weeks in this procedure.[37]

Though implants and various materials with the property of osteoinductivity and osteointegration for the improvement of its properties are used in biomedicine and it led to significant progress in

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modern medicine, it also led to the increased risk of infectious complications associated with implants,[10], [30] Thus, according to the statistics the implant-associated infections amount to 25.6% of all healthcare-associated infections in the USA.[11] One of the reasons for difficulty of the treatment of the implant-associated infection is the bacterial antibiotic resistance induced mainly by the widespread usage of antibiotics.[12, 13] Nowadays approximately 700,000 deaths per year all over the world are caused by antibiotic-resistant infections.[12] And according to the statistics, this number can increase up to 10,000,000 per year in roughly thirty years in case if there is still no effective treatment of antibiotic resistance.[12]

In the current worldwide situation, this threat might be intensified by the extensive usage of antibiotics during the COVID-19 pandemic for the prevention of secondary bacterial infections in patients. For the prevention of these problems there have been attempts of identification of new antibiotics, usage of alternatives to known antibiotics and chemical modification of existing drugs as well as other methods. One of these methods is the usage of nano-materials that represent the promising alternative to current antibiotics in the treatment of infections caused by multidrug-resistant (MDR) pathogens. Due to the certain features of nano-materials their application in medical sphere allows such advantages as bacterial annihilation, bioimaging, intracellular delivery, and treatment of cancer.[14] It has to be noted that nano-materials can demonstrate antibacterial activity either independently or in combination with antibiotics for the enhancement of their potency.[15]

Regarding this problem chemical elements that have bactericidal properties and broad-spectrum antibiotics were used. But nowadays nanotechnologies lead to significant perspectives in medicine in general and in bone pathology in particular. More and more researches take place on the basis of these perspectives in modern laboratories worldwide widening the range of such researches and their further perspectives concerning the changes of covering features of biomaterials.[6] Nanotechnologies relate to the area of nano-science i.e. the science dedicated to the study of subjects which size if less than several hundred nanometers.[7]

The critical level of control of the interphase properties of the surface can be achieved on the surface of the substrate with the help of the use of nanotechnology due to the fact that most of the biological reactions, including the reactions of the host organism, take place at the nanoscale.[8] A much larger percentage of nano-materials is located on the surface on which it is applied in comparison with micro-materials, thus increasing the distribution area of nano-structured materials. As a result of such surface and applied material scaling, almost every atom in the coating structure becomes interfacial.[9] Eventually macroscopic properties of the material are directly affected by nano-structures. As it is, self-organizing monolayers (SAM) are one of the types of nanoscale coatings that are capable of modifying the surface of biomaterials for the adaptation of their properties for specific purposes.

Nowadays various metal and metal oxide nanoparticles are used due to their antibacterial properties for treating infections caused by MDR pathogens. Among these materials are ZnO, CuO, TiO2, SiO2, MgO, Cao, Ag, Au, and Cu.[16] ZnO for example has been widely used in various researches due to its antibacterial activity and distinctive high surface area-to-volume property.[16] Moreover, ZnO is known for targeting several bacterial pathways at once instead of targeting the single one, making it rather complicated for the infectious pathogen to develop resistance against ZnO.[19] Another metal oxide nano-particle which is used due to its antibacterial activity is Silver nanoparticles (Ag NPs).[19] Though silver was used in antibacterial and antifungal therapy for a long time, its importance has been significantly increased because of the lesser possibility of bacterial resistance and wider possibilities.[20]

The clinical application of titanium and titanium alloys on the other hand was limited due to the low level of anti-infection, osteoinductivity and angiogenic abilities. In this case novel model substrate was designed which has become a combination of periodic micro/nano-pillar array and TiO2 for basically understanding the topographical bacteriostatic effects of periodic micro/nano-pillar array and the photocatalytic bactericidal activity of TiO2.[38]

Lately nano-antibiotic materials which consist of nano-particles combined with antibiotics were used in the enhancement of antibiotic activity that prevented bacterial resistance. Thus Ag NPs were applied in combination with traditionally used antibiotics for the enhancement of antibacterial activity. In a similar way, mixed with antibiotics ZnO has been used for the increasing of their synergistic effective potential.

In any event, it is biocompatibility that determines the ability of different materials to integrate into the biological tissue providing the most efficient implant functioning. Biocompatibility is the property of materials to fulfill their functions without leading to the damages of the organism. It is due to this effect clinical disorders are not caused by the implantation of the material into the body leading to the adverse tissue reactions [41]. This property of materials is necessary for an optimal therapeutic effect [26]. Consequently biocompatible materials are such materials that work or function without causing serious damage of the organism or lead to the complications harmoniously when in contact with the body or in the body.[27]

Goal

Our goal was to analyze the results of various studies related to the use of nano-coatings as well as the application of antibiotics in bone pathology and subsequently make conclusions on the topic of the best material for use in medical practice for the treatment of infectious complications on the basis of examined studies.

MATERIALS AND METHODS

During the course of the study, we searched for publications in peer-reviewed journals, carried out with the usage of the electronic databases such as PUBMED.com, RSCI (Russian Science Citation Index), and the scientific electronic library eLIBRARY.RU. The authors reviewed publications and studies on the topic of implantology and nanocoatings used in the postoperative and recovery periods. These articles have been included in the case of the presence of the evidence. Data analysis was processed only for publications officially published in the press.

RESULTS

The role of nano-coatings in traumatology and orthopedics is discussed by many authors nowadays. For example, Anil Mahapatro, author of "Bio-functional nano-coatings on metallic biomaterials" points in his work to the fact that the modification of these surfaces is highly important for interfacial control and other secondary processes. In this case self-assembled monolayers (SAMs) conduct surface modifications on a variety of surfaces with multiple functionalities. It is noted that SAMs are the most fundamental components of nanotechnology. Author notes that biofunctional nanocoatings have a major role in surface modification which emphasizing silane based nanocoatings. And nowadays the nanocoating technology of metallic biomaterials is rapidly expanding with new processes and surface engineering methods leading increasing the rate of researches.[31]

Then in the article "Evaluation of zinc-oxide nanocoating on the characteristics and antibacterial behavior of nickel-titanium alloy" the obtaining of a unique coating on NiTi substrate with the usage ZnO nanoparticles is discussed as well as its superior anti-bacterial effect against Gram-negative and Gram-positive bacteria and superior frictional performance. Authors of the article point that nanoparticles coatings can be used in future orthodontic procedures.[19]

In "Stable ZnO-doped hydroxyapatite nanocoating for anti-infection and osteogenic on titanium" pulse electrochemical in-situ method of oxidative polymerization is described which was used to produce polyperrole (PPy) from Pyrrole. This method enabled the PPy dual regulation of HA-NPs and ZnO-NPs, which led to the successful construction of a multifunctional titanium substrate with bioactive, antibacterial, angiogenic and osteoinductive HA/PPy/ZnO nanocomposite coating with physiological stability. In this experiment the composite coating was composed of uniformly distributed spherical shaped nanoparticles. As a result the composite coating could induce the apatite formation of the simulated body fluid, and the apatite arrangement demonstrated good bioactivity. Authors also noted much more important fact that the good antibacterial property was demonstrated, by the antibacterial rate of HA/PPy/ZnO composite coating against Escherichia coli and Staphylococcus aureus which was 63.5% and 72.8%, respectively. In this work on the composite coating bone marrow-derived mesenchymal stem cells (BMSCs) adhered, proliferated and differentiated, showing good osteoinductivity in fluorescence staining experiments of the composite coating.[34]

Another example is the the study named "A New Nano-Platform of Erythromycin Combined with Ag Nano-Particle ZnO Nano-Structure against Methicillin-Resistant Staphylococcus aureus" where authors describe the synthesis of ZnO nano-structure combined with Ag NPs for the preparation of an Ag-ZO (AZO) nano-composite in a low-temperature solution synthesis process. Authors note the simplicity, rapidity, and reproducibility of the of the ZnO nano-structure synthesis method. During this research the growth of MRSA clinical isolates was inhibited by the AZO sample combined with erythromycin. It demonstrated a lower risk of drug resistance than antibiotics alone. Additionally the synthesized nano-composite showed high cell viability. This leads to the conclusion that this cost-effective synthesized nano-composite can be used in different biomedical applications, as an antibacterial agent for example.[21]

Authors of the work "Enhancing the antibacterial efficacy of low-dose gentamicin with 5 minute assistance of photothermy at 50°C" presented another point of view in regard of antibiotics. They developed and researched a photothermal therapy (PTT) that assisted drug release system on the implant surface for in situ rapid disinfection under 808 nm light irradiation within a short time, in which gentamicin (Gent) has been loaded by polyethylene glycol (PEG) modified molybdenum disulfide (MoS2) on Ti surface, being encapsulated with chitosan (CS) (CS/Gent/PEG/MoS2-Ti). The coatings hyperthermia produced irradiated by 808 nm near-infrared (NIR) light did not only accelerate the local release of Gent, but also led to the reduction of the activity of bacteria, which simplified the way by which the locally released drugs entered the interior of the bacteria for the inhibition of the protein synthesis and destruction of the cell membrane. Eventually this photothermy controlled drug-loaded implant surface system provided rapid and high-efficiency in situ sterilization, as well as offered long-term prevention of local bacterial infection.[13]

In the "Characterization and cytocompatibility of anantibiotic/chitosan/cyclodextrins nanocoating on titanium implants" the development of novel ciprofloxacin loaded chitosan nanoparticle-based coating onto titanium substrates is described and characterized in case of obtaining an orthopaedic implant surface able to in situ release the antibiotic for the prevention of post-operative infections. By this method the combination of sulfobutyl ether-beta-cyclodextrin and gamma-cyclodextrin helped to obtain ciprofloxacin loaded chitosan nanoparticles. The inhibition of growth of two nosocomial Staphylococcus aureus strains was achieved by this particular antibacterial coating, with its reduction of about 20 times when compared to controls showing the possibility for the development of a new antibiotic carrier for titanium implants.[40]

The other point is shown in the article by the name of "Aluminum Protection by Using Green Zirconium Oxide Layer and Organic Coating: An Efficient and Adherent Dual System". Authors of this work demonstrated that of all structural alloys AA1100 surfaces containing ZrO2 nanocoatings have high instability of its native oxide/hydroxide interface layer, in long exposition time in the comparison with AA2024 structural alloy. Authors show that the presence of nanometric zirconium oxide film is beneficial for both substrates despite the porousness of the Zr-based nanocoatings, in comparison with the aluminum surface uniquely ground or degreased with alkaline solution. Further authors could overcome low barrier property of the zirconium oxide by the application of a further layer of an anticorrosive organic coating. It was demonstrated by authors that the samples with an ultra-thin layer of ZrO2, generated by electro-assisted technique have the superior adherence than samples with the chemical conversion treatment, due to the lower porosity found in the first case during the long-term accelerated corrosion tests and the scratch assays. As a result, the dual system was able to maintain the integrity of the metal surface and the coating adherence for 90 days, which samples without Zr-based nanocoatings could not do. Authors conclude that this system is sufficient enough alternative to chromate and phosphatizing processes due to the lack of environmental problems connected to the toxicity of chemical baths and to a large amount of waste producing.[36]

The work named Micro/nanostructured TiO2 surface with dual-functional antibacterial effects for biomedical applications presented a designed novel model substrate being a combination of periodic micro/nano-pillar array and TiO2 with the help of which understanding of the topographical bacteriostatic effects of periodic micro/nano-pillar array and the photocatalytic bactericidal activity of TiO2 can be achieved. Additionally, the authors conducted research that demonstrated how bacterial behaviors were affected by TiO2 periodic micro/nanopillar array. It was shown that TiO2 periodic micro/nano-pillar array with sub-micron motif size noticeably inhibited the adhesion, growth, and proliferation of *S. aureus* and *E. coli*. As a matter of fact it was demonstrated that limited contact area availability that generated by the special topography of TiO2 periodic micro/nano-pillararray generate, as well as the spatial confinement size-effect are the reason of significant antibacterial activity. Though these effects can't be attributed to the photocatalytic effect of TiO2 because of the dark environment where the bacteria were cultured. And although despite the fact that the TiO2 periodic micro/nano-pillar array is not lethal to *S. aureus* and *E. coli* the further researches are necessary in this area One of the reason for this is that further study could help clarify the surface topography design which is absolutely necessary for future medical implants confrontation with antibiotic-resistant implant-associated infections without using antibiotics. Such approach can be one of the ways to eliminate concerns that originate due to the widespread and excessive usage of antibiotics.[38]

It has to be noted that also a lot of works has been written recently that are dedicated to the examination of the regeneration of bone tissue. Especially a lot of articles is dedicated to the differentiation of the mesenchymal stem cells.[37]

An interesting point of view presents the article "Layer-by-layer nanocoating of antibacterial niosome on orthopedic implant" whose authors support the potential use of the designed noisome coating for orthopedic implant applications; however, noting the necessity for more investigations in the future with other preclinical studies including. The results obtained from this study show the real potential for the treatment of seated bacteria niosome by that layered formulation. The designed nano-coating on bone plate has shown prolonged drug release and heightened antibacterial activity as well as the absence of toxicity in the normal cells.[29]

Authors of the work named "Silver Nanocoating Technology in the Prevention of Prosthetic Joint Infection" point to the fact that the prevention is doubtless the general response to the increasing problem of orthopedic implant infections. In this work the ability of engineers to develop reliable, durable, non-toxic and safe biomaterials that lead to the prevention of bacterial adhesion and formation of biofilm on surfaces is discussed. Again this work points to the great potential of application of nanotechnologies and nanopatterning especially regarding antibacterial surface treatment with the help of the technologies based on AgNPs whose effectiveness was demonstrated in vitro and in vivo. AgNPs in this work demonstarated a strong antibacterial effect as well as relative inertness to the inner microflora of a patient. Though this work also showed side effects of these technologies such as toxicity and interference with osseointegration, which require further study of this problem.[28]

In spite of the positive results and perspectives shown in the aforementioned works authors of "Scientific Approaches to the Creation of Biocompatible Implant Materials" note that there are several levels of degree of implant and tissue biocompatibility.[25] The implantation in every situation is accompanied by specific morphological changes in the tissue mucosa. Authors note that aside from the implant itself the human organism has a reaction to biological materials in the form of powder, granules, or grafts which are used in orthopedics and plastic surgery. Authors emphasize the necessity of understanding that there is no material that is completely compatible with the organism with all its biomechanical and physiological properties meaning that there are no perfect implants in medical practice nowadays. And nowadays world scientists see the solution in genetic engineering which can help reproduce the organism structure with the living tissue functions and required endurance. The work shows that 3D printing, for example, can help produce materials with biological properties required for the human organism which can attribute to the goal of creating materials with optimal properties for biomedicine. Having obtained the biological structure of living tissue these materials can provide effective tissue ingrowth in the case of temporary implants, and permanent implants can be sufficiently strong.[39]

Thus among approaches to the prevention of complications during the implantation there is developing of special devices. Among such devices is cannulated cervical screw described in the work named "Cannulated Screw with Bioactive Coverage on the Basis of Natural Hydroxyapatite during Osteosynthesis of Medial Fractures of Femur's Neck". This screw was developed specifically for the accomplishment of the dynamic stability of osteosynthesis and for the purpose of accelerating rehabilitation. In the work differences in the screw design are described, especially its spiral part including the presence of bioactive coverage on the basis of natural hydroxyapatite on the surface. The application of such screw as observed by authors reduce the chance of complications during the implantation and prevents the development of osteoresorbable reaction on the "implant-bone" line.[33]

In the work "The Practicability of the Application of Vitamin D in Combination with Vitamin C for the Improvement of Bone Tissue Metabolism" authors note the importance of disease prevention on the example of osteopenia and osteoporosis problem which require the complex approach. Thus, the special place in this matter is dedicated not only to the direct treatment but also to the individual and group work with patients of risk groups and people of old age with the purpose for healthy habits formation, and lifestyle change. Besides, authors note the necessity of influence on all chains of calcium exchange with the purpose of bone tissue metabolism improvement.[35]

Nowadays despite active application of antibacterial drugs during the infectious complications of bone pathology the attention more and more is attracted by preventive medicine. The application of biocompatible nano-coatings in particular shows potential though further developments and researches are necessary regarding best material for this purpose in particular.

CONCLUSIONS

On the basis of data obtained during the analysis of scientific and research studies as well as of experimental constructive works published in the form of research articles the conclusions about high actuality of infectious complications during the applications of metallic constructions including nano-coatings during the bone pathology were made. These complications require further researches and developments of nanocoatings with safe properties with regards to antibacterial treatment as well.

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