ISSN 2616-5880 Vol. 4, Issue 6: 25-30, DOI: 10.25236/AJMC.2023.040605

Research progress on graphene oxide modification of titanium surface

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Abstract: *Titanium has been widely used in dental implants and orthopedic implants due to its excellent physical and chemical properties and good biocompatibility. However, implantation failure or implant-centered infection may still occur in titanium implants. In order to optimize implant performance, physical, chemical and biological modification of titanium surface has become a research hotspot. Graphene oxide has been increasingly used in the research and development of composite biomaterials due to its good mechanical properties, bone conductivity, bone inductivity, biocompatibility, antibacterial property and easy functionalization. In this paper, the application of graphene oxide in surface modification of titanium metal in recent years is reviewed.*

Keywords: *Graphene oxide; Titanium*

1. Introduction

Compared with other metal materials, the surface modified metal titanium (Ti) has the characteristics of non-magnetic, high corrosion resistance, high strengt-modulus ratio [1], and so on, showing more obvious advantages than other metal materials in the application of dental, orthopedic and other biomedical fields, but at present, titanium implant materials may still fail to transplant integration or occur implant-centeredInfection [2].In order to obtain better implant biomaterials, titanium implants have been modified by physical, chemical and biological means in recent years. These modifications are all aimed at improving the biological chimerism between implants and bone and reducing the bacterial adhesion on the surface of titanium implants. Among them, coating modification in biological modification has become a research hotspot of experts in recent years. However, since Ti and TiO2 are bioinert, untreated surfaces usually exhibit poor cell adhesion [3], so surface modification treatment is needed to stimulate the biological activity of titanium alloy materials. In this paper, the development process of biomedical titanium alloys was summarized, and the research progress of several common surface modified coatings of biomedical titanium alloys was introduced, and the future related research was also prospected, in order to provide reference and ideas for subsequent research.

Properties of grapheneoxide Graphene oxide (GO), as a derivative of graphene, is a flat, single-layer carbon atom nanosheet with a honeycomb two-dimensional lattice. It not only has good biocompatibility, electrical conductivity, antibacterial property, but also can promote osteogenesis, support drugs, proteins or ions, so it is used in the development of composite biological functional materials. Among existing known materials in nature, raw graphene (G) has the highest Young's modulus, and GO has more advantages in chemical synthesis, although its mechanical properties have been reduced, the reason is that the edge and surface of GO contain a large number of active oxygen-containing functional groups, including hydroxyl, carboxyl, epoxy and carbonyl groups, which can establish hydrogen bonds with water molecules, so it is close. Water is easier to adjust; These functional groups also allow GO to interact with proteins through covalent, electrostatic, hydrogen bonding, etc., making GO easier to functionalize and more biocompatible than original graphene [4].So far, a large number of studies have shown that GO can promote the adhesion, proliferation and mineralization of osteoblasts, and promote the specific differentiation of stem cells, with strong bone conduction and bone induction capabilities. Chemical modification of GO can obtain more ideal physicochemical properties, and may add new functions to it, such as osteogenesis, cell and bacterial specific reactions, etc. Therefore, GO is often used in implant surface modification

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2. Graphene oxide modification of titanium implants

At present, the research on the surface modification of titanium with graphene oxide mainly focuses on three aspects: the effect of pure graphene oxide coating, graphene oxide composite coating, and graphene oxide coating after loading proteins, drugs or ions on the bone formation and antibacterial properties of titanium implants after surface modification.

2.1 Modification of titanium surface by graphene oxide

Many scholars have studied the modification of titanium surface by graphene oxide and found that it can not only promote the adhesion, proliferation and mineralization of osteoblasts on titanium surface, induce osteogenic differentiation of stem cells, increase the antibacterial property of titanium surface, but also improve the biocompatibility and corrosion resistance of titanium.2.1.1 Osteogenic effect Zancanela et al. [5] added GO disperse liquid into the bottom pore plate containing titanium substrate and inoculated mouse osteoblasts into it, and found that compared with the control group without GO, the formation of mineralized matrix of osteoblasts in the experimental group significantly increased, indicating that the use of GO can increase the formation of mineralized nodules in titanium implants and stimulate biommineralization. Accelerate bone regeneration. Zhou et al. [6] compared the attachment, morphology, colonization and osteogenic differentiation of human periodontal ligament stem cells (PDLSCs) on GO coated titanium (GO-Ti) matrix and sodium titanate (Na-Ti) matrix, and found that when PDLSCs were inoculated on Go-Ti matrix, type I collagen, alkaline phosphatase and bone salivary were significantly higher than those inoculated on Na-Ti matrix. The levels of salivary protein and other markers related to osteogenesis were significantly increased. Pichayada et al. [7] modified the surface of titanium by anodizing and electrodepositing graphene oxide, and found that the anodized titanium coated with GO increased calcium deposition and osteopontin expression in osteoblasts compared with titanium anodized only, and the results showed increased bone formation. They also found that the graphene oxide coating not only improved the biocompatibility of titanium, but also improved the biocompatibility of titanium.It can also improve its corrosion resistance.

2.2 Antibacterial effect

Jia et al. [8-9] deposited GO on polythylene-imide modified titanium foil by evaporation assisted electrostatic self-assembly method, showing good osteogenic ability. Moreover, under the condition of no additional antibacterial agent, sterile implant surface with anti-bacterial adhesion and antibacterial film activity could still be generated, and its biocompatibility would not be significantly affected. However, Jin's team loaded four kinds of mass concentrations (20, 50, 80, 100μg/mL) of graphene oxide on the surface of pure titanium and found that different concentrations of graphene oxide all improved the hydrophilic properties of pure titanium surface. Although graphene oxide can promote the level of cell vitality, it also promoted the adhesion and growth of Staphylococcus aureus, so it was considered that pure titania-oxybene complexThe composite material has no antibacterial properties, but has good biocompatibility [10,11]. Qiu et al. [12] Graphene oxide is fixed on the surface of titanium in three ways, namely gravity action (GO-d), electrostatic action (GO-aps) and electrophoretic deposition (GO-epd). The results show that once Staphylococcus aureus exists in the form of separation but not aggregation, graphene oxide can effectively take sharp wrinkles or edges and high reactive oxygen species levelsKill them. GO-epd is effective in preventing the accumulation of Staphylococcus aureus, producing sharp wrinkles or edges, and can produce higher ROS levels. Therefore, GO-epd showed the best antibacterial activity against Staphylococcus aureus, followed by GO-APS and GO-D.

2.3 Modification Effects of graphene oxide composite coating on titanium surface

Graphene oxide is mixed with other materials as a composite coating on titanium surface, and different components can complement each other to enhance bone formation and antibacterial effects on titanium surface. Zeng et al. [13] prepared the GO/HA coating on the surface of Ti, and found that the addition of GO improved the crystallinity of deposited apatite particles and the bonding strength of titanium with the composite coating, and compared with the hydroxyapatite coating and pure titanium coating, the in vitro cell culture evaluation of the composite coating showed better biocompatibility.Lai et al. [14] prepared a uniform and crack-free GO/ chitosan/hydroxyapatite (GO/CS/HA) composite coating on the surface of titanium by electrophoretic deposition, and found that compared with HA,GO/ HA and CS/HA coatings, the wettability and bond strength of GO/CS/HA composite coating were improved. In vitro experimental results showed that the composite coating was applied the layer significantly enhanced the adhesion between cells and materials, and enhanced bone integration. Shi et al. [15] also studied the coating, and found that the nano-composite coating could not only reduce the adhesion of Staphylococcus aureus, but also effectively protect the titanium substrate from corrosion in simulated body fluid. In the incubation process with MG63 cells, the coating also showed good biocompatibility. Fathyunes et al. [16] prepared a composite coating of calcium phosphate and graphene oxide (CaP-GO) on the surface of titanium, and found that the nanohardness and modulus of the CaP-GO coating increased by 52% and 41%, respectively, compared with the titanium surface without GO coating. The adhesion strength of the CaP coating combined with GO to anodized titanium oxide increased by about 16%.Li et al. [17] used electrophoresis nanotechnology to uniformly deposit terpolymer SF/GO/HA nanocomposite coatings on titanium substrates, and found that human osteosarcoma cells MG63 showed good adhesion and proliferation behavior on the prepared coatings, and increased ALP activity. Jin et al. [11] added different concentrations of graphene oxide and silver particles to the surface of Ti substrate (T-iGO-Ag) by electroplating and ultraviolet reduction, respectively, and found that T-iGO-Ag improved the surface roughness and hydrophilicity of titanium, and had significant antibacterial effect. The coating induced reactive oxygen species, perforation, leakage, DNA/RNA release and other aspectsIn vitro, the sample was immersed in simulated body fluids, and through local surface scanning analysis, calcium and phosphorus elements were found on the surface of the sample, indicating that the composite coating has certain biological activity and biommineralization ability. The team also found that GO-Ag-Ti had a significant effect on the improvement of antibacterial activity and relative adhesion of Streptococcus mutans gingivalis and Bacillus gingivalis [18].

3. Graphene oxide modified the multifunctional structure of titanium surface to support proteins, drugs or ions

so that it is easy to functionalize, so many researchers load GO to the surface of titanium substrate in various ways, and use GO as a carrier to support proteins, drugs or ions to study the osteogenic and antibacterial effects of the modified titanium surface.

3.1 Loaded protein

La et al. [19] loaded bonemorphogeneticprotein-2 (BMP-2) onto the surface of Ti with GO coating (Ti/GO-/BMP-2) and the surface of Ti without GO coating (Ti/BMP-2) respectively, and the results of in vitro experiments showed that the surface of Ti loaded with GO coating can promote the osteogenic differentiation of human bone marrow mesenchymal stem cells (hBMMSCs), and GO can enhance the adsorption and slow release ability of BMP-2 on titanium surface. In vivo experiments showed that the cranial bone formation ability of mice implanted with Ti/GO/BMP-2 was stronger than that implanted with Ti/BMP-2, which may be due to the continuous release of BMP-2 promoted by loading GO. La et al. [20] demonstrated that GO can be used for the delivery of bone morphogenetic protein-2 (BMP-2) and substanceP (SP), and this delivery can promote the formation of bone tissue around titanium implants covered with GO.BMP-2 loaded on Ti coated with GO exhibited higher alkaline phosphatase activity in vitro osteoblasts compared to pure titanium, and titanium implants loaded with BMP-2 and SP via GO coating resulted in the greatest amount of new bone formation after implantation in mouse skulls compared to the other groups. Subbiah et al. [21] prepared an artificial matrix (FN-Tigra) composed of graphene oxide and fibronectin (Fn) on Ti substrate using electric drop technology, and co-cultured pre-osteoblasts with Ti, T-iGO(Tigra) and T-Igo-FN (Fn-Tigra), respectively, and found Tigra added to GOAnd Fn-Tigra, the proliferation ability and survival ability of cultured cells were significantly higher than that of pure Ti culture group. Moreover, when cultured on Fn-Tigra, the expression of local adhesion molecule (vinculin) in the center and surrounding region of proosteoblasts was highly activated, indicating that VINculin could promote the adhesion of osteoblasts and thus promote bone formation. In addition, it was also found that the osteoblast differentiation ability of Fn-Tigra cultured preosteoblasts was higher than that of Ti substrate cultured preosteoblasts in vitro. Han et al. [22] deposited GO on the poly-dopamine-modified Ti scaffold. The poly-dopamine-modified TI scaffold could promote the interaction between GO and titanium surface, so that GO was uniformly covered on the titanium scaffold.BMP-2 was encapsulated in gelatin microspheres and assembled on a GO/Ti scaffold, which was fixed by the functional group of GO. The results showed that the scaffold could deliver BMP-2 and induce bone regeneration. After assembling the gel microspheres containing vancomycin, it could also prevent bacterial infection. The scaffold can deliver multiple biomolecules with different physical and chemical properties independently without interfering with each other.

3.2 Drug-Loaded

Ren et al. [23] simply self-assembled GO tablets on titanium surface pretreated with alkali and loaded dexamethasone (DEX). Experimental results showed that Dex-Go-Ti could absorb a large amount of DEX and release it continuously, which significantly promoted the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells. Qiu et al. [24] found that after graphene oxide film loaded with minocycline hydrochloride (MH) was covered on the surface of titanium (MH&GO@Ti), in vitro alkaline phosphatase (ALP) activity and expression of osteogenic genes were enhanced. In vitro experiment, rBMSCs were co-cultured with Staphylococcus aureus on the surface of MH&GO@Ti, and the experimental results showed thatrBMSCs grew well on MH&GO@Ti samples with high cell coverage and almost no visible bacteria on the surface. In vivo experiments, MH&GO@Ti showed good antibacterial activity in the presence of bacteria. Ren et al. [25] modified the GO coating on the surface of Ti with alkali-hydrothermal reaction and silane coupling agent, loaded with aspirin (A), and conducted a preliminary study on the biological effects of inoculating it on mouse osteoblast MC3T3-E1. The results of torsion test showed that the bond coating and Ti remained stable under torsion shear force, and no coating was torn or shed on the sample surface. The release of aspirin onto the T-iGO surface can be maintained in 3d through π-π packing interaction. In addition, WST-8 assay and ALP activity assay confirmed that the proliferation rate of MC3T3-E1 cells on the A/T-iGO surface was significantly enhanced and the ability to differentiate into osteoblasts was significantly enhanced. Qian et al. [26] modified the surface of the titanium plate with GO and loaded minocycline hydrochloride, and studied the antibacterial activity of the sample with gram-positive Staphylococcus aureus, Streptococcus mutans and Gram-negative Escherichia coli. It was found that the GO modified titanium surface could inhibit the growth of bacteria that were in direct contact with GO, but had no inhibitory effect on bacteria that were not in direct contact with GO.GO modified titanium surface has a slow release effect on minocycline hydrochloride, and the contact killing of bacteria by GO and the release killing of bacteria by minocycline hydrochloride have a synergistic effect.

3.3 Supported ions

Xu et al. [27] prepared a bioactive coating as Sr2+ carrier on the surface of Ti by in-situ self-assembly of graphene oxide/polydopamine/strontium ion (GO/PDA/Sr2+) nanoparticle, and found that the ordered Sr2+ bound nanoparticle coating was conducive to improving mesenchymal stem cells (MSCs)The coating also has excellent protein adsorption capacity. In vitro biological evaluation showed that the synergistic effect of PDA, GO and released Sr2+ promoted the adhesion, diffusion and proliferation of MSCs growing on GO/PDA/Sr2+ coated Ti surface, promoted the expression of bone-specific genes and proteins, and accelerated extracellular matrix (ECM) mineralization. Tao et al. [28-29] used cathodic electrophoretic deposition (EPD) to prepare methyl acrylyl modified graphene oxide GO(GOMA) on Ti substrate, and used GOMA as a reservoir and release platform for zinc ions (Zn2+).Subsequently, phenylboric acid (PBA) functionalized methylacrylyl gelatin (GelMA-PBA) was prepared by in-situ radical polymerization with GOMA to prepare GOZn/GelMA-PBA coating. In vitro experiments on cell activity and alkaline phosphatase showed that GO-Zn/GelMA-PBA coating was beneficial to the adhesion, proliferation and differentiation of osteoblast. It was found that it had good antibacterial ability against Staphylococcus aureus and Pseudomonas aeruginosa, and effectively inhibited the adhesion of these two bacteria and prevented the formation of biofilm.

4. Conclusions

With the wide application of implant dentures, how to prolong the service life of implants has become a concern for many researchers. Although titanium implants have excellent physical and chemical properties and biological properties, there are still shortcomings. A variety of surface modification methods for improving their comprehensive properties continue to emerge, among which GO has been widely used in the modification of biological materials in recent years due to its superior performance, and its positive effects on the surface osteogenesis and antibacterial activities of titanium implants have been confirmed by a large number of experiments. In the future, scientists will continue to deeply explore the impact of different drugs on osteogenesis and antibacterial effects after integrating GO with titanium surface, and explore the most stable integration way of GO and titanium implant surface, in order to create implants with better performance.

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