ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 03 | March - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

OPTIMIZING TITANIUM IMPLANTS : UNVEILING THE POTENTIAL OF LOCALIZED DRUG DELIVERY IN OSSEOINTEGRATION

Dentistry

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ABSTRACT

Titanium and its alloys are the most widely used orthopaedic and dental implant materials due to their superior corrosion resistance, high biocompatibility and outstanding mechanical properties. Osseointegration is an essential factor for successful implantation. Surface modification of implants is an effective method to improve bone–implant integration. Commonly used surface modification methods include the additive modification and subtractive modification. Additive modification enhances the bioactivity of implants, whereas Subtractive modification methods helps in the formation of rough micro/nanostructure on implants to induce the adhesion, proliferation, and differentiation of osteoblasts. With advances in the biomedical field, the implant surface can be loaded with drugs to build a local drug delivery system which promotes bone formation, and provides anti-inflammatory and antibacterial effects. The local drug delivery systems such as antimicrobial drug delivery systems, anti-bone resorption drug delivery systems etc. proved to be effective method to improve osseointegration. These drug delivery systems can also be combined with traditional surface modification methods such as acid etching, anodic oxidation, surface coating technology etc to achieve enhanced osseointegration. This paper discusses about different methods of local drug delivery systems which enhance osseointegration.

KEYWORDS

Titanium, local drug delivery systems, osseointegration

INTRODUCTION

Titanium (Ti) and its alloys are the primary materials for orthopaedic and dental implants because of their high corrosion resistance, good biocompatibility and excellent mechanical properties.[1] Osseointegration is essential for the successful fixation of implants in patients. The concept of osseointegration was first put forward by Branemark et al. in the late 1960s. Branemark defined it "as a direct contact between the bone and metallic implants, without interposed soft tissue layers". Later it was modified "as a direct structural and functional connection between ordered, living bone and the surface of a load carrying implant.[2]Titanium and its alloys are considered the gold standard for clinical implant materials. The lack of bone–implant integration is the major reason that impedes the success of implants. Therefore, osseointegration of Ti-based implants needs to be improved to enhance the clinical success.[3]Surface modification of implants is an effective method to improve bone–implant integration. Commonly used surface modification methods include the additive modification and subtractive modification. Additive modification refers to the addition of extra materials to implant surface, such as active ion, inorganic/organic coating, growth factor, etc. to enhance the bioactivity of implants.[4] Subtractive modification methods includes anodic oxidation, laser treatment, acid–alkali treatment, sandblasting etc. These methods helps in the formation of rough micro/nanostructure on implants to induce the adhesion, proliferation, and differentiation of osteoblasts.[5] Many studies have suggested that osseointegration of implants can be improved by drug-assisted therapy.[6] Synthetic metabolic drugs, anticatabolic drugs, anti-inflammatory and antimicrobial drugs are proven to improve osseointegration. Synthetic metabolic drugs enhances osseo-integration by accelerating bone deposition around the implant.[7] Antimicrobials improve osseointegration by inhibiting infection. With advances in the biomedical field, the implant surface can be loaded with drugs to build a local drug delivery system which promotes bone formation, and provides anti-inflammatory and antibacterial effects. Therefore, promising method to achieve ideal osseointegration is to include a local drug delivery system on to the Ti-based implants. This article provides an overview of various local drug delivery methods incorporated onto titanium implant surfaces.

Local Drug Delivery Systems with Ti-Based Implants

1. Construction Approaches of Local Drug Delivery Systems

The main approaches to constructing drug delivery systems with Ti-based implants include sandblasting and acid etching (SLA), electrochemical anodization, layer-by-layer (LBL) self-assembly and dopamine (DA) immobilization.

Electrochemical Anodization:

Electrochemical anodization is the formation of an oxide film on the surface of metals and their alloys. This method is usually used to fabricate TiO2 nanotubes (TNTs) when constructing a drug delivery system. TNTs has the ability to regulate the behaviour of osteoblasts and stem cells and to improve osseointegration[8]

SLA:

Surface characteristics such as roughness and energy significantly influence cell differentiation, bone growth and osseointegration. SLA is most commonly used for surface modification of implants.[9] The abrasive medium material is sprayed on the surface of the implant by high-speed air flow to form a depression followed by acid etching to form smaller secondary structures and to clean impurities on the implant surface .SLA can increase the roughness of implants, helps in drug loading, and accelerate new bone formation around the implant.[10]

DA Immobilization:

DA Immobilization refers to the loading of drugs or factors on the Ti-based implants with the assistance of DA .DA has excellent biocompatibility and biodegradability in vivo.[11]

LBL Self-Assembly:

This surface modification method is based on the alternating assembly of oppositely charged polyelectrolytes to fabricate multilayer coatings .This method can release drugs layer by layer to promote osseointegration.[12]

2. Antimicrobial Drug Delivery System

The formation of bacterial biofilms on the implant surface is the main reason for implant related infections. The most commonly applied antibacterial treatment is oral antibiotics or systemic injection The researchers found that the local drug delivery system constructed on the implant surface has a high drug loading surface area and low drug delivery.

Local Delivery of Different Antimicrobials.

Vancomycin

Vancomycin (Van) is a glycopeptide. It has a good antibacterial activity for most Gram-positive bacteria due to the inhibition of the

growth and reproduction of bacteria.[13] Van is widely used to promote implant antibacterial activity and osseointegration capability .Yuan et al. fabricated a Van-loaded Ti-based implants with functional polymer coating. The implant slowly releases Van through the hyaluronidase degradation of the coating and improve osseointegration by inhibiting the attachment of bacteria and enhancing the attachment of osteoblasts.[14]

Gentamicin

Gentamicin (Gent) is an aminoglycoside antibiotic. Gent has good antibacterial activity for most Gram-negative bacteria by blocking the protein synthesis of bacteria Yang et al. found that Gent-loaded TNTs achieved desirable osseointegration in the rat model by significantly inhibiting the growth of bacteria and implant-associated infections.[15] Lee et al. fabricated a heparin-based Ti implant delivery system capable of releasing BMP-2 and Gent. This system significantly improved osseointegration by facilitating osteoblast activity and calcium deposition around the implant.[16]Escobar et al[17] constructed a Gent-loaded Ti implant and functionalized the implant with BMP-2. They found that implant could effectively inhibit bacterial proliferation and enhance osseointegration.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are oligopeptides that are involved in immune regulation.They have excellent broad-spectrum antibacterial activity.[18] AMPs can be used to enhance antimicrobial activity and bone–implant integration. Kazemzadeh-Narbat et al. constructed AMP-loaded calcium phosphate coating on Ti-based implants. They found that the osseointegration, antibacterial capability and bone conductivity of this implants were stronger than those of bare Ti.[19] Shen et al. fabricated LL37-loaded nanotubes and nanopores (NPs) on Ti substrates by the anodizing method. They concluded that the bonding ability to Ti substrate and osteogenic differentiation capability of NPs coating was stronger. The release of LL37 has markedly improved the antibacterial and osteogenic activity of implants.[20]

Other Antimicrobial Drugs

Cremer et al. prepared a porous Ti/SiO2 material containing the oral preservative chlorhexidine. They found that the release of chlorhexidine prevents the formation of bacterial biofilm on the implant surface.[21] The failure of osseointegration caused by bacterial infection could be prevented by direct grafting of antibiotic ciprofloxacin on Ti implants.[22,23] Park et al. loaded silver nanoparticles, cephalothin, minocycline (Mino) and amoxicillin on mesoporous TiO2 and confirmed that the combination of minocycline and silver nanoparticles could inhibit the growth and reproduction of bacteria.[24] Rocas et al. constructed shell-stratified, amphiphilic polyurethane–polyurea (PUUa) nanoparticles on a Ti implant, and roxithromycin was wrapped in the shell. The composite coating could promote osseointegration by suppressing bacteria growth and enhancing osteoblasts adhesion.[25]

3. Anti-Bone Resorption Drug Delivery System

Osteoclasts are mainly responsible for bone resorption. Osseo-integration can be achieved by anti-bone resorption drug delivery systems through mitigating osteoclast activity. Bisphosphate drugs such as zoledronic acid (ZA), alendronate (ALN), etc. which are commonly used to treat osteoporosis, have been proved to facilitate osseointegration of implants.[26,27]These drugs destroy the cytoskeleton of osteoclasts around the implant bone and inhibit the activity of osteoclasts. Researchers found that Ti implants loaded with bisphosphate drugs could inhibit the activity of osteoclasts from stimulating local bone regeneration and improve the osseointegration of Ti implants.[28] Recently ,Cui et al. filled the surface of a Ti implant with a new bisphosphate drug (technetium methylene diphosphonate (99Tc-MDP))-loaded poloxamer 407 hydrogel (TH/PTI). The composite scaffold inhibited the expression of genes related to osteoclasts and stimulated the expression of genes related to osteogenic differentiation.[29]

4. Bone Formation Drug Delivery System

Simvastatin (SV) is a kind of drug mainly used to reduce blood lipids. It was confirmed that it could stimulate osteoblast proliferation and differentiation and facilitate bone formation by enhancing the expression of the bone morphogenetic protein (BMP-2).[30] Yang et al. prepared porous Ti implants to release SV and proved that SV could accelerate the proliferation and differentiation of preosteoblasts and bone–implant integration by increasing the expression of ALP, type I collagen, and osteocalcin.[31] Liu et al. added hydrogel coating to SV-loaded porous Ti using 3D printing technology. The coating promoted angiogenesis and bone regeneration and improved osseointegration. Liu et al. grafted tetracycline (TC) in SV-loaded TNTs. TC is a broad-spectrum antibiotic with a strong affinity for bone minerals. The system improved the antibacterial activity ,bone targeting and osseointegration of Ti.[32] Several studies pointed out that some vitamins had certain bone targeting and could promote osteoblast maturation. Sarkar et al. constructed HA-coated Ti implant and added vitamin K2 and curcumin to it. The implant loaded with dual drugs enhanced the function of osteoblasts in vitro and improve osseointegration in vivo.[33]

5. Anti-Inflammatory Drug Delivery System

As a foreign body, implants may cause an inappropriate or excessive immune response, leading to cell or tissue damage and a series of inflammatory reactions, thus resulting in poor bone–implant integration. Studies confirmed that macrophages played an important role in regulating inflammation. Specifically, the polarization of macrophages from the M1 pro-inflammatory phenotype to the M2 anti-inflammatory phenotype inhibits inflammation.[34] Based on this property, Shen et al. confirmed that Ti/LBL/Mino enhanced the osteogenic differentiation of mesenchymal stem cells by promoting the conversion of macrophages to anti-inflammatory phenotype.[35]Ren et al. solved the inflammation due to wear particles around the implant by smearing erythromycin on Ti.[36]

The critical factor for successful implantation in vivo depends on excellent integration between the implant and bone. Osseointegration was affected by different factors such as inflammation, bacterial infection etc. during the bone healing phase after implantation. These factors may result in Ti-based implants failing to stimulate the biological activity of surrounding osteocytes, triggering infection and activating abnormal phagocytosis of macrophages. The effective method for enhancing osseointegration was to construct a Ti-implant-based local drug delivery system. The release of anti-bone resorption drugs could transform bone metabolism into bone deposition by inhibiting the absorptive activity of osteoclasts[37] whereas with the release of anti-inflammatory drugs, the system could solve aseptic loosening by mitigating local inflammatory responses.[38]

Currently, biodegradable coatings (such as PLGA, PDLLA, hydrogel, etc.) have widely been studied because of their continuous and controllable drug release.[39] Recently, with the continuous development of the field of biomedical, an increasing number of researchers use 3D printing technology to customize the local delivery systems based on Ti-based implants .But 3D printing technology has several challenges, such as high prices and difficulties in industrialization.. Though these local drug delivery systems showed desirable therapeutic effects in animal models, they can be directly applied to patients only after conducting more in vivo studies.

CONCLUSION

The construction of different local drug delivery systems, such as antimicrobial drug delivery systems, anti-bone resorption drug delivery systems etc. on Ti-based implants can effectively improve osseointegration. In present condition it is difficult to support the transformation of Ti-based drug delivery systems to the clinical stage as only limited studies were done in vivo. In future, more in vivo experiments should be carried out to promote the large-scale clinical applications of Ti-based drug delivery systems.

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