A Comprehensive Review of Surface Coatings for Enhancement of Anti-Microbial And Anti-Corrosive Properties of Titanium Implant Surface

Abstract:

Dental implants have revolutionized the field of restorative dentistry, providing a durable and long-lasting solution for replacing missing teeth. Among various biomaterials, titanium has proven to be the most suitable material for dental implants because of its incredible biocompatibility, mechanical properties, and unique surface characteristics. This scientific write-up reviews the comprehensive overview of various surface modification techniques employed to improve the osseointegration, antimicrobial properties, surface topography, and anti-corrosion behavior of titanium as a dental implant biomaterial, highlighting its role in improving implant success rates and long-term clinical outcomes.I

Lacunae on the topic of discussion:

As per our knowledge no extensive review exists that discusses the multifactorial aspects with respect to surface topography, anti-corrosion, and anti-microbial properties of commercially pure titanium or titanium alloy as a whole, altogether. This review compiles all these aspects.

Key-words: Titanium,Biomaterial, Dental Implant, Surface Modification, Surface Coating

Introduction:

Titanium is widely used as a biomaterial for dental and orthopedic implants due to its excellent biocompatibility and mechanical properties. However, the inherent properties of titanium can be further optimized through surface modifications to achieve better outcomes. Surface modifications can alter the surface topography, chemistry, and biological responses of titanium implants, influencing their osseointegration, antimicrobial properties, and corrosion resistance. This write-up explores various surface modification techniques and their implications for improving the performance of titanium implants.

1. Physical Surface Modifications:

1.1 Sandblasting and Etching:

Sandblasting involves the projection of abrasive particles onto the titanium surface, creating micro-scale roughness that promotes enhanced osseointegration. Etching involves the use of acid solutions to produce a nanoscale roughened surface. Sandblasting and etching can be combined to create a micro-nano hybrid surface, which has shown superior osseointegration and increased osteoblast activity[1].

1.2 Plasma Spraying:

Plasma spraying deposits biocompatible coatings, such as hydroxyapatite (HA) or calcium phosphate, onto the titanium surface. These coatings enhance the biological interaction with bone tissue, promoting faster osseointegration and improving implant stability[2]

Access this article online	
Website: www.ujds.in	Quick Response Code
DOI: https://doi.org/10.21276/ujds.2023.9.3.26	

[1]ANKITA SINGH, [2]ABHISHEK SARKAR, [3]SURESH SHRI POKARRAM, [4]T.P CHATURVEDI

[1-4]Faculty of Dental Sciences, IMS, BHU, Varanasi

Address for Correspondence: Dr. Ankita Singh
Associate Professor, Faculty of Dental Sciences, IMS, BHU, Varanasi-221005, Uttar Pradesh, India.
Email : ankita.singh2@bhu.ac.in

Received : 25 July, 2023, **Published :** 31 August, 2023

How to cite this article: Singh, A., Sarkar, A., Pokarram, S. S., & Chaturvedi, T. P. (2023). A Comprehensive Review of Surface Coatings for enhancement of Anti-Microbial and Anti-Corrosive Properties of Titanium Implant Surface. UNIVERSITY JOURNAL OF DENTAL SCIENCES, 9 (special is). 82-93

1.3 Anodization:

Anodization involves subjecting the titanium surface to an electrochemical process, forming a stable oxide layer with controlled nanopores. This nanostructured surface has demonstrated improved osteogenic activity and a higher degree of osseointegration[3].

2. Chemical Surface Modifications:

2.1 Acid Treatment:

Acid treatment involves the use of acidic solutions to modify the titanium surface, removing contaminants and creating a roughened topography. Acid treatment increases surface energy, promoting cell adhesion and osseointegration[4].

2.2 Surface Coating:

Surface coatings with bioactive materials, growth factors, or antimicrobial agents have been explored to improve the biological response of titanium implants. These coatings can enhance osteoblast activity, reduce bacterial adhesion, and prevent infection[5].

3. Biological Surface Modifications:

3.1 Protein Immobilization:

Protein immobilization techniques involve the attachment of bioactive proteins, such as bone morphogenetic proteins (BMPs), to the titanium surface. This stimulates cell signaling pathways, accelerating bone regeneration and osseointegration[6].

3.2 Cell Seeding:

Cell seeding techniques involve the attachment of osteogenic cells, such as mesenchymal stem cells (MSCs), onto the titanium surface before implantation. Cell-seeded implants have shown improved bone formation and integration[7].

4. Antimicrobial Properties:

The antimicrobial properties of dental implants are crucial for preventing bacterial colonization, biofilm formation, and subsequent peri-implantitis. Titanium's inherent resistance to microbial adhesion is attributed to its oxide layer, which rapidly forms upon exposure to air, known as titanium dioxide (TiO_2). TiO_2 exhibits photocatalytic properties when exposed to UV light, generating reactive oxygen species (ROS) that have antimicrobial effects against a wide range of bacteria, including Gram-positive and Gram-negative strains[8].

Biofilm-associated infections represent a medical and surgical challenge by the destruction of the adjacent tissue leading to poor vascularization, implant loosening, detachment, or even dislocations[9]. Bacteria adhere to surfaces with the help of a continuously maturing biofilm. Stage I shows rapid and reversible initial interaction between the bacterial cell surfaces and material surfaces, while in stage II, there is specific and non-specific interactions happening between proteins on the bacterial surface structures, namely fimbriae or pili, and binding molecules on the surface of the material.

Material deterioration and the spread of pathogens can both be prevented by the prevention of biofilm formation by the elaboration of antimicrobial surfaces. Thus, materials must prevent the primary adhesion of living planktonic microbial cells from their environment. Achievement of the above can be done via repelling or killing of the approaching bacteria.

Additionally, surface modifications, such as nanotexturing, have been explored to enhance the antimicrobial potential of titanium implants. Nanotextured surfaces exhibit increased surface area and altered surface energy, which can disrupt bacterial adhesion and colonization[10]. Furthermore, incorporating antimicrobial agents, such as silver nanoparticles or antimicrobial peptides, into the titanium surface has shown promising results in reducing bacterial adhesion and biofilm formation[11]

5. Surface Topography:

Titanium's surface topography plays a crucial role in osseointegration, the process by which bone integrates with the implant surface. Micro- and nano-scale features on the implant surface influence cellular responses and protein adsorption, affecting osteoblast activity and bone formation. Studies have shown that certain surface topographies, such as moderately rough or nanostructured surfaces, promote enhanced osseointegration compared to smooth surfaces [12]. On the macro scale, the use of 3D printing and laser surface texturing is used to create irregularities and pores on the titanium substrate surface, thereby increasing the bone-implant contact and consequently, osseointegration[15].

Advanced surface modification techniques, including sandblasting, acid etching, anodization, and laser treatment, are employed to create controlled surface topographies on titanium implants. These methods optimize surface roughness and energy, facilitating improved osteogenic responses and accelerating bone healing around the implant[2].

The micro-scale titanium implant surface modifications include sand-blasting, grit-blasting & acid etching.

Grit-blasting has been a reliable method to induce surface roughness in which the hard ceramic particles are ejected by compressed air at a high velocity through a nozzle. The surface roughness mainly depends on the size of the ceramic particles, ranging from 110 to 250 microns. It is imperative that the ceramic particles should have characterizations of stability and biocompatibility, thus not affecting the ingrowth of bone cells in the titanium implants. The abrasive particles that are usually used are of aluminum oxide (Al2O3), silicon oxide (SiO2), titanium oxide (TiO2), and calcium phosphate composition.

Acid-etching is a procedure in which titanium implant surfaces are roughened with strong acid solutions, namely hydrochloric acid (HCl), nitric acid (HNO3), sulfuric acid (H2SO4), hydrofluoric acid (HF), and other combined acid solutions. For instance, the purpose of acid-etching processingmostly is for removing the residual particles remaining from the previous grit-blasting processes onthe implant surfaces. Also, acid-etching readies the structure of the micro-pits with pit sizesin the range of 0.5–2 microns.[16,17].

The surface treatment employed by the combination of grit-blasting with acid-etching procedures is known as SLA. Experimental studies[18-21] reported that SLA-treated surfaces are beneficial, with increased biocompatibility in the early bone formation stage and also in cell differentiation. There is a positive effect on the activation of blood platelets and cell migration after SLA treatment due to the alteration of the surface topography of titanium implants.Studies[22-25] proved that hydrophilic surfaces can further shorten the osseointegration process. Titanium implants which are treated with SLA and are immersed in isotonic solution at low pH to produce a super-hydrophilic titanium surface. Compared with acid-etching surfaces, the super-hydrophilic surface can increase BIC in2–4 weeks[26-30]. The various nano-scale surface modifications have been discussed in brief in the next section.

6. Anti-Corrosion Properties:

Corrosion resistance is critical for the long-term success of dental implants, as it prevents the release of metal ions into the surrounding tissues, which may trigger adverse reactions and compromise the implant's stability. Titanium, in its native form, possesses excellent corrosion resistance due to the rapid formation of a passive oxide layer upon exposure to oxygen. This layer acts as a barrier against corrosive agents and protects the underlying titanium substrate from degradation[13].

Moreover, various surface treatments, such as plasma spraying, physical vapor deposition, and ion implantation, have been explored to enhance the anti-corrosion properties of titanium implants.

Plasma spraying technology is a physical method, which involves spraying melted coating material onto Ti substrate surfaces using a direct current arc plasma gun, producing a 30-micron thick coating.

It was seen with a study[31] that a three-dimensional topography formation positively had increased the mechanical interlock and tensile strength between the bone in question and implant surfaces. Titanium implants was treated using SLA and they were immersed in isotonic solution at low pH to produce a super-hydrophilic titanium surface.

Li etal.[32] fabricated nano-TiO2/Ag and nano-TiO2 coatings using a plasma-spraying technique on titanium substrates to improve the bioactive and antibacterial properties.

Anodization is a technology to change the roughness and topographic features on the surface of titanium with many influencing variables, such as oxidation duration, oxidation voltage, electrolyte solution type, electrolyte solution concentration and the subsequent heat treatment process. Nanopores and nanotubes can be induced by constant potential anodization in different acid solutions (e.g., H2SO4, HF, H3PO4, HNO3) for various time spans[33,34]. Compared with machined surfaces, anodized surfaces enhanced the bone response in biomechanical and histomorphometric experiments[35].

The anodized studies in references[34,36] possess nano-scale surfaces, enabling them to load and to deliver multifunctional molecules and growth factors, thus accelerating early bone integration. The wall thickness, diameter, and length of nanotubes directly depend on the anodization parameters such as oxide temperature, voltage, time, and electrolyte concentration[37]. Nanotubes increase the contact surface area resulting in an increase in wettability and adsorption of proteins and ions[34,38-40].

For instance, loading antibacterial ions on nanotubes can prevent biofilm formation and reduce bacteria in the peri-implant region to avoid early failure of the implant[41-43].Several experimental studies[44,45] indicated that the length of TiO2 nanotubes has an influence on biocompatibility, while their diameter has a critical effect on cell adhesion and proliferation. The best osteoconductivity was reported in 70 nm diameter nanotubes, meanwhile, 80 nm diameter nanotubes also showed improved proliferation and differentiation behavior[46-48].

These techniques create a protective coating on the titanium surface, further improving its resistance to corrosion and ion release[49,50].

Table 1. Different types of titanium implant coatings and their antibacterial effects.

Coating Types	Composition	Major Techniques	Antibacterial Efficiency seen In Vitro Studies	References
Inorganic ions/elements	Ag-doped TiO_2	Plasma Electrolytic Oxidation (PEO)	Significant reduction ($p < 0.05$) in cell numbers of Escherichia coli and Staphylococcus aureus and their metabolic activity. High silver content samples showed to have a 6-log reduction of S. aureus	Thukkaram M. et al.(2020) [51]
	Ag nanoparticles (Ag NP)-loaded calcium-phosphate solution	Plasma Electrolytic Oxidation	Antibacterial action against Staphylococcus aureus is seen (strain B 918)	Oleshko O. et al.(2020) [52]
	Zn doped HAP	Solution Precursor Plasma Spray (SPPS) process	Antibacterial action against Escherichia coli and Staphylococcus aureus is evident	Sergi R. et al.(2018) [53]
	Selenium incorporated onto microporous titanium dioxide coatings with Ca and P on titanium substrates	Micro-arc oxidation (MAO)	A minimum of 94% killing potential after 28 days was observed for Escherichia coli and Staphylococcus aureus in in-vitro studies	Zhou J. et al.(2020) [54]
	Zn/Sr-doped titanium dioxide	Micro-arc oxidation	Fewer surviving colonies of Staphylococcus aureus was observed in spread plate analysis	Zhao Q. et al.(2019) [55]
	Bismuth doped with nanohydroxyapatite	Alkali-thermal treatment done	Large zone of inhibition was being seen for Escherichia coli and Staphylococcus aureus	Ciobanu G. et al.(2019) [56]
	Samarium and Strontium on TiO_2 nanotubes	Anodization	Nearly 100% antibacterial activity was observed for Escherichia coli and Staphylococcus aureus over plate counting experiments	Zhang X. et al.(2020) [57]

		Zone of inhibition evident; was larger for Staphylococcus aureus than Escherichia coli.	
TiO_2 nanotubes doped with gallium	Anodization and solvent casting	Low concentration of live Staphylococcus aureus and Escherichia coli was observed in Live/Dead cell assay	Dong J.et al.(2019)[58]
Ag–HAP-fluoride	Sol-gel	96% reduction in Escherichia coli was observed after 6 h in spread plate results for Ag—HAP-fluoride coating which had 0.3% w/v of Ag and P/F ratio of 6	Batebi K. et al.(2018)[59]
ZnO-HAP	Spin coating	Drastic reduction in the colonies of Escherichia coli and Staphylococcus aureus was seen after 4 h of incubation	Ohtsu N. et al.(2018)[60]
Niobium doped with hydroxyapatite	Microwave irradiation done	A large zone of inhibition was seen for Escherichia coli and Bacillus subtilis	Panda S. et al.(2022)[61]
Cerium incorporated collagen-HAP	Immersion of the titanium substrate in supersaturated calcification solution (Ce-SCS)	After 24 h incubation 92.61% Escherichia coli and 73.59% Staphylococcus aureus were observed to be eradicated	Ciobanu G. et al.(2018)[62]
Calcium Titanate Iodine coating	Solution and heat treatment method that controllably incorporates 0.7% to 10.5% of Iodine into Titanium	About 99% of bactericidal activity was seen for Methicillin-resistant Staphylococcus aureus, Staphylococcus aureus, Escherichia coli and Staphylococcus epidermidis	Yamaguchi S. et al.(2021)[63]
TiN and SiC coating	Magnetron sputtering, Plasma-enhanced chemical vapor deposition system (PECVD)	Reduction was seen in number of live Porphyromonas gingivalis was observed after 4 h of incubation.	Camargo S.E.A. et al.(2020)[64]
Gentamicin loaded zinc–incorporated Halloysites (ZnHNTs)–Chitosan	Electrodeposition (EPD)	Inhibition zones of 3.11 ± 0.79 cm^2/unit area of the sample was seen in disc diffusion assay for Staphylococcus aureus	Humayun A. et al.(2020)[65]

	Gentamicin and polyacrylic acid (PAA)	Layer-by-layer assembly	About 99% of bactericidal activity wasseen present for Staphylococcus aureusand Escherichia coli	He - L. J. et al.(2020)[66]
	Chitosan/cefazolin	Electrophoretic deposition	Nearly 100% bactericidal activity against Escherichia coli was shown by the coating which had the highest drug concentration	Chen S. -T. et al.(2021)[67]
Antibiotic based	Levofloxacin loaded graphene coating	Sandblasting done with large-grit with acid-etching and salinizationalso done	Here large bacteriostatic circle diameters were seen for Staphylococcus aureus andEscherichia coli	Sun J. et al.(2021)[68]
	Chitosan here was coated with a thin layer of melittin and loaded with the antibiotics namely vancomycin and Oxacillin	Spin coating and casting methodwas followed	It was observed that the coatings were able toeradicateMethicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin - Resistant Staphylococcus aureus(VRSA) at the early stages	Zarghami V. et al. (2021)[69]
	poly L lysine (PLL)/sodium alginate (SA)/Silver nanoparticles	Electrostatic self-assembly, dip coating	A distinct ring wasseenin zone of inhibition test for Staphylococcus aureus and Staphylococcus mutans	Guo C. et al.(2020)[70]
	N-halamine based porous coating (Ti - PAA-NCl)	Alkali-heat treatment, surface grafting and NCl - functionalization	Bactericidal rate of 96% for Staphylococcus aureus and 91% Porphyromonasgingivalis was observed in contact killing assay	Wu S. et al.(2021)[71]
	Diethyl phosphite (DEP) coated Titanium ($_{pp}$(DEP)-Ti)	Plasma polymerization	The number of Staphylococcus aureus and Candida albicanscolonies decreased after 24 h	Kaleli-Can G. et al.(2020)[72]
	Phosphonate and active ester block copolymers (pDEMMP-b-pNHSMA) and PHMB	Reversible addition fragmentation chain transfer (RAFT) polymerization was observed.	Nearly 100% antibacterial activity was observed for Staphylococcus aureus and Escherichia coli	Peng J. et al.(2021)[73]
	A recombinantelastin - like peptide coating with cell - adhesive RGD sequences with a covalently attached AMP observed, RRP9W 4	Covalent immobilization of AMPs to titanium surface	The number of dead Staphylococcus epidermidis, Staphylococcus aureus,and Pseudomonas aeruginosa cells increased after 48 h	Atefyekta S. et al.(2019)[74]

Antimicrobial Peptide based	RRP9W4N incorporated into mesoporous TiO_2.	Spin-coating	Bactericidal action was seen against Staphylococcus epidermidis	Pihl M. et al.(2021)[75]
	Pectolite nanorod (NCS) with AMP-loaded collagen shell	Microarc oxidation (MAO), Spin coating	Contact killing efficiency was almost 100% for Staphylococcus aureus	Zhang L. et al.(2021)[76]
	poly (quaternary ammonium salts - co - methacrylic acid) (PQA)	Anodic Oxidation and Spray coating	Efficient antibacterial action was seen against Escherichia coli and Staphylococcus aureus	Lin J. et al.(2021)[77]
Multifunctional Coatings	P (vinylcaprolactam (VCL)–co-polyethylene glycol methacrylate (PEGMA)–co-alkyl-dimethyl tertiary amine (QAS)-co-vinyltrimethoxysilane (VTMO)) copolymer/ TiO_2 nanotube	Layer-by-layer (LbL) self-assembly method	Antibacterial action was seen at lower pH for Staphylococcus aureus and Escherichia coli	Zhang F. et al.(2022)[78]
	Nano amorphous calcium phosphate (ACP) and titanium dioxide with chitosan oligosaccharide lactate (ChOL) was used.	Anodization and anaphoretic electrodeposition was done.	Evidence of reduction by three-to-four-fold in the number of Staphylococcus aureus and Pseudomonas aeruginosa colonies was seen after 420 min	Pavlović M.R.P. et al.(2021)[79]
	poly (methacrylic acid) (PMAA) loaded onto TiO_2 nanotubes (Ti-NTs) with HHC36 peptides, with a sequence of KRWWKWWRR	- Anodization	99% of bactericidal activity was seen for Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Methicillin - resistant Staphylococcus aureus	Chen J. et al.(2020)[80]
	Yb and Er doped Ti nano - shovel/quercetin/L-arginine (TiO_2/UCN/Qr/LA)	Phototherapy	Above 90% bactericidal action against Staphylococcus aureus was observed	Zhang G. et al.(2021)[81]

Conclusion:

Surface modifications of titanium implants have emerged as a critical aspect of implantology, with the potential to significantly enhance implant performance and clinical outcomes. Various physical, chemical, and biological surface modification techniques have been developed to optimize osseointegration, antimicrobial properties, and corrosion resistance. The choice of surface modification technique depends on the specific application and desired outcomes. Further research and clinical studies are warranted to fully understand the long-term effects and benefits of these surface modifications for titanium implants.

Titanium has demonstrated exceptional performance as a dental implant biomaterial, owing to its unique combination of antimicrobial properties, surface topography optimization, and inherent anti-corrosion behavior. The ability of titanium implants to resist microbial colonization, promote osseointegration, and prevent corrosion contributes significantly to their high success rates and favorable long-term clinical outcomes.

References:

1. Geetha M, Singh AK, Asokamani R, Gogia AK. Ti based biomaterials, the ultimate choice for orthopaedic implants - A review. Prog Mater Sci. 2009;54(3):397-425.
2. Guo Y, Zhou L, Zhang W, et al. Enhancement of bioactivity of a micro-arc oxidized titanium implant with a nanotopographic surface: an in vitro study. Int J Nanomedicine. 2014;9:2843-2855.
3. Park J, Bauer S, Schmuki P, von der Mark K. Narrow window in nanoscale dependent activation of endothelial cell growth and differentiation on TiO2 nanotube surfaces. Nano Lett. 2009;9(9):3157-3164.
4. Olivares-Navarrete R, Raz P, Zhao G, et al. Integrin alpha2beta1 plays a critical role in osteoblast response to micron-scale surface structure and surface energy of titanium substrates. Proc Natl Acad Sci U S A. 2008;105(41):15767-15772.
5. Shi Z, Huang X, Cai Y, Tang R. Biomimetic Nanosheet-Coated Ti with Enhanced In Vivo Osteointegration and Antibacterial Property. ACS Appl Mater Interfaces. 2017;9(39):33424-33432.
6. Klein CP, Patka P, Wolke JG, de Blieck-Hogervorst JM, van der Lubbe HB, de Groot K. Long-term in vivo study of porous pure titanium (pTi) implants. Biomaterials. 1998;19(5):435-439.
7. Hu X, Neoh KG, Zhang J, Kang ET. Protein-functionalized polymer brushes on Ti surfaces: surface characterization and in vitro human osteoblasts compatibility. Biomaterials. 2004;25(17):4215-4227.
8. Ivanova EP, Hasan J, Webb HK, et al. Natural bactericidal surfaces: mechanical rupture of Pseudomonas aeruginosa cells by cicada wings. Small. 2012;8(16):2489-2494.
9. D. Campoccia, L. Montanaro, C.R. Arciola, The significance of infection relatedto orthopedic devices and issues of antibiotic resistance, Biomaterials 27 (2006)2331–2339,https://doi.org/10.1016/j.biomaterials. 2005.11.044
10. Mei S, Cai Y, Wang L, et al. Nanostructured titanium enhances osseointegration via bactericidal effect under osteoporotic conditions. Biol Trace Elem Res. 2019;191(2):326-334.
11. Wang X, Wu H, Liu L, Zhang W, Chen J, Wang L. The hemocompatibility, antibacterial activity, and corrosion resistance of titanium treated by hydrogen peroxide plasma immersion ion implantation and deposition. Appl Surf Sci. 2017;404:108-116.
12. Wennerberg A, Albrektsson T. On implant surfaces: a review of current knowledge and opinions. Int J Oral Maxillofac Implants. 2010;25(1):63-74.
13. Huth KC, Saugspier M, Cappello C, et al. Corrosion susceptibility of dental titanium implants. Clin Oral Implants Res. 2018;29(9):900-908.
14. Liu Y, He J, Chen L, et al. Recent advances in surface modification techniques for titanium-based dental implants. J Nanomater. 2015;2015:381759.
15. Wang Q, Zhou P, Liu S, Attarilar S, Ma RL, Zhong Y, Wang L. Multi-Scale Surface Treatments of Titanium Implants for Rapid Osseointegration: A Review. Nanomaterials (Basel). 2020 Jun 26;10(6):1244. doi: 10.3390/nano10061244. PMID: 32604854; PMCID:PMC7353126.
16. Napoli, A.;Wieland, M.; Textor, M.; Spencer, N.D. Comparative investigation of the surface properties of commercial titanium dental implants. Part I: Chemical

composition. Mater. Sci. Mater. Med. 2002, 13, 535–548.
17. Zinger, O.; Anselme, K.; Denzer, A.; Habersetzer, P.;Wieland, M.; Jeanfils, J. Time-dependent morphology and adhesion of osteoblastic cells on titanium model surfaces featuring scale-resolved topography. Biomaterials 2004, 25, 2695–2711
18. Nagasawa, M.; Cooper, L.F.; Ogino, Y.; Mendonca, D.; Liang, R. Topography influences adherent cell regulation of osteoclastogenesis topography influences adherent cell regulation of osteoclastogenesis. J. Dent. Res. 2015, 95, 319–326.
19. Ziebart, T.; Schnell, A.; Walter, C. Interactions between endothelial progenitor cells (EPC) and titanium implant surfaces. Clin. Oral Investig. 2013, 17, 301–309.
20. Lagonegro, P.; Trevisi, G.; Nasi, L.; Parisi, L.; Manfredi, E. Osteoblasts preferentially adhere to peaks on micro-structured titanium Osteoblasts preferentially adhere to peaks on micro-structured titanium. Dent. Mater. 2018, 37, 278–285.
21. Wang, X.; Wang, Y.; Bosshardt, D.D.; Miron, R.J.; Zhang, Y. The role of macrophage polarization on fibroblast behavior-an in vitro investigation on titanium surfaces. Clin. Oral Investig. 2017, 22, 847–857.
22. Zhang, J.; Liu, J.;Wang, C.; Chen, F.;Wang, X.; Lin, K. A comparative study of the osteogenic performance between the hierarchical micro/submicro-textured 3D-printed Ti6Al4V surface and the SLA surface. Bioact. Mater. 2020, 5, 9–16.
23. Donos, N.; Horvath, A.; Mezzomo, L.A.; Dedi, D.; Calciolari, E.; Mardas, N. The role of immediate provisional restorations on implants with a hydrophilic surface: A randomised, single-blind controlled clinical trial. Clin. Oral Implants Res. 2018, 29, 55–66.
24. Shibli, J.A.; Eduardo, C.; Preshaw, P.M. Efficacy of standard (SLA) and modified sandblasted and acid-etched(SLActive) dental implants in promoting immediate and/or early occlusal loading protocols: A systematicreview of prospective studies. Clin. Oral Implants Res. 2015, 26, 359–370.
25. Vasak, C.; Busenlechner, D.; Schwarze, U.Y.; Leitner, H.F.; Guzon, F.M.; Hefti, T.; Schlottig, F.; Gruber, R.Early bone apposition to hydrophilic and hydrophobic titanium implant surfaces: A histologic and histomorphometric study in minipigs. Clin. Oral Implants Res. 2014, 25, 1378–1385.
26. Alfarsi, M.A.; Hamlet, S.M.; Ivanovski, S. Titanium surface hydrophilicity modulates the human macrophage inflammatory cytokine response. J. Biomed. Mater. Res. Part A 2014, 102, 60–67.
27. Wennerberg, A.; Jimbo, R.; Stübinger, S.; Obrecht, M.; Dard, M.; Berner, S. Nanostructures and hydrophilicity influence osseointegration: A biomechanical study in the rabbit tibia. Clin. Oral Implants Res. 2014, 25, 1041–1050.
28. Lang, N.P.; Salvi, G.E.; Huynh-Ba, G.; Ivanovski, S.; Donos, N.; Bosshardt, D.D. Early osseointegration to hydrophilic and hydrophobic implant surfaces in humans. Clin. Oral Implants Res. 2011, 22, 349–356.
2.) Karabuda, Z.C.; Abdel-Haq, J.; Arisan, V. Stability, marginal bone loss and survival of standard and modified sand-blasted, acid-etched implants in bilateral edentulous spaces: A prospective 15-month evaluation. Clin. Oral Implants Res. 2011, 22, 840–849.
30. Kulterer, B.; Friedl, G.; Jandrositz, A.; Sanchez-cabo, F.; Prokesch, A.; Paar, C.; Scheideler, M.; Windhager, R.; Preisegger, K.; Trajanoski, Z. Gene expression profiling of human mesenchymal stem cells derived from bone marrow during expansion and osteoblast di erentiation. BMC Genom. 2007, 8, 70.
31. Lai, H.-C.; Zhuang, L.-F.; Zhang, Z.-Y.;Wieland, M.; Liu, X. Bone apposition around two different sandblasted, large-grit and acid-etched implant surfaces at sites with coronal circumferential defects: An experimental study in dogs. Clin. Oral Implants Res. 2009, 20, 247–253.
32. Li, B.; Liu, X.; Meng, F.; Chang, J.; Ding, C. Preparation and antibacterial properties of plasma sprayed nano-titania/silver coatings. Mater. Chem. Phys. 2009, 118, 99–104.
33. Souza, J.C.M.; Sordi, M.B.; Kanazawa, M.; Ravindran, S.; Henriques, B.; Silva, F.S.; Aparicio, C.; Cooper, L.F.Nano-scale modification of titanium implant surfaces to enhance osseointegration. Acta Biomater. 2019, 94,112–131.
34. Alves, S.A.; Patel, S.B.; Sukotjo, C.; Mathew, M.T.; Filho, P.N.; Celis, J.-P.; Rocha1, L.A.; Shokuhfar, T. Synthesisof calcium-phosphorous doped TiO2 nanotubes by anodization and reverse polarization: A promisingstrategy for an effcientbiofunctional implant surface. Appl. Surf. Sci. 2016, 399, 682–701.

35. Albrektsson, T. Resonance frequency and removal torque analysis of implants with turned and anodized surface oxides. Clin. Oral Implants Res. 2002, 13, 252–259.
36. Grotberg, J.; Hamlekhan, A.; Butt, A.; Patel, S.; Royhman, D.; Shokuhfar, T.; Sukotjo, C.; Takoudis, C.; Mathew, M.T. Thermally oxidized titania nanotubes enhance the corrosion resistance of Ti6Al4V. Mater. Sci. Eng. C Mater. Biol. Appl. 2016, 59, 677–689.
37. Ma, M.; Liu, J.; Wu, Z.; Zheng, X.; Hu, X.; Li, X. Progress of studies on fabrication of TiO2 nanotube arrays on Ti or Ti alloys by anodization. Adv. Mater. Res. 2014, 941–944, 441–444.
38. Shin, D.H.; Shokuhfar, T.; Choi, C.K.; Lee, S.-H.; Friedrich, C. Wettability changes of TiO2 nanotube surfaces. Nanotechnology 2011, 22, 315704.
39. Beltrán-Partida, E.; Moreno-Ulloa, A.; Valdez-Salas, B.; Velasquillo, C.; Carrillo, M.; Escamilla, A.; Valdez, E.; Villarreal, F. Improved osteoblast and chondrocyte adhesion and viability by surface-modified Ti6Al4V alloy with anodized TiO2 nanotubes using a super-oxidative solution. Materials (Basel) 2015, 8, 867–883.
40. Beltrán-Partida, E.; Valdez-Salas, B.; Escamilla, A.; Curiel, M.; Valdez-Salas, E.; Nedev, N.; Bastidas, J.M. Disinfection of titanium dioxide nanotubes using super-oxidized water decrease bacterial viability without disrupting osteoblast behavior. Mater. Sci. Eng. C 2016, 60, 239–245.
41. Li, H.; Cui, Q.; Feng, B.; Wang, J.; Lu, X.; Weng, J. Antibacterial activity of TiO2 nanotubes: Influence of crystal phase, morphology and Ag deposition. Appl. Surf. Sci. 2013, 284, 179–183.
42. Liu,W.; Su, P.; Iii, A.G.; Chen, S.;Wang, N.;Wang, J.; Li, H.; Zhang, Z. Optimizing stem cell functions and antibacterial properties of TiO2 nanotubes incorporated with ZnO nanoparticles: Experiments and modeling. Int. J. Nanomed. 2015, 10, 1997–2019.
43. Quirynen, M.; Van Assche, N. RCT comparing minimally with moderately rough implants. Part 2: Microbialobservations. Clin. Oral Implants Res. 2012, 23, 625–634.
44. Wang, N.; Li, H.; Lü, W.; Li, J.; Wang, J.; Zhang, Z.; Liu, Y. E. Effects of TiO2 nanotubes with different diameters on gene expression and osseointegration of implants in minipigs. Biomaterials 2011, 32, 6900–6911.
45. Su, E.P.; Justin, D.F.; Pratt, C.R.; Sarin, V.K. Effects of titanium nanotubes on the osseointegration, cell differentiation, mineralisation and antibacterial properties of orthopaedic implant surfaces. Bone Jt. J. 2018,100, 9–16.
46. Ma, M.; Liu, J.; Wu, Z.; Zheng, X.; Hu, X.; Li, X. Progress of studies on fabrication of TiO2 nanotube arrays on Ti or Ti alloys by anodization. Adv. Mater. Res. 2014, 941–944, 441–444.
47. Salou, L.; Hoornaert, A.; Louarn, G.; Layrolle, P. Enhanced osseointegration of titanium implants with nanostructured surfaces: An experimental study in rabbits. Acta Biomater. 2015, 11, 494–502.
48. VonWilmowsky, C.; Bauer, S.; Roedl, S.; Neukam, F.W.; Schmuki, P.; Schlegel, K.A. The diameter of anodic TiO2 nanotubes affects bone formation and correlates with the bone morphogenetic protein-2 expression in vivo. Clin. Oral Implants Res. 2012, 23, 359–366.
49. H. Chouirfa, H. Bouloussa, V. Migonney, C. Falentin-Daudré, Review of titanium surface modification techniques and coatings for antibacterial applications, Acta Biomaterialia, Volume 83, 2019, Pages 37-54, ISSN 1742-7061.
50. Lu X, Wu Z, Xu K, Wang X, Wang S, Qiu H, Li X and Chen J (2021) Multifunctional Coatings of Titanium Implants Toward Promoting Osseointegration and Preventing Infection: Recent Developments. Front. Bioeng. Biotechnol. 9:783816. doi: 10.3389/fbioe.2021.783816.
51. Thukkaram M., Cools P., Nikiforov A., Rigole P., Coenye T., Van Der Voort P., Du Laing G., Vercruysse C., Declercq H., Morent R., et al. Antibacterial activity of a porous Silver doped Titanium coating on Titanium substrates synthesized by plasma electrolytic oxidation. *Appl. Surf. Sci.* 2020;500:144235. doi: 10.1016/J.APSUSC.2019.144235.
52. Oleshko O., Liubchak I., Husak Y., Korniienko V., Yusupova A., Oleshko T., Banasiuk R., Szkodo M., Matros-Taranets I., Kazek-Kęsik A., et al. In Vitro Biological Characterization of Silver-Doped Anodic Oxide Coating on Titanium. *Materials.* 2020;13:4359. doi: 10.3390/ma13194359.
53. Sergi R., Bellucci D., Candidato R.T., Lusvarghi L., Bolelli G., Pawlowski L., Candiani G., Altomare L., De Nardo L., Cannillo V. Bioactive Zn-doped hydroxyapatite coatings and their antibacterial efficacy

against *Escherichia coli* and *Staphylococcus aureus*. *Surf. Coat. Technol.* 2018;352:84–91. doi: 10.1016/J.SURFCOAT.2018.08.017.

54. Zhou J., Wang X. The osteogenic, anti-oncogenic and antibacterial activities of Selenium-doped Titanium dioxide coatings on Titanium. *Surf. Coat. Technol.* 2020;403:126408. doi :10.1016/J.SURFCOAT.2020.126408.
55. Zhao Q., Yi L., Jiang L., Ma Y., Lin H., Dong J. Surface functionalization of Titanium with zinc/Strontium-doped Titanium dioxide microporous coating via microarc oxidation. *Nanomedicine.* 2019;16:149–161. doi: 10.1016/J.NANO.2018.12.006.
56. Ciobanu G., Harja M. Bismuth-doped nanohydroxyapatite coatings on Titanium implants for improved radiopacity and antimicrobial activity. *Nanomaterials.* 2019;9:1696. doi: 10.3390/nano9121696.
57. Zhang X., Huang Y., Wang B., Chang X., Yang H., Lan J., Wang S., Qiao H., Lin H., Han S. A functionalized Sm/Sr doped Titanium nanotube array on Titanium implant enables exceptional bone-implant integration and also self-antibacterial activity. *Ceram. Int.* 2020;46:14796–14807. doi:10.1016/j.ceramint.2020.03.004.
58. Dong J., Fang D., Zhang L., Shan Q., Huang Y. Gallium-doped TiO_2 nanotubes elicit anti-bacterial efficacy in vivo against *Escherichia coli* and *Staphylococcus aureus* biofilm. *Materialia.* 2019;5:100209. doi: 10.1016/J.MTLA.2019.100209.
59. Batebi K., Abbasi Khazaei B., Afshar A. Characterization of sol-gel derived Silver/fluor-hydroxyapatite composite coatings on Titanium substrate. *Surf. Coat. Technol.* 2018;352:522–528. doi: 10.1016/J.SURFCOAT.2018.08.021.
60. Ohtsu N., Kakuchi Y., Ohtsuki T. Antibacterial effect of Zinc oxide/hydroxyapatite coatings prepared by chemical solution deposition. *Appl. Surf. Sci.* 2018;445:596–600. doi:10.1016/J.APSUSC.2017.09.101.
61. Panda S., Behera B.P., Bhutia S.K., Biswas C.K., Paul S. Rare transition metal doped hydroxyapatite coating prepared via microwave irradiation improved corrosion resistance, biocompatibility and anti-biofilm property of Titanium alloy. *J. Alloys Compd.* 2022;918:165662. doi: 10.1016/j.jallcom.2022.165662.
62. Ciobanu G., Harja M. Cerium-doped hydroxyapatite/collagen coatings on Titanium for bone implants. *Ceram. Int.* 2019;45:2852–2857. doi: 10.1016/j.ceramint.2018.07.290.
63. Yamaguchi S., Le P.T.M., Shintani S.A., Takadama H., Ito M., Ferraris S., Spriano S. Iodine-loaded calcium titanate for bone repair with sustainable antibacterial activity prepared by solution and heat treatment. *Nanomaterials.* 2021;11:2199. doi: 10.3390/nano11092199.
64. Camargo S.E.A., Roy T., Iv P.H.C., Fares C., Ren F., Clark A.E., Esquivel-Upshaw J.F. Novel coatings to minimize bacterial adhesion and promote osteoblast activity for Titanium implants. *J. Funct. Biomater.* 2020;11:42. doi: 10.3390/jfb11020042.
65. Humayun A., Luo Y., Mills D.K. Electrophoretic deposition of gentamicin-loaded znhnts-chitosan on Titanium. *Coatings.* 2020;10:944. doi: 10.3390/coatings10100944.
66. He L.-J., Hao J.-C., Dai L., Zeng R.-C., Li S.-Q. Layer-by-layer assembly of gentamicin-based antibacterial multilayers on Ti alloy. *Mater. Lett.* 2020;261:127001. doi: 10.1016/j.matlet.2019.127001.
67. Chen S.-T., Chien H.-W., Cheng C.-Y., Huang H.-M., Song T.-Y., Chen Y.-C., Wu C.-H., Hsueh Y.-H., Wang Y.-H., Ou S.-F. Drug-release dynamics and antibacterial activities of chitosan/cefazolin coatings on Ti implants. *Prog. Org. Coat.* 2021;159:106385. doi: 10.1016/j.porgcoat.2021.106385.
68. Sun J., Liu X., Lyu C., Hu Y., Zou D., He Y.-S., Lu J. Synergistic antibacterial effect of graphene-coated Titanium loaded with levofloxacin. *Colloids Surf. B Biointerfaces.* 2021;208:112090. doi: 10.1016/j.colsurfb.2021.112090.
69. Zarghami V., Ghorbani M., Pooshang Bagheri K., Shokrgozar M.A. Melittin antimicrobial peptide thin layer on bone implant chitosan-antibiotic coatings and their bactericidal properties. *Mater. Chem. Phys.* 2021;263:124432. doi: 10.1016/j.matchemphys.2021.124432.
70. Guo C., Cui W., Wang X., Lu X., Zhang L., Li X., Li W., Zhang W., Chen J. Poly-l-lysine/Sodium Alginate Coating Loading NanoSilver for Improving the Antibacterial Effect and Inducing Mineralization of Dental Implants. *ACS Omega.* 2020;5:10562–10571. doi: 10.1021/acsomega.0c00986.
71. Wu S., Xu J., Zou L., Luo S., Yao R., Zheng B., Liang G., Wu D., Li Y. Long-lasting renewable antibacterial porous polymeric coatings enable Titanium biomaterials to prevent and treat peri-implant infection. *Nat. Commun.*

2021;12:3303. doi: 10.1038/s41467-021-23069-0.

72. Kaleli-Can G., Özgüzar H.F., Kahriman S., Türkal M., Göçmen J.S., Yurtçu E., Mutlu M. Improvement in antimicrobial properties of Titanium by diethyl phosphite plasma-based surface modification. *Mater. Today Commun.* 2020;25:101565. doi: 10.1016/j.mtcomm.2020.101565.
73. Peng J., Liu P., Peng W., Sun J., Dong X., Ma Z., Gan D., Liu P., Shen J. Poly(hexamethylene biguanide) (PHMB) as high-efficiency antibacterial coating for Titanium substrates. *J. Hazard. Mater.* 2021;411:125110. doi: 10.1016/j.jhazmat.2021.125110.
74. Atefyekta S., Pihl M., Lindsay C., Heilshorn S.C., Andersson M. Antibiofilm elastin-like polypeptide coatings: Functionality, stability, and selectivity. *Acta Biomater.* 2019;83:245–256. doi: 10.1016/j.actbio.2018.10.039.
75. Pihl M., Galli S., Jimbo R., Andersson M. Osseointegration and antibacterial effect of an antimicrobial peptide releasing mesoporous TiO_2 implant. *J. Biomed. Mater. Res. B Appl. Biomater.* 2021;109:1787–1795. doi: 10.1002/jbm.b.34838.
76. Zhang L., Xue Y., Gopalakrishnan S., Li K., Han Y., Rotello V.M. Antimicrobial Peptide-Loaded Pectolite Nanorods for Enhancing Wound-Healing and Biocidal Activity of Titanium. *ACS Appl. Mater. Interfaces.* 2021;13:28764–28773. doi: 10.1021/acsami.1c04895.
77. Lin J., Hu J., Wang W., Liu K., Zhou C., Liu Z., Kong S., Lin S., Deng Y., Guo Z. Thermo and light-responsive strategies of smart Titanium-containing composite material surface for enhancing bacterially anti-adhesive property. *Chem. Eng. J.* 2021;407:125783. doi: 10.1016/j.cej.2020.125783.
78. Zhang F., Hu Q., Wei Y., Meng W., Wang R., Liu J., Nie Y., Luo R., Wang Y., Shen B. Surface modification of Titanium implants by pH-Responsive coating designed for Self-Adaptive antibacterial and promoted osseointegration. *Chem. Eng. J.* 2022;435:134802. doi: 10.1016/J.CEJ.2022.134802.
79. Pavlović M.R.P., Stanojević B.P., Pavlović M.M., Mihailović M.D., Stevanović J.S., Panić V.V., Ignjatović N.L. Anodizing/anaphoretic electrodeposition of nano-calcium phosphate/chitosan lactate multifunctional coatings on Titanium with advanced corrosion resistance, bioactivity, and antibacterial properties. *ACS Biomater. Sci. Eng.* 2021;7:3088–3102. doi: 10.1021/acsbiomaterials.1c00035.
80. Chen J., Shi X., Zhu Y., Chen Y., Gao M., Gao H., Liu L., Wang L., Mao C., Wang Y. On-demand storage and release of antimicrobial peptides using Pandora's box-like nanotubes gated with a bacterial infection-responsive polymer. *Theranostics.* 2020;10:109–122. doi: 10.7150/thno.38388.
81. Zhang G., Yang Y., Shi J., Yao X., Chen W., Wei X., Zhang X., Chu P.K. Near-infrared light II-assisted rapid biofilm elimination platform for bone implants at mild temperature. *Biomaterials.* 2021;269:120634. doi: 10.1016/j.biomaterials.2020.120634.