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Dental implant surface modification for promoting peri-implant osseointegration in osteoporosis

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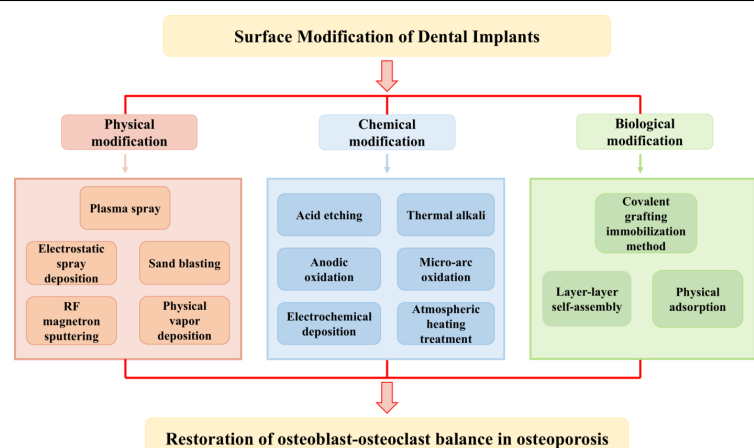
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ABSTRACT: Osteoporosis (OP) is a metabolic disease characterized by reduced bone mass, decreased bone mineral density, and increased bone fragility. This not only makes patients prone to fractures but also renders the bone tissues in the oral cavity vulnerable to damage, leading to premature loosening and loss of teeth. Implant prosthodontics is currently the best approach for managing partial and complete edentulism. When implants are placed in the oral cavity of OP patients, there is a delay in osseointegration and insufficient primary stability of dental implants, which affects the success rate of implantation. Ensuring their quick and firm integration with the bone tissue in the body of OP patients is a pressing issue that needs to be addressed in the field of oral implant prosthetics. This paper reviews commonly used methods of implant surface modification, such as physical, chemical, and biological modifications, and discusses the advantages of these technologies and the mechanisms of anti-OP effects, aiming at improving osseointegration of implants in OP patients, shortening the healing period, and enhancing the success rate of implantation. This will be significant for the research and development of new implants and for expanding the clinical indications of implant prosthodontics.

KEYWORDS: osteoporosis, oral implants, surface modification, osseointegration



1 Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone mineral density, severely reduced bone mass, and destruction of trabecular bone microarchitecture^[1]. According to the World Health Organization criteria, OP can be categorized as primary osteoporosis due to aging and ovarian decline in women, or secondary osteoporosis due to diseases and medications^[2]. Patients with OP not only have increased bone fragility and are prone to fractures, but the bone tissue surrounding the teeth in the mouth is also vulnerable to damage, leading to alveolar bone damage. This significantly affects the patient's quality of life^[3]. Dental implants have become the preferred restoration method for

edentulous and partially edentulous patients due to their aesthetics and comfort, without loss of neighboring teeth^[4,5]. Osseointegration is the formation of a direct and orderly osseous connection between the implant and the surrounding bone tissue, which is crucial for ensuring the long-term survival and normal function of the implant^[6,7]. Although clinical studies have shown that dental implants have a success rate of over 90% for 10 years of normal use^[8], in patients with OP, bone homeostasis is disrupted, with the disrupted dynamic equilibrium between osteoblasts (OB) responsible for new bone formation and osteoclasts (OC) mediating bone resorption. Thereby, the amount of new bone is less than the amount of resorbed bone^[9], which severely compromises peri-implant trabecular bone formation and bone-implant contact (BIC), resulting in fractures, poor osseointegration and implant displacement, loosening or implant failure^[10,11].

Surface modification method refers to the improvement of osseointegration by changing the physical, chemical or biological properties of the surface of the material. This includes adjustments to surface roughness, hardness, porosity, wettability, and reactivity-

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whether bioinert or bioreactive, as well as charge polarity and surface free energy. These modifications are intended to promote the activity of OB, including adhesion, spreading, and proliferation, thereby improving osseointegration^[12,13]. Thus, constructing novel implants by using appropriate surface modification techniques to achieve the purpose of regulating the bone microenvironment and improving the osseointegration strength in OP patients are critical challenges that need to be addressed to decrease the failure rate of implants in OP patients, as well as in the fields of implant dentistry and biomaterials science.

This review comprehensively compiles the results of cutting-edge advances in new implant surface modification methods to promote implant osseointegration in patients with OP. It analyzes and summarizes the mechanisms and effects of various modification methods and techniques, with a view to improving implant osseointegration under OP, shortening the healing cycle, and enhancing the success rate of implantation. This work holds substantial significance for promoting the development of new-generation implants and expanding the clinical indications for implant-based restorations.

2 Implant surface modification treatment for promoting osseointegration in osteoporotic implants

Currently, the prevalent methods for implant surface modification primarily encompass physical modifications such as plasma spraying, electrostatic spray deposition (ESD), sandblasting, radio frequency (RF) magnetron sputtering, physical vapor deposition (PVD), laser cladding, ion implantation and surface ceramization. There are also chemical modifications such as acid etching, thermal alkali (TA), anodic oxidation, micro-arc oxidation (MAO), electrochemical deposition (ED), atmospheric heating treatment, biomimetic solution deposition and sol-gel method. Moreover,

biological modifications such as covalent grafting immobilization method, layer-layer self-assembly (LBL), and physical adsorption are used^[10,14]. The above modification methods can synergistically achieve the following goals: (1) Optimization of implant surface morphology through increased surface area, roughness, and porosity; (2) Enhancement of mechanical strength, corrosion resistance, antibacterial efficacy, biocompatibility, and osteogenic capacity via compositional modification (e.g., Mg, F, and Ag) or bioactive coating/element incorporation; (3) Construction of localized controlled-release systems on the implant surface for sustained delivery of anti-osteoporotic agents and/or osteogenic growth factors, such as bisphosphonates (BPs), parathyroid hormone (PTH), transforming growth factor-beta (TGF- β), bone morphogenetic proteins (BMPs), and basic fibroblast growth factor (bFGF), thereby promoting osseointegration and improving long-term implant stability. Figure 1 summarizes the key biofunctional requirements for surface modification of OP implants, such as antimicrobial, antioxidant, and biocompatibility, along with their corresponding surface modification methods.

2.1 Physical modification

Physical modification is mainly through changing the physical structure and properties of the implant surface to achieve the purpose of optimizing the implant surface morphology, roughness, porosity, mechanical properties and biological activity^[15]. Physical modification is frequently employed as a pretreatment approach for dental implant surface modification, including techniques such as plasma spraying, ESD, sandblasting, and radio frequency magnetron sputtering.

2.1.1 Plasma spraying

Plasma spraying is a technology that utilizes a plasma gun to generate a direct current arc to heat and melt material and then spray it onto a metal surface at a high-velocity acceleration to form

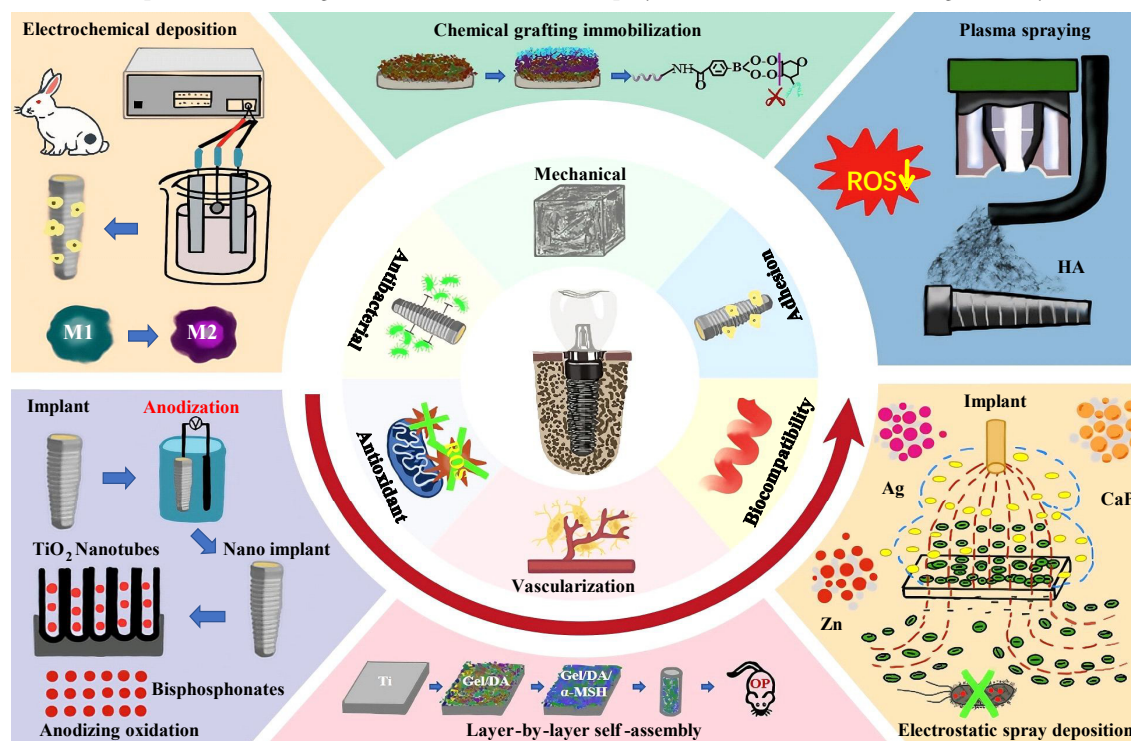


Figure 1 Multifunctional surface modification strategies for osteoporotic implants.

a coating. The main feature of plasma spraying is that its flame temperature can be higher than 10,000 K, which can melt any coating material. With high flame flow rate, powder is sprayed from the gun at high speed so that the coating material and the substrate are more closely combined^[16]. This makes the plasma spraying method more widely used in the preparation of biocompatible calcium-phosphorus composite coatings. Hydroxyapatite-coated Ti implants prepared by plasma spraying are widely used for implant surface modification due to their similarity to natural bone in composition. It was reported that compared to pure Ti implants, plasma-sprayed HA-coated Ti implants could exhibit enhanced osteoblast adhesion and proliferation in vitro. In addition, they might achieve superior bone-implant integration in vivo, demonstrating great application potential in OP patients^[17,18].

2.1.2 Electrostatic spraying deposition

ESD is a technology that utilizes a voltage difference to coat powders. The principle involves the generation of a corona discharge at the nozzle tip of the spray gun, which induces negative charging and atomization of the coating material. Subsequently, the negatively charged powder particles move along the power line flow to the positively charged substrate surface, ensuring efficient and uniform deposition^[19]. This technology can be utilized to create a uniform and dense coating by incorporating a coating material such as CaP into the coating and depositing the charged CaP particles directionally onto the implant surface by electrostatic force. Due to electrostatic repulsion, the droplets spread evenly on the surface and reduce agglomeration, thus forming a uniform and dense coating. In addition, the method can also be adjusted by spraying parameters to change the surface morphology of the coating, creating an appropriate roughness and pore structure. This facilitates nutrient transportation and promotes cell adhesion and proliferation. It is tailored to accommodate the poor blood supply and nutrient transport in bone tissue of patients with OP, thereby encouraging the growth and repair of bone tissue.

2.1.3 Sandblasting and acid etching

Sandblasting is a surface modification technique in which hard ceramic particles are propelled by compressed air through a nozzle

onto the surface of an implant. This process creates a rough texture that corresponds to the diameter of the abrasive particles^[2]. The abrasive particles produced by sandblasting have a chemically stable composition and exhibit biocompatibility, not interfering with the osseointegration process of implants. Nonetheless, the residual material from the sandblasting process can cause mechanical abrasion at the tissue-implant interface after implantation, potentially leading to adverse reactions and implant failure^[20]. Acid etching is a technique for modifying implants that employs acids, such as hydrofluoric acid (HF), nitric acid (HNO₃), sulfuric acid (H₂SO₄), or their mixtures, to alter the surface roughness of the implant. The surface of an acid-etched implant is clean and devoid of extraneous impurities, exhibiting a uniform porous structure at both the micron and submicron levels. This modification effectively increases the surface area and thus hydrophilic property of the implant. Due to the limitations of sandblasting treatment, in recent years, it has often been used in conjunction with acid etching, known as combined sandblasting and acid etching technique (SLA). SLA harnesses the benefits of both processes. Sandblasting produces a large and pitted structure, while acid etching passivates the sharp edges of the sandblast and etches out micropores, resulting in a multilayered pitted structure. This promotes OB adhesion and proliferation, thereby enhancing the osseointegration properties of the implant^[21].

2.1.4 Radio-frequency magnetron sputtering

RF magnetron sputtering is a thin-film deposition technique that employs RF-induced plasma discharge to generate energetic positive ions. These ions bombard the target material, causing sputtering of atoms or molecules, which then condense onto grounded substrate surfaces to form uniform coatings^[22]. By applying this technology, antimicrobial elements such as gallium (Ga), silver (Ag), and zinc (Zn) can be incorporated into the film, endowing the implant with antimicrobial properties and diminishing the risk of postoperative infection. As shown in Figure 2, RF magnetron sputtering was used to deposit gallium oxide (Ga₂O₃) nanocoatings onto titanium dioxide nanotubes (TNT). The antibacterial efficacy of the coating arose from positively charged

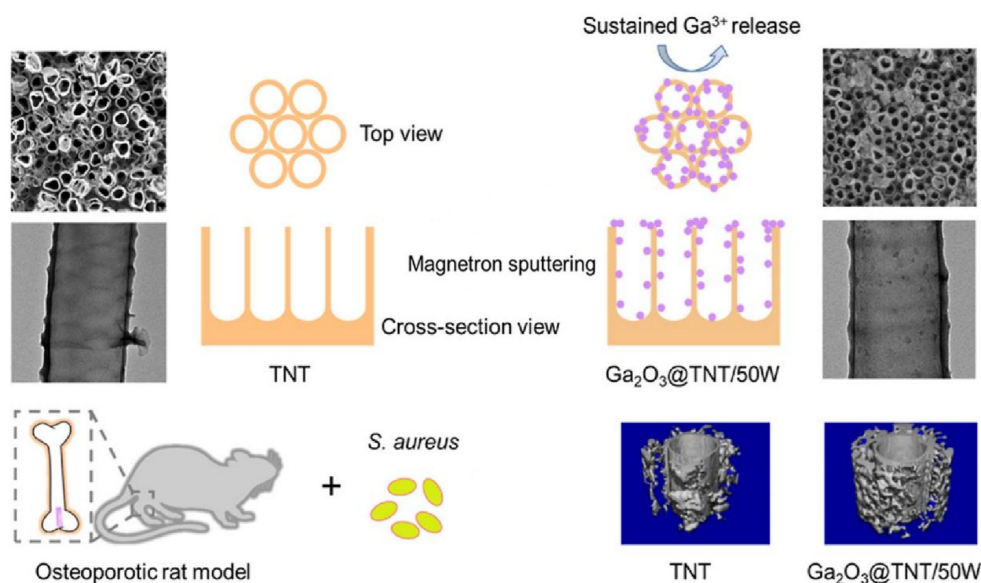


Figure 2 Schematic illustration of the antibacterial mechanisms of radio frequency magnetron sputtered Ga₂O₃-loaded TNT titanium implants in an osteoporotic rat model. Reproduced with permission from Yao, et al^[24]. Copyright © 2023, Elsevier Ltd and Techna Group S.r.l.

Ga³⁺ ions binding to anionic phospholipid head groups (e.g., phosphatidic acid, cardiolipin) on bacterial membranes, neutralizing the surface charge and disrupting the integrity of the phospholipid bilayer. Furthermore, the release of Ga³⁺ competitively inhibited bacterial iron metabolism, which compromised the membrane stability. This dual mechanism led to bactericidal rates exceeding 89% against both *Staphylococcus aureus* and *Escherichia coli*. TNT exhibited biocompatibility, while Ga³⁺ ions had osteogenic properties. Loading Ga³⁺ onto TNT surfaces not only preserved the osteoinductive capacity but also imparted localized antibacterial functionality, thereby enhancing osseointegration and infection resistance under osteoporotic conditions.

Specific cases of physical modification treatments on implant surfaces to promote peri-implant osseointegration in osteoporosis are summarized in Table 1.

Simple physical modification methods are routinely used to enhance implant surface roughness, thereby improving mechanical properties. However, there exist a few limitations. For instance, during implant grit blasting, residual abrasive particles can cause peri-implant inflammation, leading to implant failure. Coatings prepared by PVD are too thin for long-term effectiveness. Additionally, the core pathological feature of OP is the increased activity of OC and the inhibited function of OB, resulting in bone resorption being far greater than bone formation. Conventional physical modifications only promote cell anchorage by increasing surface roughness, but they have little impact on the performance of the implants themselves. They lack the release of bioactive signals and thus exhibit limited efficacy in modifying the pathological environment of OP.

2.2 Chemical modification

Chemical modification methods rely on chemical reactions such as oxidation, carbonization, or nitridation to alter the chemical composition and properties of the implant surface. These techniques can effectively regulate characteristics such as hydrophilicity and charge distribution, endowing the implant with biocompatibility, corrosion resistance, antibacterial properties, and the ability to release drugs^[28]. This fosters protein adsorption, cell adhesion, proliferation, and differentiation, creating a favorable chemical microenvironment for osseointegration. The primary techniques include TA treatment, anodic oxidation, MAO, and ED^[29].

2.2.1 Thermal alkali treatment

As a commonly used chemical modification method, TA treatment typically involves precisely placing the implant into an alkaline solution system with a specific concentration and heating the reaction system to a set temperature range, generally between 60°C and 100°C. In this TA environment, hydroxide ions (OH⁻) in the alkaline solution chemically react with the metal atoms on the implant surface, promoting the formation of a rough, porous structure rich in HA-like substances on the implant surface. This unique microstructure significantly expands the surface area of the implant. From a microscopic perspective, it resembles the construction of an intricate three-dimensional network on the implant surface, providing more abundant sites for cell adhesion, proliferation, and differentiation.

2.2.2 Anodizing oxidation

Anodic oxidation is an electrochemical modification method in

which a metal or alloy, serving as the anode, is placed in an electrolyte. An electrochemical reaction occurs under an applied electric field, forming an oxide layer on the anode's surface^[30]. The anodic oxidation method can produce TiO₂ nanotubes of varying sizes with well-ordered arrangements. These TiO₂ nanotubes excel not only in promoting the adhesion, spreading, proliferation, and differentiation of OB but also serve as storage platforms for OP drugs, growth factors, or other bioactive substances, contributed by their nanoscale pores. As shown in Figure 3, TNTs were synthesized on a Ti substrate through the anodic oxidation technique. Subsequently, irisin (IR) was deposited onto the surface of the TNTs, and a TNT-IR-LBL multilayer film structure was created using the LBL approach. This assembly was then implanted into OP rats to assess its osseointegration potential. As an exercise-induced myokine, Irisin regulates bone metabolic balance by inhibiting the bone resorption marker β -crosslaps and upregulating the levels of bone formation markers, including CoL-1, RUNX-2, OPN, and ALP. Alternatively, it might promote osteogenic differentiation by activating the Wnt/ β -catenin signaling pathway and inhibiting sclerostin (Sost). The TNT structure, prepared through anodic oxidation, enhanced cellular responses and served as a platform for drug loading. Concurrently, the LBL-assembled multilayer film facilitated sustained drug release from the TNTs. By integrating TNT arrays with the multilayer film structure, a drug release platform was established, enabling localized and controlled slow release of Irisin. This approach enhances osseointegration within the primary OP microenvironment.

2.2.3 Micro-arc oxidation

MAO, also known as Plasma Electrolytic Oxidation (PEO), is an electrochemical surface modification technology. This process involves applying a high-voltage electric field in an electrolyte to induce plasma discharge reactions on the surface of the metal substrate, thereby forming a uniform oxide ceramic layer^[32]. The coating system exhibits multiple superior properties, such as strong adhesion to the substrate, excellent mechanical strength, corrosion resistance, biocompatibility, and controllable degradability. Additionally, the porous morphology and controllable degradation characteristics of MAO coatings enable the gradual release of bioactive ions such as Mg²⁺ and Zn²⁺, simultaneously promoting OB proliferation while inhibiting OC differentiation, thereby improving osseointegration in OP environments.

2.2.4 Electrochemical deposition

The fundamental principle of ED involves applying an external electric field to drive the directional migration of metal cations in the electrolyte towards the cathode interface. In the process, controlled reduction occurs, followed by crystallization and deposition under the electric field, ultimately forming the coating layer^[33]. Compared to PVD, ED offers higher deposition efficiency, milder process conditions, lower energy consumption, and relatively simpler wastewater treatment, making it suitable for large-scale production. By precisely regulating key ED process parameters such as voltage, current density, electrolyte composition, and deposition time, it is possible to achieve synergistic optimization of coating thickness gradients, pore topological structures, and chemical compositions, thereby producing specifically functionalized coatings tailored for patients with OP.

Specific cases of chemical modification treatments on implant surfaces to promote peri-implant osseointegration in osteoporosis

Table 1 Research on promoting peri-implant osseointegration in osteoporosis through physical modification of implant surfaces.

Modification method	Cell/Animal models	Base material composition	Coating material composition	Experimental results	Method advantages	Anti-OP principle or mechanism	References
Plasma spraying	BMSCs	TC4	Experimental group: H ₂ O ₂ -induced HA coatings containing 30wt% Ce (30%Ce-HA), 10wt% Ce (10% Ce-HA), and Ce-free coating (HA) Control group: TC4 having HA coating without H ₂ O ₂ induction treatment	In the experimental group, the 30%Ce-HA group exhibited the highest cell viability and lowest ROS generation. Compared to HA coatings without Ce prepared under H ₂ O ₂ induction (52.9 ± 6.1% by day 3 and 53.4 ± 5.0% by day 7), the 30%Ce-HA group showed the cell viability of 76.2 ± 5.9% by day 3 and 72.1 ± 6.9% by day 7 - an increase of 43% for day 3 and 36% for day 7	The high-temperature and high-speed jet stream enabled rapid melting and solidification of HA powder on the substrate surface, forming a mechanically interlocked structure with the substrate, thereby significantly enhancing the bonding strength between the coating and the substrate; Ce substituted Ca in HA to form a Ce-HA solid solution, maintaining the crystal structure stability of HA	CeO ₂ possessed antioxidant properties that could upregulate the Wnt/β-catenin signaling pathway or effectively maintain superoxide dismutase (SOD) activity, inhibiting intracellular reactive oxygen species (ROS) and malondialdehyde (MDA) production, alleviating H ₂ O ₂ -induced oxidative stress damage, and promoting BMSCs osteogenic differentiation; CeO ₂ could effectively inhibit OC formation and activity by increasing the OPG/RANKL ratio, thereby reducing bone resorption	Li ^[24]
			Experimental group: CaP nanoparticles (nCaP) coating, BP coating, nCaP/BP coating Control group: Uncoated Ti	The nCaP/BP coating group showed the highest bone volume fraction (BV%) (nCaP coating: 31.52 ± 5.66%; BP coating: 44.69 ± 1.94%; nCaP/BP coating: 47.04 ± 11.64%; uncoated sample: 25.62 ± 8.97%)	Compared to plasma spraying where high temperatures could easily cause HA decomposition, ESD operated at low temperatures, thereby preserving the chemical stability and bioactivity of CaP; nCaP was co-deposited with organic biomolecules such as collagen, growth factors, peptides, or drugs to precisely construct multifunctional coatings	The nCaP coating activated Wnt ligands by releasing Ca ²⁺ and PO ₄ ³⁻ ions and inhibited GSK-3β, stabilizes β-catenin, besides promotion of the expression of osteogenesis-related genes Runx2 and Osterix, and enhancement of the migration ability of OB toward the coating surface; BPs could bind to nCaP through specific side chains R1 and R2 groups, inhibiting OC-mediated bone resorption and increasing peri-implant bone mass	
SLA	Sprague-Dawley rats	Ti	Experimental group: Dopa coating, Zoledronic acid (ZA) coating, Dopa and ZA co-modified coating Control group: Uncoated Ti	The removal torque values in the experimental groups were significantly higher than those in the control group after 8 weeks of implantation, with no significant differences observed among the experimental groups themselves	Surface modification via the SLA method simultaneously enhanced the implant surface roughness and constructed nanoscale cavities, with the formed cavity structures effectively loading Dopa particles	The Dopa coating reduced the expression of NFATc1 and c-Fos genes by activating D2 receptors, while the ZA coating decreased OC generation and attenuated bone resorption by suppressing the expression of NF-κB, MAPK, and NFATc1	Ma ^[26]
			Experimental group: CaP coating, Type I collagen coating Control group: Uncoated Ti	The OP rats experimental group displayed higher BV% (CaP coating: 61.96 ± 11.09%; type I collagen coating: 64.94 ± 7.82%; uncoated sample: 60.44 ± 12.60%) and bone area fraction (BA%) (CaP coating: 46.95 ± 12.49%; type I collagen coating: 51.51 ± 9.62%; uncoated sample: 43.82 ± 6.84%)	Sandblasting increased the surface roughness of implants; RF magnetron sputtering allowed precise control of the Ca/P ratio in coatings by adjusting parameters such as RF power, working pressure, and sputtering time; ESD was performed at room temperature or low temperature, avoiding the destruction of the triple-helix structure of collagen caused by traditional high-temperature processes and preserving its natural bioactivity	The CaP coating surface exhibited protein adsorption effects, while increased concentrations of Ca ²⁺ and PO ₄ ³⁻ induced a bone-like apatite crystal deposition layer, which significantly promoted OB adhesion and interfacial response on the implant surface, thereby optimizing the osseointegration process; The type I collagen coating could drive the early proliferation and osteogenic differentiation of human mesenchymal stem cells (hMSCs) via upregulating ALP activity and the mRNA expression of Runx2 and osteocalcin	
Sandblasting; RF magnetron sputtering; ESD	Wistar rats	Ti	Experimental group: CaP coating, Type I collagen coating Control group: Uncoated Ti	The OP rats experimental group displayed higher BV% (CaP coating: 61.96 ± 11.09%; type I collagen coating: 64.94 ± 7.82%; uncoated sample: 60.44 ± 12.60%) and bone area fraction (BA%) (CaP coating: 46.95 ± 12.49%; type I collagen coating: 51.51 ± 9.62%; uncoated sample: 43.82 ± 6.84%)	Sandblasting increased the surface roughness of implants; RF magnetron sputtering allowed precise control of the Ca/P ratio in coatings by adjusting parameters such as RF power, working pressure, and sputtering time; ESD was performed at room temperature or low temperature, avoiding the destruction of the triple-helix structure of collagen caused by traditional high-temperature processes and preserving its natural bioactivity	The CaP coating surface exhibited protein adsorption effects, while increased concentrations of Ca ²⁺ and PO ₄ ³⁻ induced a bone-like apatite crystal deposition layer, which significantly promoted OB adhesion and interfacial response on the implant surface, thereby optimizing the osseointegration process; The type I collagen coating could drive the early proliferation and osteogenic differentiation of human mesenchymal stem cells (hMSCs) via upregulating ALP activity and the mRNA expression of Runx2 and osteocalcin	Alghamdi ^[27]

a: Schematic illustration of the TNT-IR-LBL synthetic process



b: The nanoporous multilayer coating on the TNT array substrates to promote bone regeneration in senile osteoporosis rats

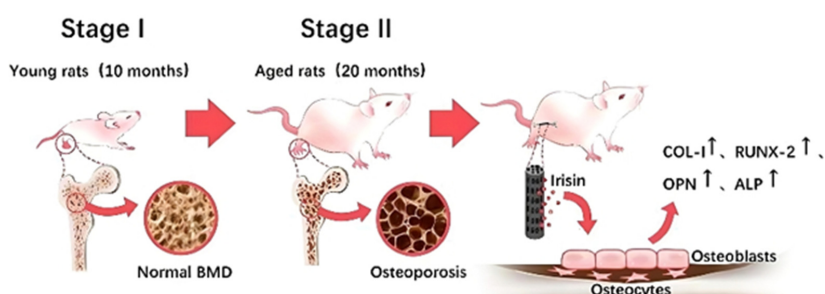


Figure 3 Schematic illustration of anodizing preparation and animal implantation process for TNT-IR-LBL titanium-based implants. Reproduced with permission from Li et al^[30]. Copyright © 2023, Elsevier Ltd.

are summarized in Table 2.

The above analysis indicates that chemical modification methods can promote early osteogenesis in OP patients. However, the OP environment differs from the normal bone microenvironment, characterized by excessive ROS accumulation, decreased pH, and abnormal immune function. Traditional chemical modification strategies cannot simultaneously address the synergistic requirements of ROS scavenging, immune regulation, and vascular regeneration, and exhibit uncontrolled coating degradation and ion release, necessitating further research.

2.3 Biological modification

Biomodification involves immobilizing specific proteins or growth factors onto the surface of implants to impart bioactivity. This process actively induces the adhesion, proliferation, and differentiation of OB, thereby promoting osseointegration and shortening the healing period. The most used methods currently include chemical grafting immobilization, LBL assembly, and physical adsorption.

2.3.1 Covalent grafting immobilization method

In chemistry, grafting refers to the connection of one or more

molecular chains from a chemical substance to another molecular chain, resulting in alterations to the molecular structure. This modification is achieved by introducing new molecules onto the original molecular chain or forming reinforced covalent bonds between molecular chains^[39]. Under OP conditions, surface modification of implants through chemically bonded grafting can enhance osseointegration. For instance, osteogenic molecules can undergo specific chemical reactions with the ROS-responsive crosslinker NBC^[40]. When the ROS levels in the implantation microenvironment rise, this triggers the cleavage of chemical bonds, releasing the osteogenic molecules and protecting OB from oxidative stress damage, thereby accelerating bone repair rates under OP conditions.

2.3.2 Layer-by-layer self-assembly

LBL is a process that employs a layer-by-layer alternating deposition technique, relying on weak interactions between molecular layers such as electrostatic attraction, hydrogen bonding, and coordination bonds, to facilitate spontaneous association between layers. This results in the formation of molecular aggregates or supramolecular structures with a complete architecture, stable performance, and specific functionalities^[41]. As

Table 2 Research on promoting peri-implant osseointegration in osteoporosis through chemical modification of implant surfaces.

Modification method	Base material composition	Cell/Animal models	Coating material composition	Experimental results	Method advantages	Anti-OP principle or mechanism	References
TA	MSCs; Sprague-Dawley rats	Ti	Experimental group: Chitosan/siRNA complex targeting the Ckip-1 gene (CS/siCkip-1) Control group: Chitosan/non-targeting siRNA complex for the Ckip-1 gene (CS/siNC), CS, Unloaded Ti	At 12 weeks post-implantation, the experimental group's ultimate shear strength (N/mm ²) (CS/siCkip-1: 2.17 ± 0.20 N/mm ² ; CS/siNC: 1.31 ± 0.11 N/mm ² ; CS: 1.26 ± 0.12 N/mm ² ; unloaded: 1.13 ± 0.09 N/mm ²) and maximum pull-out force (N) (CS/siCkip-1: 93.05 ± 8.85 N; CS/siNC: 56.30 ± 5.01 N; CS: 54.03 ± 5.55 N; unloaded: 48.53 ± 4.17 N) were significantly higher than the control group	TA enabled the Ti surface to possess a microporous/nanofiber network structure with pore sizes ranging from 100–400 nm, endowing the implant with super hydrophilicity and negative charge. It facilitated the physical adsorption of positively charged CS/siRNA complexes, allowing uniform loading of CS/siCkip-1 on the implant surface and achieving efficient siRNA delivery	CS could carry a large amount of siRNA without cytotoxicity; Ckip-1 specifically enhanced the E3 ligase activity of Smurf1, leading to Runx2 degradation and reduced OB differentiation; siRNA could target and silence Ckip-1, thereby relieving its inhibitory effect on OB differentiation and promoting bone formation under OP conditions	Zhang ^[4]
Anodic oxidation	MC3T3-E1, RAW264.7; Sprague-Dawley rats	TC4	Experimental group: Mesoporous TiO ₂ layer containing ZA (ZA-MTL) Control group: Mesoporous TiO ₂ layer (MTL), Unloaded TC4	ZA-MTL exhibited the highest expression levels of Coll α1, ALP, OCN, and BMP2, while showing the lowest expression levels of RANK, TRAP, and CTSC; the BIC values in the ZA-MTL were 1.45 times higher than those in the MTL group and 2.64 times higher than those in the Unloaded TC4 group, and the BV/TV values were 1.3 times higher than those in the MTL group and 1.8 times higher than those in the Unloaded TC4 group	The mesoporous TiO ₂ layer parameters, including pore depth (pore diameter 15 nm, depth 30 μm), surface area (112.3 m ² /g), volume (0.32 cm ³ /g), and water contact angle (18.3°), could be optimized as needed to achieve excellent hydrophilicity, which facilitated cell adhesion and enables the loading of high doses of ZA, thereby realizing the localized sustained delivery of ZA	The ZA-loaded mesoporous TiO ₂ layer enhanced the expression of osteogenic genes Col1α1, OCN, BMP2 and inhibited the adhesion and proliferation of RAW264.7 and the expression of osteoclastic genes RANK, TRAP, CTSC, synergistically promoting bone formation with suppression of bone resorption	Liu ^[3]
Anodic oxidation	Sprague-Dawley rats	Ti	Experimental group: TiO ₂ nanotubes containing Sr, TiO ₂ nanotubes containing Co, TiO ₂ nanotubes containing Sr and Co Control group: TiO ₂ nanotubes, Unloaded Ti	The TiO ₂ nanotube group containing Sr and Co exhibited the highest BV/TV, Tb.Th, and Tb.N values in the OP rat model; the control group showed fewer newly formed trabeculae, mainly concentrated on the sidewalls of the implant threads, while the experimental group displayed newly formed trabecular structures not only on the sidewalls but also within the thread cavities of the implants	The nanotube structure facilitated the penetration and growth of cellular pseudopodia, endowing cells with excellent extensibility and cytoskeletal morphology; the nanotube morphology could guide and enhance cell migration on the implant surface, collectively promoting OB proliferation, differentiation, and bone matrix production, thereby enhancing osseointegration	Sr stimulated the calcium-sensing receptor (CaR) in OB, triggering related mitogenic signals and enhancing matrix mineralization; Co promoted angiogenesis by stabilizing HIF-1α and activating VEGF, thereby improving vascular defects in OP and the bone metabolic microenvironment	Yang ^[6]
MAO	HUVECs, hBMSCs; Sprague-Dawley rats	Ti	Experimental group: Zn-TiO ₂ group: (Sr/(Sr+Ca)=0.4); 1SrZn-TiO ₂ group: (Sr/(Sr+Ca)=1.4); 2SrZn-TiO ₂ group: (Sr/(Sr+Ca)=2.4); 3SrZn-TiO ₂ group: (Sr/(Sr+Ca)=3.4) Control group: TiO ₂ group	The 2SrZn-TiO ₂ group exhibited the highest BV/TV and Tb.Th values, while the 3SrZn-TiO ₂ group demonstrated the highest peak push-out force load	The porous coating, prepared using MAO, provided anchoring points for cell proliferation and adhesion, while the porous structure facilitated nutrient infiltration and promoted angiogenesis; by regulating the electrolyte composition and process parameters, the types and concentrations of doped elements as well as surface morphological characteristics could be precisely controlled, thereby endowing the implant with multiple biological functionalities such as promoting osseointegration, antibacterial properties, and anti-inflammatory effects	Sr could increase the secretion of VEGF and Ang-1 in HUVECs and BMSCs, which was beneficial for creating a favorable osseointegration microenvironment during the early stages of implant placement; Zn exhibited excellent antibacterial properties and could prevent peri-implantitis by inhibiting bacterial biofilm formation on the implant surface	Yan ^[7]

(To be continued on the next page)

(Continued)

Modification method	Base material composition	Cell/Animal models	Coating material composition	Experimental results	Method advantages	Anti-OP principle or mechanism	References
ED	Ti	Sprague-Dawley rats	Experimental group: 10%Zn-HA coating, 10%Mg-HA coating, 10%Sr-HA coating Control group: HA coating	The experimental groups had significantly higher values of BV/TV (10%Zn-HA: $28.6 \pm 1.2\%$; 10%Mg-HA: $30.3 \pm 1.5\%$; 10%Sr-HA: $40.2 \pm 2.4\%$; HA: $23.8 \pm 1.2\%$), Tb.N (10%Zn-HA: $382.2 \pm 13.8 \text{ mm}^{-3}$; 10%Mg-HA: $427.7 \pm 16.8 \text{ mm}^{-3}$; 10%Sr-HA: $503.9 \pm 15.4 \text{ mm}^{-3}$; HA: $226.2 \pm 7.3 \text{ mm}^{-3}$) and Tb.Th (10%Zn-HA: $90.4 \pm 3.5 \mu\text{m}$; 10%Mg-HA: $95.7 \pm 3.4 \mu\text{m}$; 10%Sr-HA: $116.3 \pm 4.1 \mu\text{m}$; HA: $77.6 \pm 3.7 \mu\text{m}$) than the control group	The ED coating preparation process could maintain the crystal structure stability of HA while achieving uniform ion distribution, avoiding local concentration deviations of metallic elements; the low-temperature process reduced the thermal expansion coefficient difference between the coating and substrate, minimizing the risk of coating cracking or delamination; specific voltage and deposition time could be regulated to optimize the crystallinity of the coating, balancing the dissolution rate and stability	Zn²⁺ partially replaced Ca²⁺ in HA, increasing the dissolution rate of the coating; The released Zn²⁺ could enhance local bone tissue repair capacity and antibacterial properties; Mg²⁺ is strongly involved in bone metabolism, both as a mitogen factor for OB, which proliferate in the presence of Mg²⁺, and as protective factor from excessive bone resorption, and decreased implant stability; Sr²⁺ stimulated OB differentiation and promoted bone matrix mineralization, while inhibiting OC differentiation and reducing bone loss	Tao ^[6]

shown in Figure 4, the LBL technique was initially utilized to create a gelatin/dextranamine (Gel/DA) multilayer film structure on the Ti surface, embedding α -MSH within the Gel/DA multilayer. Following this, PEG-NBC was synthesized through chemical methods, and the boronic acid groups within the PEG-NBC molecules coordinated with the polyhydroxy structures on the DA molecular chains to form a ROS-responsive PEG-NBC- α -MSH-Gel/DA functional coating. When ROS concentrations abnormally increased at the implantation site, the coordination bonds in the Gel/DA multilayer film broke, triggering the controlled release of α -MSH. This intelligent release mechanism effectively activated the osteogenic differentiation signaling pathway of MSCs in the osteoporotic microenvironment, promoting bone defect repair. Compared to simple physical adsorption or chemical grafting, LBL allows for the stepwise deposition of natural polyelectrolytes such as chitosan and hyaluronic acid. This results in a multilayer film structure capable of loading growth factors and drug molecules, thereby constructing biocompatible drug delivery carriers. LBL overcomes the limitations of traditional physical adsorption methods, which are susceptible to environmental factors like pH and ionic strength, by employing multilayer barriers and charge-balancing mechanisms to reduce the risk of rapid drug release.

Specific cases of biological modification treatments on implant surfaces to promote peri-implant osseointegration in osteoporosis are summarized in Table 3.

Biological modification methods have become the preferred strategy for optimizing implant osseointegration due to their intelligent response to OP pathological environments and targeted regulation advantages. However, some biomolecules may introduce microorganisms and infectious agents into the host during implantation, posing risks of biogenic infection. In recent years, localized drug delivery systems based on injectable hydrogels and drug-loaded nanoparticles can achieve targeted ROS scavenging

and immunomodulation of the microenvironment, demonstrating remarkable potential to reverse OP pathological conditions. These systems may serve as ideal candidate materials for OP bone tissue regeneration, facilitating early-stage bone microenvironment remodeling in osteoporotic bone defects^[46].

3 Discussion

This review summarizes the specific applications of currently used implant surface modification methods in the OP setting. Among them, the core of physical modification is to mimic the microenvironment of natural bone tissue by altering the surface morphology of the implant, such as the preparation of rough and porous surface structures and calcium-phosphorus composite coatings, to improve the abrasion resistance, corrosion resistance, and biological properties of the implant, and to provide more suitable conditions for the attachment and growth of OB, to accelerate the formation and maturation of the bone tissues^[47]. Currently, these modification methods have achieved better results under normal bone conditions. However, in OP, its effectiveness may be limited by the relatively low number and activity of osteoblasts due to the low bone density. Therefore, physical modification is usually used in conjunction with chemical and biological modification.

Chemical modification methods show versatility and flexibility in implant surface modification. Chemical modification can be done by coating the implant surface with bioactive coatings such as HA, bioactive glass, or metal ion coatings doped with Mg^{2+} , Zn^{2+} , Sr^{2+} , etc., which promotes osteogenesis, accelerates early osteogenesis, with inhibition of inflammatory factors, and long-term bone metabolic homeostasis^[48-50]. The anodic oxidation method forms a micro-nanoscale surface by constructing TiO_2 nanotubes on the surface of the implant^[51,52], which endows the implant with a great

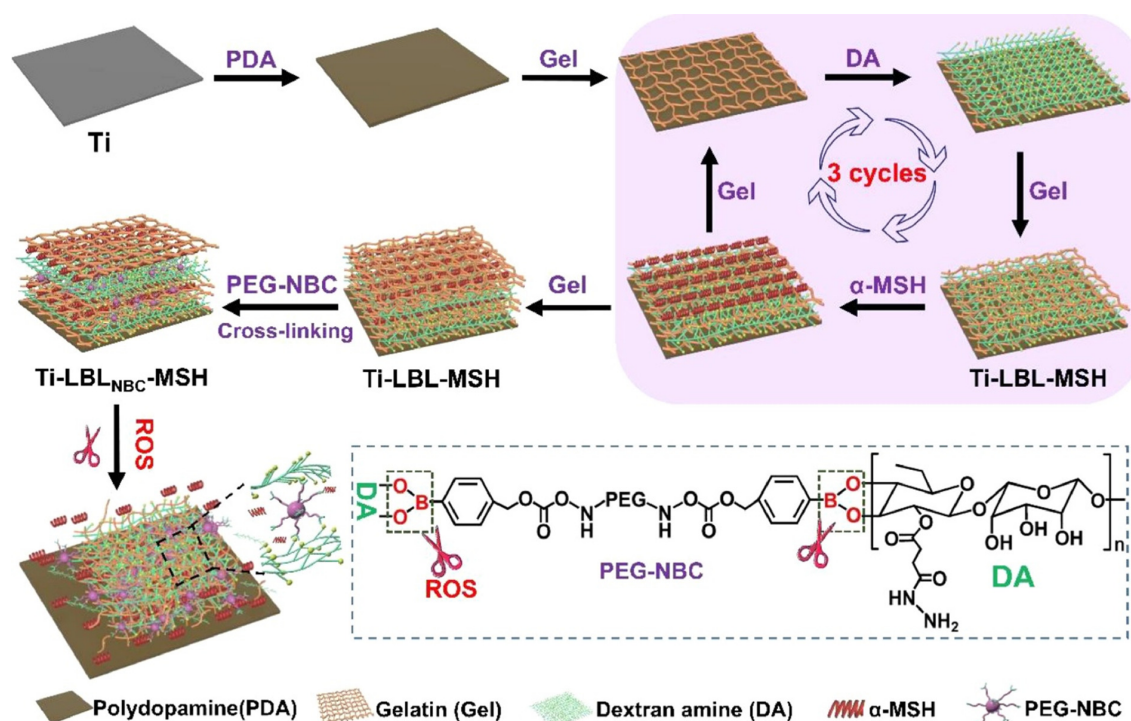


Figure 4 Schematic illustration of a biomimetic multilayer titanium implant responsive to reactive oxygen species for in situ delivery of alpha melanocyte stimulating hormone (α -MSH). Reproduced with permission from Chen, et al^[46]. Copyright © 2021 Elsevier Ltd.

Table 3 Research on promoting peri-implant osseointegration in osteoporosis through biological modification of implant surfaces.

Modification method	Base material composition	Cell/Animal models	Coating material composition	Experimental results	Method advantages	Anti-OP principle or mechanism	References
Covalent grafting immobilization method	Ti	MSCs; Sprague-Dawley rats	Experimental group: HA/p-OGP/Apt19S coating Control group: HA/p-OGP coating, HA coating, unloaded	The number of migrating MSCs in the experimental group was significantly higher than that in the control group; the expression levels of migration-related proteins Cdc42, p-FAK/FAK, Integrin $\alpha 5$, and Integrin $\beta 1$ in the experimental group were significantly upregulated, being 1.62 times, 1.56 times, 1.27 times, and 1.46 times those of the pure unloaded, respectively	During the circulatory process in vivo, the grafted material was less susceptible to enzymatic degradation, oxidation, and other effects, ensuring its integrity and functionality before reaching the target site. The ROS-responsive system constructed through grafting enabled rapid release of Apt19S, thereby facilitating swift recruitment of MSCs	p-OGP could directly regulate the proliferation and differentiation of MSCs and OBs; Apt19S was a regulatory molecule responsible for MSC recruitment, which guided the migration of MSCs to the implantation site by binding to ALP on the surface of MSCs; combined with the osteogenic synergistic effect of HA and p-OGP, the ROS-responsive release of Apt19S recruited MSCs, significantly enhanced bone regeneration efficiency under OP conditions	Chen ^[43]
			Experimental group: Calcitonin/Bone Morphogenetic Protein 2/Chitosan-Gelatin multilayer film (CT/BMP2-CS/Gel) Control group: CT-CS/Gel multilayer film structure, BMP2-CS/Gel multilayer film, CS/Gel multilayer film, unloaded	Compared to the unloaded group, the CT/BMP2-CS/Gel multilayer membranes exhibited increased expression of osteogenic genes ALP, OCN, OPN, BMP2, Runx2, Osterix, OPG by 1.6 times, 1.53 times, 1.81 times, 2.0 times, 1.2 times, 1.84 times, and 1.2 times, respectively	The CS/Gel multilayer film structure served as a bionic reservoir to regulate the localized delivery of CT and BMP2 around the implant, achieving the desired concentration and maintaining their bioactivity over an extended period	CT up-regulated BMP2 expression; BMP2, a potent osteoinductive growth factor, up-regulated mRNA expression of Runx2, DLX5, and Osterix; Through the BMP2/Smads/Runx2/Osterix and BMP2/Smads/Msx2/Osterix signaling pathways, it regulated the transcription of downstream osteogenic genes ALP, OCN, and OPN, promoting osteogenic differentiation of MSCs and improving osseointegration under OP conditions	
LBL	Polyether ether ketone (PEEK)	BMSCs; New Zealand white rabbit	Experimental group: 5-layer poly sodium styrenesulfonate (PSS) and poly allylamine hydrochloride (PAH) multilayer films, 10-layer PSS/PAH multilayer films, 20-layer PSS/PAH multilayer films Control group: unloaded	When the number of multilayer films increased from 5 layers to 20 layers, the contact angle on the implant surface decreased from 39.7° to 21.7°; Only scattered bone was observed around the control group, while continuous bone formation appeared around the 20-layer PEEK	Negatively charged PSS was used to encapsulate solid particles to enhance the stability of colloidal systems, while positively charged PAH was employed to strengthen protein and cell adsorption; The functional multilayer films constructed through repeated adsorption of PSS and PAH could impart stable surface modifications and excellent mechanical properties to implants	The self-assembled multilayer film formed by negatively charged PSS and positively charged PAH served as a site for bone cell growth; The PSS/PAH multilayer film structure on the PEEK surface enhanced the hydrophilicity of the implant surface by increasing the number of layers, thereby improving osteoblast adhesion, proliferation, and differentiation capabilities	Liu ^[45]
			Experimental group: PEG-NBC- α -MSH-Gel/DA multilayer film Control group: PEG-NBC-Gel/DA multilayer film, α -MSH multilayer film, Gel/DA multilayer film, unloaded	The experimental group showed only minimal α -MSH release when soaked in PBS without H ₂ O ₂ , whereas significant α -MSH release was observed when soaked in PBS containing H ₂ O ₂ ; The mRNA expression of Runx2, OCN, OPG, OPN, and COL in MSCs of the experimental group reached their highest levels	The PEG-NBC- α -MSH-Gel/DA multilayer film could maintain the biological activity of α -MSH over an extended period; After cross-linking with PEG-NBC, α -MSH remained in a physically stable state and could rapidly release therapeutically effective concentrations of α -MSH when ROS levels were excessive, sustaining localized treatment	PEG-NBC could be utilized to control drug release and prolong the drug's half-life; As an endogenous neuropeptide, α -MSH promoted osteogenic differentiation by stimulating cyclic adenosine monophosphate (cAMP); When the multilayer film was exposed to a pathological environment with ROS, the Gel/DA multilayer film on the Ti implant would be disrupted, enabling the sustained and controlled release of α -MSH from the multilayer film; This process through Runx2-mediated positive feedback regulation of the GSK-3 β / β -catenin signaling pathway, thereby promoting the differentiation of local MSCs and inhibiting OC activity	
LBL	Ti	MSCs, RAW264.7; Sprague-Dawley rats	Experimental group: PEG-NBC-Gel/DA multilayer film, α -MSH multilayer film, Gel/DA multilayer film, unloaded				Chen ^[42]

specific surface area, and the structure can adsorb or encapsulate a large number of drug molecules. By adjusting the parameters such as electrolyte composition, voltage, temperature and time of the anodic oxidation method, the pore size, pore depth and pore arrangement can be precisely controlled to modulate the release rate of anti-OP drug. In addition, topographies prepared on the implant surface using anodic oxidation can enhance the antioxidant properties of implants by influencing the oxidative stress microenvironment^[53,54]. This property is particularly important for OP patients, supporting the use of relevant implants in OP patients.

The biological modification approach focuses more on regulating the metabolic activity of bone cells through a controlled drug delivery system (CDDS) and the release of bioactive factors. Drug delivery systems enable precise regulation of osteocyte growth and differentiation through controlled release rates and dosages of anti-OP agents. The currently utilized anti-OP pharmaceuticals in clinical settings encompass BPs, PTH, estrogen and selective estrogen receptor modulators, statins, icariin, quercetin, insulin, and simvastatin, etc. Among them, BPs represent the first-line therapeutic agents for postmenopausal OP. Through cellular uptake and biochemical processes, it can inhibit FPPS, a key enzyme in the mevalonate pathway, thereby blocking protein prenylation. This disruption impairs osteoclast cytoskeletal formation and ruffled border function, ultimately inducing osteoclast apoptosis^[55]. While PTH, estrogen, and statins exhibit pleiotropic anti-osteoporotic effects, their significant side effects necessitate careful dosage considerations, typically positioning them as alternatives or adjuncts to BPs. Traditional Chinese medicines, such as icariin and quercetin, hold substantial promise in anti-osteoporosis therapy, with their advantages warranting further investigation. The application of the anti-OP agents in implant surface modification demonstrates favorable outcomes not only in the promotion of osteogenesis and the inhibition of bone resorption but also circumvents the adverse effects associated with systemic administration. Currently, the most used surface modification method for loading anti-OP drugs is the LBL method. This method has the potential to leverage weak intermolecular interactions, such as electrostatic forces, hydrogen bonds, and coordination bonds, and select well biocompatible materials to construct multilayered and functionally diverse membrane structure. Encapsulating the anti-OP drugs within these membrane layers can achieve drug loading. Meanwhile, precise control over the thickness and composition of the membrane layers allows for the regulation of drug loading, release rate, and duration, thereby extending the therapeutic efficacy. In addition, biomodification methods can load osteoinductive growth factors that regulate osteoblast signaling pathways onto the implant surface to achieve long-term regulation of osteoblast metabolic activities to improve osseointegration. It was found that the BMP-2/Smad-4 signaling pathway could promote osteogenic gene expression and OB differentiation through cooperative action with Runx2. By loading bioactive BMP-2 and Smad-4 onto implant surfaces using the LBL method, the bone integration effect under OP conditions would be enhanced^[56].

Despite the above advantages and advances, there are some limitations to the modification of implants using surface modification methods. Firstly, for example, when using plasma spraying to prepare HA coatings, due to thermal expansion coefficient (CTE) mismatch between the metal substrate and the HA coating, the bonding strength of the coating may be affected. Coating peeling or degradation may form sharp edges or

microcracks, inducing stress concentration and increasing implant fracture risk^[18]. Peeling or degradation of these coatings sometimes result in the formation of sharp edges or microcracks, which can trigger stress concentrations and increase the risk of implant fracture. Secondly, HA-coated implants are more susceptible to bacterial colonization than titanium implants or natural teeth due to the superior surface roughness and hydrophilicity of HA compared to pure Ti implants. Additionally, the long-term release kinetics and potential toxicity of metal ion-containing coatings, which are prepared through chemical modification, have not yet been verified. Lastly, while drug release control coatings created using the biomodification method can regulate the rate of drug release, prolonged use of anti-OP drugs may still result in adverse effects such as jawbone necrosis, implant loosening, pain, numbness, and sensory deficits^[57]. Anchoring functional bioactive macromolecules such as extracellular matrix (ECM) components or analogs, proteins, and growth factors on metal implant surfaces can regulate cell behavior and promote bone healing around implants that provides mechanical support. However, this approach cannot prevent soft tissue invasion. Guided bone regeneration (GBR) membranes spontaneously and independently simulate physiological processes in vivo by acting as physical barriers to create exclusive repair space for bone cells. Combining both strategies overcomes limitations in osteoporotic bone defect repair materials^[58].

Therefore, although a single modification strategy can enhance the initial bone-bonding rate, it is difficult to overcome the fundamental problems of bone metabolism imbalance and decreased mechanical adaptability caused by OP. Future research directions may focus on the following aspects: developing new chemical bonding technologies to enhance coating-substrate bond strength, breaking through traditional single-function modification thinking, promote the leap from "passive osseointegration" to "active regeneration induction" of implants at material-cell-tissue multi-levels, constructing multistage sustained-release systems to solve bioactive molecular decay in vivo that can achieve sustainable release of anti-OP drugs, achieving large-scale material production simultaneously with modification, conducting long-term clinical studies to compare coating performance and evaluate new implant coating success rates. In addition, different patients have dissimilar behavioral habits, stress levels, and mental health status, all of which can affect the osteogenic performance of materials^[59,60].

4 Conclusion

This review summarizes applications of various surface modification techniques in improving osseointegration capacity of implants for OP patients and discusses advantages and limitations of existing modification methods. Current research on modification methods has evolved from single physical morphology control to composite biological coatings. Different modification techniques exhibit distinct mechanisms and effects, but all promote implant-bone integration to some extent, receiving preliminary validation in constructed OP animal models. However, a few limitations persist, requiring further optimization of modification technologies and enhancement of clinical outcomes. Current studies are confined to in vivo and in vitro validation. Most previous research focused solely on material effects on bone tissue, neglecting bodily responses to materials. During clinical trials, there are individual differences among patients. In addition, OP patients experience excessively

long osseointegration periods, high clinical translation time costs, significant individual variations, and considerable clinical translation difficulties. Future efforts should prioritize convergence of materials science, dental medicine and artificial intelligence, establishing interdisciplinary collaborative innovation systems. Through intelligent material design, bionic structure optimization and machine learning-driven surface functionalization, precision therapeutic solutions combining mechanical compatibility and bioactivity are promising for OP patients.

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Author contribution

B.L. : conceptualization, literature search, original draft preparation. X.C. : figure generation, visualization, manuscript formatting. S.Z. : data curation, visualization, manuscript formatting. Y.C. : literature search. H.X. : checking references formatting. Z.P. : writing and editing, funding acquisition. O.L. : oversight of research direction, critical review of theoretical framework. Q.P. : oversight of research direction, manuscript structure refinement, funding acquisition.

Ethics approval and consent

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N/A

Competing interest

The authors declare that they have no competing interests.

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