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REVIEW ARTICLE

Role of implants surface modification in osseointegration: A systematic review

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Abstract

Long-term and stable fixation of implants is one of the most important points for a successful orthopedic surgery in the field of endoprosthesis. Osseointegration (OI), functional connection between bone and implants, is considered as a pivotal process of cementless implant fixation and integration, respectively. OI is affected by various factors of which the property of implants is of high significance. The modification of implants surface for better OI has raised increasing attention in modern orthopedic medicine. Here, the process of OI and the interactions between implants and ambient bone tissues were emblazed. The knowledge regarding the contemporary surface modification strategies was systematically analyzed and reviewed, including materials used for the fabrication of implants, advanced modification techniques, and key factors in the design of porous implants structure. We discussed the superiority of current surface modification programs and concluded that the problems remain to be solved. The primary intention of this systematic review is to provide comprehensive reference information and an extensive overview for better fabrication and design of orthopedic implants.

KEYWORDS

biomaterials, orthopedic implants, osseointegration, surface modification

1 | INTRODUCTION

The prevalence of osteoarthritis (OA) increases with the aging population. According to the Global Burden of Disease (GBD), the global age-standardized incidence of knee OA and hip OA in 2010 was 3.8% and 0.85%, respectively, which is expected to increase rapidly over the coming years (Cross et al., 2014; Lawrence et al., 2008). Hence, total joint replacement (TJR) has become a cost-effective solution for reducing pain and rehabilitating joint function. In this situation, implants play a more and more important role in modern orthopedic surgery. However, failure of implants and, in this case, the needed revision remain to be a significant clinical challenge, which results in much higher complication and mortality rates than primary TJR (Gwam et al., 2017; Hamilton, Howie, Burnett, Simpson, [nbtilde] & Patton, 2015).

Aseptic loosening is the most common factor for revision surgeries, as it accounts for one-third of them (Gothesen et al., 2013; Prkic, Welsink, The, van den Bekerom, & Eygendaal, 2017). For a long-term and reliable fixation of implants, osseointegration (OI) has been

Abbreviations: Al, aluminum; ALP, alkaline phosphatase; AM, additive manufacturing; BMSCs, bone marrow-derived stem cells; CoCr, cobalt–chromium; CpTi, commercially pure titanium; CVD, chemical vapor deposition; ECMs, extracellular matrices; GBD, Global Burden of Disease; HA, hydroxyapatite; MoM, metal-on-metal; MSCs, mesenchymal stem cells; OA, osteoarthritis; OI, osseointegration; PVD, physical vapor deposition; PS, plasma spraying; PEEK, polyetheretherketone; STL, standard triangulate language; Ta, tantalum; Ti, titanium; V, vanadium; VEGF, vascular endothelial growth factor; Y-TZP, yttrium oxide-stabilized zirconia; ZrO_2, zirconia.

proven to be a significant solution by numerous in vivo trials over the past few decades (Davies, 2003; Kienapfel, Sprey, Wilke, & Griss, 1999; Pilliar, 2005). The definition of OI is "direct structural and functional connection between living bone and the surface of an artificial implant" (Brånemark, Brånemark, Rydevik, & Myers, 2001). Since the importance of OI was recognized, a great number of strategies have been developed to accelerate OI and achieve a more rapid and firm fixation. It is demonstrated that the OI process can be influenced by a variety of factors, which might be generally divided into two aspects: the environment of the bone–implant interface and the design of the implant itself. The environmental factors include loading conditions, host bone properties, interface distance, the concentration of local osteoblast and osteoclast, and systemic illness (diabetes, rheumatoid arthritis, and smoking) (Annibali, Pranno, Cristalli, la Monaca, & Polimeni, 2016; Li, He, Hua, & Hu, 2017; Shibamoto et al., 2018). The second aspect consists of materials; surface coating; topology; macro-, micro-, and nanostructure of the implants, and so on. (Rasouli, Barhoum, & Uludag, 2018). There have been many kinds of fabrication methods to modify the surface of implants in order to change the surrounding environment for a better OI.

In spite of the excellent in vivo results have been proven, there are still lots of problems that need to be solved, and the mechanism of OI remains still unclear. This present review aimed to describe the process of OI and summarize the current implant surface and its modification for promoting OI. In the end, we discussed several dilemmas that researchers were facing and proposed the prospects of the design and manufacture strategies for modifying future orthopedic implants.

2 | THE PROCESS OF OSSEOINTEGRATION

OI is a dynamic process involving a sequence of cascade responses in which the properties of implant surface play an important role (Figure 1). Bone healing around implants involves a cascade of cellular and extracellular biological events (Mavrogenis, Dimitriou, Parvizi, & Babis, 2009). There exists an inflammatory response, which takes place as soon as the implant is placed into the body, leading to the release of various proteins such as growth factors and cytokines that form a blood clot (Lotz, Berger, Schwartz, & Boyan, 2018; Terheyden, Lang, Bierbaum, & Stadlinger, 2012). In a few minutes, the proteins and lipids will be absorbed by the implant surface from the blood clot. These proteins coated on the surface may act as a signal for cell migration and proliferation (Rivera-Chacon et al., 2013). The specific

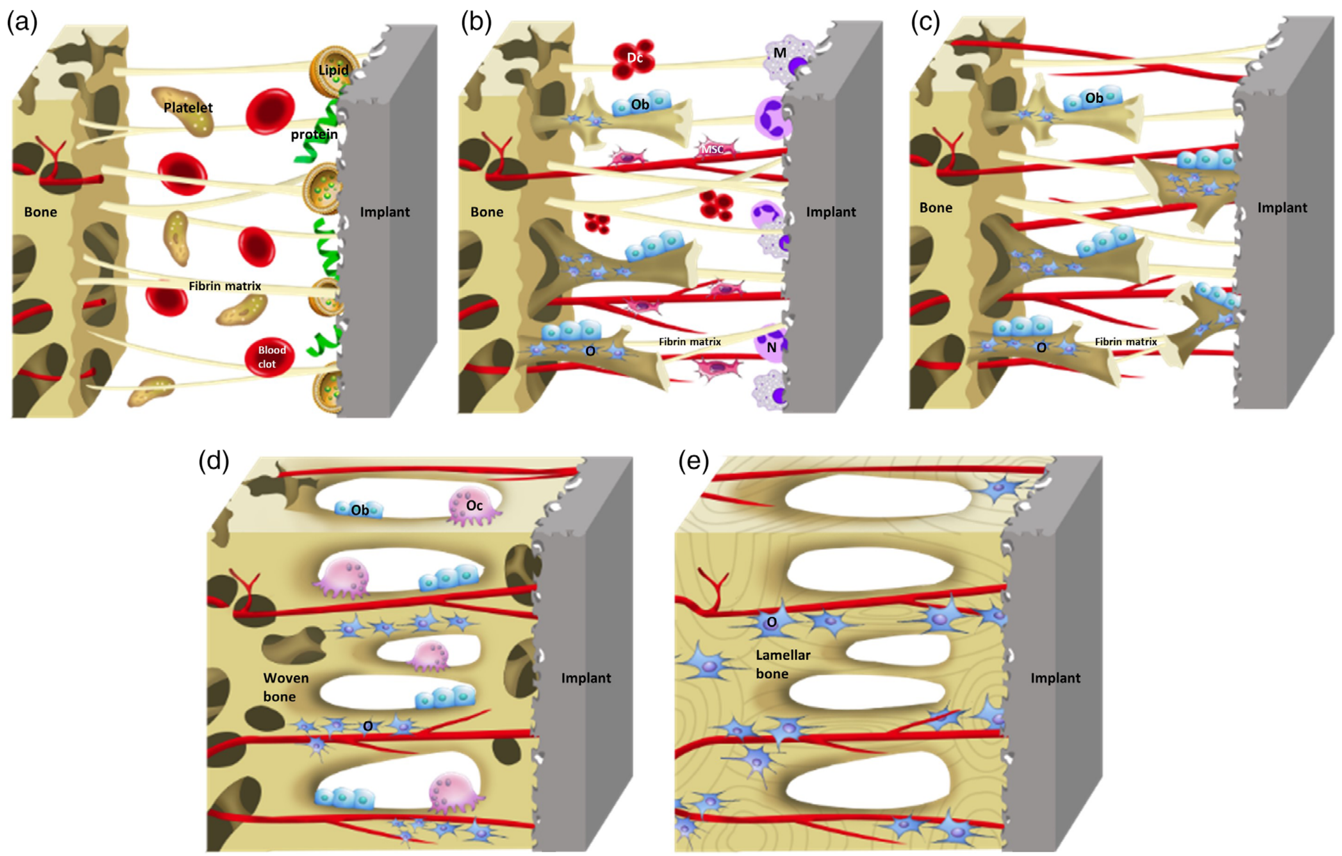

FIGURE 1 Schematic of the process of implants OI. The process of OI includes the formation of the blood clot and fibrin matrix (a). Angiogenesis and woven bone formation (b). Distance osteogenesis and contact osteogenesis (c). Newborn woven bones fill up the gap and bone remodeling (d). Woven bones transform into lamellar bones (e). Dc, decomposed clot; M, macrophage; MSC, mesenchymal stem cell; N, neutrophil; O, osteocyte; Ob, osteoblast; Oc, osteoclast;

types of proteins and firmness of adhesion depend largely on the characteristics of the surface of the implant, such as topographic features, roughness, and hydrophilicity (Boyan, Lotz, & Schwartz, 2017; Gittens, Olivares-Navarrete, Schwartz, & Boyan, 2014; Pegueroles, Tonda-Turo, Planell, Gil, & Aparicio, 2012; Wang et al., 2016). Subsequently, blood platelets facilitate the formation of the fibrin matrix, which serves as "a bridge" for cell migration and attachment (Marx, 2004; Mavrogenis et al., 2009).

A total of 2-3 days after implant placement, macrophages and neutrophils adhere to the implants through the "bridge," removing the pathogens and necrotic tissue and decomposing the blood clot to make space for new blood vessels (Caplan & Dennis, 2006; Davies, 2003). After 4 days, angiogenesis occurs in the gap between the implant and host bone with nondifferentiated mesenchymal stem cells (MSCs) gathering around the vessel structure. Under the influence of growth factors and cytokines, MSCs differentiate into osteoblasts, which can produce the extracellular matrix and form immature woven bone (Berglundh, Abrahamsson, Lang, & Lindhe, 2003; Meyer et al., 2004). However, MSCs can also differentiate into fibroblasts that may stimulate the formation of a fibrous membrane on the implant surface and impede the process of bone ingrowth (Razzouk & Schoor, 2012). It is affected by the surface properties and surrounding cell communication (Boyan, Cheng, Olivares-Navarrete, & Schwartz, 2016; Ma et al., 2018).

Woven bone formation keeps on taking place over 1–2 weeks after implantation. Since the movement of MSCs is guided by the fibrin bridge, there are two types of osteogenesis according to which MSCs adhere to. Contact osteogenesis is defined as bone formation initiated directly on the surface of the implant. On the other hand, distance osteogenesis arises on the bones or tissues surrounding the implant, which can migrate to the implant surface through the fibrin bridge (Davies, 1996; Osborn & Newesely, 1980). It is demonstrated by Choi et al. that two osteogenesis processes act interactively, and the surrounding bone that undergoes distance osteogenesis after implantation can deliver signals inducing contact osteogenesis (Choi, Sim, & Yeo, 2017).

After 2 weeks, the bone–implant gap is filled up by newborn woven bone and the subsequent procedure of OI is bone apposition and remodeling. During this process, osteoclasts resorb the newly formed bone to eliminate the microcracks and optimize the surface for lamellar bone (Mulari, Qu, Härkönen, & Väänänen, 2004). Osteoclasts establish a sealing zone and create various microtopography and nanotopography, which contain biochemical information, leading osteoblasts to find the position that needs new bone formation (Minkin & Marinho, 1999). Osteoclasts and osteoblasts cooperate in a harmony way, and the fragile provisional woven bone transforms gradually into parallel fiber bone and then into the lamellar bone. This dynamic process exists continuously over 1 year or longer, which is necessary for long-term fixation.

3 | MATERIALS

Materials for orthopedic implants have experienced a significant advancement over the decade. Depending on the nature of materials used for fabrication, implants available now can be roughly divided into four groups: metals, ceramics, polymers, and hybrids (Table 1). It is demonstrated that materials with similar mechanical properties as host bones can improve the amount and speed of bone ingrowth (Mukherjee & Gupta, 2017; Samira et al., 2015).

3.1 | Metals

Metals and alloys have been used for many years and still occupy the major position in orthopedic surgeries because of their biomechanical properties. Recently, many kinds of bioactive metals that can facilitate the OI process have raised increasing concern in orthopedic research.

3.1.1 | Titanium and titanium alloy

Titanium (Ti) has become the material of choice for implants since it was found to have great potential to fuse with bone by Bothe et al. in 1940 (Bothe, 1940). Owing to its excellent mechanical properties such as high strength, corrosion resistance, low modulus of elasticity, and the abundant amount in natural mineral deposits, Ti is currently the most commonly used commercial material for load-bearing implants in the world (Geetha, Singh, Asokamani, & Gogia, 2009; Shen & Brinson,

TABLE 1 Classification of commonly used materials and their characteristics

Types	Implant materials	Advantages	Disadvantages	Ref.
Metal based	Titanium	Excellent mechanical properties; biocompatibility	Allergic reactions	Takemoto et al. (2005)
	Titanium alloys	Plasticity; corrosion resistance		Niinomi (1998)
	Tantalum	Biocompatibility; high coefficient of friction	Rare and expensive	Wang et al. (2016)
	Cobalt–chromium alloy	Corrosion resistance; stable	Brittle	Roach (2007)
Ceramics based	Zirconia (ZrO_2)	Biocompatibility; corrosion and scratch resistance; hardly cause allergic reactions	Aging progress	Sivaraman, Chopra, Narayan, and Balakrishnan (2018)
	Alumina (Al_2O_3)	High mechanical strength; stiffness	Bioinert	Camilo et al. (2017)
Polymer-based	Polyetheretherketone (PEEK)	Similar elastic modulus to bones; radiolucency; plasticity	Bioinert; lack of antibacterial activity	Mishra and Chowdhary (2019)

2011; Xue, Krishna, Bandyopadhyay, & Bose, 2007). Commercially pure Ti (CpTi) exhibits four different grades with the increase of oxygen content: pure Grade I, Grade II, Grade III, and Grade IV Ti. Other elements such as nitrogen, carbon, iron, and hydrogen also increase but do not vary much between the grades (Lautenschlager & Monaghan, 1993). These small changes of the composition significantly improve the mechanical properties of pure Ti from Grade I to Grade IV (McCracken, 1999). The formation of a stable oxide layer on the pure Ti has been proved to be responsible for the CpTi biocompatibility and enhancement the corrosion resistance ability (Saini, Singh, Arora, Arora, & Jain, 2015; Tiainen, Wohlfahrt, Verket, Lyngstadaas, & Haugen, 2012). However, it makes Ti hard to be carved.

Nowadays, for higher porous structure and better plasticity, titanium alloys have been introduced into the market. Ti6Al4V (titanium; 6% aluminum; 4% vanadium) occupies the most important position among all the Ti alloys. Aluminum is able to increase the strength of the alloy and decrease its density at the same time while vanadium can prevent aluminum from corrosion (Roach, 2007).

3.1.2 | Tantalum

Tantalum (Ta) is a highly inert and corrosion-resistant material with an extremely high melting point (3,017°C). Different from Ti, Ta is highly conductive to heat and electricity and has been proven to be more biocompatible than Ti (Cachinho & Correia, 2008). Oxidation reaction on the Ta surface facilitates osteoblasts' adhesion, proliferation, and differentiation, and it is more excellent than commonly used Ti6Al4V (Miyaza et al., 2002; Stiehler et al., 2008). Therefore, Ta has emerged as an essential component for acetabular reconstruction in revision hip arthroplasty because of its rapid and long-term fixation (Issack, 2013; Paprosky, Perona, & Lawrence, 1994).

Ta can also be fabricated into highly porous implants. Owing to its high volumetric porosity, Ta is known as the trabecular metal. The elastic modulus of porous Ta is similar to that of subchondral bone, which assists it in reducing stress shielding and preserving bone stock (Meneghini, Ford, McCollough, Hanssen, & Lewallen, 2010). Simultaneously, the high coefficient of friction enables porous Ta to exhibit superior initial stability than conventional cementless prosthesis (Meneghini, Meyer, Buckley, Hanssen, & Lewallen, 2010). However, highly porous tantalum structure is so thin that it is difficult to manufacture accurate inner topography (Zardiackas et al., 2001). What's more, rare in storage and high costs in purification and fabrication hinder its wide range of applications. As a consequence, Ta is constantly produced as a powder and coated on the surface of other implants, which also shows satisfying consequents (Shi et al., 2017; Zhou, Hu, & Lin, 2018).

3.1.3 | Cobalt–chromium alloy

Cobalt–chromium (CoCr) alloy is commonly utilized in metal-on-metal (MoM) Total Hip Arthroplasty (THA) for its high wear and corrosion resistance. It is also found to have an excellent combination of material toughness and yield strength, ductility, and hardness (Navarro, Michiardi, Castaño, & Planell, 2008). Cobalt increases the strength of alloy, whereas chromium is a component that enhances the corrosion resistance (Camilo et al., 2017). However, adding more than 30% chromium makes this alloy hard to cast and results in a brittle phase (Christian, Oliver, Paustenbach, Kreider, & Finley, 2014). As a result, the CoCr alloys used to construct MoM implants regularly contain ~64% Co, ~28% Cr, and small amounts of other metals: molybdenum, aluminum, nickel, manganese, iron, and lanthanum. Viennot et al. demonstrated that CoCr alloys not only exhibit high corrosion resistance but also found to be electrochemically equivalent after multiple castings (Viennot, Dalard, Lissac, & Grosgogeat, 2005). However, the OI and biocompatibility of CoCr are often considered inferior to Ti alloys (Jakobsen, Baas, Jakobsen, & Soballe, 2010). Another issue related to CoCr alloys is that the degradation of the biomaterials will produce plenty of nanosized particles, which may cause allergic reactions and cytotoxicity (Learmonth, Gheduzzi, & Vail, 2006). It is reported that patients with MoM CoCr implants typically have elevated blood Co and Cr concentrations (Engh Jr et al., 2009). But the biological relevance between particles and complications has not been thoroughly evaluated and Christian et al. suggested that the Co/Cr concentrations in the blood and tissue of MoM implant patients are too low to increase the risk of systemic disease (Christian et al., 2014).

3.2 | Ceramics

Ceramic is an inorganic material that has been manufactured by sintering and compacting solid particles at high temperature. It has been remarkably improved in terms of its mechanical properties since its first application in the 1970s (Sedel, 2000). As it barely induces wear debris and allergic reaction, ceramic is widely fabricated as femoral head and acetabular liner in clinical practice.

3.2.1 | Zirconia

Zirconia (ZrO_2), the oxide form of zirconium, is a ceramic, which has been considered as a biomedical implant since 1969 (Hulbert, Klawitte, & Bowman, 1972). ZrO_2 ceramics are commonly used as femoral component heads in total hip replacement as they exhibit superior corrosion and scratch resistance to reduce aseptic loosening caused by particles of debris (Clarke et al., 2003). In addition, it is reported that ZrO_2 is quite biocompatible and hardly cause an allergic reaction to human beings (Christel et al., 1988). Thanks to its white tooth-like color and esthetic appearance, ZrO_2 is emerging as a promising alternative implant in dentistry (Mishra & Chowdhary, 2019). It is well known that ZrO_2 has three different types of crystallographic status depending on temperature. Pure ZrO_2 is monoclinic (M), which will transform into tetragonal (T) with the ambient temperature increasing to 1170°C, whereas the T transforms into cubic (C) at 2370°C (Brett, 1981). The T phase is a metastable phase with the highest strength. The phase transformation from T to M (T–M) results in a volume expansion of 3–4%, resisting the propagation of cracks. However, this advantage will be lost once T transforms extensively into M. The phase transformation could finally increase the formation of cracks and decrease surface hardness, which is obviously undesirable for clinical implants (Catledge et al., 2003). Under the severe environment of moisture and stress, ZrO_2 ceramics undergo an increasing transformation of T phase into M phase, which is known as "aging" of the material (Catledge et al., 2003; Lughi & Sergo, 2010). In order to prevent or retard this phenomenon, various oxides are added to ZrO_2 to stabilize the T phases (Lakusta et al., 2018). Currently, 3 mol% yttrium oxide (yttria)-stabilized ZrO_2 (Y-TZP) is the ceramic of choice because of its almost 100% T microstructure (Kelly & Denry, 2008).

3.2.2 | Aluminum oxide

Aluminum oxide (Al_2O_3), also called alumina, is a kind of polycrystalline ceramic that is obtained from aluminum oxide powder and fabricated into implants at a very high temperature. Al_2O_3 has been introduced into total hip replacement since 1971 by Boutin (Boutin, 1971). Unlike ZrO_2, Al_2O_3 is a very stable and chemically inert material and does not need to be chemically stabilized. Desai et al. explained that the low electric conductivity and thermal conductivity of Al_2O_3 are mainly due to the robust ionic and covalent chemical bonds between Al^{3+} and O^{2-} (Desai, Wu, Rohlfing, & Wang, 1997). It is well acknowledged that Al_2O_3 is a material with extremely hard and scratch resistance, low coefficient of friction, and high level of stiffness. The wettable and hydrophilic properties of Al_2O_3 play an important part in the lubrication process and make it possible to fabricate large-diameter femoral heads. The major disadvantages of Al_2O_3 include the brittleness and the chipping during prosthesis insertion. The incidence of squeaking is another problem that disturbs the patients despite the fact that it does not affect patient function (Tai et al., 2015). In addition, Al_2O_3 is considered to be inert and exhibits osteogenic potential. It is reported that a fibrous membrane consisting mostly fibroblasts is induced when Al_2O_3 is implanted (Gibon et al., 2017).

3.3 | Polymers

Implants based on polymers provide excellent properties such as low elastic modulus, biocompatibility, and higher elongation to fracture. Polymers are now mostly used as screws or coating materials in orthopedic implants, and the articular prosthesis made from polymers requires more scientific attention.

3.3.1 | Polyetheretherketone

Polyetheretherketone (PEEK) is a semicrystalline thermoplastic material that is produced from the step-growth alkylation reaction of bisphenolates. Since first introduced in the 1990s by AcroMed, PEEK has been widely used in spine, orthopedics, and arthroscopy surgery because of its chemical resistance, mechanical properties, and imaging characteristics (Kurtz & Devine, 2007; Uzumcugil, Yalcinkaya, Ozturkmen, Dikmen, & Caniklioglu, 2012). PEEK's modulus of elasticity is 3.6 GPa, which can be increased to 18 GPa by reinforcing it with carbon fibers, leading it to be more closer to that of cortical bone (18 GPa) than Ti alloys (~110 GPa) (Ponnappan et al., 2009; Ramakrishna, Mayer, Wintermantel, & Leong, 2001). This provides the potential to decrease stress shielding. Because of its radiolucency, PEEK can be imaged by X-ray, CT scan, and MRI in contradiction with Ti, which makes it possible to evaluate the process of postoperative OI precisely (Ponnappan et al., 2009). Similar to many polymers, PEEK can be repeatedly sterilized by autoclaving and be manufactured into complicated shapes by machining and heat contouring to adapt to the individual application (Abu Bakar, Cheang, & Khor, 2003). In spite of all these advantages, some studies demonstrated that PEEK's bioinert and smooth surface hinders OI and induces the formation of fibrous encapsulation (Najeeb, BDS, BDS, & BDS, 2016). Besides, PEEK lacks antibacterial activity on the surface, and detachment of coating materials sometimes results in inflammation and osteolysis (Campoccia, Montanaro, & Arciola, 2006). Therefore, the development of proper coating and modification of implants surface of PEEK to overcome these drawbacks seems to be a focal point in the future.

4 | SURFACE MODIFICATION TECHNIQUES

It has been proved by numerous studies that the properties of implant surface could influence the ambient environment, which is of high importance for OI (Huanhuan, Pengjie, Sheng, Binchen, & Li, 2017; Kang, Jeong, Huh, Park, & Cho, 2018; Kargupta et al., 2014). Modification techniques have experienced constant development and evolution with the purpose of increasing surface roughness, physically mimicking host bone structure, and improving implants biocompatibility. These modification techniques can be divided into three categories depending on the characteristics brought on the surface: physical, chemical, and biological (Table 2). These techniques can be utilized either individually or in combination. Each method has its own specific advantages and limitations, and it is essential to choose an appropriate method in terms of implant materials, applying situations and fabricating procedures.

4.1 | Physical techniques

Physical surface modification exploits dry transformation technology to change the topography or morphology of the surface of the implant in order to create a favorable environment for OI. Currently, commonly used and effective physical techniques include grit blasting, additive manufacturing (AM), vapor deposition, plasma spraying, and so on.

TABLE 2 Summary of fabrication techniques

Category	Techniques	Features	Ref.
Physical techniques	Grit blasting	Forcing particles against the surface; simple and low cost; promote the attachment both of osteocytes and bacterial	Jemat, Ghazali, Razali, and Otsuka (2015)
	Additive manufacturing (AM)	Creating complex 3D structures; uncomplicated process; energy and materials saving	Yuan, Ding, and Wen (2019)
	Plasma spraying (PS)	Thermal technique; economical and safety	Tang et al. (2013)
	Physical vapor deposition (PVD)	Vacuum deposition; utilize all types of inorganic and some organic materials; strong adhesion	Feddes, Wolke, Vredenberg, and Jansen (2004)
	Machining	A simple method to increase roughness; slow and inefficient	Salou, Hoornaert, Louarn, and Layrolle (2015)
	Laser treatment	Achieving complex and precise topography; rapid and clean	Hindy, Farahmand, and Tabatabaei (2017)
Chemical techniques	Anodic oxidation (anodization)	An accelerated electrochemical process; enhancing the corrosion resistance; creating nanometer features	Hall et al. (2017)
	Sol–gel	Low temperature technique; drugs delivery	Adams et al. (2009)
	Chemical vapor deposition (CVD)	Generating a fine and solid film; creating both homogeneous and hierarchical structures	Li et al. (2013)
	Acid etching	Removing materials and fabricating roughness; depending on acid concentration, temperature, and time	Jemat et al. (2015)
	Alkali treatment	Extending uniformly; do not damage mechanical properties;	Yao et al. (2019)
Biological techniques	Cells	AMSCs, BMSCs, MSCs, embryonic stem cells	Heng et al. (2011)
	Proteins	VEGF, ECM	Lewallen et al. (2015)

4.1.1 | Grit blasting

Grit blasting is one of typical physical surface modification techniques that force abrasive particles (i.e., sand, alumina, hydroxyapatite, TiO_2) against the implant surface through a pressurized projection by means of compressed air. Grit blasting is a kind of simple and low-cost technique that is usually used to roughen the surface, thereby facilitating cell adhesion. The topography and roughness of surface mainly depend on the size, shape, and properties of the particles applied. Abe et al. evaluated the mechanical and histological differences of grit-blasted implants in dogs and demonstrated that grit blasting facilitated the use of bare implants (Abe, Nishimura, & Izumisawa, 2008).

Following grit blasting, acid-etching can help to clean the residuary particles. Herrero-Climent et al. reported that the combination of grit blasting and acid-etching accelerated the process of osteogenesis at the different implantation procedures (Herrero-Climent et al., 2013). The disadvantage of grit blasting is that the fabricated rough surface can also promote the attachment of bacteria (Jemat, Ghazali, et al., 2015).

4.1.2 | Additive manufacturing

AM, known as 3D printing or rapid prototyping, is a rising technology possessing the capability of creating complex 3D structures at the micrometer or nanometer scale. AM is a group of layer-by-layer fabricating processes of which selective laser melting and electron beam melting are mostly widespread. The procedure of AM begins with the creation of the 3D object model through computer-aided design. This 3D model file would be saved as a standard triangulate language (stereolithography, STL) format and be sliced into 2D layers parallel to the manufacturing platform by using a slicing algorithm. Finally, a fine metallic powder layer would be melted by powerful energy (laser beam or electron beam according to different techniques) and be made into a 3D structure in a layer-by-layer process following the STL files. The advantages of AM are as follows: (a) this technology can theoretically deal with any material that is difficult to be machined as long as it is available in powder form; (b) AM could generate customized, complex, and precise shapes for an individual patient; (c) it is an uncomplicated process from design to fabrication, which can reduce the waste of energy and materials. Slots et al. demonstrated that the implants underwent a rapid AM possessing clinically relevant mechanical strength and pure chemical character (Slots et al., 2017). Meanwhile, they contributed to the adhesion of MSCs, deposition of collagen, and secretion of alkaline phosphatase (ALP).

4.1.3 | Plasma spraying

Plasma spraying (PS) is one of the thermal spraying techniques in which molten materials are coated onto a surface. During the spraying process, materials are loaded into a plasma jet and melted with the temperature around 1,000°C. Then, the melted materials are emanated from a plasma torch under vacuum, reduced or atmospheric pressure, and finally, rapidly solidify and form a deposit. PS can create a broad thickness range of coatings (range from nanometers to several millimeters). This technology is an economical and safe method, and chemical compositions scarcely remain on the surface during fabrication (Coelho et al., 2012). Several studies demonstrated that PS coatings could improve the biocompatibility of implants and promote OI (Stewart, Welter, & Goldberg, 2004; Veerachamy, Hameed, Sen, Dash, & Manivasagam, 2018). Hydroxyapatite (HA) is commonly applied in PS processes. Vahabzadeh et al. reported that both stability and chemistry can be influenced significantly in vivo and in vitro by the plasma-sprayed HA coatings on Ti implants (Vahabzadeh, Roy, Bandyopadhyay, & Bose, 2015). But the loss of crystallinity of HA during spraying cannot be ignored and invokes further research studies (Zyman, Cao, & Zhang, 1993).

4.1.4 | Physical vapor deposition

Physical vapor deposition (PVD) represents a category of vacuum deposition strategies that produce vaporizing materials and coat it on the substrates. In this procedure, materials are transformed from condensed status into vapor status and, in the end, deposit on the surface in the form of condensed status. Sputtering deposition is one of the most commonly used PVD technologies in orthopedic and dental implants. During the sputtering process, bombardment of ions removes local substrate ions from the surface and makes space for coatings (Feddes et al., 2004). PVD has the ability to utilize all types of inorganic materials and some organic materials. The strong adhesion of the coatings to the surface is another prominent feature of this method. Shevtsov et al. evaluated the effect of PVD silver coating on porous implants. An in vitro study showed that silver-coated implants provided protection from bacterial growth and more angiogenesis could be observed compared with the control group (Shevtsov et al., 2019). Zykova et al. acknowledged that HA coatings on Ti alloy in the presence of magnetron-sputtered alumina bond coats exhibited higher corrosion resistance and better biocompatibility (Zykova et al., 2015).

4.2 | Chemical techniques

The hypothesis behind chemical surface modification is the possibility to achieve a chemical bond between the coat and the bone due to the chemical similarities between the bone itself and the foreign material (Albrektsson & Wennerberg, 2019). Chemical surface modification can result in the alteration of implants surface by various chemical reactions such as oxidation, carbonization, or nitridation. Advanced chemical surface modification techniques include anodic oxidation, acid, and alkali treatment, chemical vapor deposition, and sol–gel deposition.

4.2.1 | Anodic oxidation

Anodic oxidation (anodization) is an accelerated electrochemical process in which oxide film is applied to the anode metal implants surface while immersed in an electrolyte bath. The anodic oxidation used to be a kind of technology for enhancing the corrosion resistance of screw implants. However, owing to the developed control of voltage, concentration, and temperature, it is now ordinarily utilized to increase the thickness of the TiO_2 layer and fabricate controllable nanostructures on titanium implant surfaces. The nanometer features of surfaces created by anodic oxidation significantly improve the bioactivity and promote OI of Ti implants (Hall et al., 2017). Anodic oxidation of Ti implants will change the crystalline structure and chemical composition of the oxide film, which greatly influence the cell response to the implants (Krasicka-Cydzik, 2004). Wang et al. reported that Ti alloys exhibited different colors when anodized at different voltages (yellow at 60 V and pink at 65 V), and this technology increased the grain formation, roughness, and hydrophilicity (Wang et al., 2019). Yamada et al. combined anodic oxidation and sandblasting to modify the Ti surface and demonstrated that it enhanced the strength of early-stage OI (Yamada et al., 2013).

4.2.2 | Sol–gel

Sol–gel refers to a technology that forms an oxide or solid compound by sol–gelation and thermal treatment. In this procedure, organic or inorganic compounds undergo hydrolysis polymerization and turn into a colloidal solution (sol), which is gradually changed into a gel-like diphasic system. Then the remaining liquid is removed by a drying process, which will shrink the structure. Afterward, a thermal treatment is used to promote polycondensation and enhance mechanical properties. The solution can be transformed into a ceramic or aerogel depending on different manipulations. One of the advantages of the approach is that it is a low-temperature technique that allows excellent control of coatings' chemical composition. Another important feature of the sol–gel technique is that the coatings can be composed of drugs, and the drugs are released at a controlled speed. Adams et al. produced a vancomycin-containing sol–gel film on Ti alloy, which exhibited predictable release kinetics and successfully treated the bacterial infection in a rat osteomyelitis model (Adams et al., 2009). In addition, the sol–gel method combined with different coating processes can create bioactive coatings with a multiple-layer hierarchy, which corresponds with the bone structure (Zemtsova et al., 2017).

4.2.3 | Chemical vapor deposition

Chemical vapor deposition (CVD) implies the processes in which gaseous precursors undergo chemical reaction at a heated surface and generate a fine solid film. Being similar to PVD, CVD also involves the procedure of deposition and condensation of evaporated materials. However, CVD deposits the coatings with the chemical bonding, whereas PVD relies on physical forces. Regularly, the by-products accompanied by the chemical reaction can be removed by gas flow through the reaction chamber. This technology is widely used in the semiconductor industry to produce thin films. CVD processing is able to create films of both homogeneous and hierarchical structure and of controllable composition (Li et al., 2013). Recently, CVD technology realized the production of inexpensive, high-quality diamond thin film, which showed significant physical characteristics and OI potential (Metzler et al., 2013; Nistor & May, 2017). Park et al. obtained a functionalized polymer nanolayer on Ti implants surface via initiated CVD, which displayed increased protein adsorption, higher ALP activities, and higher calcium deposition (Park et al., 2015).

4.3 | Biological techniques

Contrary to the indirect osteogenesis-stimulated methods (physical and chemical), biological techniques, including cell seeding and biological coatings, directly promote the osteoblast attachment, proliferation, and differentiation. Since physical and chemical techniques have shown significant results, biological techniques are frequently used as a supplemental strategy to enhance the OI. Various cells and proteins have been seeded onto porous implants surface: bone marrow-derived stem cells (BMSCs), MSCs, embryonic stem cells, vascular endothelial growth factor (VEGF), and so on (de Peppo et al., 2012; Gafni et al., 2004; Huang, Kaigler, Rice, Krebsbach, & Mooney, 2005). The effects of biological techniques vary in terms of the density, position, differentiation potential of the seeded cells, and the design of the substrates (Heng et al., 2011; Schipper, Marra, Zhang, Donnenberg, & Rubin, 2008).

Nowadays, there have been an increasing number of in vivo and in vitro experiments verifying the consequences of biological techniques. Vandrovcova et al. incorporated lactoferrin into artificial extracellular matrices (ECMs) of collagen type I fibrils and coated the collagen–lactoferrin fibrillary onto the poly(lactic glycolic acid) surface. The results demonstrated that this coating component promoted adhesion, growth, and osteogenic differentiation of Saos-2 cells (Vandrovcova et al., 2015). Zhang et al. seeded the scaffold with autologous MSCs and reported that the application of MSCs enhanced the bone formation and mineralization in the experimental group compared with cell-free scaffolds (Zhang, Zhang, Wang, Lyu, & Wu, 2017).

In spite of the exciting effectiveness of biological techniques, there are still some problems remaining to be solved. The detached cells and proteins could penetrate into ambient tissue or space, which is able to cause unexpected side effects and the formation of the fibrous membrane (Pallu et al., 2009). What's more, there are a few long-term in vivo trials of biological technologies. The long-term effects and transformation process of the cells seeded on joint, especially upon a high load-bearing environment, require more exploration.

5 | POROUS STRUCTURE

Bone is a 3D inhomogeneous structure with complicated topography. Porous implants that have a similar hierarchical structure on multiple scales with bone may facilitate OI. These pores enhance the permeability of implants and create the space for nutrient exchanges, which grant better biocompatibility and OI potential for implants. It is demonstrated by numerous studies that highly porous implants exhibit faster and firmer new bone formation compared with solid implants (Cheng et al., 2018; Lee, Wen, Gubbi, & Romanos, 2018). The principal parameters to evaluate the porous implants include porosity, pore size, pore interconnectivity, and pore geometry. These parameters determine the mechanical properties and play a key role in the biological performance of the implants.

5.1 | Porosity

Porosity is defined as the percentage of void space in a solid structure. Total porosity is calculated by a gravimetric method according to the equation:

$$P=\left(1-\frac{\rho_{\text{Structure}}}{\rho_{\text{Material}}}\right)\cdot 100\%,$$

where the ρ structure is the density of the porous structure and the ρ material is the density of bulk material (Leon, 1998). The porosity of cancellous bone ranges from 30% to 95% (Buckwalter, Glimcher, Cooper, & Recker, 1996). In general, an increase in the porosity can expand the surface area available to cell adhesion and enhance the potential for vascularization and perfusion (Karageorgiou & Kaplan, 2005). Hadjicharalambous et al. indicated that ZrO_2 ceramics with higher porosity favored better cell spreading and growth and contributed to the osteogenic differentiation (Hadjicharalambous et al., 2015). However, high porosity can also decrease the mechanical properties and reduce corrosion resistance (Hollister, 2005). Therefore, it is of great importance to reach a balance point for optimizing the design of the implants.

5.2 | Pore size

Pore size is another critical parameter when designing porous implants. But, the most appropriate pore size remains controversial in the literature. The well-recognized minimum pore size needs to be 100 μm, which allow the generation of mineralized bone and migration of osteocyte (Sundelacruz & Kaplan, 2009). Implants with pores of 200–350 μm size benefit the capillary formation, while fibrous tissue tends to grow into pore sizes of 10-75 μm (Itala et al., 2001; Karageorgiou & Kaplan, 2005). Although the increase of pore size can reduce Young's modulus and yield strength, it can also decrease the stiffness and strength of implants (Ran et al., 2018). Most of the studies claimed that pores sized between 100 μm and 400 μm were favorable for OI (Tsuchiya et al., 2008; Zaharin et al., 2018). However, Taniguchi et al. evaluated the effect of different pore sizes (300, 600, and 900 μm) on in vivo bone ingrowth in rabbits. These implants had a constant porosity of 65%. They demonstrated that the implants with a pore size of 600 μm had a significantly higher fixation ability while bone growth of implants with a pore size of 300 μm was lower than other implants (Taniguchi et al., 2016). Kuhne et al. reported that 500-μm implants showed better bone formation in the cancellous bone bed of the rabbit femoral condyle than 200-μm implants (Kuhne et al., 1994). As a result, the exact suitable pore size calls for more exploration.

5.3 | Pore interconnectivity

Besides porosity and pore size, the role of pore interconnectivity cannot be ignored. Permeability, described as the ability to press substance through the porous material, is closely related to the pore interconnectivity. An open cellular and high interconnectivity porous structure facilitates the exchange of cells, proteins, and nutrients, which is essential for the process of OI. The implants with well-designed interconnected pores showed a much more effective way in the circulation of cell fluid and nutrition than those with random architecture (Park, Kim, Jeon, Koh, & Kim, 2009). The depth of tissue integration can be impeded when cell channels are sealed or closed and it is negative for long-term fixation (Jones et al., 2009). Mitsak et al. suggested that a more permeable scaffold with regular architecture stimulated the formation of bone in vivo (Mitsak, Kemppainen, Harris, & Hollister, 2011).

5.4 | Pore geometry

Compared with the other three parameters discussed above, the amounts of studies involving pore geometry are relatively small since the shape of the pores is difficult to control during the traditional fabrication process. However, AM makes it possible to create porous implants with predefined, complex pore geometry (Van Bael et al., 2011). Pore geometry has shown to influence cell behavior (Fu, Rahaman, Bal, & Brown, 2009a). It is also demonstrated that the shape optimization of pore might increase the permeability and accelerate the speed of bone–tissue ingrowth (Jeong & Hollister, 2010). Chang et al. assessed the histological response within porous HA implants depending on pore geometry: cylindrical type, sponge type, and cross type. The results showed that porous HA with cylindrical pores exhibited the best osteoconductivity (Chang et al., 2000). Fu et al. reported that scaffolds with cellular-type microstructure showed far better ability to support cell proliferation into the pores and cell function compared with that of lamellar-type microstructure (Fu, Rahaman, Bal, & Brown, 2009b). However, the optimal geometry is still in dispute because the research studies on pore geometry are insufficient and the mechanism of how the pore geometry affects cell behavior remains unclear.

6 | DISCUSSION

OI is a complicated and complex process in which the immune system plays a vital role. It is inevitable that the insertion of prosthesis into bone tissue will cause the immune reaction. The complement system is rapidly activated after the implantation and greatly influences the bone formation and bone resorption as the immune and skeletal systems share signal pathways and interact closely (Greenblatt & Shim, 2013; Modinger et al., 2018). Macrophages, a type of mononuclear phagocyte, are the precursors of osteoclasts that have increased much interest in the field of osteoimmunology. Macrophages that reside in bone and bone marrow can differentiate into osteoclasts during bone remodeling (Chen et al., 2016). What's more, they contribute to the genesis of osteoblasts and provide the trophic support for bone anabolism (Batoon, Millard, Raggatt, & Pettit, 2017). Various orthopedic implants with antibacterial surfaces that are already used, for example, coating with silver, showed better OI potential as well (Orapiriyakul, Young, Damiati, & Tsimbouri, 2018). However, it is to remind that the OI process may differ from animals and human so that it must be carefully considered when applying for the clinical practice (Abrahamsson, Berglundh, Linder, Lang, & Lindhe, 2004; Bosshardt et al., 2011). Additionally, different positions of implants may undergo individual OI process. Huja et al. demonstrated that the bone formation rate of the femur is much higher than that of mandible and maxilla (Huja & Beck, 2008). It is confirmed that the load-bearing bone will adapt to the pressure by remodeling, thus facilitating the OI (Barak, Lieberman, & Hublin, 2011). In such circumstances, early weight bearing after TJR in a proper way is rational and commendatory.

Materials are the most important components as they determine the principal characteristics of implants. Qualified materials should possess the following properties: (a) enough mechanical strength to sustain pressure and bump; (b) highly corrosion resistance to prevent abrasion; (c) strong plasticity ensures that they can be manufactured into complicated shapes; (d) they should be provided with biocompatibility and will not cause allergy or immunological rejection. At present, Ti is the most commonly used implant material. However, there have been worries about body allergic reactions to TI (Goutam, Giriyapura, Mishra, & Gupta, 2014; Olmedo, Paparella, Brandizzi, & Cabrini, 2010). Olmedo et al. reported that the dissemination of Ti particles from orthopedic implants would invade the liver, lungs, and spleen (Olmedo, Guglielmotti, & Cabrini, 2002). Even though this hypothesis is only based on the isolated case and the evidence of titanium as a cause of host reaction in patients remains unproven, the association between the release of Ti particles and hypersensitivity cannot be ignored (Javed, al-Hezaimi, Almas, & Romanos, 2013).

Forming an oxide layer on the surface of implants by various techniques is frequently used to increase corrosion resistance and enhance biocompatibility (Jiang, Zhang, Zhou, Lin, & Liu, 2018). Polymer-based materials have been considered as an alternative to replace metals, for example, PEEK, PMMA, and PE, since they hardly give rise to allergic reactions. Carpenter et al. suggested that porous PEEK structures provide a more favorable mechanical environment for bone formation and maintenance under spinal load magnitudes than porous 3D printer Ti (Carpenter et al., 2018). On the other hand, the unmodified PEEK is less osteoconductive and bioactive than Ti (Najeeb et al., 2016). Therefore, the hybrid materials that best integrate those contributions will be a new trend in optimizing the design of implants. A nanosilver/polymer-coated Ti implant was studied by Zeng et al. and it exhibited excellent antibacterial and osteoinductive activities (Zeng et al., 2019).

Definite evidence is emerging that the topography of the implant surface could affect OI to a great extent by modifying the mechanical properties of implants and influencing cell responses. Fibroblasts adhere more strongly to smooth surfaces while rough surfaces facilitate the adhesion and proliferation of osteoblasts, which demonstrates that different types of cells prefer various microenvironments (Cochran, Schenk, Lussi, Higginbottom, & Buser, 1998). Porous implants are believed much more appropriate for OI than for solid implants. The size of pores has been shown to play a key role in adhesion, proliferation, and differentiation of cells. Smaller pores may prevent cell infiltration and impede the interaction between cells since there is no enough space to accommodate more cells (Oh, Kim, Im, & Lee, 2010; Oh, Park, Kim, & Lee, 2007). However, too big pore size will hinder cell adhesion to the implants when accelerating the infiltration too much (Lee, Ahn, Kim, & Cho, 2010). Moreover, the larger pores could decrease the mechanical properties and initiate more fatigue cracks, which will lead to a clinical failure (Dewidar & Lim, 2008; Ishihara et al., 2000). Another dilemma regarding pore size is that the distribution of them. It is still unclear whether the homogenous pore size performs better than the heterogeneous pore size. The effect of pore geometry on OI attracts more attention since the precise geometry is now available with the development of fabrication techniques. The potential mechanism of how the geometry affects the OI is hypothesized to the fact that diverse geometries provide distinct anchorages for cells, which are significant for adhesion and proliferation (Perez & Mestres, 2016). Besides, the geometry of pores would change the angles of struts interconnectivity, which is known to be able to influence the cellular behavior (Kemppainen & Hollister, 2010). Inappropriate shapes and angels may increase the shear strength and slice the osteocytes when performing the implantation, which is unfavorable for OI. In addition, the properties of bones and cell responses may differ from age, gender groups, and locations of implants. Such a difference should be taken into consideration when designing the porous structure.

7 | CONCLUSION AND FUTURE PROSPECTS

Aseptic loosening and formation of fibrous encapsulation have become the principal reasons for the failure of orthopedic implants. Surface modification is used to modify the physical, chemical, and biological properties of implants surface in order to promote OI and achieve better clinical effects. In this review, we concluded the advanced and commonly used strategies for surface modification currently. In spite of the fact that exciting progress has been made, there are still many limitations calling for further investigations. Firstly, there are no general rules about standard implant roughness and also there are no standard measurement methods for the characterization of the implant roughness. Secondly, OI is immune-mediated progress, which is driven by the complement system and macrophages and characterized by tissue reparative features (Park & Davies, 2000). However, it remains to be controversy that how to find a balance between promoting OI and foreign body reaction. What's more, increasing porosity leads to diminished strength and fracture at relatively low loads. Optimal design of the porous implants requires more examination. Last but not least, most of the present studies are in vitro tested or tested in small animals. Human joints are extremely complicated structures that would be influenced by many types of factors, for example, ligaments, soft tissues, muscles, and general factors. The gap between experimental results and clinical application remains to be bridged.

In conclusion, surface modification is an enduring and paramount business for orthopedic doctors and researchers. The present review summarized the factors contributing to OI and brought potential insight into the creation of new orthopedic implants.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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