Biomaterials Science

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Biomater. Sci.*, 2018, **6**, 1312

A review of nanostructured surfaces and materials for dental implants: surface coating, patterning and functionalization for improved performance

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The emerging field of nanostructured implants has enormous scope in the areas of medical science and dental implants. Surface nanofeatures provide significant potential solutions to medical problems by the introduction of better biomaterials, improved implant design, and surface engineering techniques such as coating, patterning, functionalization and molecular grafting at the nanoscale. This review is of an interdisciplinary nature, addressing the history and development of dental implants and the emerging area of nanotechnology in dental implants. After a brief introduction to nanotechnology in dental implants and the main classes of dental implants, an overview of different types of nanomaterials (*i.e.* metals, metal oxides, ceramics, polymers and hydrides) used in dental implant together with their unique properties, the influence of elemental compositions, and surface morphologies and possible applications are presented from a chemical point of view. In the core of this review, the dental implant materials, physical and chemical fabrication techniques and the role of nanotechnology in achieving ideal dental implants have been discussed. Finally, the critical parameters in dental implant design and available data on the current dental implant surfaces that use nanotopography in clinical dentistry have been discussed.

Received 6th January 2018,
Accepted 11th April 2018

DOI: 10.1039/c8bm00021b

rsc.li/biomaterials-science

1. Introduction

Dental implants are a common solution to deal with the loss of teeth. It can greatly improve the lives of the people who need them. However, there are two crucial issues that concern dentists: implant-related infection and the separation of implants from the bone. While the importance of osseointegration for the success of dental implants has been recognized, more investigations are needed to improve and accelerate osseointegration and achieve interfacial mechanical properties in harmony with the bone tissue. With increasing age, adults lose their permanent teeth, and a large number of dental implants are used to replace missing teeth annually.[1,2] Periodontal disease, gum disease, failed root canal or agenesis and accidents are among the reasons that can lead to tooth loss. The conventional solution is to replace the missing teeth with the dental implant, which has a long history.[3] Dental implants are now considered the most advanced solution for missing teeth. The early dental implants were made of bone, stone, shells, carved bamboo pegs and metals such as Au and Cu (Fig. 1).[4,5] The ancient Chinese used carved bamboo pegs to replace missing teeth 4000 years ago.[6] The practitioners also tried to replace the lost teeth with animal teeth, or even human teeth purchased from slaves or poor people. The earliest studies on tooth transplantation reported that slaves in ancient Egypt gave their teeth to their Pharaohs.[7] Replacing a tooth with an animal one is classified as a heteroplastic implant, while a tooth from another human is a homoplastic implant. In most cases, these kinds of replacement teeth would be rejected by the host and would lead to infection.[5,8–10] For a long period of time, metallic dental implants have been successfully used; however, serious limitations related to inadequate similarity in their osseointegration and their mechanical properties in comparison with their bone have been recognized. Table 1 summarizes the history and development of dental implants since 2500 BC.

In the 18th century, researchers began to perform experiments with gold and alloys, often with poor outcomes. Titanium chambers embedded in rabbit bone was the first successful example of the modern dental implant reported in 1952 by Branemark.[24] Dental implants based on Branemark's work were introduced in 1971.[25] The recognition of the

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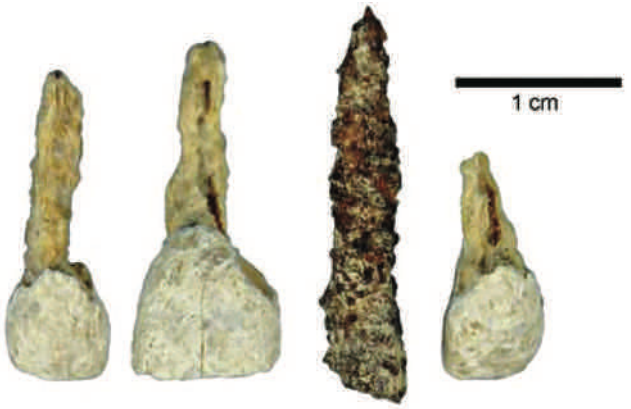

Fig. 1 The early dental implants were made of bone, stone, and metals. Dental crowns (parts of the teeth visible in the mouth) are completely preserved, although the enamel appears to be damaged by erosion (demineralization potentially caused by soil acidity).[10] Copyright, 2014, Antiquity Publications Ltd.

osseointegration phenomenon was a turning point in the history of dental implants. It was recognized that during this process, bone adheres to metal surfaces such as titanium (Ti) and grow without being impeded.[26–28] In 1982, the US Food and Drug Administration (FDA) approved Ti dental implants.[3] Following the evolution of dental implants, ceramic and ceramic-like elements surface treatments have been used to increase the osseointegration phenomenon.[29,30]

Today, due to the success of the procedures and the resulting high demand for dental implants, intense research is being performed in the fields of construction techniques, materials, design, and characterization of implants. In 2003, more than 1.3 million procedures were performed in Europe and more than 700 000 in the United States.[31] In the US alone, 5.5 million implants were placed in 2006. As reported in 2006, about 1 million artificial hips and knees are implanted each year in the United States.[32] Worldwide, there are more than 80 companies producing 220 various dental implants.[33] By one account, the dental implant market in the US is projected to reach $5 billion by 2018.[34] By another account, from the American Academy of Implant Dentistry (AAID), the value of the American and European market for dental implants is forecast to grow to $4.2 billion by 2022.

A dental implant is an artificial tooth root that periodontists place into the jaw with the aim of holding a replacement tooth (the crown) or supporting a prosthesis. Dental implant

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features can be classified into three broad categories: (i) physicochemical properties, (ii) topographic properties, and (iii) mechanical properties. These properties are inter-related and a change in any of these features can affect the others.[35] Two different kinds of reactions can happen after dental implantation. Fibro-osseous integration, *i.e.*, the development of a soft tissue fibrous capsule around the metal implant, is the first reaction. Direct contact between the bone and dental implant surface without interposing soft tissue, so-called osseointegration, is the second reaction to an implant.[35] The rate and quality of osseointegration are significantly affected by implant features such as surface composition, hydrophilicity, surface roughness topography, and geometry.[30]

Patients, and increasingly dentists, are demanding shorter treatment times. Until the 1990s, dental implants had primarily machined surfaces. The healing time for microtopographic dental implants (*e.g.* machined implants) is about 3 to 6 months depending on the anatomical location and the quality of the bone.[36] Recent nanotechnology research on dental implants has been geared toward reducing the time needed to wait before loading.[30,37–39] Therefore, the implant surface (topography) and tissue interface are becoming critical factors.[37] Surface topography of the implant is regulated, at best, at the micro level, but tissue reaction is predominantly associated with processes controlled at the nano level.

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Table 1 History and development of dental implants

Date	Innovation	Ref.
2500 BC	Egyptians used gold wire ligatures for tooth stabilization	9
500 BC	Etruscans replaced teeth with oxen bones	9
500 BC	Phoenicians used gold wire to stabilize teeth that were periodontally loose	11
600 AD	The Mayan population used pieces of shells as implants to replace mandibular teeth	11
800 AD	Stone implants were prepared and placed in the mandible	11
1700s	J. Hunter transplanted teeth from one human to another	11
1809	J. Maggiolo performed the first implant placement into a fresh extraction socket by using a gold tub	12
1913	E. J. Greenfield placed a hollow cylinder of Pt–Ir (24-gauge) soldered with 24-karat gold as an artificial root in the jaw-bone	13
1930s	Alvin and Moses Strock used orthopedic screw fixtures made of vitallium placed in both humans and dogs to restore missing teeth.	13
1938	P. B. Adams patented a cylindrical endosseous implant	14
1940s	M. Formiggini and F. Zepponi developed a post-type endosseous implant.	15
1940s	G. Dahl developed a subperiosteal implant	15
1952	Osseointegration discovered by Branermark	9
1960s	R. Chercheve developed a double-helical spiral implant made of Co–Cr	16
1968	L. Linkow developed a thin and long blade implant to treat partial and total edentulism	17
1981	Schroeder and Lendermann introduced titanium plasma spray	18
1983	The first ceramic CAD/CAM solutions or prosthodontic restorations were developed	19
1988	The All-on-4® treatment concept was introduced, which uses a reduced number of implants to treat full arches	20
2005	Nobel Guide/Nobel Clinician introduced the first comprehensive concepts for 3D treatment planning	21
2005	Immediate Function received clearance by the U.S. Food and Drug Administration (FDA)	22
2011	Thommen Medical introduced hydrophilic surfaces that speed early osseointegration	23

Controlling interfacial responses at the nano level should be well-understood and controlled for developing ideal implants that eliminate rejection and promote adhesion and integration to the surrounding tissue.[40–43] Chemical engineering of implant surfaces, creating a nanostructured surface and wettability of the implant surface leads to better control of cell adhesion, cell colonization, and subsequent activity and ultimately, control of these factors leads to better osseointegration and reduces the healing time.[44] The nanostructured surface, due to structural similarity to natural extracellular matrices (ECM), has been shown to improve cell responses such as adhesion, growth, survival, and differentiation that are required to improve osseointegration. There are tremendous numbers of surface morphologies and chemical modification techniques to enhance the level of peri-implant bone regeneration and accelerate osseointegration.[38,39]

Dental implants based on the emerging nanotechnology field overcome the main limitations of traditional dental implants *via* improving and accelerating osseointegration and

achieving mechanical properties reminiscent of bone tissue. This review focuses on recently applied nanostructured materials in dentistry, effective design of dental implants and the role of nanotechnology in achieving ideal dental implants and future prospects in the development of dental implants.

2. Nanotechnology and dental implants

The 21st century's leading technology, nanotechnology, involves the design and application of size- and structure-dependent properties of the materials at the nanoscale.[45–48] According to the European Commission's recommendation, a "nanomaterial" is defined as "a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range of 1 to 100 nm".[49] In recent years, nanotechnology has found useful applications in various fields,[50–64] such as preventive dentistry, disease diagnostics and monitoring at an early stage, drug development and targeting, the design of microbial resistant and biocompatible dental implants and clinical tools and devices for oral health care.[65] Nanotechnology has considerable potential for the introduction of better implants by design and interfacial engineering such as surface etching and patterning techniques,[66–68] surface functionalization techniques (doping elements,[69] layer-by-layer assembly,[70] reverse polarization anodization,[71] surface coating techniques[72,73]), particularly on the micro and nanoscale.

New coating technologies have been developed for using titanium dioxide nanotubes, hydroxyapatite and related calcium phosphates (CaP). The dissolution of CaP coatings in the implant increases the ionic strength and leads to blood saturation and biological apatite crystal precipitation onto the implant surfaces.[74] Titanium nanotubes can also be applied as a drug delivery vehicle. The TiO_2 nanotubes loaded with anti-inflammatory drugs provide a gradual release of the drugs after implant surgery, maintain effective drug concentrations at the site of action and reduce possible side effects when the drug is injected or taken orally.[75]

Nanoscale modification of dental implant surfaces may cause a change in the topography as well as the chemistry of surfaces. A better understanding of the role of nanotopography leads to more significant osseointegration by nanoscale modification of the surface of the implant.[40] Cell behaviour is affected by both the dimension and the density of the nanostructures.[76] Surface nanopatterning, nanocoating, and functionalization can drastically improve cellular and tissue responses that may benefit osseointegration and dental implant procedures. Depending on the surface morphology of the dental implants, cell spreading may be increased or decreased. Alteration in the wettability or surface energy of a biomaterial is considered as the likely basis for changing cell interactions with the surface. The nanotopography is linked to increased gene expression and is indicative of faster osteoblastic differentiation. Selectivity of cell adhesion is an interesting feature attributed to nanoscale surface modification. Recent studies have observed a relative lowering of fibroblast adhesion compared to osteoblast adhesion on the micro- and nanostructured surfaces.[77] Dental implants with nanoscale modification lead to changed cell behaviour, indicated by changes in cellular protein adsorption, when compared to conventional dental implants.[40] Another significant outcome with nanoscale surface alteration is the reduced bacterial adhesion and proliferation. There was a noticeable reduction in bacterial colonization on nanostructured dental implants regardless of the fact that these surfaces stimulate osteoblast adhesion and differentiation.[78] Fibroblast adhesion was lower on the nanoscale surface in comparison with conventional surfaces.[79] Furthermore, nanoscale structures displayed a reduction in fibroblast proliferation.[80,81] The micro- and nanoscale surface properties of the implant, including wettability, roughness, and chemistry could affect bone formation.[82] Engineering and control of surface features are necessary to control specific protein adsorption, cell adhesion, differentiation of stem cells and osseointegration. Nanotechnology helps in creating unique surface topographies, chemical compositions and provides the ability to predict biological interactions and the ideal surface for a specific biological response.[30,42,83]

Lowering the failure rate of dental implants is the major driving force for employing nanotechnology in the growing global dental implant market. This has been made possible by enhanced osseointegration and bone healing, and reduced infections in new implants. However, the control of the surface properties at the protein and cell levels (*i.e.*, nanoscale), is an important challenge for scientists and dental implant manufacturers.[40] Other concerns are being raised that are related to the safety of nanomaterials in a variety of applications such as surface coatings, patterning, and functionalization.

There is always the risk of nanoparticle detachment and toxicity of the debris.[40] Nanoparticles have a large surface area to volume ratio, which could cause an increased rate of absorption *via* the skin, and other relevant tissues. This could lead to undesirable effects in the human body, and it is also possible to accumulate non-degradable nanoparticles in the body.[84] Many studies have reported that spherical solid nanomaterials can easily enter the lungs and reach the alveoli and subsequently lead inflammation in the respiratory tract and systemic effects.[85,86] If these nanomaterials enter the bloodstream, they may result in cardiovascular and other extrapulmonary effects. The generation of reactive molecules *via* penetration into skin could lead to cell damage.[44]

3. Classification of nanostructured dental implants

Dental implants have seen significant improvements over the last decade, with the major problem being related to osseointegration since the properties of the metals are different from

Table 2 Main classifications of dental implants based on the materials used for fabrication

Type	Implant material	Ref.
Metal-based implant	Titanium	30
	Titanium alloys	124
	Tantalum	125
	Gold alloys	126
	Stainless steel	127
	Cobalt chromium alloy	128
Ceramics-based implant	Bioglass	129
	β-Tricalcium phosphate	130
	Zirconia (ZrO_2)	131
	Zirconia (ZrO_2)-toughened alumina (Al_2O_3)	132
	Alumina (Al_2O_3)	133
	Hydroxyapatite (HA)	134
Polymer-based implant	Polymethylmethacrylate (PMMA)	135
	Polytetrafluoroethylene (PTFE)	136
	Polyethylene (PE)	106
	Polysulfone (PSF)	137
	Polyurethane (PU)	137
	Polyether ether ketone (PEEK)	138

those of human bone. A large number of nanostructured dental implants are under development or available in the market. They can be classified into several categories based on (i) the form, shape and type of prosthesis connection of the implant;[3,87] (ii) the nature of materials used for fabrication (Table 2); (iii) the biological responses they are intended to elicit upon implantation (Table 3).[88,89]

3.1. Nanomaterials used in dental implants

Four groups of materials used in the fabrication of dental implants are metals, ceramics, polymers and hybrid materials (Table 2). Micro/nanostructured metals and metal alloys have been used for many years in orthopedic surgeries and dental implants due to their biomechanical properties that facilitate processing and finishing, and provide adequate strength, toughness and sterility by the common sterilization methods. Nanostructured metals such as titanium and its alloys (Ti-6Al-4V) have been used in the fabrication of new dental implants. However, nanostructured metals of gold alloys, stainless steel, Co–Cr and Ni–Cr alloys are still the metals of choice for the fabrication of prosthetic components of the implants.[89] By changing the surface topography of metals and metal alloys, a dental implant may overcome the disadvantage of this class of materials and add unique functionality. Titanium surface coatings having nanopores with diameters of 30, 150 and 300 nm promote adhesion and osteogenic differentiation of human mesenchymal stem cells and rapid osseointegration.[90] Nanostructured titanium implants without any alloying elements have been considered for many biomedical applications, where the recognized toxicological effects of the alloying elements can be avoided.[91] However, the alloying elements must be present in the conventional titanium implants to provide high strength and corrosion resistance. Recent investigations have shown that commercially pure grades of titanium implants can be nanostructured to achieve enhanced mechanical properties that exceed those of many titanium alloys.[92,93]

Table 3 Types of nanostructured materials based on their interactions with the body

Types of materials	Body responses	Nanostructured materials	Ref.
Bioinert	Fibrous capsule is formed surrounding the biomaterial	Nanostructured stainless steel	141
		Nanostructured Co–Cr alloy	142
		Nanostructured zirconia	143
		Nanostructured alumina	144
Bioactive	Osseointegration is induced by the bioactive material. Ionic changes and biomaterial resorption occur on the surface of bioactive materials	Nanostructured titanium	145 and 146
		Nanostructured niobium	147
		Nanostructured tantalum	148
		Nanostructured hydroxyapatite	149
		Nanostructured calcium phosphate	150
		Nanostructured bioactive glass	151

Ceramics are inorganic materials that have been manufactured by compacting and sintering the starting materials at elevated temperatures. Ceramics are used in micro/nanostructured dental implants due to their unique properties, including their inertness (*i.e.*, low biodegradation), high strength, outstanding corrosion resistance, minimal thermal and electrical conductivity with a wide range of material specific elastic properties and excellent aesthetics.[94,95] However, certain limitations, especially their inferior mechanical properties, low ductility, inherent brittleness, and particularly fracture toughness, impede their widespread commercial applications. There are particular problems in the design of porous implants or implants with rough and porous surfaces to obtain better osseointegration. Increasing porosity leads to diminished strength and fracture at relatively low loads.[96] Hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), zirconia (ZrO_2), and alumina (Al_2O_3) are known as important implant ceramic materials. Among all the ceramic materials, HA has often been considered as an ideal candidate for use in load-bearing applications due to bonding for osseointegration.[97,98] Coating the HA implants with nanostructured layers is applied to obtain the favored mechanical characteristics and enhance the surface reactivity including osteoblast adhesion, mineralization and proliferation.[73] Zirconia (ZrO_2) and alumina (Al_2O_3) have revealed excellent biocompatibility. Al_2O_3 shows high hardness and wear resistance while ZrO_2 displays fracture toughness and higher strength and the composites made from both Al_2O_3 and ZrO_2 have higher fracture toughness and ductility than the individual constituents.[99,100]

One of the challenges of ceramic implants is the problem related to the production of ceramic pieces with complex shapes while conserving precise dimensional control of the

topographies from the nano to the microscale and suitable features of materials. For example, while fabricating porous alumina dental implants to favor bone ingrowth, it has been shown that the residual undesirable surface microporosity adjacent to the gingival cuff causes an inflammatory response that inhibits the formation of an appropriate biological seal and leads to clinical failure.[101] Although conflicting reports exist about the influence of ceramic coatings and nano- and/or microtopography on the osseointegration of dental implants, the prevailing philosophy is that they may considerably affect the bone growth and attachment on implant surfaces and increase the success of dental implants by rapid return to function. There is a serious need for more investigations in this field, including both *in vitro* and *in vivo* models, that would finally result in clinical application.[101] A significant scientific challenge with ceramic-based dental implants is to fabricate metallo-ceramic hydride implants that will combine the benefits of ceramics, especially their inertness, with a mechanical reaction comparable with those of dental implant alloys.

Implants based on polymeric materials such as polytetrafluoroethylene (PTFE),[102] polyethylene terephthalate (PET),[103] polyurethane (PU),[104] polyether ether ketone (PEEK),[105] polyethylene (PE),[106] polymethylmethacrylate (PMMA),[107] ultra-high-molecular-weight polyethylene (UHMW-PE),[108] polypropylene (PP),[109] polysulfone (PSF),[110] polydimethylsiloxane (PDS),[111] and silicone rubber (SR)[112] have been developed for the substitution of missing dental roots and implants. In general, polymeric materials provide required properties in the development of dental roots and implants such as lower strengths and elastic moduli with magnitudes closer to soft tissues, ideal porosity, thermal and electrical passiveness, biocompatibility, easy handling, low cost of fabrication and higher elongation to fracture compared with other classes of biomaterials.[88,96,113] However, implants based on polymers are more difficult to sterilize by ethylene oxide or autoclaving. Upon exposure to semi-clean oral environments, electrostatic interaction with polymer surfaces can gather dust or other particulates. Elastic deformation of porous polymers can close open regions intended for tissue ingrowth.[96]

Hybrid dental implants with a nanostructured surface can provide the required antimicrobial and osteogenic effects.[114,115] Hybrid dental implants are composed of the mixture of two or more materials, involving the combination of a matrix material and secondary particles or thin films. The matrix can be derived from a biocompatible polymer, metal or ceramic. Surface modifications of the implant either by novel ceramic coatings or by patterning the implant's surfaces have been used for better binding to bone and occlusive surfaces that offer toughness during mastication. Possible designs for a hybrid dental implant with graded coatings are depicted in Fig. 2. Nanomaterials such as nanofibers, nanotubes, nanorods, and nanospheres provide high surface area per unit mass, which allow easier addition of surface functional groups and increase cellular interactions, ultimately enhancing the success of the dental implants.[116–118] The deposition of a

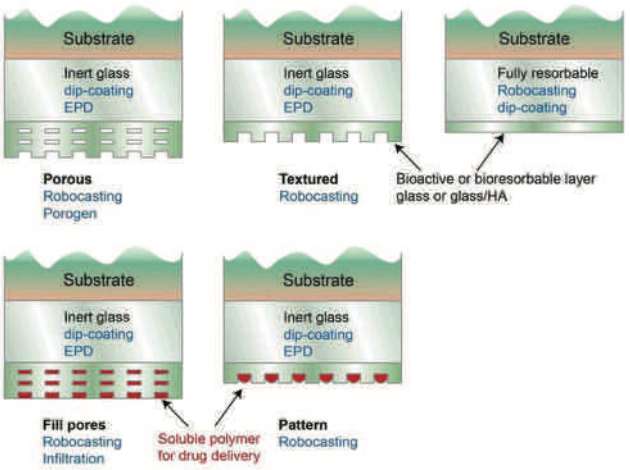

Fig. 2 Possible designs for a hybrid dental implant with graded coatings. Good adhesion and long-term stability can be obtained *via* the outer layer, which can be designed with varied thickness and porosity and different combinations of organic and an inorganic materials and, if necessary, be encapsulated in a bioresorbable component such as a glass (fabricated by pulsed-laser deposition or electrophoretic deposition, EPD) or a polymer (by means of robocasting or dip-coating).[101] Copyright, 2011, Quintessence Publishing Co.

silver coordination polymer compound onto a titanium implant can be used as light-stable, nanostructured and antibacterial coatings for dental implants and restorative materials.[119] Ag-implanted TiO_2 with a nanostructured surface has been used for improving the antimicrobial and osteogenic effect.[114] Incorporation of Zn into TiO_2 coating on titanium improves the antibacterial activity and bone marrow stem cell functions.[115] Coating a graphene/zinc oxide nanocomposite film onto artificial acrylic teeth surfaces protect dental implant surfaces against cariogenic *Streptococcus* mutants.[120] A HA/collagen nanocomposite coated on a titanium rod was used for achieving rapid osseointegration.[121] Carbon nanofiber fillers can be incorporated into vinyl siloxanes to improve osteoblast adhesion and integration (osteoconductive functionality).[117] A gelatin-gold nanocomposite coating on titanium enhances the biocompatibility of dental implants.[122] Coating ZrO_2–Ag and ZrO_2–Cu on titanium implants provides antibacterial activity.[123]

3.2. Bioactivity of dental implant materials

After implantation of a synthetic material, tissue shows various reactions to the implant depending on the material type and topography. Bioinert materials (*e.g.*, titanium, stainless steel, alumina, stabilised zirconia, and ultrahigh molecular weight polyethylene) have minimal interactions (bonding) with the surrounding tissue. Other materials have shown the ability for a series of biophysical and biochemical reactions with surrounding tissues, forming an interfacial chemical bond that fixes so-called "bioactive materials". A real chemical bonding ability with soft tissues has been shown in some bioactive ceramics like bioactive glasses of certain com-

positions. However, bioactive ceramics in the bulk form are not recommended for load-bearing applications due to their flexural strength, strain-to-failure and fracture toughness being less than that of bone, and their elastic moduli being greater than that of bone.[139] CaP ceramics are considered to be bioactive and osteoconductive. The ion-exchange reaction between the bioactive implant and surrounding body fluids forms a biologically active carbonate hydroxyapatite (HA) layer on the implant that is similar to the mineral phase in bone.[140] There are also "bioresorbable" bioactive materials that start to dissolve (resorb) upon placement within the human body and are slowly replaced by advancing tissue. Examples of this type of material are tricalcium phosphate [$Ca_3(PO_4)_2$] and polylactic–polyglycolic acid copolymers.

4. Nanofabrication techniques for dental implants

Current implant procedures include the endosseous type of dental implants with nanoscale surface characteristics.[35] Understanding and controlling surface and bulk material properties and interfacial reactions at the nanoscale is important to the development of new implant surfaces that will reduce failure and enhance adhesion and integration to the surrounding tissue. Several studies have been performed on surface treatments for roughness at the nanometer scale in *in vitro* and *in vivo* animal models.[152–155] However, the roles of surface chemistry and surface roughness on osseointegration are still not fully understood. During the initial stages of implant development, the focus was on the effects of surface modification at the micro-level, and more recently it shifted to the nanolevel to study the effects of roughness on the cellular responses. By engineering the surface of implants, it is possible to improve the stability and wettability, to accelerate osseointegration, stimulate and reduce the healing/loading time after surgery and improve the retention of tissue.

Nanotechnologies are increasingly used for surface modifications of dental implants. There are several techniques to modify the bulk and surface properties of dental implants to create varied surface roughness from the micro to nanoscale.[2,30,37,156–166] These methods can be divided into three groups: (i) surface etching and patterning techniques, (ii) surface functionalization techniques, and (iii) surface coating techniques,[167,168] which can be undertaken by various chemical and physical techniques.[139] The physical techniques include the compaction of nanoparticles, self-assembly of monolayers, ion-beam assisted deposition, magnetron sputtering deposition, plasma spraying deposition, pulsed laser deposition, physical vapour deposition, and hot isostatic pressing. Chemical techniques include peroxidation, acid etching, alkali treatment, nanoparticle deposition, biomimetic processes, electrochemical deposition, micro-arc oxidation (MAO) and electrophoretic deposition, lithography and contact printing.[169] Combinations of these techniques could also be applied; for example, acid etching after grit-blasting so as to remove the contamination *via* blasting residues on implant surfaces.[167,168] It is likely that perfect surface coating and functionalization will not be generated by a single technique or material; a combination of techniques/materials can generate layers that blend inorganic and organic phases, with thicknesses ranging from the micro to nanometer scale, and chemically and topographically textured surfaces. Each technique has advantages and limitations and no single technique can generate composite layers combining inorganic and organic materials to create nanotextured surfaces.

The modification of implant surfaces using physical and chemical nanocoating has become an important tool to overcome the limitations of non-optimal release kinetics, antimicrobial resistance, high susceptibility to mechanical abrasion and delamination, toxicity, and high manufacturing costs.[170] Nanocomposite coatings on dental implants have been developed to attain improvements in bioactivity, protection against metal ion release, biocompatibility, an improved environment and structure for osseointegration. A 'composite' approach allows one to manipulate the mechanical properties, such as strength and Young's modulus, to match the natural bone, with the incorporation of secondary nanoparticles.[171] This approach is currently being explored in the development of a new generation of nanocoatings involving HA,[172] pectins,[173] cubic zirconia,[174] ultra-nanocrystalline diamond,[175] carbon nanotube (CNTs),[176] poly(lactide-*co*-glycolide)/bioactive glass/hydroxyapatite coating,[171,177] and TiO_2 [178] to promote osseointegration. Table 4 lists a number of physical and chemical surface fabrication and modification techniques used in dental implants.

4.1. Physical fabrication techniques

Physical surface modifications are typically used for the dry transformation of passive inert implants into smart implant surfaces that actively instruct the physiological environment towards the regeneration of bone tissue. Fig. 3–14 show some examples of the physical surface modification techniques of dental implants.

4.1.1. Machining. Until the 1990s, dental implants had primarily machined surfaces, which imply a turned, milled, or polished manufacturing process. Typical surface roughness values for machined titanium implant surfaces were 300–1000 nm, with a mostly amorphous layer of TiO_2 that was 2–10 nm thick. Based on the sterilization process, the TiO_2 layer could be crystallized into a rutile crystal structure. Further, the thickness and temperature are important in the phase composition.[139] Imperfections along these machined surfaces enable osteogenic cells to attach and to deposit bone, thus generating a bone-to-implant interface.[36] The healing time of machined implants is about 3 to 6 months, depending on the anatomical location and the quality of the bone.[9] Multiple dental prostheses can be machined using computer-aided machining (CAM) systems but the implementation of such devices is very expensive.[179] Machining of titanium is slow and inefficient, which greatly limits this approach.

Table 4 Dental implant surface fabrication techniques and examples of their application

Fabrication technique	Metal/implant	Surface morphology	Response of nanostructured implants	Ref.
Machining	Titanium	Regular array of TiO_2 nanotubes 37 nm in diameter and 160 nm thick with an average roughness of 0.5 μm	Improved bone-to-implant contact, bone growth, and osseointegration	241
Grit blasting	Titanium was grit-blasted with particles of different sizes 22–28 μm and 180–220 μm	Different grit blasting procedures gave distinctly different patterns: Group 1 had a homogenous surface structure. Group 2 had a less homogenous surface structure. Group 3 exhibited a main surface structure similar to that of group 2, but with a smoother appearance.	Group 1 showed the lowest retention in bone. Group 2 implant showed a significantly better functional attachment ($p < 0.001$) than the other two groups	242
Laser treatment	Titanium and its alloys	Created 3-D structures with multiphase compositions at the micrometer and nanometer scale	Enhanced *in vitro* osteogenic cell attachment, growth, and differentiation	243 and 244
Plasma spraying	Titanium	Nanocrystalline hydroxyapatite coatings composed of spherical crystallites ranging from 20–200 nm	Enhanced osteoblast adhesion	245
Sputtering Deposition (SD)	Ti6Al4V implant alloy	Nanocrystalline hydroxyapatite coating of approximately 300 and 400 nm in size	Achieved rapid ingrowth and recrystallization of the bone mineral phase	246
Lithograph	Titanium	Topographical nanostructures with well-defined shapes (semispherical protrusions) and variable sizes (60 nm, 120 nm and 220 nm)	Implant surfaces with 60 nm features demonstrated significantly higher bone-implant contact (BIC, 76%) compared with the 120 nm (45%) and control (57%) surfaces.	68
Ion-Beam Assisted Deposition (IBAD)	Alumina-blasted/acid-etched Ti-6Al-4V implant	Nano-thick (20–50 nm) bioactive (Ca- and P-based) ceramic layers	Improved biomechanical fixation and BIC at early implantation times	247
Acid etching and grit-blasting	Titanium	Nanorough topography	Early biomechanical fixation and improved bone-to-implant contact	248 and 249
Anodization	Titanium	TiO_2 nanotube	Higher nanometer scale roughness, low contact angle and high surface energy on nanoporous surfaces enhanced the osteoblast-material interactions	250 and 251
Oxidative nanopatterning	Titanium	Nanoporous structures 5–100 nm	Promoted the proliferation of essential osteoblastic cells and simultaneously inhibited the growth of unwanted fibroblastic cells.	252 and 253
Micro-Arc Oxidation (MAO)	Ultrafine-grained (~200–500 nm) and coarse-grained Ti	Nanocrystalline hydroxyapatite and α-$Ca_3(PO_4)_2$ phases	Improved the bioactivity of Ti surfaces	254
Sol–Gel combined with electrospinning	Titanium	Sol–gel-derived hydroxyapatite nanofiber	Promoted human osteoblast proliferation.	255
Chemical Vapor Deposition (CVD)	Silicon nitride (Si_3N_4)	Nanocrystalline diamond coatings	Improved human osteoblast proliferation and the stimulation of differentiated markers, like ALP activity and matrix mineralization	256
Self-Assembled Monolayers (SAMs) (*e.g.* molecular self-assembly)	The native oxide surfaces of Ti or Ti-6Al-4V	Self-assembled monolayers of α,ω-diphosphonic acids	Effective for osteoblast binding and proliferation	257
Alkali hydrothermal treatment	Titanium	Nanoporous, nanoplate and nanofiber-like structures	The Ti surface with a nanofibre-like structure showed better apatite-inducing ability than the nanoporous or nanoplate surface structures.	258

Currently, materials with low reactivity and high setting expansion are used to compensate for the high casting shrinkage of titanium.[180]

4.1.2. Grit blasting. Sandblasting, which is also called grid blasting, is one of the most commonly used surface modification techniques, due to it is simplicity and low price. It is generally used for descaling and surface roughening of commercial implants, thereby increasing the surface area of the implant for better osseointegration. Surface topography achieved by shot peening depends greatly on the size of the particle used. Typically, micro or nanoparticles (sand, alumina, hydroxyapatite, titania) are typically projected through a nozzle at high velocity by means of compressed air. Depending on the size and shape of the nanoparticles and on

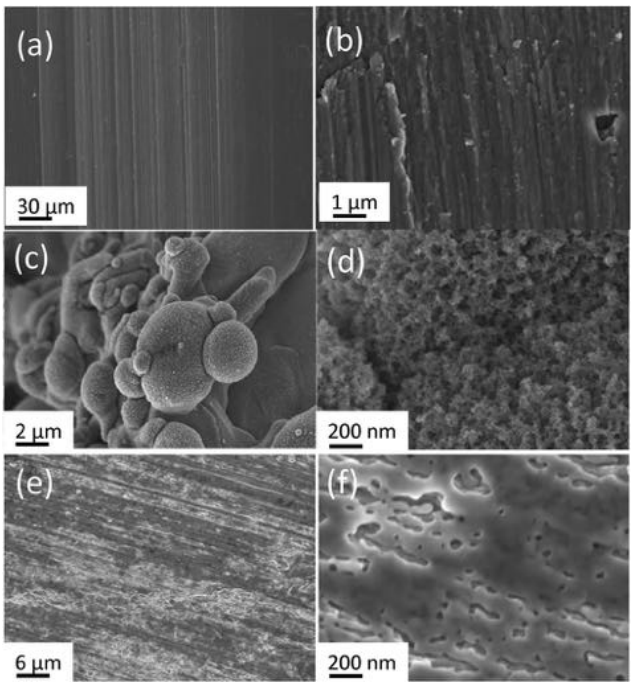

Fig. 3 Physical surface modification techniques for dental implants. SEM image of (a, b) the machined implant surface, (c, d) Brånemark BioHelix implant modified by laser processing, (e, f) sputter CaP coated titanium implant. Copyright, 2011 INTECH.[139]

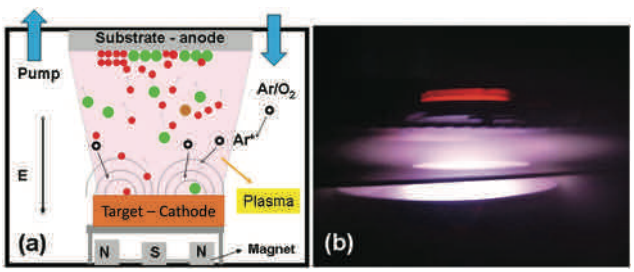

Fig. 4 (a) Schematic exhibiting the RF sputtering process. (b) The actual arcing and deposition process of our RF sputtering system. Copyright, 2011, INTECH.[192]

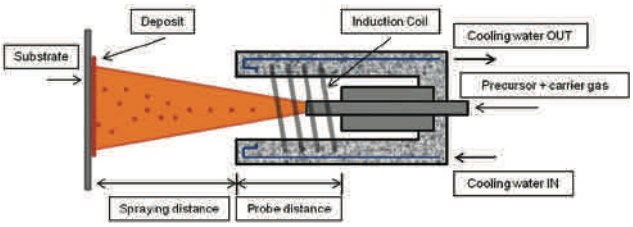

Fig. 5 Schematic representation of a RF plasma torch. The PS technique involves the projection of precursor materials into the hot plasma jet generated by a plasma torch. Copyright 2012, MDPI publisher.[193]

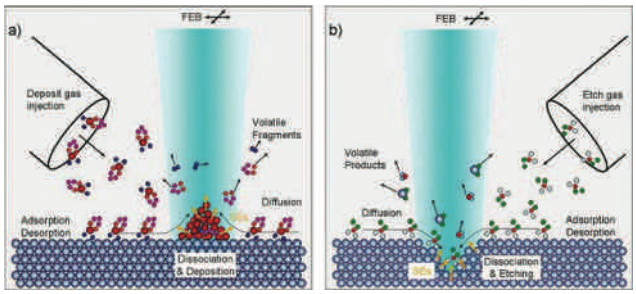

Fig. 6 Basic elements and principles of gas-assisted focused electron beam and ion beam fabrication: (a) electron beam induced deposition, (b) electron beam induced etching.[197] In the ion source materials in the form of a gas, an evaporated solid, or a solution (liquid) are ionized. Copyright 2008, American Institute of Physics.

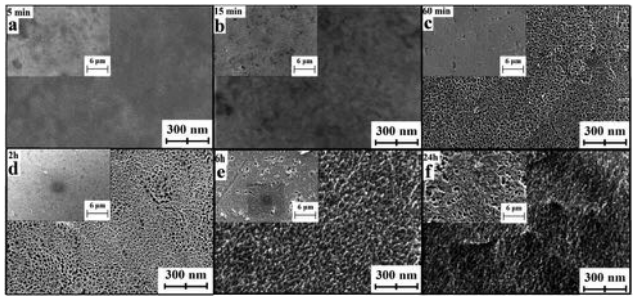

Fig. 7 Ultrafine grained titanium etched in H_2SO_4/H_2O_2 solutions for 5 min (a), 15 min (b), 1 h (c), 2 h (d), 6 h (e) and 24 h (f). Copyright 2017, MDPI publisher.[208]

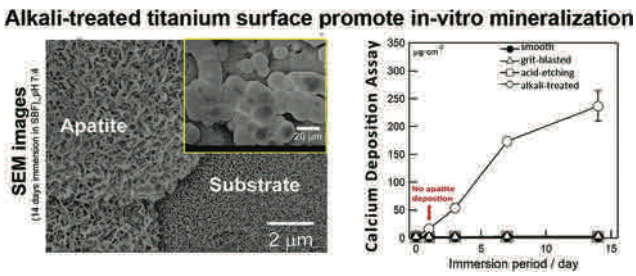

Fig. 8 The effects of surface alkali-based treatment of titanium implants: (a) SEM images of the Ti implant (substrate) after apatite formation. (b) The ability of the alkali treated Ti implant to promote *in vitro* mineralization and *in vivo* bone formation, compared with other surface functionalization techniques. Copyright 2017, Elsevier.[213]

their velocity, erosion and material tearing of the implant surface are inflicted. In general, the blasting particles should be chemically stable, biocompatible and should not hamper the osseointegration of the dental implants.[30] Titanium and titanium-alloy dental implants are blasted with air-propelled hard ceramic particles such as Al_2O_3, TiO_2 or $Ca_2P_2O_7$.[181] Some recent studies have found that the HA coating on the as-machined surfaces has outcomes comparable to or more favorable than those obtained with grit-blasted implants.[182] The

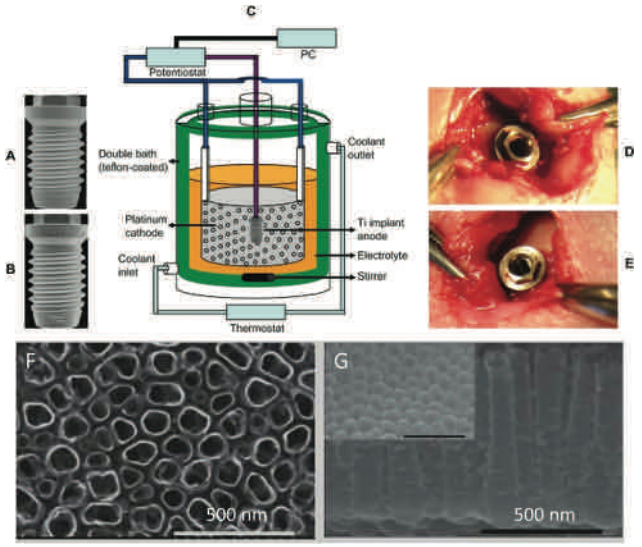

Fig. 9 Electrochemical growth behavior TiO_2 nanotubes on the surfaces of a blasted and screw-shaped titanium implant. (A) the TiO_2 nanotube-fabricated TEST implant (B) the blasted CONTROL implant. (C) Electrochemical cell Setup. (D) One nanotube implant and (E) one blasted implant. (F, G) Nanotube implants formed in 1 M H_3PO_4 + 0.4 wt% HF. (F) SEM image (top view) of the nanotube implants. (G) SEM image (cross-section) and bottom view (inset) of the nanotube implants.[219] Copyright 2010, Dove Medical Press Ltd.

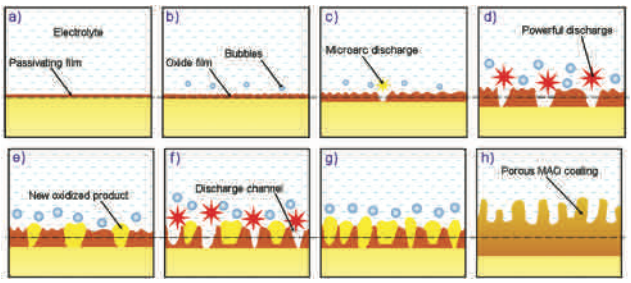

Fig. 10 Schematic of the fabrication steps for MAO porous coating. (a) The formation of the passivating film; (b) liberation of bubbles and formation of the porous insulating oxide; (c) the action of the spark discharges; (d) the action of powerful arc discharges; (e–f) the newly generated oxide coating is formed and thickened; (g–h) the porous ceramic oxide coating is gradually formed.[221] Copyright 2017, PubMed Central Canada.

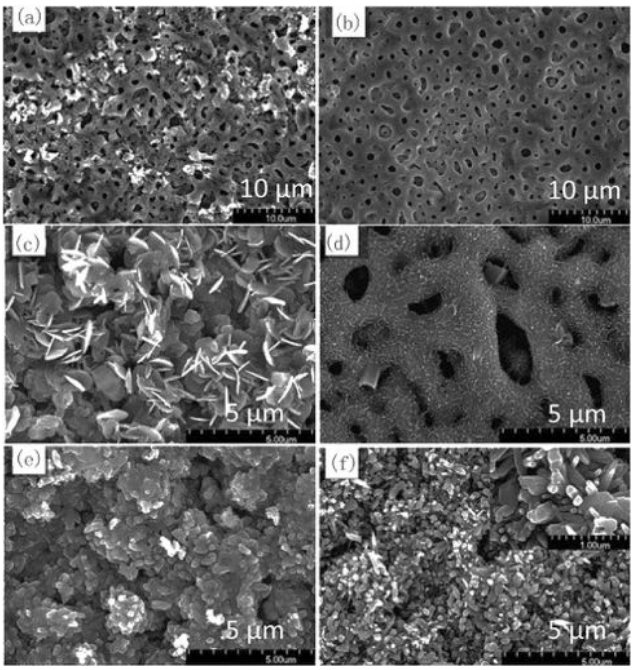

Fig. 11 SEM images of the micro-Arc oxidation (MAO)-treated dental implants were produced using different voltages (V) and frequencies (F): (a) 175V-200F-MAO, (b) 175V-500F-MAO, (c) 175V-200F-HT, (d) 175V-500F-HT, (e) 175V-200F-HTP and (f) 175V-500F-HTP groups. Copyright 2010, Elsevier.[226]

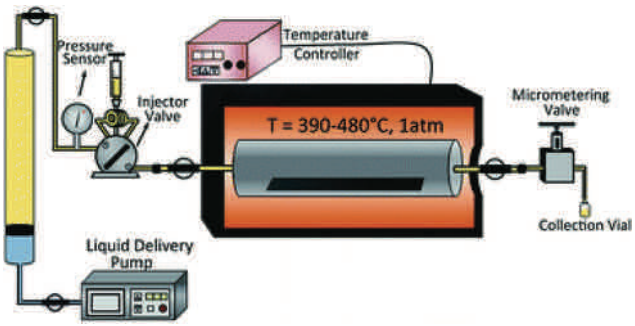

Fig. 12 Schematic of the experimental set up of the liquid injection metal–organic vapour deposition technique. Copyright 2012, Royal Society of Chemistry.[230]

grit blasting method is effective at controlling surface roughness but not in terms of osseointegration itself. Typical values of the average surface roughness are in the range from 300 nm to 3 μm.[183] Bacteria will tend to accumulate more on the rough surface compared to smooth surface substrate.[184]

4.1.3. Laser treatment. Laser treatment is a physical fabrication technique to create 3-D structures at the micrometer and nanometer scale (Fig. 3). This technique is the method of choice to achieve complex selective surface topography with high resolution.[139] It has various benefits over machining, which needs chemical agents and a complex manufacturing system. The advantages of laser technology include the following: (i) a rapid and extremely clean nanofabrication technique; (ii) suitability for the selective changes in implant; (iii) precise, targeted and guided surface roughening.[35] In laser treatment, only the valley and parts of the flank of the implant threads can be laser treated while the residual part was left as-machined.[139] Other advantages of this technology are the ability to generate complex and precise selective surface geometry with high resolution cleanly and rapidly.[185] Hallgren and coworkers[186] showed that the removal torque value was larger for the laser-treated implant (52 N cm) compared to the machined surface implant (35 N cm) after 12 weeks of healing.

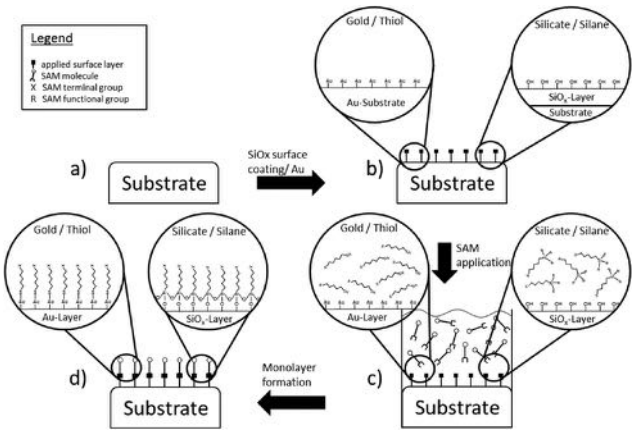

Fig. 13 Biological activation of inert ceramics using tailored SAMs on implant surfaces. The scheme for the fabrication of a SAM is depicted with respect to a silicate-silane and a gold–thiol monolayer assembly.[234] Copyright 2014, PubMed Central Canada.

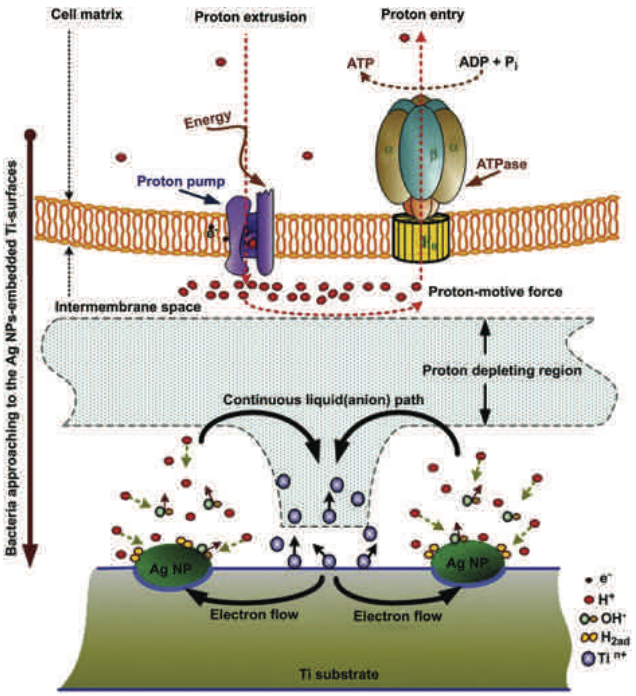

Fig. 14 Possible antimicrobial activity of Ag nanoparticle-embedded surfaces.[272] Copyright 2011, Elsevier.

The combination of laser-treatment with acid etching has proven to have improved osseointegration by about 50%, compared to the laser-treated surface with bone-implant contact.[187]

4.1.4. Sputtering deposition (SD). Sputtering is one of the physical vapour deposition (PVD) technologies used in dental implants. In this procedure, atoms or molecules of some materials are ejected in a vacuum chamber, becoming precursors for coating due to the bombardment with high-energy ions. The deposition of films is dependent on various sputtering parameters including the following: the material properties, sputtering power and time, gas flow and working pressure. Antibacterial agents can be effectively incorporated into implant materials by the magnetron sputtering (MS) process. The desired antibacterial ability can be preserved under optimum processing parameters. Bai *et al.*[188] employed MS to fabricate Ti–Ag composite coatings with different Ag contents (1.2–21.6 at%) by means of co-sputtering Ti–Ag targets. Zhang *et al.*[189] introduced the novel duplex-treatment method by combining MS with micro-arc oxidation (MAO) to fabricate the Ag-containing bioactive antibacterial coatings. Wolke *et al.*[190] concluded that the HA coating deposited by MS was dense and uniform. Sugita *et al.*[191] obtained pico to nanometer thin TiO_2 coatings on micro-roughened metal surfaces. A slow rate of sputter deposition has been used to achieve a thin titanium oxide coating (6.3–300 nm) deposited on the implant surface. Fig. 4 exhibits a schematic diagram of the radio frequency (RF) sputtering process, which can be used to deposit thin films of CaP on metal surfaces. The strong adhesion of the coating to the metal surface is the main benefit of this method. The Ca : P ratio and the crystalline nature of the coating can be easily changed.[35]

4.1.5. Plasma spraying (PS). The plasma-spraying (PS) technique involves the projection of precursor materials into the hot plasma jet generated by a plasma torch (Fig. 5) under vacuum, reduced or atmospheric pressure. Argon and oxygen are the common gases used for these applications. Upon impingement of precursor materials (powders particles) onto the implant surface, an adherent coating is formed by melting and sintering.[193] The main advantage of plasma-spraying is the possibility of coating various nanostructured films, *e.g.* Au, Ti, and Ag, on a wide range of materials such as ceramics, metals or polymers at a thickness <100 nm.[35] Lower power can be used to activate a plasma discharge at low pressure with cheaper and simpler power generators.[194] The PS technique provides several other benefits in comparison with wet fabrication techniques, including the lack of chemical residuals on implant surfaces, and reduced chemical waste and safety concerns during manufacturing.[195]

4.1.6. Ion-beam assisted deposition (IBAD). A typical ion-beam assisted deposition (IBAD) includes two main elements: (i) electron or ion bombarded precursor materials that vaporize forming an elemental cloud that covers the surface of a substrate and (ii) an ion gun that treats the substrate with highly energetic gas ions (*e.g.* inert Ar^+ ions or reactive O_2^+ ions) to prompt adhesion of the precursors from the elemental cloud.[193] It uses a beam of high-energy (~10 keV) ions to irradiate the implant surface in a vacuum chamber (Fig. 6). As a result of the collision between incident ions and substrate ions, the incident ions lose energy and fall to rest on the near-surface region of the metal. This technique is typically used to deposit very thin ceramic films on ceramics, polymers or metals. The advantages of this technique include the following: (i) it is an ultraclean process that results in the synthesis

of high purity layers; (ii) there is excellent adhesion between the implanted surface and substrate; (iii) it is a deposition process that does not affect the bulk properties of the substrate; (v) it is a reproducible and controllable method.[196] The deposited nanolayers are typically amorphous, and therefore heat treatment of the implant might be needed. The final crystallinity of the deposited layer is dependent on the time, temperature and amount of water vapour present during the coating. Ion-beam-assisted deposition has a low deposition rate compared to plasma sputtering.

4.2. Chemical nanofabrication techniques

Chemical nanofabrication techniques include (i) anodic oxidation (anodization), (ii) acid treatment, (iii) alkali treatment, (iv) chemical etching with hydrogen peroxide, (v) sol–gel treatment, and (vi) chemical vapor deposition.[35] Among these techniques, the easiest technique is the immersion of the material in a solution containing the chosen molecules to enhance film formation on the surface. Surface etching and the chemical deposition of nanoparticles in surface coatings have been used in the development of easy-to-clean surface properties of the tooth surface. These surface treatments can help with the detachment of bacteria and adsorbed salivary proteins under the influence of physiological shearing forces in the mouth.[198,199]

4.2.1. Acid etching. A variety of chemical treatments such as solvent cleaning, wet chemical etching, and passivation treatments have been employed for modifying the implant surfaces. Acid etching can remove grains and grain boundaries of the implant surface. The selective removal of material and the resulting roughness are dependent on the bulk material, certain phases, the surface microstructure, impurities on the surface, the acid, and the soaking time (Fig. 7). The acid etched implants give greater resistance in reverse torque removal and better osseointegration compared to the machined surface implants.[184] The degree of etching is dependent on the acid concentration, temperature, and treatment time (typically from 1 to 60 min). The surfaces are generally considered minimally rough as the typical average surface roughness (S_a) values are 300–1000 nm. There have been few analyses of the surface layer but, speculatively, a titanium hydride layer could possibly be found because of the presence of hydrogen ions in the acid. The surface oxide was formed as a native amorphous titanium oxide with a thickness of around 10 nm.[200] Nano pit networks (pit diameter 20–100 nm) can effectively be fabricated on titanium, tantalum, and Ti6Al4V and CrCoMo alloys by combining strong acids or bases and oxidants.[201] The sandblasted/acid-etched surface had a greater bone-implant contact percentage in comparison with the machined surface. This difference was statistically significant at only 30 and 60 days after healing.[202] Li *et al.* showed in a minipig model in which sandblasted/acid-etched implants exhibited superior bone anchorage compared to machined and acid-etched implants since removal torque values were significantly enhanced in sandblasted/acid-etched surface implants.[203] The use of H_2O_2 with acid etching was shown to create amorphous TiO_2 nanostructures on the implant surface.[204] The surface treatment with H_2O_2/HCl passivated surfaces (30% HNO_3) and heat-treated surfaces increased the adsorption of cell-adhesive RGD peptides on the surface.[205] Xie *et al.*[206] fabricated micro/nanostructured titanium implants using sandblasting followed by H_2O_2 treatment. Reactive oxygen species detected on the dental implant surface cause remarkable wettability and the enhancement of cell differentiation and gene expression. Implant treatment with HF creates discrete nanostructures on TiO_2 grit-blasted surfaces.[207] However, complex chemical changes by acid treatments induced by these methods may require careful inspection. Nazarov *et al.*[208] studied the effect of the etching time and the etching medium (acidic or basic piranha solutions) on the surface relief and morphology of ultrafine grained Ti implant surfaces. The results showed that the etching medium and time can control micro-, nano-, or hierarchical micro/nanostructures on the surface.

4.2.2. Alkali treatment. Alkali treatment (*e.g.* NaOH treatment) is a popular surface treatment method among dental researchers. Titanium nanostructures with a sodium titanate gel layer outward from the surface have been seen after NaOH treatment.[209] Formation of the gel-like layer over the implant surface allows for HA deposition. H_2O_2 produces a titania gel layer. This behaviour has also been seen with other metals such as zirconium and aluminium.[210] Alkali treatment results in the growth of a nanostructured and bioactive sodium titanate layer on implant surfaces. Upon immersion in simulated body fluid (SBF), a bioactive surface can nucleate CaP crystals. Through ion exchange, the release of Na ions from sodium titanate results in the formation of Ti–OH. The Ti–OH with negative charge reacts with Ca^{2+} from SBF leading to calcium titanate production. In calcium titanate, P and Ca ions can develop into apatite crystals that can facilitate suitable conditions for bone marrow cell differentiation.[35,211] Pattanayak *et al.*[212] found that only the Ti metals heat-treated after exposure to the strong acid solutions with pH < 1.1, or strong alkali solutions with pH higher than 13.6 formed the apatite on their surfaces in SBF within 3 days, while no apatite was formed upon exposure to solutions with an intermediate pH value. The apatite formation is attributed to the magnitude of the positive or negative surface charge developed on the Ti implant, while the absence of apatite formation at an intermediate pH is attributed to its neutral surface charge.[212] Ti surfaces with either acid-etching treatment or alkali-based treatment evoked robust bone formation around Ti implants. Such information may be utilized for the advancement of biomaterials research for bone implants in the future. Fig. 8 shows the effect of the surface alkali-based treatment of titanium implants on the ability to promote *in vitro* mineralization and *in vivo* bone formation.

4.2.3. Anodization or anodic oxidization. The anodization technique is commonly applied to fabricate nanostructures with diameters <100 nm on titanium implant surfaces.[214] Anodization or "anodic oxidization" is an electrochemical

deposition process carried out in an electrolyte. The deposition process is tailored by varying different process parameters to control the structural and chemical properties of the surface, including electrolyte composition, current, anode potential and temperature.[215,216] Micro- or nanoporous surfaces could be fabricated by the potentiostatic or galvanostatic anodization of titanium in strong acids (H_2SO_4, H_3PO_4, HNO_3, HF) at a high current density (200 A m^{-2}) or potential (100 V). The thickness of the surface oxide layer was more than 1000 nm.[30] Smooth titanium surfaces can be successfully transformed into nanotubular structures with diameters <100 nm with the help of anodization.[214] The bone reaction to anodized implants has been investigated with various species and healing times and most often compared to the original machined surface. Significantly higher bone to implant contact has been found along with increased biomechanical removal torque values for phosphorous containing anodized surfaces in comparison with the machined surfaces in dog and rabbit models.[217,218] The electrochemical growth behavior and surface oxide properties are controlled by several process parameters, including nature of the substrate, forming voltage, electrolyte related parameters (ion content, concentration, temperature, pH the current density, the distance between the anode and cathode), and circulation speed. Electrochemical growth behaviour of TiO_2 nanotubes on the surfaces of blasted and screw-shaped titanium implants is shown in Fig. 9 for a typical case. Controlling the nanotube diameters can lead the transition from cell adhesion and spreading enhancement (observed for 15–30 nm TiO_2 nanotubes) to growth decay (≥50 nm diameter).[1]

4.2.4. Micro-arc oxidation (MAO). The MAO method is a high voltage plasma-assisted anodic oxidation process. MAO is a relatively convenient technique for fabricating firmly adherent oxide ceramic layers on the surfaces of valve metal, for example, Ti, Ta, Mg, Al, Zr, and their alloys. The MAO process uses a power supply to control the coating process. The non-working side of the dental implant is connected to a copper conductor and treated as the anode, and the stainless steel electrolytic bath works as the cathode, filled with electrolyte. In the MAO process, (i) the passivating film is formed when the specimen is immersed in the electrolyte (Fig. 10a). (ii) With increasing voltage, small oxygen bubbles evolve and a porous insulating oxide layer grows on the implant surface.[220] (iii) When the applied voltage surpasses a certain limit, a breakdown in the insulating oxide coating occurs (Fig. 10c). (iv) The ions from the electrolyte and the other elements from the implant surface diffuse into the breakdown regions, forming a porous oxide coating, and (v) the discharge sparks gradually grow bigger, and the micro-arc discharges are transformed into powerful arc discharges (Fig. 10d). Finally, the porous ceramic oxide coating is formed with the continuous formation and breakdown of the oxide coating at the large discharge channels (Fig. 10).[221] The composition of the electrolytes has a dramatic effect on the porosity and thickness of the coated layer. Necula *et al.*[222] have successfully prepared Ag-bearing TiO_2 coatings with different contents of Ag NPs by MAO in the electrolyte, including calcium acetate (CA), calcium glycerophosphate (Ca-GP) with Ag NPs. Yao *et al.*[223] have used MAO to fabricate a Cu-doped TiO_2 coating in the working electrolyte. Muhaffel *et al.*[224] have also used MAO to prepare outer HA layers and inner TiO_2 layers in β-glycerophosphate disodium salt pentahydrate (β-GP) and CA electrolyte with diverse amounts of added $AgNO_3$ (0.1 g L^{-1} and 0.4 g L^{-1}). Jan *et al.*[69] electrodeposited tiny Pd–Ag–HAp nanoparticles on a TiO_2 barrier layer for dental implant application. Micro-arc oxidation (MAO), also called plasma electrolytic oxidation (PEO), has been widely applied to fabricate porous and robust coatings on biodegradable magnesium and its alloys. Yu *et al.* deposited Mg-containing hydroxyapatite coatings on Ti-6A1-4V alloy for dental materials. In this study, plasma electrolytic oxidation (PEO) was performed in electrolytes containing Mg at 280 V for 3 min.[72] MAO or PEO processes for doping functionalized elements (Sr, Si, Mn, Mg, Zn) into Ti implants have been reviewed.[225]

Park *et al.*[226] evaluated the conditions affecting the MAO on CP–Ti with AC-type rectangular electric pulses. The 175V-200F-MAO, 175V-500F-MAO groups were produced using different voltages and frequencies. The fabrication of the HA was influenced by a hydrothermal treatment (HT) after the MAO process either in an alkaline solution to form HT-treated groups or in a 0.002 M β-glycerophosphate disodium salt pentahydrate (β-GP) solution to fabricate HTP-treated groups. Discrete rod-like crystallites (100–500 nm) and crystallites that were aggregated and undefined in shape, were formed in the 175V-500F-HTP group (Fig. 11e).

4.2.5. Wet chemical deposition "sol–gel". Wet chemical deposition methods are alternatives to physical deposition methods, which preserve biomolecule activity. One of the most important advantages of wet chemical deposition is that drugs can be incorporated into the coatings. Wet chemical depositions have several benefits including the simplicity of the experimental setup, mild chemical conditions of preparation and the possibility to coat a complex 3D-geometry onto the implants (such as porous implants).[193] Biomimetic modification is one of the coating techniques used to obtain successful osseointegration. The classical biomimetic coating, for example, Ca–P coating, typically requires an immersion period ranging from 14 to 28 days with replenishment of simulated body fluid (SBF). Biomimetically produced apatite surfaces, *e.g.*, rough and porous calcium-deficient apatite layers, may be useful in facilitating early bone ingrowth into porous surfaces. Biomimetic Sr and Si-ion substituted apatite films deposited on Ti implants further promote early bone formation.[139] Sol–gel methods combine different coating process such as dip and spin coatings, following sintering. This is applicable for substrates with complex geometry and can be used for depositing a wide range of metal oxides on metallic and nonmetallic substrates. Sol–gel methods attain the deposition of nm-scale calcium phosphate accretions on the implant surface. The sol–gel method is based on colloidal suspensions of solid particles (1–500 nm) in a liquid solution (a sol). It is one of the widely used methods for depositing CaP, TiO_2, TiO_2-CaP composite

and silica-based coatings on implant surfaces.[35] The sol can be deposited on the substrate surface *via* various techniques such as dip-coating, spin-coating or spraying. The coating is put on the target surface while still in gel form, after drying only the precursor materials, and is formed as a thin layer.[227]

4.2.6. Chemical vapor deposition (CVD). CVD has been used to deposit diamond nanoparticles on Ti dental implants to provide ultrahigh hardness, enhanced toughness, and good adhesion (Fig. 12).[73] CVD differs from PVD in the processes employed; CVD only uses chemical bonding to deposit the layer while PVD uses physical forces. CVD utilizes a mixed source material while PVD utilizes a pure source material. For CVD, the precursor eventually decomposes and leaves the desired layer of the source material in the substrate. HA is a bioactive ceramic with a crystal structure similar to that of a native bone and teeth minerals.[73]

Some problems such as the poor mechanical properties and processing problems related to HA deposition have led to applications of HA as powder, coating, porous bodies, and non-load-bearing implants. Popescu *et al.*[228] successfully modified metallic surfaces at the nanoscale level by the process of chemical vapor deposition; a Ca–P–O bio-ceramic nanocoating was deposited on the titanium-based dental implant by CVD.[229] Nanostructured Ca–P–O bio-ceramic coatings on metals will promote better attachment to the bone while optimizing abrasion resistance, bond strength, and dissolution rate. CVD may be used for metalloceramic coatings, which will provide continuous variation from a nanocrystalline metallic bond at the interface to the hard-ceramic bond on the surface. One advantage of the graded bonding structure is the ability to overcome adhesion problems associated with ceramic hard coatings on metallic substrates, while exhibiting enhanced surface hardness and wear resistance.[73]

4.2.7. Self-assembled monolayers (SAMs). SAMs are formed spontaneously on surfaces by the adsorption of molecules onto some specific substrate, exposing the functional end group at the interface (Fig. 13).[231,232] The exposed group could be osteoinductive moieties or a cell-adhesive molecule. SAM and subsequent chemical functionalization is an effective approach to create a bioactive tissue-facing surface layer. An example of this is the use of cell adhesive peptide (Arg-Gly-Asp, RGD) domains appended to SAMs composed of polyethylene glycol (PEG) on the Ti surfaces.[233] This chemical reactiveness on the outward surface can be affected by specific tailored head and tail ends of SAM molecules.[234]

Molecular grafting and chemical treatment of surfaces are considered as complementary methods for coating dental implants to enhance cell adhesion and enhance mineralization and the production of matrix and marker proteins. With covalent bonding, for example, linker molecules can enhance the adhesion of attachment proteins, signalling domains,[24,204,205] antibiotics, and growth factors such as human epidermal-growth factor (EGF) or recombinant human bone morphogenetic protein-2 (rhBMP-2) to implant surfaces.[207,208] However, the activity of grated biomolecules is strongly dependent on their spatial orientation on the surface. The native oxide layer without any treatment on the surface of metallic implants usually exhibits relatively low contact angles with water.[68] Immobilizing biocompatible anchor molecules (BAM) makes surfaces more attractive for cells with osteogenic potential. The selection of an appropriate method for the immobilization of BAM depends on several factors such as the stability, molecular weight and structure of BAM and the number of BAMs desired. ECM components like laminin,[235] fibronectin,[236] heparin,[237] collagen,[238] as well as antibiotics[239] and growth factors[240] have been successfully covalently bound to Ti surfaces.

5. Addressing infection risk in dental implants

The main reason for dental implant failures is related to infections.[259] The main treatment against infections is the administering of antibiotics; therefore, an obvious strategy is antibacterial coatings and covalently attached antimicrobial molecules on implant surfaces (Fig. 7). Once the bacteria adhere to implant surfaces, they secrete a protective polysaccharide leading to biofilm formation that acts as a barrier against the penetration of antibiotics, leading to failure to eradicate the infection, the spread of antibiotic resistance and chronic infections.[260,261] Due to the decreased efficiency of antibiotics with resistant strains, it may be necessary to introduce alternative strategies. Given the difficulty of dealing with bacteria after biofilm formation, an effective method to deal with infections is the prevention of their binding to surfaces in the first place.[262]

Therefore, nanostructures on the surface may be an alternative strategy to prevent bacterial adhesion. The size and shape of nanoparticles are crucial factors for antimicrobial activity.[263–265] Studies have shown that nano-rough TiO_2 nanotubes and Ti thin films had a significant reduction in infections, adhesion and biofilm formation. Implants with nanoscale surface topography have antimicrobial activity against oral infections (*S. epidermis, S. aureus*, and *P. aeruginosa*). More interestingly, the TiO_2 nanotubes can also be modified with Ag nanoparticles to prevent infection for the life of the implant.[266] Ag nanoparticles have antimicrobial properties, and they can be embedded at concertations that can eradicate microbes but not damage healthy cells and tissues. Ag nanoparticles can help to inhibit biofilm formation[266] through the induction of reactive oxygen species (ROS) (Fig. 14). The ROS *via* the free radical chain reaction leads to the selective peroxidation of cell walls and membranes, and the destruction of the DNA structure of infectious agents without any harm to the bone, stem or immune cells.[267–271]

6. Osseointegration

Brånemark suggested a new definition of osseointegration in 1985: "Osseointegration is defined as a direct structural and

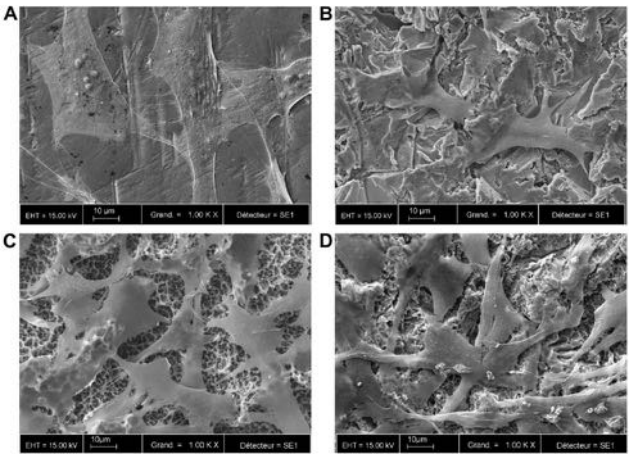

Fig. 15 SEM micrographs of the MC3T3-E1 cells grown on different implant surfaces for 2 days. (A) Smooth-Ti implant, (B) alumina-Ti implant, (C) sandblasted and acid etched (SLA) Ti implant and (D) biphasic calcium phosphate ceramic grit-blasted (BCP-Ti) implant. Magnification ×1000. Scale bar = 10 μm. A uniform layer of osteoblasts covered all surfaces.[161] Copyright 2008, Elsevier.

functional connection between ordered, living bone and the surface of a load-carrying implant".[273] This phenomenon leads to the proper functioning of implants. Osseointegration depends on parameters such as biomaterial type, implant design, surface treatments, surgical techniques, bone type and patient care.[87] There are several possible interactions between the bone and implant surfaces of different topographies. Nano/composite coatings on the implant are required to improve osseointegration, inflammatory responses, osteolysis and achieve antimicrobial activity.[274] Fig. 15 shows osteoblast cell-line MC3T3-R1 after 2 days of culturing on the various surfaces.[161]

HA is considered to be a bioactive and osteoconductive material. HA and similar CaPs are commonly used for coating Ti implants to improve biocompatibility and enhance osseointegration.[275–277] Several studies have shown that calcium and phosphate ions are released from CaP-coatings and lead to the precipitation of apatite and the incorporation of biological molecules such as growth factors. These deposits provide a substrate for cell adhesion, differentiation into osteoblasts and the synthesis of mineralized collagen, the ECM of bone tissue and ultimately lead to improved osseointegration.[278–281] Different types of methods have been suggested for CaP coatings. An appropriate method provides a homogeneous dissolution rate, such as the electrochemical coating method as compared with the plasma spray method.[282,283] Dental implants have also been coated with immobilized molecules such as fibronectin, collagen, arginine–glycine–aspartic acid to improve osteoblast cells attachment.[2,284,285]

Lee *et al.*[286] functionalized TiO_2 with vitamin B_6 (pyridoxal 5′-phosphate (PLP)) to promote the osteointegration of bone and dental implants. The functionalized TiO_2 implant exhibited increased hydrophilicity, promoted adhesion, migration, and the proliferation of diverse cell types, and finally enhanced bone-to-implant integration *in vivo*.[286] PLP *via* its aldehyde group of Schiff-base formations promoted the surface binding of serum albumin and other plasma proteins, provided a suitable platform for osteoblast adhesion, delayed platelet activation and retarded blood coagulation.[287] Ingrassia *et al.* studied cell-mediated functionalization to modify the surface of the implant. They functionalized Ti implants using human induced pluripotent stem cell-derived mesenchymal progenitor (iPSC-MP) cells. The results showed that these functionalizations stimulated the proliferation of human iPSC-MP cells, affected the expression of genes involved in development and differentiation, and promoted the release of alkaline phosphatase.[288] Yusa *et al.* functionalized TiO_2 with zinc to investigate the osteoblast differentiation of human dental pulp stem cells (DPSCs) on functionalized titanium (Zn–Ti). Zinc has an important role in the differentiation of osteoblasts and bone modeling. DPSCs cultured on Zn–Ti showed significantly upregulated gene expression levels of runt-related transcription factor 2 (Runx2), osteopontin (OPN), vascular endothelial growth factor A (VEGF A), osteoblast-related genes of type I collagen, bone morphogenetic protein 2 (BMP2), and ALP, in comparison with the control. These findings suggest that the combination of the modified Ti and DPSCs provides a novel method for bone regeneration.[289]

Many events must be controlled to gain and accelerate the osseointegration of dental implants. Nanoscale modulation of osseointegration can be achieved *via* the following: (i) selectivity in osteoblast adhesion and decreased fibroblast adhesion *via* the control of surface energy, wettability (contact angle) and surface roughness. (ii) The control of cell behavior (adhesion. proliferation and differentiation) by anisotropy and nanostructure dimensions. (iii) Rapid differentiation of adhered cells along the osteoblast lineage. (iv) An increase in alkaline phosphatase activity and calcium mineralization. (v) A decrease in bacterial colonization by nanostructured ZnO or TiO_2. (iv) The control of protein adsorption and immunity response.

7. Critical parameters in dental implant design

After >40 years since the introduction of dental implants, there is still some way to go to achieve ideal dental implants. Further investigations are needed into implant materials, design parameters, surface engineering, roughness, biocompatibility, osseointegration and other characteristics of dental implants. The physical, chemical and mechanical properties determine the performance and efficiency of implants in biological systems. The level of osseointegration is considered as a marker of biocompatibility, it is defined as an appropriate interaction of the dental implant with the surrounding tissues.[290] Since the implant surface plays an important role in interactions with biological molecules, proteins and cells, the

new generation of dental implants are focused on surface engineering to accelerate and improve osseointegration.[291] In addition to the nature of biomaterials, implant features such as shape, length, the diameter of the implants and surface characteristics were shown to have a critical role in osseointegration.[292–295]

Micro and nanotechnology are providing important progress in the field of the precision engineering of surfaces to control surface chemistry, crystal structure, physical properties, chemical and surface morphology. Some researchers have studied the impact of surface properties on the osteoblastic cells adhesion and osseointegration phenomena. The effect of the implant surface is not entirely clear, but studies have shown that the osteoblastic cells quickly adhere to rough surfaces of Ti implants in comparison with the smooth surface of the implant (Fig. 15).[296,297] The impact of various surface factors such as surface morphology, topography, roughness, the existence of impurities, chemical composition, and surface energy was investigated,[298–301] and it was found that controlling the surface properties leads to better implant osseointegration.[302]

Implant surface characteristics such as roughness, wettability, electrical charge, chemical composition, surface energy, residual stresses and morphology influence the attraction, repulsion, adsorption, and absorption of proteins and cells in order to impact osseointegration. Initial cellular interactions are dependent on the physicochemical properties of surfaces including heterogeneity, the presence of functional groups, wettability, topography, charge and roughness.[303]

7.1. Biocompatibility

The concept of biocompatibility is defined as the compatibility of the material with a biological environment.[304] Long-term contact with tissue and the ability to perform specific functions are key features for dental implants. Indeed, biocompatibility is determined through the study of interactions between implant and *in vitro* and *in vivo* tissue tests. The physical, chemical and mechanical characteristics are essential for biocompatibility.[87,305] Ti implants have been used since 1970. The biocompatibility of these implants depends on the spontaneous formation of the oxide layer on the surface of the implants; this thin layer protects the implant against corrosion reactions or degradation in a wide range of environmental conditions.[306]

The analysis of the biocompatibility of micro and nanostructured dental implants typically involves the following: (i) *in vitro* studies on surface roughness, wettability, composition, crystalline structures, apatite-forming ability in SBF, number and thickness of the coating layers, mechanical stability, and dynamic resistance to corrosion. (ii) *In vivo* tests such as the microscopic analysis of tissue quality around the implant, quantification of mechanical resistance after osseointegration of the implant, corrosion resistance, toxicity assessment, bending strength, density, toughness, average grain size, micro-hardness, Young's modulus, inertia assay, analysis of human clinical trials.[135,211,307–312]

7.2. Chemical composition

Through the proper choice of materials, processing and surface coating provide better control of the cellular response and the adsorption of specific proteins, and trigger mechanisms involved in osseointegration. Cells react differently to the chemical composition of the material and induce different responses. Surface composition and surface modification through coating play critical roles in the stability and reactivity of implants. The existence of contamination is acceptable only in small quantities.[87] Different materials are used to manufacture the implant and among the metallic biomaterials, pure Ti, α + β type Ti-6Al-4 V and extra low level of interstitial content (ELI) alloys are widely used due to their specific strengths and corrosion resistance in dental implant applications. Other metals, polymers, ceramics and carbon are used in the construction of dental implants.[156,313] Ti is not considered to be a completely bioinert material, and several studies have shown it to be potentially hazardous in the body, resulting in allergic responses in some people.[314–317] Ceramic materials have been used in the manufacture of oral implants for more than 4 decades.[318] Appropriate features, such as excellent biocompatibility, good corrosion resistance, high wear resistance, high strength and similar osseointegration in comparison to Ti or HA, have indicated that alumina (α-Al_2O_3) is a good candidate for oral implant materials.[319] The survival rate of these implants was lower compared to Ti implants.[320–322] Zirconia has been considered for dental implants due to its high mechanical resistance[323,324] and many studies have been done on manufacturing techniques (powder injection moulding, hot isostatic pressing, *etc.*) as well as new derivatives (such as yttria partially stabilized tetragonal zirconia polycrystals (Y-TZP) and zirconia-toughened alumina (ZTA)).[318,325] There is, however, some concern about the long-term survival rate of zirconia.[326,327]

In the past few years, the study of nanomaterials has received tremendous impetus due to their unique physical and chemical properties, biological properties, and functionality. Recently, nanostructured materials have been used for improving the antimicrobial and osteogenic effect. An important aspect of nanoparticles is their large surface area to volume ratio, where a large contact surface is expected to enhance their good antibacterial properties.

7.3. Wettability and surface energy

The wettability of the implant surface is predicted by the contact angle between the interface of the droplet and the horizontal surface. When the contact angle is >90 degrees the surface is hydrophobic, and with a contact angle <90 degrees the surface is hydrophilic. Implant surface wettability affects the interaction with the biological environment. Highly hydrophilic surfaces compared to hydrophobic surfaces have better interactions with biological molecules and cells. Complete moistening indicates biocompatibility, hydrophilicity, and high surface energy.[87,328] Most implant surfaces currently in clinical use are hydrophobic.[329,330] A hydrophilic surface is

suitable for blood coagulation in comparison with a hydrophobic surface. Therefore, dental implants manufactured with highly hydrophilic and rough implant surfaces are more favorable for osteointegration in comparison with the conventional ones.[331] Hydrophilic properties are affected by the chemical composition of the dental implant. Overall, hydrophilic surfaces are considered ideal surfaces in comparison with hydrophobic surfaces in light of their interactions with cells, tissues and biological fluids. Fig. 16 shows the sample surfaces under different treatments and their effects on water contact angle.

Wetting is reduced on microstructured surfaces.[333] The wetting behaviour of the surface should be considered at the micro- and nanoscales.[328] Fig. 17A schematically shows how hydrophilic surfaces interact closely with biological fluids, providing normal protein adsorption to the surface and following interactions with cell receptors. Fig. 17B shows how the hydrophobic surfaces are prone to hydrocarbon contamination, causing the trapping of air bubbles that can hinder protein adsorption and cell receptor adhesion/activation.

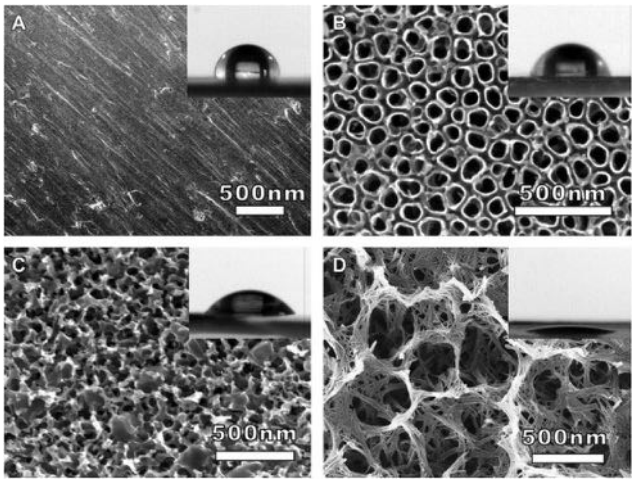

Fig. 16 SEM images of the sample surface under different treatments. (A) A blank Ti substrate and the corresponding water contact angle (inset). (B) TiO_2 nanotubes (anodized at 20 V), and the corresponding water contact angle (inset). (C) The sponge-like structure of TiO_2 (anodized at 50 V), and the corresponding water contact angle (inset). (D) The nano/micro nest-like structure of TiO_2 prepared by alkaline hydrothermal treatment, and the corresponding water contact angle (inset).[332] Copyright 2014, Elsevier.

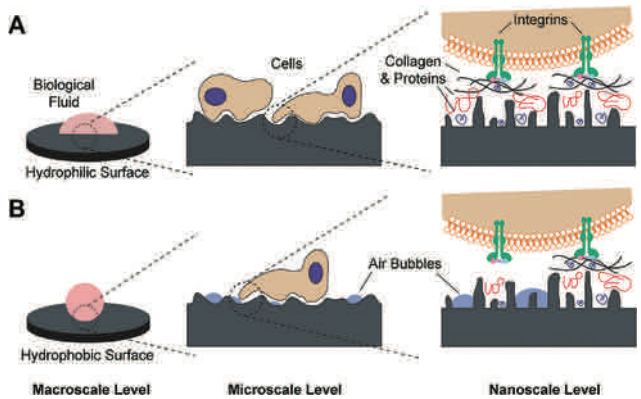

Fig. 17 Schematic of the possible interactions with hydrophilic (A) and hydrophobic surfaces (B) at different length scales.[328] Copyright 2014, Elsevier.

Surface energy has a critical role in the interactions between biomaterial surfaces with proteins, cells, and bacteria. There is a relationship between critical surface tension and biocompatibility. Surfaces with surface tension between 20 to 30 dynes cm^{-2} show a low adsorption; above this, the implant exhibits greater adsorption.[87] Nanomaterials with a high surface energy exhibit a greater number of favourable sites for macromolecular adsorption. The surface chemical composition of dental implants also affects the hydrophilicity of the surface. Table 5 shows the effect of chemical composition and surface roughness of the dental implant surface on the wettability.

Contamination is the main reason for the reduced hydrophilicity of Ti implant surfaces. Rupp *et al.* reported that by enhancing the surface free energy and hydrophilicity through the chemical modification of Ti surfaces, there was reduced hydrocarbon contamination.[334] Hannig *et al.*[199] investigated the effects of a low surface free energy (about 18–20 mJ m^{-2}) organic/inorganic nanocomposite coating (NANOMER®, INM, Saarbrücken, Germany) on enamel as well as titanium specimens for biofilm management at the tooth surface and easy-to-clean surface properties. This nanocomposite coating strongly reduced biofilm formation on the dental implant surface, providing an easy-to-clean surface property. Therefore, nanocoating can facilitate the detachment of adsorbed salivary proteins and adherent bacteria under the influence of shearing forces in the mouth (Fig. 18).[199]

7.4. Surface roughness

The effects of surface topography on osseointegration success and the mechanical stability of dental implants have been extensively explored.[26,296,298,335] Most commercial dental implants have surface roughness of about 0.5–1 μm.[2,336–338] Roughness at the nanoscale promotes protein adsorption, osteoblast cell attachment and the ability for the incorporation of growth factors.[30,165] At the macroscale, the implant should provide an appropriate mechanical fixation with bone. At the

Table 5 The effect of chemical composition and surface roughness on the wettability of the dental implant surface.[30] Copyright 2007, Elsevier

Type of implant	Surface roughness (μm)	Contact angle (°)
cpTi	R_a = 0.22 ± 0.01	55.4 ± 4.1
Ti6Al4V	R_a = 0.23 ± 0.01	56.3 ± 2.7
TPS	R_a = 7.01 ± 2.09	n.d.
SLA	S_a = 1.15 ± 0.05	138.3 ± 4.2
Modified SLA	S_a = 1.16 ± 0.04	00
Plasma-sprayed HA coating	R_a = 1.06 ± 0.21	57.4 ± 3.2
Biomimetic CaP coating	R_a = 1.83 ± 0.64	13.4 ± 0.17

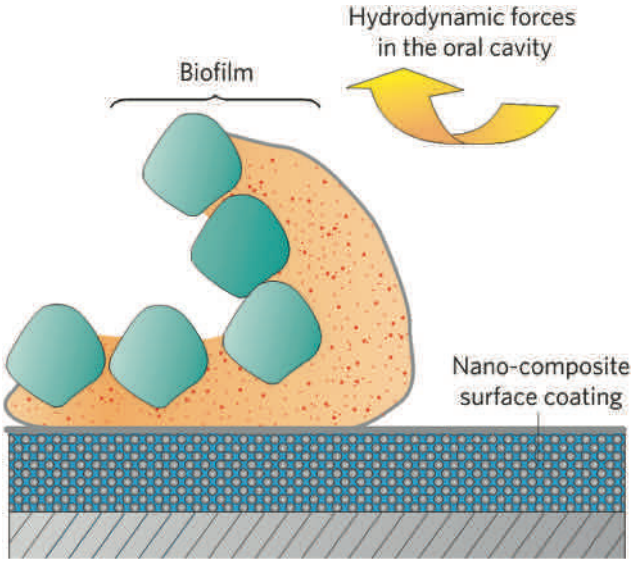

Fig. 18 Easy-to-clean nanocomposite surface coating. The low-surface-free-energy coating (blue) leads poor protein–protein binding. Shear forces in the mouth (yellow arrow) cause easy detachment of the biofilm (pellicle and bacterial) from the outer layer of the surface.[198] Copyright 2010, Nature.

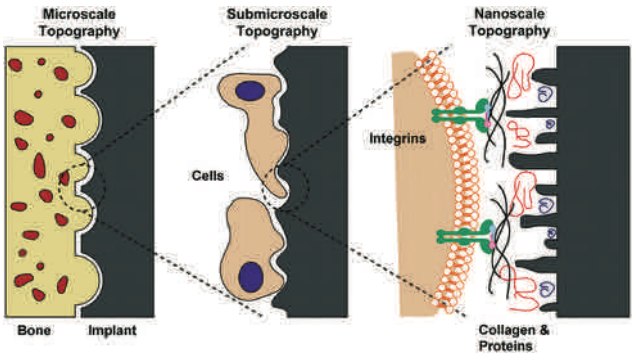

Fig. 19 Schematic of the interactions between bone and the implant surface at different topographical scales.[340] Copyright 2011, Elsevier.

microscale, micro- and submicron features exhibited on the surface can directly interact with mesenchymal stem cells and osteoblast cells. At the nanoscale, receptors on the cell membrane, such as integrins, can distinguish adsorbed proteins on the surface, which in turn are controlled by the nanostructures on the surface (see Fig. 19).[339,340]

The surface roughness effects on gene expression, the production of growth factors, cytokines and the response of the adjacent skeletal tissue play a crucial role in the success of the implants.[341] Cells, proteins and other biological molecules have different responses to the implant surfaces with roughness on the nano, micro, and macro levels. It is expected that increasing the surface area of the implant with nanoroughness provides many binding sites for cell attachment, thus leading to success, and provides easier and more rapid osseointegration.[342–344] Studies have shown that rough surface topography influences and enhances primary stability.[345] Surfaces with nanoroughness present a larger surface area and provide a firmer mechanical bond to the surrounding tissues.[346]

Surface roughness prompts focal adhesion and acts as a guide for cytoskeletal assembly, membrane receptor organization and morphology, and the proliferation of different cell types.[43,347,348] Moreover, rough implant surfaces have been shown to improve the adsorption extracellular matrix molecules such as the adsorption of fibronectin and albumin in *in vitro* experiments. Nanostructures such as nanofibers, sharp tips and nanotubes interact with cells and influence cell proliferation.[347,349,350]

Fibroblasts adhere more strongly to smooth surfaces, accumulate on the smooth surfaces and avoid rough surfaces. The surfaces with moderate roughness exhibit greater ability for osteoblast proliferation and collagen synthesis compared to other surfaces.[351,352] Epithelial cells are more attracted to rough surfaces in comparison with smooth surfaces. Osteoblast cells attach more easily to rough surfaces similar to those found on commercial implants with treated surfaces. Nanoscale features alter osteoblastic adherence, proliferation, differentiation, and matrix production.[353]

Studies have shown that microstructured surfaces are appropriate for osteoblast-like cells.[161] Up-regulation of osteoblast proliferation was observed on the nanoscale surface of materials such as alumina, Ti, and CaP.[354] Nanoscale modification of the implant surface may alter the surface reactivity.[355] A wide range of cell types including epithelial cells, fibroblasts, myocytes, and osteoblasts respond differently to the effect of surface nanotopography.[356,357] Therefore, nanotopography may modulate and control the growth, proliferation, and biological function of osteoblasts. Macrophages prefer to attach to rough surfaces. There are no general rules about standard implant roughness and also there are no standard measurement methods for the characterization of the implant roughness. There are different ideas about the optimal physicochemical properties and surface geometries for cell attachment. Identifying the optimal surface for molecules in a biological environmental with implant interface is an important challenge in tissue engineering.[358] These different modifications, which result in a variety of surface chemistries and topographies, have led to different responses by biological molecules and osteoblast cells.[359] The nanostructure is able to alter the *in vitro* proliferation and function of osteoblast cells and is optimal with a nanodot diameter of approximately 50 nm. These results will lead to the continuation of the design of functional surfaces that modulate cell behaviour and stimulate cell maturation to attain the perfect dental implant candidate.

Much research has been conducted on the evaluation of the effects of implant surface topographies on stem cell differentiation.[360,361] Hirano *et al.* investigated the proliferation and osteogenic differentiation of human mesenchymal stem cells on Zr and Ti with different surface topographies. The results

suggest that the creation of micro- and nano-topographies on Zr and Ti enhance the proliferation and differentiation of hMSCs, ALP activity and the expression of Runx2.[360] Sandrine *et al.* investigated adhesion and osteogenic differentiation of human mesenchymal stem cells on Ti with nanopores 30, 150 and 300 nm in diameter. The results indicated that Ti with nanopores of 30 nm and Ti with nanopores with 150 nm induced osteoblastic differentiation while Ti with nanopores of 300 nm had a limited effect. Generally, Ti with 30 nm nanopores may promote early osteoblastic differentiation and rapid osseointegration of Ti implants.[362]

8. Conclusion and future prospects

Inadequate bone formation around implants and osseointegration, exacerbated by microbial infection, is the most likely reason for implant failure. With recent progress in surface engineering at the nanoscale, we can now better control the complex biological events such as the adsorption of proteins, blood clot formation, migration, adhesion, and differentiation of cells. A major problem with current dental implants is the achievement of mechanical properties similar to bone tissue. There are still no available optimized implant surface modification methods and protocols for clinical application. Nanotechnology has brought new insight into the production of the second generation of implants, and through the manipulation and engineering of bone implants to mimic the natural topography, nanomaterials processing is truly a new frontier. Nanotechnology can fabricate a new generation of implant materials with high efficiency, low cost and high surface area to volume to ratio. Scientists are still looking to produce an implant similar to the structure of the tooth, which can provide the best biological response in terms of structure, surface chemistry and function. There is the need for more research into the interaction of cells with implant surfaces, as well the influence of different chemical compositions and nanopatterns in the interactions of biological molecules and cells with implant surface, and the stimulation of osseointegration and bone formation. Despite many promising studies applying nanotechnology for implant surface engineering, the development of dental implants with interesting properties is still challenging. Nanotoxicity and the potential human health risk of nanoparticles should be carefully evaluated; therefore, more research needs to be conducted in order to achieve the ideal dental implant.

Abbreviations

AAID	American academy of implant dentistry
BAM	Biocompatible anchor molecules
BCP	Biphasic calcium phosphate
CA	Calcium acetate
Ca-GP	Calcium glycerophosphate
CaP	Calcium phosphate
CNTs	Carbon nanotubes
CVD	Chemical vapor deposition
EGF	Epidermal-growth factor
ECMs	Extracellular matrices
FDA	Food and drug administration
HA	Hydroxyapatite
IBAD	Ion-beam assisted deposition
MS	Magnetron sputtering
MAO	Micro-arc oxidation
NPs	Nanoparticles
PVD	Physical vapor deposition
PS	Plasma-spraying
PDS	Polydimethylsiloxane
PEEK	Polyether ether ketone
PE	Polyethylene
PEG	Polyethylene glycol
PET	Polyethylene terephthalate
PMMA	Polymethylmethacrylate
PP	Polypropylene
PSF	Polysulfone
PTFE	Polytetrafluoroethylene
PU	Polyurethane
RF	Radio frequency
rhBMP-2	Recombinant human bone morphogenetic protein-2
SLA	Sandblasted with acid etched
SAMs	Self-assembled monolayers
SR	Silicone rubber
SBF	Simulated body fluid
SD	Sputtering deposition
S_a	Surface roughness
UHMW-PE	Ultra-high-molecular-weight polyethylene
β-GP	β-Glycerophosphate disodium salt pentahydrate

Conflicts of interest

There are no conflicts to declare.

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