# Implant surface characteristics and their effect on osseointegration

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### VERIFIABLE CPD PAPER

#### IN BRIEF

- Explores the effect of various dental implant surfaces on osseointegration.
- Explains different materials, designs and surface characteristics that are available for dental implants.
- Discusses the techniques that are used to modify dental implant surfaces to provide more predictable outcomes.

Aim The aim of this literature review is to find current knowledge of dental implants focusing on materials, designs and surface modifications and to understand which implant surfaces have more predictable clinical outcomes. Research material and methods An electronic search using PubMed/Medline, Scopus and The Cochrane Library databases from 1950 onwards was conducted using keywords and terms. Published papers were then obtained online or from specialist libraries. References from individual published papers were also searched for relevant publications. Results Different designs, materials and methods to modify surfaces of implants have been discussed in this paper. Many laboratory studies using animal models reported improved biological outcomes with surface modification of implants at the microscopic level. Despite pure titanium being commercially the prime material of choice, ceramics have the potential to become the next generation of dental implants. Presently there is not sufficient scientific evidence for routine use of ceramic implants. Conclusions Pure titanium is the ideal material for implants. Rough implant surfaces are believed to deliver better osseointegration compared with smooth surfaces however, results from different studies vary. It is not clear which combination of different surface modifications provide a more predictable outcome. More standardised high quality prospective studies are required to prove which implant surfaces have the optimum properties for replacing missing teeth.

### INTRODUCTION

A glossary of biomaterial definitions describes a medical implant as a device fabricated from one or more materials that is purposely inserted within the body with the aim to integrate with the surrounding tissue.1 The first implants used to replace missing teeth probably date back to the end of the first century AD.2 Crubzy et al.3 described a piece of metal that they believed to have served as a dental implant, found in the maxilla of a male over 30 years of age who was alive at the end of the first century AD. They concluded that it was fashioned from wrought iron or non-alloy steel. Lack of periapical pathoses and close apposition to the bone were significant findings, suggesting this implant achieved successful osseointegration. However, it took until 1960s for modern implants to emerge. It was only at

that time when Brånemark and co-workers gave rise to the concept of osseointegration.<sup>4</sup> Endosseous implants are now being used for single tooth replacement,<sup>5</sup> bridgework,<sup>6</sup> complete-arch reconstructions<sup>7</sup> and complete removable overdentures,<sup>8</sup> or to reconstruct maxillofacial defects.<sup>9</sup> Implant dentistry is continuously evolving as new levels of biological technology continue to drive enhancement in implant surface materials and designs.

Although the main purpose of surface modification of implants is to achieve better osseointegration, a shortened period of healing is desirable for both the clinician and the patient. <sup>10</sup> Pure titanium is commercially the prime material of choice in implant dentistry; however the reported success rates vary and the reasons for this are not always clear.

### RESEARCH MATERIALS AND METHOD

### **Case definition**

Any variation of osseointegrated dental implant surfaces in terms of design, shape, modification, material or characteristics placed in humans or intended to be placed in humans to replace missing teeth.

### Search strategy

In February 2014, PubMed/Medline, Scopus and The Cochrane Library databases were searched from 1950 onwards to identify the potential relevant literature on dental implant surface characteristics.

The following terms were used to conduct the search:

'dental implant\$' OR 'oral implant\$' OR 'osseointegrated dental implant\$' OR 'osseointegrated oral implant\$' OR 'implant surface\$' OR 'implant surface characteristics' OR 'implant surface design\$' OR 'implant surface modification\$' OR 'dental implant material\$' OR 'oral implant material\$' OR 'dental implant shape\$' OR 'oral implant shape\$'.

The initial search generated 38,797 papers. Then the search was limited to clinical trials, observational studies and laboratory studies, which produced 2,727 articles. Two independent operators reviewed titles and abstracts for further investigations. Only studies published in English in peerreviewed journals were selected using the following criteria.

### Inclusion criteria

Retrospective or prospective observational studies, clinical trials, case studies, cohort

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Author(s)	Study	Type of implant	Method of analysis	Effects observed	
Wenneberg <i>et al.</i> <sup>28</sup>	ln vivo	surface(s) 25 μm or 250 μm Al <sub>2</sub> O <sub>3</sub> blasted	Histomorphometric and mechanical	A highly increased surface roughness is a short-term disadvantage for bone tissue	
Hehn and Vassos 40	Clinical trial	HA-coated Ti alloy implants	Life table methodology	11 implants failed in eight patients, 97.8% success rate reported	
Siegele and Soltesz 49	In vivo	Five different types	Finite-element	Conical or stepped implant surfaces imply higher stresses than cylindrical or screw-shaped	
Ivanoff et al. 50	In vivo	Screw-shaped (vari- ous diameters)	Mechanical and histomorphometric	Statistically significant increase of removal torque with increasing implant diameter	
Wong <i>et al</i> . <sup>53</sup>	In vivo	Sandblasted, acid etched, HA-coated	Mechanical and morphometric	HA-coated implants showed superior osseointegration	
Lan <i>et al</i> . <sup>54</sup>	In vitro	1) Triangular 2) Trapezoidal	Biomechanical and finite-element	Trapezoidal implants provided greater primary stability and lower concentration of bone stress	
Schwarz <i>et al.</i> <sup>56</sup>	In vitro	Five different surfaces	Histological	Surface roughness affects chondrocyte proliferation, differentiation, and matrix synthesis	
Brett <i>et al.</i> <sup>59</sup>	In vitro	1) SLA; 2) TPS; 3) Smooth surface	Photoelectron spectroscopy, SEM	SLA surface delayed bone cell growth. TPS surface elicited the greatest increase in cell numbers.	
Braceras <i>et al</i> . <sup>66</sup>	In vivo	1) CO; 2) SLA; 3) Untreated	Energy dispersive spectroscopy	Low-density bone arising from bone towards the implant was onl present on the CO samples	
Park and Davis <sup>67</sup>	In vivo	Micro-roughened machined surfaces	Histological	Micro-roughened surfaces showed more platelets than machined surfaces	
Trisi <i>et al</i> . <sup>68</sup>	In vivo	Machined and Osseotite	Histomorphometric	The actual bone-to-implant contact for Osseotite was greater tha in machined surface implant	
Cochrane <i>et al</i> . <sup>70</sup>	Clinical trial	SLA	Clinical and radiographic	The success rate for these implants, as judged by abutment placement, was 99.3%	
Ogiso <i>et al</i> . <sup>71</sup>	In vivo	A high-density HA-coated ceramic	Light and electron microscopy	HA-coated ceramic implant had no structural changes during five years of function	
Vercaigne <i>et al</i> . <sup>74</sup>	In vivo	TiO <sub>2</sub> -gritblasted and Ca-P coated	Histological and histomorphometric	Significantly greater BIC for the CaP-1 and CaP-4 implants	
Gan <i>et al</i> . <sup>76</sup>	In vivo	Sol-gel coated	Histological and histomorphometric	Both types of sol-gel coatings significantly enhanced the early ra of bone ingrowth and fixation	
Gali <i>et al</i> . <sup>77</sup>	In vivo	1) TPS, 2) SLA	Roughness testing and SEM	Osteoblasts on SLA appeared more elongated and spindle shaped than those on TPS	
Bornstein <i>et al</i> . <sup>78</sup>	In vivo	Modified SLA <i>versus</i> standard SLA	Histological and histomorphometric	Significantly greater BIC for modified SLA.	
Ivanoff <i>et al</i> . <sup>79</sup>	In vivo	TiO <sub>2</sub> blasted and turned	Histological	Significantly higher BIC for the blasted implants.	
Wenneberg <i>et al</i> . <sup>82</sup>	In vivo	$25$ - $\mu$ m $Al_2O_3$ blasted and $TiO_2$	Mechanical and histomorphometric	The blasted specimens exhibited a statistically significant higher BIC after 12 weeks	
Rasmusson <i>et al</i> . <sup>83</sup>	Clinical trial	Titanium dioxide- blasted implants	Clinical	A cumulative survival rate of 96.9% after ten years of follow-up was reported	
Sul <i>et al</i> . <sup>84</sup>	In vivo	Turned	Histological	The test implants demonstrated a greater bone response than control implants	
Ivanoff <i>et al</i> . <sup>85</sup>	Case-control	Screw-type turned and oxidized	Histological	Significantly higher bone-to-implant contact for the oxidized implants than turned implants	
Degidi <i>et al</i> . <sup>86</sup>	Clinical trial	TiUnite porous ano- dized surface	Clinical	98% and 96% survival rates was reported for implants placed in healed and post-extraction sites	
Rossi <i>et al</i> . <sup>87</sup>	RCT	TiUnite versus machined-surfaced	Clinical and radiographic	A success rate of 95.5% for TiUnite surfaces and 85.5% for machined-surfaces was reported	
Ellingsen <i>et al</i> . <sup>88</sup>	In vivo	Fluoride modified	Histomorphometric	The evaluations demonstrated higher bone-to-implant contact for fluoride-modified implants	
Lamolle <i>et al</i> . <sup>90</sup>	In vitro	Fluoride modified	Histomorphometric	Submerging Ti implants in a weak HF solution improved biocompatibility of implant surfaces	
Hallgren <i>et al</i> . <sup>92</sup>	In vivo	Laser machined <i>versus</i> turned	Mechanical and histomorphometric	Significantly more bone-to-implant contact was found for the laser-machined implants	
Guarnieri <i>et al</i> . <sup>93</sup>	Clinical trial	Laser micro-textured	Clinical	The survival rate was reported 95.6% two years after installation	
Yang <i>et al</i> (2011) <sup>102</sup>	In vitro	Simvastatin-coated	Histological and histometrical	Simvastatin-coated surfaces accelerated osteogenic differentiation of preosteoblasts	
Herr <i>et al</i> (2008) <sup>103</sup>	In vitro	Tetracycline-coated	SEM analysis	Tetracycline-HCl treatment removed the smear and killing the bacteria around implant surfaces	

studies, laboratory studies and review papers conducted on dental implants investigating the effect of different implant surface characteristics on osseointegration.

### **Exclusion criteria**

Studies with unclear sample size or dubious aim and case definition, which did not investigate the effect of implant surface characteristics on clinical performance, were excluded.

Table 1 demonstrates the characteristics of included papers.

### **OSSEOINTEGRATION**

Osseointegration was initially defined at the light microscope level as 'a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant'. Zarb and Albrektsson suggested a more clinical description as a process of rigid fixation of an alloplastic material when asymptomatically maintained in bone during functional loading. Subsequently, they proposed objective criteria for determining implant success.

Surgical instrumentation of mature bone to create space for placement of an implant results in vascular trauma. The osteotomy site is filled with blood and implant surfaces are covered by it.14 Proteins and other biomolecules may be absorbed onto the implant surface.15 Several studies demonstrated that there is an amorphous layer of unmineralised collagen and proteoglycans between bone and implant surface. 16-18 A large number of adhesive proteins such as fibronectin, vitronectin, osteopontin, fibrinogen and thrombospondin are involved in the cell adhesion mechanism. All these proteins contain the tripeptide arginine-glycine-aspartic acid, which is recognised by integrin receptors on the cell surface.19

Cooper *et al.* studied the effect of surface topography on the ability of osteoblast cultures to produce a mineralising matrix and they concluded that cells respond differently to various surfaces.<sup>20</sup> If the implant surface is less than optimal, osteogenic potential will be reduced.<sup>21</sup> It is not clear whether bone grows from the osteotomy site walls toward the implant surface or along the implant surface itself.<sup>22</sup>

At the microscopic level, the biomechanical interlocking between implant and bone can be influenced by the topography of an implant surface.<sup>23</sup> Experimental studies have shown that for metallic implants with porous surfaces optimum bone growth requires a pore size between 50 and 400 µm.<sup>24</sup>

### EVALUATION OF THE OSSEOINTEGRATED SURFACES

The quality of integrated interfaces is most often assessed with biomechanical testing and histomorphometric analysis.<sup>25,26</sup> There are generally three types of biomechanical tests: pull-out, push-out and torque measurement.<sup>27</sup>

Histomorphometric analyses often present bone-implant contact as a percentage of the total implant length and as a percentage of three consecutive 'best threads' length.<sup>28</sup>

### **IMPLANT MATERIALS**

Gold, silver, aluminium, platinum and porcelain were amongst the first industrial implants used for replacing teeth.<sup>29</sup> Most of these materials are no longer used as they caused marked foreign body or inflammatory reaction with formation of fibrous tissue.<sup>30</sup>

From a chemical point of view, dental implants are being produced within the following three groups: metals, ceramics and polymers.<sup>31</sup>

Implants are also categorised by biocompatibility based on the type of biological response they elicit in the long-term interaction with the host tissue. The three major type of biocompatibility of implants are:

- Biotolerant: the material is not necessarily rejected by host tissue but surrounded by a fibrous capsule
- Bioinert: materials allow close apposition of bone on their surface
- Bioactive: formation of new bone onto their surface takes place and ion exchange with host tissue leads to the formation of chemical bonds along the interface.<sup>32</sup>

### Metals

Titanium and titanium alloys have become the preferred materials of choice for dental implants. Pure titanium forms a surface oxide layer immediately (9–10 seconds) after exposure to air which can reach a thickness of between 2–10 nm in one second. This stable surface oxide layer of titanium is biocompatible<sup>33,34</sup> and provides high corrosion resistance, <sup>35,36</sup> high passivity and resistance to chemical attack. The modulus of elasticity of titanium and its alloys are comparable to that of bone.<sup>37,38</sup>

### **Ceramics**

Ceramic materials used for dental implants are either bioactive or bioinert. Lacefield<sup>39</sup> investigated various types of ceramic materials available for dental implants. The most popular is plasma-sprayed hydroxyapatite (HA) ceramic. It has been claimed that plasma-sprayed HA and other bioactive ceramic coatings can enhance cohesive chemical bonding with bone compared with uncoated metal implants.<sup>39</sup>

The entire implant can be made up of ceramic, or metal implants can be coated with ceramic. Flexural strength and various degrees of solubility are the main concerns regarding full ceramic implants hence ceramic coated metal implants are usually the preferred choice.<sup>39</sup> Achieving strong adhesion between the ceramic coating and metal surface of implant is important to avoid fragmentation. Hot isostatic pressing and surface-induced mineralisation (SIM) are methods used for this purpose.

Although in a six-year clinical study conducted by Hahn and Vassos<sup>40</sup>, the success rate of HA-coated implants was reported to be 97.8%, degradation of the ceramic coating, which could affect the longevity and success of these implants,<sup>41</sup> has given rise to concern.<sup>42</sup>

### **Polymers**

Historically, a variety of polymers have been tried in implant dentistry. Polyurethane, polymethylmethacrylate, polyamide fibres and polytetrafluoroethylene are some example of these polymers.43 The intension was to mimic the micro-movement of periodontal ligaments and transfer stress more favourably to bone using these materials.44 Research suggested no statistically significant difference of polymers compared to rigid implants.44 However, several studies45,46 reported adverse immunological reactions using polymers as well as lack of adhesion of these materials to living tissues, hence polymers are no longer used for coating dental implants.; however, they are sometimes used as a shock absorber component incorporated into some rigid implant superstructures.47

### **IMPLANT SURFACE DESIGN**

A 3D structure involving form, configuration, shape, macrostructure and micro-irregularities will contribute toward the design of an implant. Several different types of implant surface designs have been shown in Table 2. The main objective for designing the surface is to improve long-term success of the osseointegrated interface and accomplish uncomplicated prosthetic replacement. Presence or absence of threads, macro irregularities and shape of the implant are widely considered in the design of dental implants.<sup>48</sup>

The prosthetic interface which connects the superstructure abutments to the body of implant can be either external or internal. Hexagonal design is the most common external connection used in the design of dental implants. Other external connectors are octagonal and the spline interface. Some implant systems have a Morse taper interface, which is an internal connector. Other internal connectors include hexagonal and octagonal.

Dental implants are also categorised as having threaded and non-threaded surfaces. It is believed that threads play an important role in primary stability and long-term success of dental implants.<sup>49</sup> Threads will maximise primary contact, enhance primary stability, increase implant surface area and help stress distribution in the bone.<sup>50,51</sup> Direct bone apposition to implant surface at surgical placement is the desirable outcome but inevitably some gaps may occur. In an animal study in rabbits using non-porous surface implants it was claimed that a maximum gap of 0.35 mm is critical if direct bone-implant contact is to be achieved after healing.<sup>52</sup> Some studies have suggested that initial gaps can be enhanced by using calcium phosphate coating on implant surfaces, provided limitation of micro-movements is less than 150 µm.<sup>53</sup>

Lan *et al.*<sup>54</sup> carried out a biomechanical analysis of alveolar bone stress around implants with different thread designs. Their results suggested that a thread pitch exceeding 0.8 mm is appropriate for a screwed implant and that for clinical cases requiring greater bone-implant interface trapezoid-threaded implants with a thread pitch of 1.6 mm were more stable and generated less stress than other thread designs.

The concept of double threaded or triplethreaded implants has been recently introduced and is believed to provide faster thread penetration into the bone, generate less heat upon placement and hence improved primary stability. These implants require more torque for placement thus have tighter contact with bone, which could be indicated for type IV (cancellous) bone (Table 2).<sup>26</sup>

### **SURFACE TOPOGRAPHY**

Implant surface topography pays an important role in the osseointegration of titanium implants<sup>55</sup> and includes macroscopic, microscopic and nanometric characteristics of the implant surface. Schwartz *et* al.<sup>56</sup> investigated the reaction of osteogenic cells to different surfaces and they found that osteoblast proliferation was increased on rough surfaces. Albrektsson and Wennerberg demonstrated that the differentiation and adhesion of osteoblasts is enhanced on rough surfaces, whilst fibroblast adhesion is weaker.<sup>23</sup>

Depending on the dimension of different surface characteristics, implant surface roughness is divided into macro, micro and nano roughness.

- Macro roughness: this feature can range from millimetres to microns. The implant geometry, including threaded screw and macro porous, are directly related to this scale. An appropriate macro roughness can directly improve the initial implant stability and long-term fixation by mechanical interlocking of the rough surface irregularities and the bone.<sup>28,57</sup>
- Micro roughness: frequently ranges from 1–10 microns. In a systematic review

- by Junker *et* al.<sup>58</sup>, it was emphasised that at the micron-level optimal surface topography results in superior growth of and interlocking of bone at the implant interface.
- Nano roughness: nanoscale topographies are widely used in implant dentistry. This technology uses nano-sized materials with a size of 1–100 nm on the implant surface. This microscopic roughness is believed to promote absorption of proteins and adhesion of osteoblasts hence improved osseointegration.<sup>59</sup>

### Nanotopography

At the nanoscale, a more textured surface topography increases the surface energy, which in turn increases the wettability of the surface to blood and adhesion of cells to the surface. Nanotopography can promote the process of cell differentiation, migration and proliferation by accelerating wound healing thereby, enhancing osseointegration following implant placement. 60,61

There are various methods to create nanometre-scale topography; the most widely used being grit blasting, ionisation and acid etching. Studies have demonstrated that biphasic calcium phosphate grit-blasted surfaces can provide a more rapid osseointegration in comparison to smooth surfaces. Application of calcium phosphate coatings can also promote osseointegration by plasma spraying, biomimetic and electrophoretic deposition.62 An electrochemical process consisting of deposition of calcium phosphates from saturated solutions releases calcium and phosphate ions from these coatings which help in the precipitation of biological apatite nanocrystals with the incorporation of various proteins, which in turn promotes cell adhesion, osteoblast differentiation and the synthesis of mineralised collagen, the extracellular matrix of bone tissue. Osteoclast cells absorb calcium phosphate coatings and this activates these cells to produce bone tissue, thus direct bone-implant contact is promoted without the intervention of a connective tissue layer, leading to biomechanical fixation of dental implants.<sup>62</sup>

### METHODS OF SURFACE MODIFICA-TIONS OF IMPLANT SURFACES

### Mechanical methods

Grinding, blasting, machining and polishing generally result in rough or smooth surfaces, which can improve adhesion, proliferation and differentiation of cells.<sup>63</sup>

### Chemical methods

Chemical treatment with acids or alkali, sol gel, hydrogen peroxide treatment,

anodisation and chemical vapour deposition are chemical surface modification methods used to alter surface roughness and composition and enhance surface energy.<sup>64</sup>

### Physical methods

Plasma spraying, ion deposition and sputtering are some of the physical methods used for implant surface modification. Plasma spraying includes vacuum plasma spraying and atmospheric plasma spraying. A method used to deposit thin films on implant surfaces is sputtering and is believed to improve biological activity and mechanical properties.<sup>56</sup>

### SURFACE TREATMENT METHODS FOR TITANIUM IMPLANTS

### Machined dental implants (turned surface)

Originally described by Brannemark,11 turned surface implants were the first generation of dental implants. Although the surface appears to be relatively smooth, scanning electron microscopy analysis showed grooves and ridges created during the manufacturing process. One disadvantage regarding the morphology of non-threaded (machined) implants is that the surface defects provide resistance to bone interlocking, which delays the process of osseointegration as a result of osteoblastic growth along the existing surface grooves. The techniques described by Brannemark, burying followed by a six month healing period before loading, improve the clinical outcomes from this type of implant.58

Clinical studies and systematic reviews have indicated a positive correlation between surface roughness and bone-implant contact. Experimental studies clearly indicated that significantly greater bone deposition is formed around HA coated or oxidised implants, hence these implants should be preferred over machined dental implants when used in poor bone quality sites.<sup>58</sup>

### **Etched surfaces**

Strong acids are used for roughening the surface of titanium implants. Acid etching removes the oxide layer of titanium implants in addition to parts of the underlying material. 60 The higher the acid concentration, temperature and treatment time, the more of the material surface is removed. A mixture of HNO<sub>3</sub> and HF or a mixture of HCl and H<sub>2</sub>SO<sub>4</sub> is the most commonly used solution for acid etching of titanium implant surfaces. 65 Treating surfaces with acids provides homogeneous irregularities, increased surface area and enhanced bioadhesion. 66

Lower surface energy and reduced possibility of contamination are some advantages

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etched titanium	SPI® Element (Thommen Medical, Switzerland)	Pl® Element hommen Medical,	NobelActive® (Nobel Biocare, Sweden) TiUnite oxidised titanium	Brånemark® Standard (Nobel Biocare, Sweden) Turned titanium		Table 2 Several dif
Sand-blasted, acid-etched	Neoss (Neoss, UK)	Neoss (Neoss, UK)	Nobel Active® (Nobel Biocare, Sweden). TiUnite oxidised titanium	Brånemark® Mk II (Nobel Biocare, Sweden)  Turned titanium		ferent types of impl
TPS titanium	Seven (Sweden & Martina, Italy)	Seven (Sweden & Martina, Italy)	NobleReplace® Select (Nobel Biocare, Sweden) TiUnite oxidised titanium	Brånemark® Mk III (Nobel Biocare, Sweden) Turned titanium		Several different types of implant designs and surface characteristics
Sand-blasted titanium	Southern® (Southern Implants, South Africa)	Southern® (Southern Implants,	Nobel Speedy Groovy (Nobel Biocare Sweden) TiUnite oxidised titanium	Brånemark® Mk III (Nobel Biocare, Sweden) TiUnite oxidised titanium		ce characteristics
Sand-blasted titanium	Southern® (Southern Implants, South Africa)	Southern® (Southern Implants, South	NobelReplace® Groovy (Nobel Biocare, Sweden) TiUnite oxidised titanium	Brånemark® Mk IV (Nobel Biocare, Sweden) Turned titanium		
Acid-etched ceramic	Straumann® PURE, ZLA™ (Straumann, Switzerland)	Straumann® PURE, ZLA"	Implantium® SLA (Dentium, Korea) Titanium	Brånemark® Mk IV (Nobel Biocare, Sweden) TiUnite oxidised titanium		
Acid-etched zirconium	CeraRoot® 11 ICE (Oral Iceberg, Spain)	CeraRoot® 11 ICE (Oral Iceberg, Spain)	Straumann® BL (Straumann, Switzerland) SLActive titanium	Ankylos Plus® (Dentsply- Germany) Grit-blasted and etched titanium	AIIIII	
Sand-blasted acidetched titanium	SwissPlus® (Zimmer, USA)	SwissPlus® (Zimmer, USA)	Straumann® TL (Straumann, Switzerland) SLA/ SLActive titanium	Astra® (Astra Tech, Sweden) TIO2-blast titanium		
Sand-blasted acidetched titanium	WINSIX® implant (Winsix, UK)	WINSIX® implant (Winsix, UK)	Straumann® TL (Straumann, Switzerland) Roxolid SLActive titanium	Astra® (Astra Tech, Sweden) TiO <sub>2</sub> -blast titanium		
Sand-blasted acidetched titanium	WINSIX® implant (Winsix, UK)	WINSIX® implant (Winsix, UK)	MegaGen EZ Plus (MegaGen, South Korea) Titanium	IMZ® (Friedrichsfeld, Germany) TPS titanium		

of this technique as no particles are encrusted in the surface. It facilitates osteoblastic retention and allows them to migrate toward the implant surface. Rapid osseointegration with long-term success has been reported when titanium surface was roughened by acids.<sup>55</sup>

### **Dual-etched surfaces**

Dual acid-etching is a technique used to roughen the surface of implant by immersing the titanium implants for several minutes in a mixture of concentrated HCl and H<sub>2</sub>SO<sub>4</sub> heated above 100 °C. This method enhances the osteoconductive process through the attachment of osteogenic cells and fibrin, resulting in direct bone formation.67 It has been hypothesised that a specific topography is achieved by dual acid etching of implants, which enables them to attach to the fibrin scaffold, to promote the adhesion of osteogenic cells hence promoting bone apposition.68 This fibrin adhesion guides osteoblastic migration along the surface.69 Cochran et al.70 reported higher boneimplant contact and less bone resorption with dual acid etched surfaces.

### Hydroxyapatite coated surfaces

At the implant bone interface a coating with hydroxyapatite  $(\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2)$  can be considered as bioactive because of the consequence of events that result in formation of a calcium phosphate rich layer on the surface through a solid solution ion exchange. The calcium phosphate incorporated layer will gradually be developed via octacalcium phosphate in a biologically equivalent hydroxyapatite that will be incorporated in the developing bone. The control of the c

According to Biesbrock and Edgerton, <sup>72</sup> there are some concerns regarding HA coated implants including microbial adhesion, osseous breakdown and coating failure. However, the authors proposed that these implants could be beneficial in grafted bone or type IV bone where more rapid bone implant contact is needed. Also where short implants are indicated HA coating may be useful.

It is worth mentioning that in a comparative study by Vercaigne *et al.*<sup>73</sup> it was demonstrated that bone reaction to chemical composition of HA-coated implants was more profound than implant surface roughness, although signs of degradation were also observed.

### Sol-gel coated implants

This low cost and simple procedure is used to deposit homogenous chemical compositions on surfaces with large dimensions and complex designs.<sup>74</sup> The sol-gel method is capable of enhancing chemical homogeneity in the production of HA coating to a high level.<sup>75</sup>

In a short-term *in vivo* laboratory study by Gan *et al.*<sup>76</sup> better osseointegration with no adverse effect was evaluated after analysing the bone tissue around the implant surface using sol-gel method.

## Sandblasted and acid-etched surface (SLA and modified-SLA) implants

The SLA implant surface is produced after sandblasting with large grit particles of 250-500 µm followed by etching with acids. Macrostructures are created after sandblasting in addition to micro-irregularities supplemented by acid etching.77 A histomorphometric study by Bornstein et al.78 demonstrated that modified SLA surfaces showed significantly more bone apposition than standard SLA surfaces after two weeks healing but both surface types showed the same apposition after four weeks, with an increasing apposition between two and four weeks. They suggested that the acid-etched modified implants may be of benefit for patients undergoing early loading implant techniques.

### **Grit-blasted surfaces**

Titanium dioxide particles with sizes of 0.25-0.50 µm are used to grit-blast the machine turned implant giving a rough surface compared with the turned implant. In a human study using microimplants, Ivanoff et al.79 showed enhanced osseointegration in the mandible but not in the maxilla. These results compared well with previous animal studies.80-82 In a ten-year prospective study of TiO<sub>2</sub> grit blasted implants a success rate of 96.9% was reported by Rasmusson et al.83, and these implants had a higher success rate than unblasted, machine turned implants. There is a tendency for more predictable clinical results with grit-blasted roughened implant surfaces than implants with machined surfaces.

### **Oxidised surfaces**

Sul et~al.84 described anodisation as a process used to alter the topography and composition of the surface by increasing the thickness of the titanium oxide layer, roughness and an enlarged surface area. This moderately rough surface was reported to enhance osteoblast cell adhesion to titanium implants. Ivanoff et al.85 demonstrated that a faster integration of the implant in the bone could be achieved as a result of ossteoconductive properties of the anodised design. A ten-year follow-up of immediately loaded implants with porous anodised surfaces reported a cumulative 65.26% success rate and 97.96% survival rate.86 In a randomised clinical trial, anodised implant survival rates were reported to be higher than machined implants (95.5% and 85.5% respectively).<sup>87</sup>

### Fluoride treatment

Ellingsen88 in an animal study reported that surface modification with fluoride significantly increased the retention of titanium implants after four and eight-week healing periods. He stated that titanium is very reactive to fluoride, forming TiF, providing more firm bone to implant contact when compared to grit-blasted implants with a shorter healing time. Surface modified implant surfaces with fluoride also resisted a greater removal torque than grit-blasted implants. In a parallel in vitro - in vivo study using TiO, gritblasted titanium implants by Cooper et al.89 (human mesenchymal cells in vitro and the rat tibia model in vivo), results suggested that fluoride ion treatment of TiO, grit-blasted titanium substrates enhances osteoblastic differentiation of human mesenchymal stem cells in vitro and significantly increased the bone-to-implant contact in vivo. Lamolle et al.90 demonstrated that fluoride modified titanium surfaces improved the biocompatibility of implant surfaces and Schade et al.91 also demonstrated that fluoride treated pure titanium implants showed the highest retention in bone, using the rabbit pull out model. Surface modification using laser ablation

Laser ablation is another method employed for surface modification of dental implants. Microstructures with increased hardness, corrosion resistance, and a high degree of purity with standard roughness and a thicker oxide layer are features reported to enhance the titanium implant surfaces. Para In a two-year retrospective clinical study, 95.6% survival rate for immediately loaded laser microtextured implants placed into fresh extraction sockets in the anterior maxilla was reported by Guarniari and co-workers.

### Sputter deposition

Sputtering is a vacuum process whereby molecules of a material are ejected by bombardment of high-energy ions. Radio frequency sputtering and Magnetron sputtering are methods used to deposit hydroxyapatite on implant surfaces. Animal studies by Vercaigne *et* al. <sup>94</sup> demonstrated higher bone implant contact rates with sputter coated implants.

### Bioactive drugs incorporated dental implants

In attempt to improve and accelerate osseointegration several osteogenic drugs have been applied to implant surfaces.

### **Bisphosphonates**

In experimental studies bisphosphonates have been shown to increase bone density

around implant sites when incorporated on to the implant surface.<sup>95,96</sup> However, achieving the controlled release of anti-resorptive drugs from an implant surface is challenging.

### Simvastatin

Simvastatin is a drug which reduces serum cholesterol concentration; it inhibits 3-hydroxy-3-methylglutaryl coenzyme reductase to decrease cholesterol biosynthesis by the liver.<sup>97</sup> In an animal study in rats, simvastatin increased cancellous bone intensity as well as its compressive intensity.<sup>98</sup> Mundy *et al.*<sup>99</sup> suggested simvastatin could promote bone formation by inducing expression of the bone morphogenetic protein (BMP-2) gene. The effect of simvastatin on implant surfaces was investigated in several laboratory studies and they all reported potential for improved osseointegration.<sup>100-102</sup>

### Antibiotic coating

Herr *et al.*<sup>103</sup> investigated the effect of tetracycline on implant surfaces and found that, in addition to killing microorganisms that contaminate implant surfaces, it can also effectively remove the smear layer, increase cell proliferation and inhibit collagenase activity hence promote enhanced attachment and bone healing.

### Synthetic peptide coating

Petzold *et* al. <sup>104</sup> found that proline-rich synthetic peptide coated titanium implants have potential to promote osseointegration and bone healing in rabbit models.

### FUTURE OF DENTAL IMPLANT SURFACES

### Ceramic implants

Although ceramic materials for the purpose of oral implants were introduced about 30–40 years ago, the interest in such implants had fallen due to inferior mechanical properties and low survival rates. <sup>105,106</sup> Introduction of zirconia implants which exhibit good mechanical and physical properties has raised the interest in the recent years. <sup>107–110</sup>

Lately, the outcome of ceramic implants has been assessed based on the available clinical data from retrospective and prospective studies and high survival rates of up to 98% after an observation period of 12–56 months. <sup>111</sup> However, from a critical point of view and comments from systematic reviews <sup>108,110</sup> the short observation periods, insufficient number of implants placed and low level of evidence extracted from those studies indicate a scarcity of clinical data that would support the use of zirconia implants. Zirconia may have the potential

to become the material of choice in implant dentistry, however adequate clinical research must be conducted prior to its use in routine clinical procedures.

#### **Nanotubes**

Nanotubes are submicron structures, which possibly increase osseointegration. The idea is taken from osteoblastic response to nanofiber alumina. 112 The adsorption of proteins, which mediate osteoblastic adhesion, such as vitronectin and fibronectin, are freed on nanophase substances thus may provide improved osteoblast interaction.<sup>113</sup> Titanium oxide nanotubes range between 15-100 nm and can be tailored though anodisation.114 A space of 30 nm was found to be an effective diameter for rapid bone deposition and improved cellular activity.115 Furthermore, nanotubes have been proposed as a drug delivery system for various therapeutic indications, For example, the inner substructures could be filled with drugs, chemicals and biomolecules.116 Nanotubes seem to be a promising method for the future of implant dentistry due to the low-cost, flexible manufacturing and possibility of usage as a drug delivery system.117

### **CONCLUSIONS**

Conclusions from systematic reviews are conflicting. While a review by Junker et al.58 suggests there is sufficient evidence that rough surfaces produce a predictable osseointegration, a Cochrane based review by Esposito et al. 118 indicated there is limited proof, showing that smooth (turned) surfaces are less prone to bone resorption. There is a lack of quality randomised control trials to detect true differences between implant surfaces. Further investigations are required, as the influence of the various patterns of surface modification on osseointegration remains unclear. It is yet to be proved what characteristics of surfaces irregularities are more important and which combination could provide a more predictable osseointegration.

- Williams D F. Definitions in Biomaterials. Amsterdam: Elsevier, 1987.
- Becker M J. Ancient dental implants: a recently proposed example from France evaluated with other spurious examples. Int J Oral Maxillofac Implants 1999; 14: 19–29.
- 3. Crubézy E, Murail P, Girard L, Bernadou J-P. False teeth of the Roman world. *Nature* 1998; **391:** 29.
- Brånemark P-I, Adell R, Breine U, Hansson B O, Lindström J, Ohlsson Å. Intra-osseous anchorage of dental prostheses: I. experimental studies. Scand J Plast Reconstr Surg 1969; 3: 81–100.
- Sabri R. Four single-tooth implants as supernumerary premolars in the treatment of diastemas and microdontia: report of a case. *Int J Oral Maxillofac Implants* 1998; 13: 706–709.
- Knabe C, Hoffmeister B. The use of implant-supported ceramometal titanium prostheses following sinus lift and augmentation procedures: a clinical

- report. Int J Oral Maxillofac Implants 1998; 13:
- Balshi T J, Wolfinger G J, Balshi S F. Analysis of 356 pterygomaxillary implants in edentulous arches for fixed prosthesis anchorage. *Int J Oral Maxillofac Implants* 1999; 14: 398–406.
- Mericske-Stern R. Treatment outcomes with implant-supported overdentures: clinical considerations. J Prosthet Dent 1998; 79: 66-73.
- Tolman D E, Desjardins R P, Jackson I T, Brånemark P-I. Complex craniofacial reconstruction using an implant-supported prosthesis: case report with long-term follow-up. Int J Oral Maxillofac Implants 1997: 12: 243-251.
- Wennerberg A, Albrektsson T. Suggested guidelines for the topographic evaluation of implant surfaces. Int J Oral Maxillofac Implants 2000; 15: 331–344.
- Brånemark P I. Introduction to osseointegration. In Brånemark P I (ed) Tissue integrated prostheses: osseointegration in clinical dentistry. pp 11–76. Chicago: Quintessence Publishing Co., 1985.
- 12. Zarb G, Albrektsson T. Osseointegration: a requiem for the periodontal ligament. *Int J Periodontics Rest Dept* 1991: 11: 88–91
- Zarb G A, Albrektsson T. Towards optimized treatment outcomes for dental implants. J Prosthet Dent 1998; 80: 639–640.
- Cooper L F. Biologic determinants of bone formation for osseointegration: clues for future clinical improvements. J Prosthet Dent 1998; 80: 439–449.
- Kasemo B, Lausmaa J. Biomaterial and implant surfaces: a surface science approach. Int J Oral Maxillofac Implants 1988; 3: 247–259.
- Klinger M M, Rahemtulla F, Prince C W, Lucas L C, Lemons J E. Proteoglycans at the bone-implant interface. Crit Rev Oral Biol Med 1998; 9: 449–463.
- Albrektsson T, Brånemark P, Hansson H-A et al.
   The interface zone of inorganic implants in vivo: titanium implants in bone. Ann Biomed Eng 1983; 11: 1–27.
- Albrektsson T O, Johansson C B, Sennerby L. Biological aspects of implant dentistry: osseointegration. *Periodontol 2000*; 1994: 4: 58–73.
- Ruoslahti E, Pierschbacher M D. New perspectives in cell adhesion: RGD and integrins. Science 1987; 238: 491–497.
- Cooper L F, Masuda T, Whitson S W, Yliheikkilä P, Felton D A. Formation of mineralizing osteoblast cultures on machined, titanium oxide grit-blasted, and plasma-sprayed titanium surfaces. *Int J Oral Maxillofac Implants* 1999; 14: 37–47.
- Kieswetter K, Schwartz Z, Dean D, Boyan B. The role of implant surface characteristics in the healing of bone. Crit Rev Oral Biol Med 1996; 7: 329–345.
- 22. Davies J E. Mechanisms of endosseous integration. Int J Prosthodont 1998; 11: 391–401.
- Albrektsson T, Wennerberg A. Oral implant surfaces: part 1review focusing on topographic and chemical properties of different surfaces and in vivo responses to them. Int J Prosthodont 2004; 17: 536–543.
- Bobyn J D, Pilliar R M, Cameron H U, Weatherly G C.
   The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone.
   Clin Orthop Relat Res 1980: 150: 263–270.
- Cooper L F, Masuda T, Yliheikkilä P K, Felton D A. Generalizations regarding the process and phenomenon of osseointegration. Part II. In vitro studies. Int I Oral Maxillofac Implants 1998: 13: 163–174
- Masuda T, Yliheikkilä P K, Felton D A, Cooper L F. Generalizations regarding the process and phenomenon of osseointegration. Part I. In vivo studies. Int J Oral Maxillofac Implants 1998; 13: 17–29.
- Sykaras N, Iacopino A M, Marker V A, Triplett R G, Woody R D. Implant materials, designs, and surface topographies: their effect on osseointegration. A literature review. Int J Oral Maxillofac Implants 2000; 15: 675–690.
- Wennerberg A, Albrektsson T, Andersson B. Bone tissue response to commercially pure titanium implants blasted with fine and coarse particles of aluminum oxide. Int J Oral Maxillofac Implants 1996; 11: 38–45.
- 29. Marziani L. Subperiosteal implantation of supporting framework for a prosthesis. *Dtsch Zahnärztl Z* 1955;

- **10:** 1115-1129.
- Donath K, Laaß M, Günzl H J. The histopathology of different foreign-body reactions in oral soft tissue and bone tissue. Virchows Archiv A Pathol Anat Histopathol 1992; 420: 131–7.
- LeGeros R Z, Craig R G. Strategies to affect bone remodeling: osteointegration. J Bone Miner Research 1993; 8(Suppl 2): 5583–5596.
- 32. Pilliar R. Dental implants: materials and design. *J Can Dent Assoc* 1990; **56:** 857–861.
- Lautenschlager E P, Monaghan P. Titanium and titanium alloys as dental materials. *Int Dent J* 1993;
   43: 245–353
- Ducheyne P. Titanium and calcium phosphate ceramic dental implants, surfaces, coatings and interfaces. J Oral Implantol 1988; 14: 325–340.
- Donley T G, Gillette W B. Titanium endosseous implant-soft tissue interface: a literature review. J Periodontol 1991; 62: 153–160.
- Parr G R, Gardner L K, Toth R W. Titanium: the mystery metal of implant dentistry. Dental materials aspects. J Prosthet Dent 1985; 54: 410–414.
- Kasemo B, Lausmaa J. Metal selection and surface characteristics. In Branemark P I (ed) Tissue integrated prostheses: osseointegration in clinical dentistry. pp102. Chicago: Quintessence, 1985.
- 38. Meffert R M, Langer B, Fritz M E. Dental implants: a review. *J Periodontol* 1992; **63:** 859–870.
- Lacefield WR. Current status of ceramic coatings for dental implants. *Implant Dent* 1998; 7: 315–322.
- Hahn J, Vassos D M. Long-term efficacy of hydroxyapatite-coated cylindrical implants. *Implant Dent* 1997; 6: 111–115.
- 41. Zablotsky M H. Hydroxyapatite coatings in implant dentistry. *Implant Dent* 1992; 1: 253–257.
- Albrektsson T. Hydroxyapatite-coated implants: a case against their use. J Oral Maxillofac Surg 1998; 56: 1312–1326.
- 43. Lemons J. Dental implant biomaterials. *J Am Dent Assoc* 1990; **121:** 716–719.
- Meijer G, Heethaar J, Cune M, De Putter C, Van Blitterswijk C. Flexible (Polyactive) versus rigid (hydroxyapatite) dental implants. *Int J Oral Maxillofacial Surg* 1997; 26: 135–140.
- Kawahara H. Cellular responses to implant materials: biological, physical and chemical factors. *Int Dent J* 1983; 33: 350–375.
- Chapman R, Kirsch A. Variations in occlusal forces with a resilient internal implant shock absorber. Int J Oral Maxillofac Implants 1989; 5: 369–374.
- Steigenga J T, Al-Shammari K F, Nociti F H, Misch C E, Wang H L. Dental implant design and its relationship to long-term implant success. *Implant Dent* 2003: 12: 306–317.
- Ivanoff C J, Sennerby L, Lekholm U. Influence of initial implant mobility on the integration of titanium implants. An experimental study in rabbits. Clin Oral Implants Res 1996; 7: 120–127.
- Siegele D, Soltesz U. Numerical investigations of the influence of implant shape on stress distribution in the jaw bone. *Int J Oral Maxillofac Implants* 1989; 4: 443–440.
- Ivanoff C-J, Sennerby L, Johansson C, Rangert B, Lekholm U. Influence of implant diameters on the integration of screw implants: An experimental study in rabbits. Int J Oral Maxillofac Surg 1997; 26: 141–148.
- Carlsson L, Röstlund T, Albrektsson B, Albrektsson T. Implant fixation improved by close fit. Cylindrical implant-bone interface studied in rabbits. Acta Orthop Scand 1988; 59: 272–275.
- Tisdel C L, Goldberg V M, Parr J A, Bensusan J S, Staikoff L S, Stevenson S. The influence of a hydroxyapatite and tricalcium-phosphate coating on bone growth into titanium fiber-metal implants. J Bone Joint Surg Am 1994; 76: 159–171.
- Wong M, Eulenberger J, Schenk R, Hunziker E. Effect of surface topology on the osseointegration of implant materials in trabecular bone. *J Biomed Mater Res* 1995; 29: 1567–1575.
- 54. Lan T H, Du J K, Pan C Y, Lee H E, Chung W H. Biomechanical analysis of alveolar bone stress around implants with different thread designs and pitches in the mandibular molar area. Clin Oral Investig 2012; 16: 363–369.
- 55. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq

- Y. Surface treatments of titanium dental implants for rapid osseointegration. *Dent Mater* 2007; **23:** 844–854.
- Schwartz Z, Martin J Y, Dean D D, Simpson J, Cochran D L, Boyan B D. Effect of titanium surface roughness on chondrocyte proliferation, matrix production, and differentiation depends on the state of cell maturation. J Biomed Mater Res 1996; 30: 145-155.
- Shalabi M M, Gortemaker A, Van't Hof M A, Jansen J, Creugers N H. Implant surface roughness and bone healing: a systematic review. J Dent Res 2006; 85: 496–500.
- Junker R, Dimakis A, Thoneick M, Jansen J A. Effects of implant surface coatings and composition on bone integration: a systematic review. *Clin Oral Implants Res* 2009; 20(Suppl 4): 185–206.
- Brett P M, Harle J, Salih V et al. Roughness response genes in osteoblasts. Bone 2004; 35: 124–33. 60. Dohan-Ehrenfest D M, Coelho P G, Kang B-S, Sul Y-T, Albrektsson T. Classification of osseointegrated implant surfaces: materials, chemistry and topography. Trends Biotechnol 2010; 28: 198–206.
- Dalby M J, Andar A, Nag A et al. Genomic expression of mesenchymal stem cells to altered nanoscale topographies. J R Soc Interface 2008; 5: 1055–65.
- Lavenus S, Louarn G, Layrolle P. Nanotechnology and dental implants. Int J Biomater 2010; 2010: 91537.
- Le Guehennec L, Lopez-Heredia M-A, Enkel B, Weiss P, Amouriq Y, Layrolle P. Osteoblastic cell behaviour on different titanium implant surfaces. Acta Biomater 2008; 4: 535–543.
- Bagno A, Di Bello C. Surface treatments and roughness properties of Ti-based biomaterials. J Mater Sci Mater Med 2004; 15: 935–949.
- MacDonald D E, Rapuano B E, Deo N, Stranick M, Somasundaran P, Boskey A L. Thermal and chemical modification of titaniumaluminumvanadium implant materials: effects on surface properties, glycoprotein adsorption, and MG63 cell attachment. Biomaterials 2004; 25: 3135–3146.
- Braceras I, De Maeztu M A, Alava J I, Gay-Escoda C. In vivo low-density bone apposition on different implant surface materials. Int J Oral Maxillofac Surgery 2009; 38: 274–278.
- Park J Y, Davies J E. Red blood cell and platelet interactions with titanium implant surfaces. Clin Oral Implants Res 2000; 11: 530–539.
- Trisi P, Lazzara R, Rao W, Rebaudi A. Bone-implant contact and bone quality: evaluation of expected and actual bone contact on machined and osseotite implant surfaces. Int J Periodontics Restorative Dent 2002: 22: 535-545.
- Cameron H U, Pilliar R M, Macnab I. The rate of bone ingrowth into porous metal. J Biomed Mater Res 1976; 10: 295–302.
- Cochran D L, Buser D, Ten Bruggenkate C M et al.
   The use of reduced healing times on ITI® implants with a sandblasted and acid-etched (SLA) surface: early results from clinical trials on ITI and SLA implants. Clin Oral Implants Res 2002; 13: 144–153.
- Ogiso M, Tabata T, Ichijo T, Borgese D. Examination of human bone surrounded by a dense hydroxyapatite dental implant after long-term use. J Long term Eff Med Implants 1991; 2: 235–247.
- Biesbrock A R, Edgerton M. Evaluation of the clinical predictability of hydroxyapatite-coated endosseous dental implants: a review of the literature. *Int J Oral Maxillofac Implants* 1995; 10: 712–720.
- 73. Misch CE. Divisions of available bone in implant dentistry. *Int J Oral Implantol* 1990; **7:** 9–17.
- Vercaigne S, Wolke J G, Naert I, Jansen JA. A histological evaluation of TiO<sub>2</sub>-gritblasted and Ca-P magnetron sputter coated implants placed into the trabecular bone of the goat: part 2. Clin Oral Implants Res 2000; 11: 314–324.
- Milev A, Kannangara G, Ben-Nissan B. Morphological stability of hydroxyapatite precursor. Materials Letters 2003; 57: 1960–1965.
- Gan L, Wang J, Tache A, Valiquette N, Deporter D, Pilliar R. Calcium phosphate solgelderived thin films on porous-surfaced implants for enhanced osteoconductivity. Part II: short-term in vivo studies. Biomaterials 2004; 25: 5313–5321.
- 77. Galli C, Guizzardi S, Passeri G *et al.* Comparison of human mandibular osteoblasts grown on two

- commercially available titanium implant surfaces. *J Periodontol* 2005; **76:** 364–372.
- Bornstein M M, Valderrama P, Jones A A, Wilson T G, Seibl R, Cochran D L. Bone apposition around two different sandblasted and acid-etched titanium implant surfaces: a histomorphometric study in canine mandibles. Clin Oral Implants Res 2008; 19: 233-241.
- Ivanoff C J, Widmark G, Hallgren C, Sennerby L, Wennerberg A. Histologic evaluation of the bone integration of TiO<sub>2</sub> blasted and turned titanium microimplants in humans. Clin Oral Implants Res 2001; 12: 128–134.
- Gotfredsen K, Nimb L, Hjörting-Hansen E, Jensen J S, Holmén A. Histomorphometric and removal torque analysis for TiO<sub>2</sub>-blasted titanium implants. An experimental study on dogs. Clin Oral Implants Res 1992; 3: 77–84.
- Gotfredsen K, Wennerberg A, Johansson C, Skovgaard LT, Hjørting-Hansen E. Anchorage of TiO<sub>2</sub>-blasted, HA-coated, and machined implants: an experimental study with rabbits. *J Biomed Mater Res* 1995; 29: 1223–1231.
- Wennerberg A, Albrektsson T, Johansson C, Andersson B. Experimental study of turned and grit-blasted screw-shaped implants with special emphasis on effects of blasting material and surface topography. *Biomaterials* 1996; 17: 15–22.
- 83. Rasmusson L, Roos J, Bystedt H. A 10-year followup study of titanium dioxide-blasted implants. *Clin Implant Dent Relat Res* 2005; **7:** 36–42.
- Sul Y T, Johansson C B, Röser K, Albrektsson T.
   Qualitative and quantitative observations of bone
   tissue reactions to anodised implants. *Biomaterials* 2002; 23: 1809–1817.
- Ivanoff C J, Widmark G, Johansson C, Wennerberg A. Histologic evaluation of bone response to oxidized and turned titanium micro-implants in human jawbone. *Int J Oral Maxillofac Implants* 2003; 18: 341–348.
- Degidi M, Nardi D, Piattelli A. 10-year follow-up of immediately loaded implants with TiUnite porous anodized surface. Clin Implant Dent Relat Res 2012; 14: 828–838.
- Rocci A, Martignoni M, Gottlow J. Immediate loading of Brånemark System® TiUnite™ and machined-surface implants in the posterior mandible: a randomized open-ended clinical trial. Clin Implant Dent Relat Res 2003; 5(s1): 57-63.
- Ellingsen J E, Johansson C B, Wennerberg A, Holmén A. Improved retention and bone-to implant contact with fluoride-modified titanium implants. *Int J Oral Maxillofac Implants* 2004; 19: 659–666.
- Cooper L F, Zhou Y, Takebe J et al. Fluoride modification effects on osteoblast behaviour and bone formation at titanium oxide grit-blasted c.p. titanium endosseous implants. Biomaterials 2006; 27: 926–936.
- Lamolle S F, Monjo M, Rubert M, Haugen H J, Lyngstadaas S P, Ellingsen J E. The effect of hydrofluoric acid treatment of titanium surface on nanostructural and chemical changes and the growth of MC3T3-E1 cells. Biomaterials 2009; 30: 736-742.
- Schade R, Sikiri- M D, Lamolle S et al. Biomimetic organic – inorganic nanocomposite coatings for titanium implants in vitro and in vivo – biological testing. J Biomed Mater Res A 2010; 95: 691–700.
- Hallgren C, Reimers H, Chakarov D, Gold J, Wennerberg A. An in vivo study of bone response to implants topographically modified by laser micromachining. *Biomaterials* 2003; 24: 701–710.
- Guarnieri R, Placella R, Testarelli L, Iorio-Siciliano V, Grande M. Clinical, radiographic, and esthetic evaluation of Immediately loaded laser microtextured implants placed into fresh extraction sockets in the anterior maxilla: a 2-Year retrospective multicentric study. *Implant Dent* 2014; 23: 144–154.
- Vercaigne S, Wolke J G, Naert I, Jansen J A. Bone healing capacity of titanium plasma-sprayed and hydroxylapatite-coated oral implants. Clin Oral implants Res 1998; 9: 261–271.
- Josse S, Faucheux C, Soueidan A et al. Novel biomaterials for bisphosphonate delivery. Biomaterials 2005; 26: 2073–2080.
- 96. Kajiwara H, Yamaza T, Yoshinari M *et al.* The bisphosphonate pamidronate on the surface of titanium

- stimulates bone formation around tibial implants in rats. *Biomaterials* 2005; **26:** 581–587.
- 97. Goldstein J L, Brown M S. Regulation of the mevalonate pathway. *Nature* 1990; **343**: 425–430.
- Oxlund H, Andreassen T T. Simvastatin treatment partially prevents ovariectomy-induced bone loss while increasing cortical bone formation. *Bone* 2004; 34: 609–618.
- 99. Mundy G, Garrett R, Harris S *et al.* Stimulation of bone formation *in vitro* and in rodents by statins. *Science* 1999; **286:** 1946–1949.
- Ayukawa Y, Okamura A, Koyano K. Simvastatin promotes osteogenesis around titanium implants. Clin Oral Implants Research 2004; 15: 346–350.
- Du Z, Chen J, Yan F, Xiao Y. Effects of Simvastatin on bone healing around titanium implants in osteoporotic rats. Clin Oral Implants Res 2009; 20: 145–150.
- 102. Yang F, Zhao S F, Zhang F, He F M, Yang G L. Simvastatin-loaded porous implant surfaces stimulate preosteoblasts differentiation: an in vitro study. Oral Surg Oral Med Oral Path Oral Radiol Endod 2011; 111: 551-556.
- 103. Herr Y, Woo J, Kwon Y, Park J, Heo S, Chung J. Implant surface conditioning with tetracycline-HCI: a SEM study. Key Eng Mater 2008; 361: 849–852.
- 104. Petzold C, Monjo M, Rubert M et al. Effect of proline-rich synthetic peptide-coated titanium

- implants on bone healing in a rabbit model. *Int J Oral Maxillofac Implants* 2013; **28:** e547–555.
- 105. McKinney RV Jr, Koth D L. The single-crystal sapphire endosteal dental implant: material characteristics and 18-month experimental animal trials. *J Prosthet Dent* 1982; **47:** 69–84.
- 106. Koth D L, McKinney RV Jr, Steflik D E, Davis Q B. Clinical and statistical analyses of human clinical trials with the single crystal aluminum oxide endosteal dental implant: five-year results. J Prosthet Dent 1988; 60: 226–234.
- Kohal R J, Att W, Bächle M, Butz F. Ceramic abutments and ceramic oral implants. An update. Periodontology 2000; 2008: 47: 224–243.
- 108. Wenz H J, Bartsch J, Wolfart S, Kern M. Osseointegration and clinical success of zirconia dental implants: a systematic review. Int J Prosthodont 2008; 21: 27–36.
- 109. Özkurt Z, Kazazoglu E. Zirconia dental implants: a literature review. *J Oral Implantol* 2011; **37:** 367–76.
- 110. Andreiotelli M, Wenz H J, Kohal R J. Are ceramic implants a viable alternative to titanium implants? A systematic literature review. Clin Oral Implants Res 2009; 20(s4): 32–47.
- Depprich R, Naujoks C, Ommerborn M, Schwarz F, Kübler N R, Handschel J. Current findings regarding zirconia implants. Clin Implant Dent Relat Res 2014; 16: 124–137.

- 112. Price R L, Gutwein L G, Kaledin L, Tepper F, Webster T J. Osteoblast function on nanophase alumina materials: Influence of chemistry, phase, and topography. J Biomed Mater Res A 2003; 67: 1284–1293.
- Webster T J, Ergun C, Doremus R H, Siegel R W, Bizios R. Enhanced functions of osteoblasts on nanophase ceramics. *Biomaterials* 2000; 21: 1803–1810.
- 114. Bauer S, Kleber S, Schmuki P. TiO<sub>2</sub> nanotubes: Tailoring the geometry in H<sub>3</sub>O<sub>4</sub>HF electrolytes. Electrochem Commun 2006; 8: 1321–1325.
- 115. Park J, Bauer S, von der Mark K, Schmuki P. Nanosize and vitality: TiO<sub>2</sub> nanotube diameter directs cell fate. Nano Lett 2007; 7: 1686–1691.
- 116. Yao C, Balasundaram G, Webster T. Use of anodized titanium in drug delivery applications. *Mater Res Soc Symp Proc* 2007; 951: e12–28.
- 117. von Wilmowsky C, Schwarz S, Kerl J M et al. Reconstruction of a mandibular defect with autogenous, autoclaved bone grafts and tissue engineering: an in vivo pilot study. J Biomed Mater Res A 2010; 93: 1510–1518.
- 118. Esposito M, Murray-Curtis L, Grusovin M, Coulthard P, Worthington H. Interventions for replacing missing teeth: different types of dental implants. Cochrane Database Syst Rev. 2007; 17: CD003815. Update in: Cochrane Database Syst Rev 2014; 7: CD003815