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Review

# Advancing dental implant surface technology – From micron- to nanotopography

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ABSTRACT

Current trends in clinical dental implant therapy include use of endosseous dental implant surfaces embellished with nanoscale topographies. The goal of this review is to consider the role of nanoscale topographic modification of titanium substrates for the purpose of improving osseointegration. Nanotechnology offers engineers and biologists new ways of interacting with relevant biological processes. Moreover, nanotechnology has provided means of understanding and achieving cell specific functions. The various techniques that can impart nanoscale topographic features to titanium endosseous implants are described. Existing data supporting the role of nanotopography suggest that critical steps in osseointegration can be modulated by nanoscale modification of the implant surface. Important distinctions between nanoscale and micron-scale modification of the implant surface are presently considered. The advantages and disadvantages of nanoscale modification of the dental implant surface are discussed. Finally, available data concerning the current dental implant surfaces that utilize nanotopography in clinical dentistry are described. Nanoscale modification of titanium endosseous implant surfaces can alter cellular and tissue responses that may benefit osseointegration and dental implant therapy.



## 1. Introduction

Current dental implant success has evolved from modest results of the middle of the past century. Beginning in the late 1960s the focused efforts of PI Branemark led to the detailed microscopic characterization of interfacial bone formation at machined titanium endosseous implants [1,2]. These concepts of osseointegration focused the profession on a proscribed surgical technique and the biocompatible nature of the machined titanium surface. Bone formation at the endosseous implant surface was considered a positive outcome that was contrasted to fibrous encapsulation, a negative and undesired result [3]. The main clinical advantage of osseointegration was the predictable clinical result that occurred when an osseous interface was reproducibly formed and maintained at the titanium surface of load bearing dental implants [4].

Over two decades later, osseointegration is widely accepted in clinical dentistry as the basis for dental implant success. The low rate of implant failure in dense bone of the parasymphyseal mandible [5–8] has not been fully recapitulated by subsequent data from studies involving more challenging clinical situations [9,10]. Anecdotal reports of difficulty in achieving high rates of implant success in selected patient populations (e.g. smokers and diabetics) were supported by initial reports [11–13]. The cause of these failures, while not precisely determined, was largely attributed to a failure in bone formation in support of osseointegration. Challenging osseointegration with new protocols such as immediate placement and immediate loading may require further control of bone formation and osseointegration [9].

Failure to achieve osseointegration at a high rate can be attributed to one or more implant, local anatomic, local biologic, systemic or functional factors [5,8]. Clinical control of all of these factors is represented by multidisciplinary treatment planning procedures. While it is presently acknowledged that these, as well as clinician-related factors, are important determinants of endosseous implants success, a major interest in implant design factors is evident and clinical efforts to improve implant success have been focused on increasing the amount of bone that forms at the endosseous implant surface.

Implant surface character is one implant design factor affecting the rate and extent of osseointegration [14–18]. The process of osseointegration is now well described both histologically and at

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the cellular level. The adhesion of a fibrin blood clot and the population of the implant surface by blood-derived cells and mesenchymal stem cells is orchestrated in a manner that results in osteoid formation and its subsequent mineralization [19–21]. A seamless progression of changing cell populations and elaboration and modification of the tissue/implant interface eventually results in bone forming in direct contact with the implant surface. Precisely how much of the implant surface directly contacts bone, how rapidly this bone accrual occurs, and the mechanical nature of the bone/implant connection is influenced by the nature of the implant surface itself [22].

The character of the implant surface is implicated in this complex process of osseointegration in a number of different ways. Early investigations revealed the biocompatible nature of the cpTitanium implant [23], and revealed some pragmatic advantages for cpTitanium over other suitable materials [24]. Molecular investigations have contributed to defining cellular responses to titanium as "compatible" and advantageous. For example, Suska and colleagues [25] showed relatively low inflammatory signaling within cells in tissues adjacent to cpTitanium implants and suggested that this is a part of the osseointegration process. During the first 10–20 years of applied endosseous implant experience, the concept that cpTitanium implant biocompatibility supported clinical osseointegration success dominated clinical thinking. Subsequently, experiments with surface topography encouraged new considerations of improvements in bone formation at the implant surface.

## 2. Micron-scale surface topography

The significance of micron-scale topography was highlighted in an important report by Buser and colleagues [26] that compared various surface preparations of cpTitanium to an electropolished surface negative control and a hydroxyapatite coated positive control group. The observation that a micron-scale rough surface prepared by grit blasting and subsequent acid etching was capable of rapid and increased bone accrual reiterated an earlier report that a $TiO_2$ grit blasted surface also supported more rapid and increased bone accrual at cpTitanium implants [27]. These early observations indicated that the cpTitanium surface could be modified to enhance bone accrual and suggested that cpTitanium was not only "bioinert" or "biocompatible", but could influence cellular activity or tissue responses leading to greater osteogenesis.

At least three different lines of thinking have evolved to better interpret or explain how surface topography at the micron-scale can increase bone-to-implant contact. One is the biomechanical theory of Hansson and Norton [28], the second is the concept of contact osteogenesis [29], and the third is a surface signaling hypothesis supported by many cell culture investigations [14,30,31].

Hansson has elegantly described the theoretical interaction of bone with the implant surface and mathematically defined the role of surface roughness at the micron-scale within this hypothetical construct [28]. The result of the theoretical calculations – that an implant surface should be densely covered with pits of approximately 1.5 μm depth and 3–5 μm diameter – is supported by data collected in a series of studies on implant topography effects on bone-to-implant contact [32,33]. There is an appreciation that mechanical interlocking of bone is essential to the improved performance of endosseous implants. One possible explanation is given by the adaptation of bone to mechanical loading played by the osteocytes acting as mechanosensors [34,35]. Evidence of the important relevance of increased bone-to-implant contact has been provided by measurement of the physical interaction of micron-level rough implants with bone using push-out or torque removal assays [36,37]. What has not been fully elucidated is how mechanical signaling in the unmineralized tissue of forming bone and adjacent connective tissue is affected by the implant surface. The bonding of bone to the implant surface is not implicated as a mechanism of enhancing the early physical associations of the implant with bone.

A principal role for fibrin clot stabilization by the implant surface exemplifies one role that microscale surface roughness may play in improved osseointegration [38]. Described is a physical interlocking of fibrin fibers with the surface features which promotes the directed ongrowth of bone forming cells directly at the implant/bone interface. Topographic enhancement may aid in stabilization of fragile extracellular matrix scaffolds for conduction of cells toward and onto the implant surface (contact guidance) [39].

Several investigators have further described surface topography-specific effects on titanium-adherent osteoblastic cell behavior [40–43]. The overriding theme of these investigations is that surface adhesion-mediated control of cell function underscores the positive influences on bone formation. Many investigations have contributed to the understanding that there is a range of micron-level surface topography that enhances the adherent osteoblasts' differentiation and extracellular matrix formation/mineralization [44]. Together these investigations have shown that increased surface topography effectively enhances extracellular matrix synthesis of adherent cells and provides a faster and more reliable osseointegration response [43,45–57].

A clearly defined role for extracellular matrix proteins-receptors (integrin) has been proposed to transduce topography-specific signals to the adherent cells [40]. One possible way that topography may alter cellular differentiation is through imposed changes in cell shape [58]. Micron-level topography effects on increased bone-to-implant contact are observed in vivo [26,59], and in human clinical histology [60]. Limited evidence that integrins are involved in cellular responses to implant surfaces has been obtained using MG63 cell culture studies [61].

Micron-scale topographic modification of the cpTitanium surface is accepted in the endosseous dental implant marketplace [32,33]. The belief that micron-level surface topography results in greater accrual of bone at the implant surface is supported by some clinical evidence [62,63]. Yet, these surfaces have been generally interpreted to be biocompatible devices with limited ability to directly affect the initial fate of surrounding tissues (e.g. impose bone formation or prevent bone resorption).

Today, a growing aspect of endosseous implant surface research is focused on further enhancing the activity of bone forming cells at the tissue implant interface. This desire for "bioactivity" has been addressed using a variety of different approaches. Clearly, cpTitanium surfaces can be modified to direct specific cellular responses such as osteogenesis. More specifically, cpTitanium implant surfaces can be made to direct the osteoinduction of adherent progenitor cells. While one approach is the immobilization of bioactive peptides or growth factors and notably the BMPs [64,65], other approaches have embraced the use of nanoscale surface engineering to induce intrinsic osteoinductive signaling of the surface adherent cells. The purpose of this review is to explore how nanotechnology applications to the cpTitanium implant surface may provide new opportunities to create endosseous implant surfaces with greater specific control of adherent cell and adjacent tissue fate.

## 3. Nanotechnology and surface science

Nanotechnology has been defined as "the creation of functional materials, devices and systems through control of matter on the nanometer length scale (1–100 nm), and exploitation of novel phenomena and properties (physical, chemical, and biological) at that length scale" (National Aeronautics and Space Administration). Nanotechnology involves materials that have a nano-sized

topography or are composed of nano-sized materials. These materials have a size range between 1 and 100 nm ($10^{-9}$ m) (Fig. 1). Nanotechnology often involves one-dimensional concepts (nanodots and nanowires) or the self-assembly of more complex structures (nanotubes). Materials are also classified according to their form and structure as nanostructures, nanocrystals, nanocoatings, nanoparticles, and nanofibers [66].

Application of nanotechnology to the dental implant surface involves a two dimensional association of surface features (across and away from the mean surface plane) (Fig. 2). These nanofeatures can be arranged in an organized manner (isotropic) or unorganized manner (anisotropic), often depending on the method of manufacture. Of the surface topographies that have been applied to a dental implant surface, the topography is often characteristically anisotropic. Isotropic features such as nanogrooves or nanopits that are created largely by optical methods are not readily applied to complex screw shaped objects. When these concepts are applied to the endosseous implant surface, implied is the embellishment of the surface with nanometer-scale features that lead to novel physicochemical behavior (e.g. bone bonding) or biochemical events (e.g. altered protein adsorption, cell adhesion with changes in cell behavior).

Nanoscale modification of the titanium endosseous implant surface may affect both the topography as well as the chemistry of the surface. Specific chemical modification of cpTitanium could be the targeted goal of nanoscale modification. In fact, a complicating feature of nanoscale manipulation of any material is that there are inherent chemical changes of the bulk material surface. Albrektsson and Wennerberg [32] divided implant surface quality into three categories: (1) mechanical properties, (2) topographic properties, and (3) physicochemical properties. They indicated that these characteristics are related and by changing any of these groups the others will also be affected. This important observation is likely to be even more relevant to the discussions of nanotopographic modifications of the endosseous cpTitanium surface. One frequently encountered limitation to studies comparing nano- and micron-level surface topography is that it can be extremely difficult to isolate chemistry or charge effects induced by the nanotopography. When atomic level control of material assembly is approached, the surface properties are influenced by quantum phenomena that do not govern traditional bulk material behavior [67]. It is very difficult but important to distinguish distinct topography-specific effects from allied changes in surface energy or chemical reactivity.

Nanotechnology requires novel ways of manipulating matter in the atomic scale. Several approaches are currently prevalent in the experimental application to endosseous implants (Table 1). One approach involves the physical method of compaction of nanoparticles of $TiO_2$ vs micron-level particles to yield surfaces with nanoscale grain boundaries [54]. An advantage of this method is

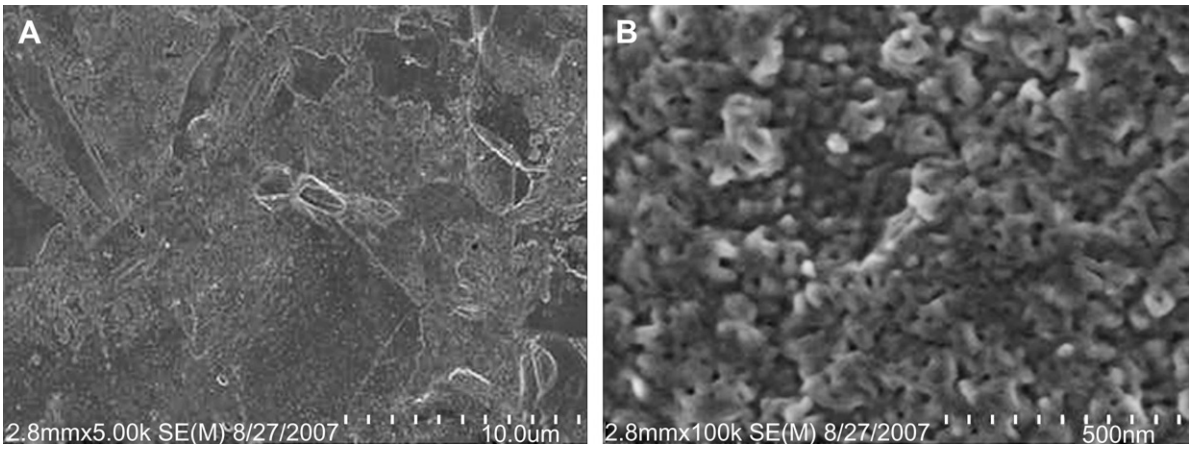


**Fig. 1.** Nanoscale in perspective. The scanning electron micrograph at 5000× (A) fails to represent true nanoscale features of a titanium implant surface. 100,000× image (D) shows the complex nanoscale surface; here produced by titania sol–gel deposition.

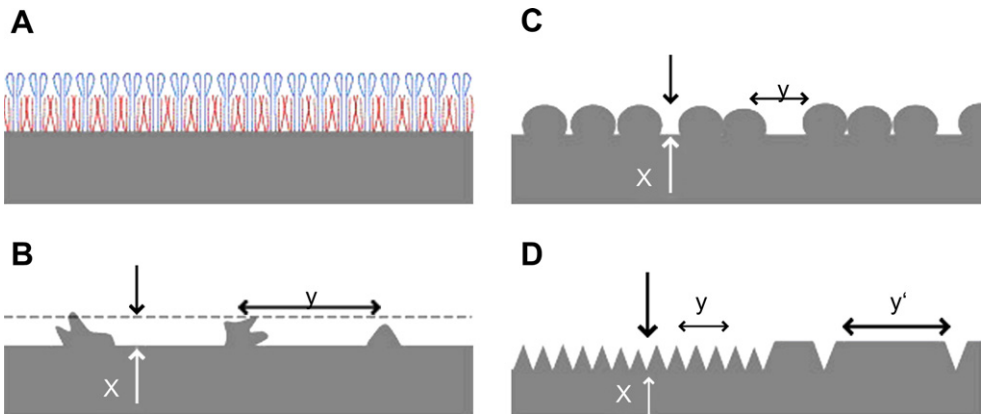


**Fig. 2.** Nanoscale surface modification. (A) Self-assembled monolayers (SAMs) can change the topography and chemistry of a surface to impart novel physical and/or biochemical properties. (B) Deposition or chemical modification techniques can apply nanoscale features ($x \leq 100$ nm) in a manner that are distributed in micron-scale ($y > 100$ nm). (C) Other deposition or compaction methods can place nanoscale features in nanoscale distribution. The cell response to surfaces represented by (B) or (C) may be different. (D) Isotropic surfaces can be created in the nanoscale ($x \leq 100$ nm) by subtractive or additive methods. The distribution can be in either the nano- ($y$) or micron-scale ($y'$). It is thought that some nanosurfaces mimic natural cell environments.

**Table 1**
Methods for creating nanofeatures on cpTitanium implants

| Methods | Characteristics |
|---|---|
| *Self-assembly of monolayers* | |
| | The exposed functional end group could be a molecule with different functions (an osteoinductive or cell adhesive molecule). |
| *Physical approaches* | |
| Compaction of nanoparticles | Conserves the chemistry of the surface among different topographies. Not readily applied over implant surfaces. |
| Ion beam deposition | Can impart nanofeatures to the surface based on the material used. |
| *Chemical methods* | |
| Acid etching | Combined with other methods (sandblasting and/or peroxidation) can impart nanofeatures to the surface and remove contaminants. |
| Peroxidation | Produces a titania gel layer. Both chemical and topography changes are imparted. |
| Alkali treatment (NaOH) | Produces a sodium titanate gel layer allowing hydroxyapatite deposition. Both chemical and topography changes are imparted. |
| Anodization | Can impart nanofeatures to the surface creating a new oxide layer (based on the material used). |
| *Nanoparticle deposition* | |
| Sol–gel (colloidal particle adsorption) | Creates a thin-film of controlled chemical characteristics. Atomic-scale interactions display strong physical interactions. |
| Discrete crystalline deposition | Superimposes a nanoscale surface topographical complexity on the surface. |
| *Lithography and contact printing technique* | Many different shapes and materials can be applied over the surface. Approaches are labor intensive and require considerable development prior to clinical translation and application on implant surface. |

that it conserves the chemistry of the surface among different topographies.

Second is the process of molecular self-assembly. Self-assembled monolayers (SAMs) are formed by the spontaneous chemisorption and vertical close-packed positioning of molecules onto some specific substrata, exposing only the end-chain group(s) at the interface [68]. The exposed functional end group could be an osteoinductive or cell adhesive molecule. An example of this is the use of cell adhesive peptide domains (RGD domains) appended to SAMs composed of polyethylene glycol (PEG) and applied to the titanium implant surfaces [69].

A third method is the chemical treatment of different surfaces to expose reactive groups on the material surface and create nanoscale topography. This is popular among current dental implant investigators. NaOH treatment catalyzes the production of titanium nanostructures outward from the titanium surface [70]. Treatment with a NaOH solution produces a sodium titanate gel layer on the Ti surface while $H_2O_2$ produces a titania gel layer. The NaOH treatment creates a gel-like layer over the material allowing hydroxyapatite deposition. This behavior has also been seen with other metals such as zirconium and aluminum [71–73]. Titanium oxide nanotubes chemically treated with NaOH accelerated HA crystal growth in a simulated body fluid (SBF) [48]. The kinetics of HA formation is significantly accelerated by the presence of the nanostructure associated to the NaOH treatment. Both chemical and topography changes are imparted.

Chemical treatments (peroxidation ($H_2O_2$) or acid oxidation, such as hydrofluoric acid) have also been used to create nanotopography [15,72,73]. The use of $H_2O_2$ with acid etching has been shown to create novel nanostructures of amorphous titanium oxide on the implant surface [74]. It was found that the treatment of the implant surface with $H_2O_2$/HCl increased the adsorption of RGD peptides onto the surface followed by passivated surfaces (30% $HNO_3$) and heat-treated surfaces [75]. These surface treatments also increased the mineralization in the same order. Treatment with hydrofluoric acid also creates discrete nanostructures on $TiO_2$ grit blasted surfaces [76]. Several cell culture studies [41,77,78], preclinical investigations [46,79], and clinical studies [18] support the observation that hydrofluoric acid treatment of $TiO_2$ grit blasted titanium implants is associated with rapid bone accrual at the implant surface. Complex chemical changes induced by these methods may require careful inspection.

The deposition of nanoparticles onto the titanium surface represents a fourth approach to imparting nanofeatures to a titanium dental implant [80]. Sol–gel transformation techniques achieve deposition of nanometer-scale calcium phosphate accretions to the implant surface [81,82]. Alumina, titania, zirconia and other materials can also be applied [83]. Owing to their resultant atomic-scale interactions, the accretions display strong physical interactions [80,84–86]. In a modified approach, Nishimura and colleagues [87] recently demonstrated a directed approach to assembly of $CaPO_4$ nanofeatures on dual acid-etched cpTitanium implant surfaces. The deposition of discrete 20–40 nm nanoparticles on an acid-etched titanium surface led to increased mechanical interlocking with bone and the early healing of bone at the endosseous implant surface in a rat model.

One of the main concerns related to coating the implant surface is the risk of coating detachment and toxicity of related debris. This question was addressed by Gutwein and Webster [47] who evaluated the relationship of particle size and cell viability and proliferation compared to micron-particles. Nanoparticles of titania and alumina had less negative impact in cell viability and proliferation. There may be an advantage to nanoscale modification of surfaces using sol–gel coating methods. The quantum interaction of high electron density at the atomic level can enforce high bond strength between the substrate and nanoscale coating. Examples of this have been reported for the calcium phosphate (CaP)/discrete crystalline deposition (DCD) sol–gel coating of Ti alloy implant surfaces [88].

A fifth approach to creating nanoscale topography on Titanium is the use of optical methods (typically lithography) reliant on wavelength specific dimensions to achieve the appropriate

nanoscale modification [70]. These approaches are labor intensive methods that require considerable development prior to clinical translation. The present use of lasers to promote micron-level groove on an implant surface can produce micron-level, not nanoscale, modification of the implant surface [89]. Another method of depositing nanoscale material on to the implant surface involves ion beam deposition (e.g. hydroxyapatite) [90]. All are relevant to the endosseous dental implant surface and experimental examples of each can be identified (below).

Nanotopography has been shown to influence cell adhesion, proliferation, differentiation and cell specific adhesion. Related changes in chemistry and nanostructure impart important chemical changes and permit biomimetic relationships between alloplastic surfaces and tissues. It is speculated that alloplastic nanosurfaces possess topographic elements scaled to naturally occurring substrates.

## 4. Biomimetics and nanotechnology

The recapitulation of natural cellular environments can be achieved at the nanoscale. Nanoscale modification of an implant surface could contribute to the mimicry of cellular environments to favor the process of rapid bone accrual. For example, cell adhesion to basement membranes is an often cited example of nanoscale biomimetics. The structure of the epithelial basement membrane contains pores approximating 70–100 nm [91]. It is suggested that the surface roughness of bone is approximately 32 nm making it within the nanoscale range of current nanotechnology investigations [92–95]. These in vivo examples further exemplify an anisotropic arrangement of nanofeatures. Intentionally placing molecular structures at such resolution on an endosseous implant may be achieved with anisotropic arrangements. The result may be changes in physical properties including enhanced magnetic, catalytic, optical, electrical, mechanical, and biological properties when compared to conventional formulations of the same material [96].

## 5. Nanotopography alters cellular responses

Surface nanotopography appears to affect cell interactions at surfaces and alter cell behavior when compared to conventional sized topography (Fig. 3) [97–99]. Different physical relationships exist between cells and nano- vs cell and micron-scale surface features. Nanotopography specific effects on cellular behavior have been demonstrated using a wide range of different cell types including epithelial cells, fibroblasts, myocytes and osteoblasts. Nanostructured surfaces possess unique properties that alter cell adhesion by direct (cell–surface interactions) and indirect (affecting protein–surface interactions) mechanisms. Evidence has been gathered using several models and surface systems (Tables 2 and 3).

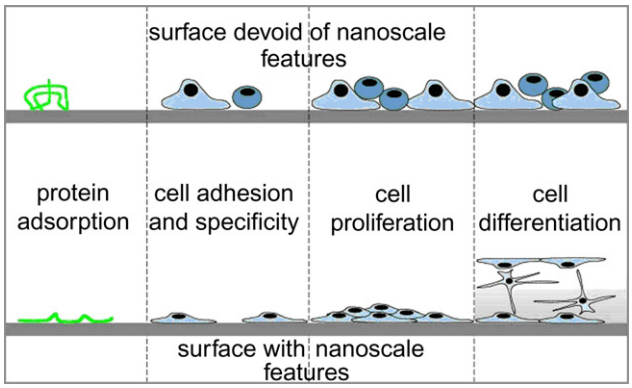


**Fig. 3.** Depiction of broad range of nanoscale topography effects observed in cellular protein adsorption is altered by nanoscale modification of bulk material. Both cell specificity and extent of cell adhesion are altered. Depending on the nano-architecture cell spreading may be increased or decreased. By presently undefined mechanisms, cell proliferation appears to be enhanced by nanoscale topography. For osteoblast, several investigators have shown nanoscale topography enhances osteoblast differentiation.

### 5.1. Protein/surface interactions – surface wettability

The changes in initial protein–surface interaction are believed to control osteoblast adhesion [108]. This is a critical aspect of the osseointegration process. When implants come into contact with a biological environment, protein adsorption (e.g. plasma fibronectin) that occurs immediately will mediate subsequent cell attachment and proliferation. Cell binding to protein domains of adhesive extracellular matrix proteins involves receptors termed integrin receptors that transmit signals through a collection of proteins on the cytoplasmic face of the contact, termed focal contacts [130]. Surface effects are often mediated through integrins that bind the RGD motif in cell attachment proteins [131]. The RGD motif of cell adhesive proteins such as fibronectin or vitronectin is important in mediating cell adhesion of osteoblasts and other cells to synthetic material surfaces [132]. Nanofeatures could alter the conformation of these RGD containing proteins, a phenomenon known to affect cell adhesion and behavior [133].

Changing the surface energy or wettability of a biomaterial represents a classical approach to altering cell interactions with the surface. Extracellular matrix protein adsorption onto surfaces (to subsequently modulate cell adhesion) is dramatically affected by surface energy. Interestingly, many studies of self-assembled monolayers (SAMs) have demonstrated that hydrophobic groups are more likely to adsorb albumin and that albumin is not replaced by ECM proteins, blocking cell adhesion. Hydrophobic surfaces adsorbed fibrinogen [134], while hydrophilic surfaces allowed an interchange of adsorbed albumin by ECM proteins [135].

Nanoscale topography is a powerful way of altering protein interactions with a surface. Webster and colleagues [53,109] observed an increased vitronectin adsorption on nanostructured surfaces when compared to conventional surfaces. They also found an increased osteoblast adhesion when compared to other cell types, such as fibroblasts, on the nanosurfaces [109]. Another study suggested higher adsorption of fibronectin on hydrophilic SAMs surfaces with greater focal adhesion formation (integrin binding) evident in the osteoblast cells adhered to the hydrophilic SAM treated surfaces [68]. Lim and colleagues [93] more directly related protein adsorption, cell adhesion and the active process of attachment by measurement of increased focal adhesion kinase (FAK) activity. In a study using SAMs biofunctionalized with RGD, Cavalcanti-Adam and colleagues [133] also found that the spacing among the nanofeatures modulates focal adhesion (FA) formation; cells cultured on a 58 nm nanopattern formed normal FA, whereas those plated on a 108 nm nanopattern failed to develop FA. Surface roughness at the nanoscale is an important determinant of protein interactions that ultimately direct cell activity in control of tissue formation at implant surfaces [136].

### 5.2. Cell adhesion, spreading and motility

Irrespective of the surface-adsorbed proteins, cells are remarkable in their ability to sense nanostructure (Fig. 4). Nanofeatures of a surface affect both cell adhesion and cell motility. Both of these cell traits are attributed, in part, to the function of integrins. Underlying substratum topography influences cell behaviors by both direct and indirect interactions [137]. Indirect interactions are enacted by the interposed adherent proteins described above. Direct interactions involving the integrin receptors with the surface

**Table 2**
Reported osteoblast responses to nanosurfaces – in vitro

| Size/nanofeature | Cell response | Material/fabrication | Cell culture model | Ref. |
|---|---|---|---|---|
| 14, 29, 45 nm nanopits | Change in signaling | Poly(L-lactic acid) and polystyrene (50/50 w/w)/polymer demixing | hFOB | [94] |
| Ion beam coating thickness ~60 nm SG coating thickness of 70 nm | Change in signaling | $Ti_6Al_4V$/ion beam implantation of Zn or Mg or SG coating with HA | Human bone-derived cells | [100] |
| 12 nn ridges/0.2–2 mm separation | Changes in cell cytoskeleton | Ti/PLD | Osteoblast – rat calvaria | [101] |
| Pits with 120 nm ∅, spacing of 300 nm in orthogonal or hexagonal arrangement | Changes in cell cytoskeleton | PMMA/EBL in silica | hMSCs | [102] |
| Pits with 120 nm ∅. The pitch between the pits was 300 nm. Hexagonal and square pit arrangements | Changes in cell cytoskeleton – restriction of spreading – filopodia | PMMA/EBL in poly(carbonate) | hMSCs | [103] |
| Alumina (23-nm average ∅), titania (32-nm average ∅) | Decreased apoptosis | Particles diluted in growth media at concentrations of 10,000, 1000, and 100 mg/ml as well as 10,000, 5500, and 1000 mg/ml | Human osteoblasts | [47] |
| RMS roughness values from 0.5 to 13 nm | Decreased proliferation | Gradients of polymer crystallinity were fabricated on films of poly(L-lactic acid)/gradient in annealing temperature. | Osteoblast – MC3T3-E1 | [104] |
| 0.5–2.4 μm – Ti<br>0.5–1.4 μm – $Ti_6A1_4V$<br>0.2–0.4 μm – $Co_{28}Cr_6Mo$ | Increased adhesion | Ti, $Ti_6Al_4V$, and CoCrMo alloys/compaction | Human osteoblasts | [54] |
| 7–40 nm | Increased adhesion | Nobium oxidation of cpTi/sol–gel coating | Osteoblast – MC3T3-E1 | [105] |
| HA, Ti-coated HA annealed in air, and Ti-coated HA annealed in $N_2 + H_2$ possessed Sq of 5, 32, and 28 nm, respectively | Increased adhesion | HA/compaction/Ti coating ($CaTiO_3$) | Human osteoblasts | [106] |
| Nanograined/not shown | Increased adhesion | HA, TCP, or $CaTiO_3$/compaction | Human osteoblasts | [107] |
| nm HA and HA functionalized with RGD | Increased adhesion | Sintering | Human osteoblasts | [108] |
| Alumina (23-nm ∅ diameter), titania (32-nm ∅ diameter) | Increased adhesion | Titania or alumina powders/compaction | Osteoblasts from neonatal rat calvaria | [53] |
| Alumina (24 and 45 nm average ∅), titania (39 and 97 nm average ∅) and HA (67-nm) powders | Increased adhesion | Titania, alumina or HA powders/compaction | Osteoblasts from neonatal rat calvaria<br>Fibroblasts | [109] |
| Nanotubes of 3.4 ± 0.3 nm | Increased adhesion | cpTi coated with helical rosette nanotubes featuring lysine side chains (HRN-K1) | Human fetal osteoblast | [110] |
| Self-assembled nanowires 50–100 wide | Increased adhesion | Ti mesh/NaOH treatment | MSCs and mice | [111] |
| Alumina nanofibers with 2 nm in ∅ and ~50 nm in length alumina nanospherical grain size (<100 nm) powder | Increased adhesion – Ca deposition | Alumina grain or nanofibers/compaction | Human osteoblasts | [49] |
| 5–50 nm pores | Increased adhesion – Ca deposition | $Ti_6Al_4$ V/$H_2SO_4$/$H_2O_2$ 70/30% followed by coating of $TiO_2$ | Osteoblast – MC3T3-E1 | [112] |
| Nanophase titania (32-nm average ∅) powders | Increased adhesion – Ca deposition | PLGA mixed with titania (in various proportions)/cured in air | Human osteoblasts | [113] |
| 11–85 nm | Increased adhesion – differentiation | Polystyrene–polybromostyrene/polymer demixing | hFOB | [93] |
| | Increased adhesion – differentiation – Ca deposition | Nanophase titania/(PLGA) composites | Human osteoblasts | [67] |
| ~100 nm/nanotubes | Increased Adhesion – Proliferation – Differentiation | titania/anodization | primary rat bone marrow MSCs | [114] |
| ~100 nm/nanopores | Increased adhesion – proliferation – differentiation – Ca deposition | Alumina sheets/anodization | Primary murine bone marrow MSCs | [115] |
| ~100 nm features on Ti | Increased differentiation | cpTi/$TiO_2$ blasting/HF treatment | Osteoblast – MC3T3-E1 and Ratus novergicus | [78] |
| 100–200 nm difference among groups | Increased differentiation | PMMA/Colloidal lithography and polymer demixing | Primary human osteoprogenitors | [116] |

(*continued on next page*)

**Table 2** (*continued*)

| Size/nanofeature | Cell response | Material/fabrication | Cell culture model | Ref. |
|---|---|---|---|---|
| 20–50 nm surface features | Increased differentiation | cpTi and $Ti_6Al_4V$/oxidation with $H_2SO_4/H_2O_2$ | Primary rat calvaria derived osteoblasts | [117] |
| Elongated HA nanocrystals, with a mean length of about 100 nm | Increased differentiation | $Ti_{13}Nb_{13}Zr$/mechanomaking process or $Ti_6Al_4V$ followed by $HF/HNO_3$ acid etch CaP coating | hMSCs | [118] |
| Parallel ridges/channels (microstructured)/ nanostructured HA (100 nm). | Increased differentiation | Photolithography/nanostructured HAP (biomimetic) on silicon microstructures | Saos-2 and MG63 cell lines | [119] |
| Alumina nanofibers with 2 nm in ∅ and ~50 nm in length | Increased differentiation – Ca deposition | Alumina nanofibers/compaction/Sintered at 400, 600, 800, 1000, or 1200 °C | Human osteoblast | [56] |
| 20–50 nm surface features | Increased differentiation – Ca deposition | cpTi/oxidation with $H_2SO_4/H_2O_2$ | Primary rat calvaria derived osteoblasts | [120] |
| Alumina (24-nm average ∅), titania (39-nm average ∅) and HA (67-nm) powders | Increased differentiation – Ca deposition | Titania, alumina or HA powders/compaction | Osteoblasts from neonatal rat calvaria | [52] |
| Island height of about 90 nm | Increased filopodia | Polystyrene and polybromostyrene/ polymer demixing | Human bone marrow cells | [121] |
| Nanofibers (60–100 nm) | Increased osteoblast specificity | Carbon nanofibers/compaction | Human osteoblasts | [50,122] |
| Alumina (23-nm average ∅), titania (49-nm average ∅) and HA (67-nm) powders | Increased osteoblast specificity | Poly(L-lactic) acid or PMMA powder mixed with titania, alumina or HA (in various proportions)/compaction | Neonatal rat calvaria osteoblasts Rat skin fibroblasts | [123] |
| Nanophase titania (32-nm average ∅) powders | Increased osteoblast specificity | PLGA mixed with titania (in various proportions)/cured in air | Human osteoblasts | [124] |
| ~160 nm pores | Increased proliferation | Alumina/EBE | Human osteoblasts | [125] |
| AAT texture showed micropores and an overlapped nanometric net of filaments | Increased proliferation | cpTi/alkali etching process with CaP solution (biomimetic) | Osteoblast-like MG63 | [126] |

cpTi – commercially pure titanium, PLGA – poly(lactic-*co*-glycolic) acid, EBL – electron beam lithography, EBE – electron beam evaporation, HF – hydrofluoric acid treatment, PLD – pulsed laser deposition, PMMA – polymethyl methacrylate, SG – sol–gel, and Ti – titanium.

may also transmit signals to control adhesion, spreading and motility.

Nanofeatures of an alloplastic surface may have unique attributes affecting cell interactions. Both the dimension and the density of the nanofeatures affect cell behavior [133]. In a well controlled investigation of titanium nanostructure, Andersson and colleagues [138] compared cell morphology and cytokine production on titanium substrates with 15 mm wide and 185 nm deep grooves vs Ti substrates with 100 nm high, 168 nm diameter hemispherical nanopillars. The cells appeared partially aligned to the grooves and had a cytokine release similar to that found from cells on flat surfaces. Cells on hemispherical pillars had a smaller area and had more membrane projections compared to cells. Morphological changes correlated with diminished protein secretion. It has been suggested that 70–100 nm features of an implant surface are scaled to function directly with the focal adhesion of cells.

**Table 3**
Reported osteoblast responses to nanosurfaces – in vivo

| Size/nanofeature | Tissue response | Material/fabrication | Animal/cell culture model | Ref. |
|---|---|---|---|---|
| 3 μm CaP coating | Elimination of tissue fibrous encapsulation and foreign body giant cell response | PLGA/CaP coated with CaP | Ratus novergicus | [127] |
| 8 nm diameter and 100 nm length | Enhanced bone formation | PLGA mixed with Ti nanotubes | Ratus novergicus | [128] |
| AAT texture showed micropores and an overlapped nanometric net of filaments | Increased bone-to-implant contact | cpTi/alkali etching process with CaP solution (biomimetic) | Sheep | [126] |
| Not shown | Increased bone-to-implant contact | cpTi/HA – ion beam assisted deposition (IBAD) | Rabbit | [129] |
| ~100 nm features on Ti | Increased bone-to-implant contact | cpTi/$TiO_2$ blasting/HF treatment | Dog | [79] |
| ~100 nm features on Ti | Increased differentiation | cpTi/$TiO_2$ blasting/HF treatment | Ratus novergicus | [78] |
| Not shown | Increased osseoactivity | cpTi/HA – ion beam assisted deposition (IBAD) | Dog | [90] |
| Discrete deposition of HA nanoparticles (20–40 nm) on Ti substrate | Increased push-out test resistance | cpTi/dual acid etch/coated with CaP by DCD | Ratus novergicus | [87] |
| Not shown | Increased removal torque – bone-to-implant contact – bone volume | cpTi/Sandblast/HA – ion beam assisted deposition (IBAD) | Rabbit | [96] |
| 20–100 nm range of the features (HA) | Increased tensile test resistance | cpTi and $Ti_6Al_4V$/acid etch/coated with CaP by DCD | Ratus novergicus | [88] |

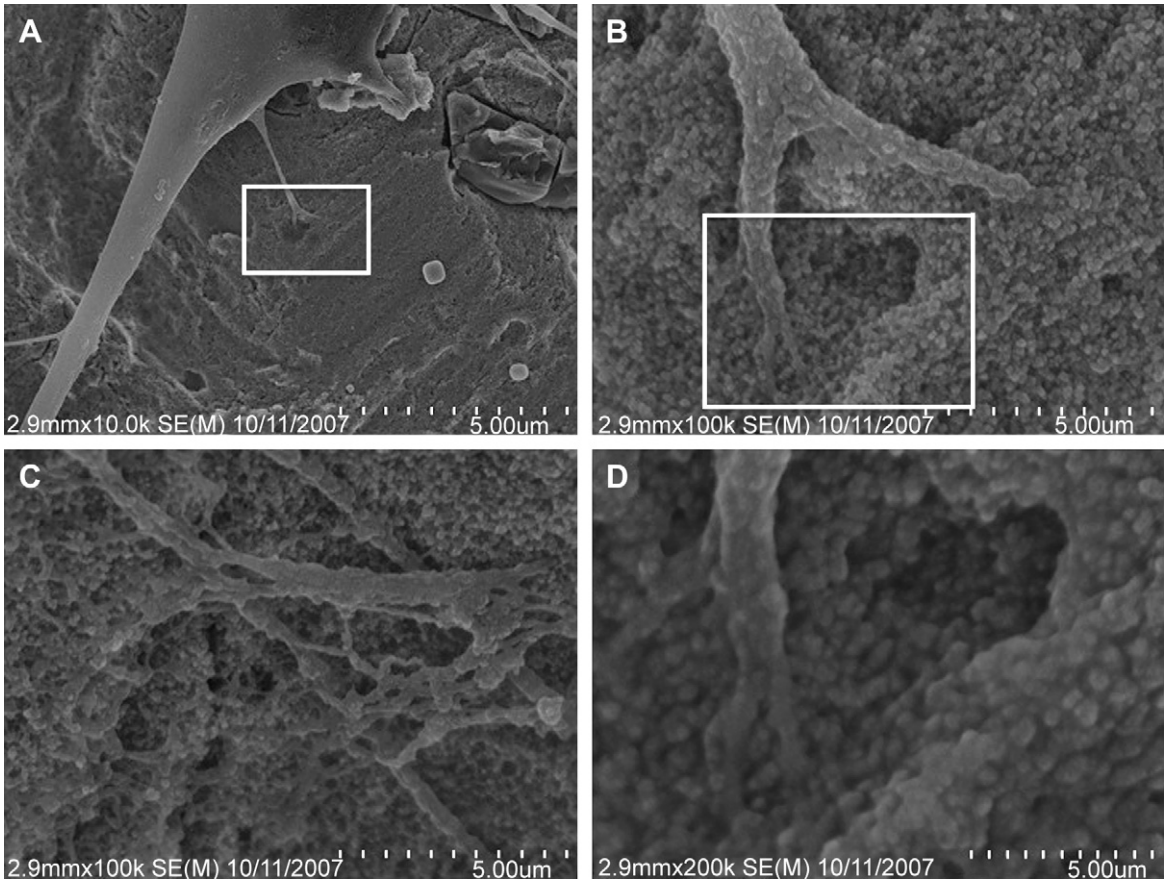


**Fig. 4.** Nanoscale topography-cell interactions. There is apparent affinity of cells for nanoscale features. Here, 20–40 nm features produced by $H_2O_2/H_2SO_4$ treatment are interactive points for lamellipodia of spreading cells. The cause and effect relationship is a current point of investigation. (A) 10,000× image of adherent cell, (B) and (C) represent 100,000× images of the same adherent cell and (D) 200,000× magnification of the cell with nanofeatures. (B) higher magnification of the rectangle in (A). (D) higher magnification of the rectangle in (B).

Cells respond differently to the scale of roughness. Osteoprogenitor cell adhesion was enhanced on poly-L-lactide (PLLA) and polystyrene (PS) surface with nanoscale and micron-scale roughness compared to smooth surfaces. OCT-1 osteoblast-like cells grew along the surface with two different nanoscale surfaces (PLLA) and grew inside micron-scale pits of PS [139]. Similar conclusions were made when comparing nano- and micron-scale grain boundary effects on osteoblast cell adhesion and proliferation [54]. Some greater details of the relationship between surface nanofeatures and cell adhesion are emerging. Teixeira and colleagues [140] demonstrated that when cells bridge submicron-scale patterns, integrin binding was limited to substrate-adsorbed proteins on the top of the ridges. Geometrical constraints imposed by topographic features smaller than focal adhesion architecture (approximately 300 nm) actually confine the cell attachment apparatus to the top of the topographic feature. Therefore, on the nanoscale patterns, integrin occupancy within a focal adhesion may be spatially segregated whereas on microscale ridges there are no constraints on integrin–ligand binding. While the current understanding of nanotopography effects on adherent osteoblast behavior requires further clarification, nanotopography may work at a linear scale that facilitates the mechanotransduction signaling mechanisms of the adherent osteoblast.

Several investigations demonstrate that cell spreading is restricted on nanoscale surfaces. For example, Dalby and co-workers [116] investigated primary human osteoblast cell behavior on nanopitted surfaces. High pit density reduced cell spreading and ordered arrays of nanopits were effective in this regard. Randomization of the pits led to more cell spreading.

Nanotopography presents an opportunity to modulate cell adhesion and spreading both positively and negatively. When Lim and co-workers [93] compared osteoblast adhesion on PLLA substrates with 3–45 nm nanofeatures they demonstrated that cell adhesion was positively affected by nanotopography and interdependent on substratum surface characteristics of topography and surface chemistry. Lim and colleagues [94] further demonstrated that 14–29 nm pits favorably supported adherent cell integrin signaling when compared to 45 nm pits. In contrast, Cai and co-workers [141] found no major differences in fibronectin adsorption or cell proliferation on 2 vs 20 nm titanium films. There may be cell-type specific responses to nanofeatures of a given surface.

Teixeira and colleagues [142] have also shown that, depending on cell culture conditions, corneal cell integrins aligned either parallel to or perpendicular with the isotropic nanofeatures. Cellular responses to nanoscale and submicron-topographic cues are context dependent. Given the relatively anisotropic nature of natural cellular substrates, the significance of such findings remains to be defined. Nonetheless, these and other studies show that cell adhesion through integrins is sensitive to nanoscale features.

Cells adherent to nanotopographies may possess altered motility. Recent reports demonstrated that fibroblast and MSCs motility varied remarkably across a small range of nanostructures [143,144]. Hansen and colleagues [92] cultured MC3T3-E1 osteoblastic cells on nanotopographic surfaces (11–38 nm high islands). Using atomic force microscopy (AFM), they measured relatively higher cellular modulus values for cells on surfaces with nanofeatures compared with cells on flat control surfaces. They concluded that nanoscale topography affects the actual mechanical

properties of the individual cell. This may be attributed to the resultant integrin-based remodeling of the cytoskeleton or more complex biophysical changes in the cell membrane. The ability to control cell motility or spreading may be valuable in future engineering of the implant–bone–mucosa interface or the mucosa–epithelial interface at the dental implant abutment.

### 5.3. Proliferation

Apparently, nanoscale features can increase adherent cell proliferation. Zhao and co-workers [145] used three different approaches (electrochemical machining, anodization and chemical etching) to produce reproducible submicron-scale structures on Ti surfaces and observed an inverse relationship between cell proliferation and cell differentiation with the diminishing scale of surface features. Webster and colleagues [52] also observed increased osteoblast proliferation on the nanoscale (alumina, titania and hydroxyapatite) materials tested.

It is not fully understood how nanostructured surfaces modulate the adherent osteoblast response. At the simplest of levels, the proliferation rate of adherent cells has been measured as an index of cytocompatibility. Suggested is the concept that surface-to-cell signaling results in increased rate of proliferation. The mechanism(s) affecting this process is not defined, however, it can be speculated that many of the events associated with adhesion can affect signaling pathways that control proliferation. One example is the cross-talk between integrin signaling and the predominant MAP kinase pathways affecting cell proliferation [146].

### 5.4. Selectivity of adhesion

An interesting feature of nanoscale topographic surfaces is the selectivity of cell adhesion. Several investigators have demonstrated the relative diminution of fibroblast adhesion compared to osteoblast adhesion when nano- and micron-structured surfaces were evaluated [49,123]. For example, on nano-sized materials, the affinity ratio between osteoblasts and fibroblasts was 3 to 1. In the conventional materials the ratio was 1 to 1 [109]. Similar results with other cell types such as smooth muscle cells and chondrocytes have been reported [122]. This could have important implications in specification of tissue responses at bone and mucosal surfaces of the dental implant/abutment assembly.

Bacterial adhesion and proliferation is also diminished on nanophase materials [147]. Decreased bacterial colonization on nanostructured $TiO_2$ and ZnO is observed even though these surfaces promote osteoblast adhesion and differentiation. These initial observations imply that further development of the implant and the implant abutment surface can be explored in terms of biofilm accumulation and peri-implantitis.

The function of other cells types on nanostructured surfaces has also been addressed by Webster and co-workers [53]. They measured on nanoscale surface an increase in osteoclast function measured by tartrate resistant acid phosphatase (TRAP) synthesis and formation of resorption pits. The TRAP synthesis on nanophase hydroxyapatite was more than twice that measured on conventional hydroxyapatite. This increased osteoclastic activity may be important for the formation and maintenance of healthy new bone juxtaposed to a dental implant.

### 5.5. Differentiation

In addition to supporting osteoblast-specific adhesion and adherent cellular proliferation, it is important to the process of osseointegration that the adherent mesenchymal cells differentiate rapidly along the osteoblast lineage. Early indications of nanoscale topography advantages were reported by Webster et al. [51]. They revealed that alkaline phosphatase synthesis and calcium mineral content increased in cell layers formed on nano-sized materials after 21 and 28 days.

To date few studies have evaluated the gene expression pattern indicative of differentiation of osteoblasts on nanostructured surfaces. Immunolabeled osteopontin and BSP were found in higher concentration in nanostructured surfaces [117]. Isa and co-workers [41] compared adherent palatal mesenchyme cell differentiation when cultured on a hydrophilic micron-scale topography cpTi surface or a nanoscale cpTi surface. Both surfaces supported osteoblastic differentiation, however, Runx2 expression (the key transcription factor controlling osteoblast differentiation) was increased on the nanoscale surface only. A recent in vitro and in vivo study has also demonstrated the upregulation in Runx2 expression [78]. Also, many other genes are upregulated in nanostructured surfaces as a response to Runx2 levels, such as BSP, OPN, OCN (Fig. 5).

Increased bone formation was measured for nanoscale rough implant surfaces in animal models [148]. In a series of studies the same group found early bone formation and increased torque removal when implant surfaces were added with nano-hydroxyapatite or titania [149].

## 6. Nanotechnology alters surface reactivity

Nanoscale modification of the implant surface may alter the endosseous implants surface reactivity. Existing reports suggest that little bone bonding occurs at endosseous titanium implants, particularly during the early phases of bone formation [150]. Nanoscale modifications of topography appear to change the chemical reactivity of bulk materials [151]. Ellingsen [152] demonstrated that the calcium phosphate precipitation on grit blasted titanium was dramatically altered by HF surface treatment that creates nanoscale topographic surface features. When the physical interaction of such titanium disks with bone was measured by a pull-off test, bonding of bone to the HF treated titanium surface was evident [153]. Bone bonding may be a benefit attributed to titanium implants through nanoscale surface modification.

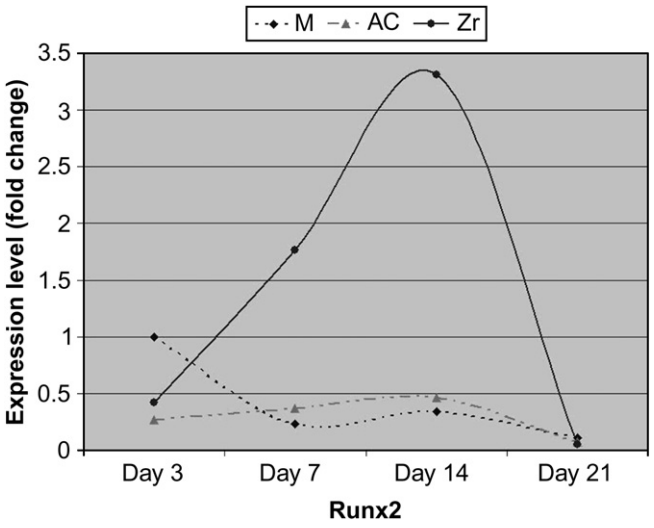


**Fig. 5.** Effect on surface treatment (topography) on osteoblast differentiation. Osteoblasts were cultured on titanium disks treated by machining (Ra = 86.52 nm), acid etching to provide a micron-rough surface (Ra = 388.40), and with zirconia sol–gel deposition (Ra = 89.71 nm) to produce a nanoscale topography with pore sizes ranging from 20 to 40 nm. During the 21 days, expression of the key osteoblast differentiation factor, Runx2, was determined by real-time PCR. The results are plotted as fold change in expression level (compared to day 3 machined surface) vs culture duration (days). The marked elevation in Runx2 levels for the nanoscale surface reflects data for other nanoscale surfaces [78]. M – machined surface, Ac – acid-etched surface, and Zr – nanozirconia surface.

Biomimetic features of nanoscale modifications to the endosseous surface tissue–implant interface also address molecular (not cellular) interactions with tissues. Davies [29,150] described the formation of bone/implant bonding at solid surfaces as a four-stage process comprising the adsorption of non-collagenous bone proteins to the solid surface. Critical to the process is the initiation of mineralization by the adsorbed proteins and incipient surface directed mineralization. In a recent study, Mendes and colleagues [88] concluded that the traditional "bioactive" lithomorphic materials such as CAPs and bioactive glasses are not obligatory to promote bone bonding, but rather that a surface should have a submicron-surface complexity into which the bony cement line matrix can be deposited, and with which it can interact. Nanoscale topography may provide biomimetic surfaces that support hydroxyapatite mineral formation [154], and related organic phase guidance of bone mineralization [155].

## 7. The relative value of nanoscale and micron-scale roughness

The development of an implant/bone interface may be influenced by both nanoscale and micron-scale parameters of topography. The role of surface parameters (both bulk chemistry and topography) requires consideration of molecular (ionic and biomolecular) interactions with the surface, cell adhesion phenomenon and local biomechanical features of the established interface. It is clear that nanoscale modification will affect the chemical reactivity of an endosseous implant surface and alter the ionic and biomolecular interactions with the surface. Proposed changes include enhanced wettability, altered protein adsorption, and potential mineralization phenomenon. Changes in wettability and altered protein adsorption lead to altered cell adhesion, likely involving both integrin and non-integrin receptors. The potential for mineralization and epitaxic crystal growth in support of early bone bonding could dramatically alter the biomechanical environment of the healing implant in favor of stability.

Various reports support the concept that nanotopography enhances osteoblastic differentiation which could also promote stability and favorably alter the biomechanical environment for healing (see Tables 2 and 3). However, initial clinical stability may require additional considerations of micron-scale topography and overall implant design. The pioneering investigations of Meirelles and co-workers [148,149] suggest that nanometer-scale topography alone is not sufficient to assure robust osseointegration. Investigations which have isolated nanometer-scale topography as an experimental variable in osseointegration have required additional consideration of endosseous implant stability. It is possible that micron-level roughness is of additional value to the process of osseointegration. The theoretical consideration of how forming tissues interlock with micron-level topographic elements [29], and how mechanical stimulation of forming tissues is imparted by such topographic elements [28] represent ideas that may not be fully displaced by the introduction of nanotopographic modification to the endosseous implant surface.

## 8. Nanostructured surfaces for implant dentistry

There are many different methods to impart nanoscale features to the implant surface (see Table 1). Several of these methods have already been used to modify implants available commercially. Others are advancing through the research and development process.

As indicated above, positive bone responses occur at nanostructured surfaces tested in vitro and in vivo. Presently, only a few nanoscale surface topography modifications have been used to enhance bone responses at clinical dental implants. The OsseoSpeed surface (Astra Tech AB, Molndal, Sweden) possesses

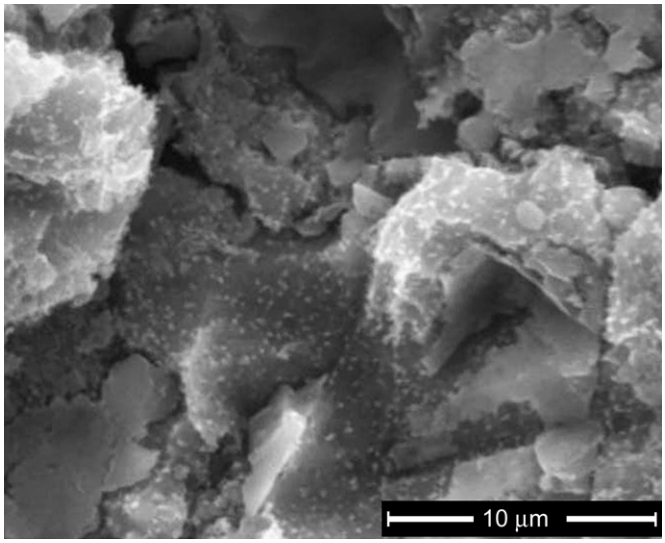


**Fig. 6.** Scanning electron microscopic evaluation of an OsseoSpeed implant. 2500× magnification of the $TiO_2$ grit blasted and HF treated implant surface. Note that the $TiO_2$ grit blasted surface is randomly covered with surface features of approximately 100 nm imparted by the HF etching.

nanostructured features created by $TiO_2$ blasting followed by a proprietary hydrofluoric acid treatment [44,77]. Across a micron-rough titanium surface, 50–100 nm surface accretions of titanium oxide are observed by scanning electron microscope (SEM) analysis (Fig. 6). Greater osteoblastic gene expression (Runx2, Osterix, Alkaline Phosphatase and Bone Sialoprotein) was measured in cells adherent to the nanoscale HF treated surface compared to the micron-scale surface [78]. This nanotopography is associated with the elevated levels of gene expression that indicate rapid osteoblastic differentiation. Most recent investigations show that this nanoscale surface modification promotes high levels of IGF-2 and BMP2 and BMP6 expression by adherent human mesenchymal stem cells for prolonged periods of time in culture.

Other studies concerning this nanoscale surface modification have demonstrated an increased bone formation, torque removal value [46]. In the rabbit tibia model of osseointegration, histomorphometric evaluations demonstrated higher bone-to-implant contact for the nanoscale OsseoSpeed implants compared to the micron-scale TiOblast implants (Astra Tech AB, Molndal, Sweden) at 1 month ($35 \pm 14\%$ vs $26 \pm 8\%$) and 3 months ($39 \pm 11\%$ vs $31 \pm 6\%$) after placement. Berglundh and colleagues [79] used a gap model of osseointegration in the canine mandible to demonstrate the amount of new bone that formed in the voids within the first 2 weeks of healing was greater for HF-modified (OsseoSpeed) implants than at TiOblast implants and concluded that the nanoscale surface promotes osseointegration in the early phase of healing following implant installation.

Clinical evaluation of this implant surface preceded clinical launch and a report of the first data was provided in 2006 [18]. Six-hundred and thirty four patients received 1860 OsseoSpeed™ implants. The initial report indicated 4% surfaces had signs of inflammation (BOP) with plaque present on 12% of sites. Twenty-one patients have lost a total of 25 implants (15 in maxilla and 10 in mandible) for a CISR of 98.7% from placement. Evaluation of this effectiveness trial performed in more than 100 practices is ongoing. High success in challenging situations such as immediate placement and loading was also reported [156].

Another nanoscale surface implant presently available in the clinical marketplace involves a CaP nanoparticle modification of a minimally rough titanium alloy implant (Nanotite, 3i Implant Innovations, Palm Beach Gardens, FL). The surface has been

described as being created by a particulate sol–gel deposition method using discrete crystalline deposition (DCD) of calcium phosphate (CaP) (nominal crystal size 20 nm) with surface coverage of approximately 50%. The suggested nanofeature size of the tightly adherent adsorbed CaP/DCD crystal is 50–100 nm. Mendes and co-workers [88] measured bone ingrowth for implants modified using this technology in a rat tibia model using a well defined bone chamber model. The extent of bone ingrowth was 26.95% and 29.73% for cpTi and Ti alloy modified surfaces compared to the 12.01% cpTi and 16.97% Ti alloy chambers. In a related presentation, Mendes and colleagues [88] showed bone-bonding behavior; DCD, surfaces had statistically greater tensile detachment force (e.g. 11.30 N nanoscale DCD vs 1.90 N control).

The nanoscale CaP surface created by DCD (Nanotite, 3i) was further evaluated [157]. The histologic evaluation of clinical implants revealed bone-to-implant contact of $19 \pm 14.2\%$ and $32.2 \pm 18.5\%$ for the Osseotite (3i) control and the Nanotite (3i) experimental implants, respectively. Other clinical studies are ongoing to determine the safety and performance of this implant with nanoscale topography. For example, Goené and co-workers [158] observed greater bone formation at 4 and 8 weeks and concluded that the addition of a nanometer-scale calcium phosphate treatment to a dual acid-etched implant surface appeared to increase the extent of bone development after 4 and 8 weeks of healing. The authors suggest that this rapid accrual of bone at the implant expedites the implant healing period and supports early loading protocols.

Ion beam assisted deposition (IBAD) has also been used to create a commercially available dental implant surface [90]. This technique creates a thin-film over the implant surface by deposition of the chemical element of interest. In one available study, the bone formation (measured by tetracycline labeling quantification) was higher in the experimental group than in the control group (sand-blasted/acid-etched) after 2 (13.56% vs 24.04%) and 4 weeks (14.22% vs 27.39%) [90]. An example of this type of surface modification is presented on the Nanotite surface of Bicon Implants (Nanotite, Bicon Inc., Boston, MA). These very different chemical and physical approaches all impart nanoscale features to existing endosseous cpTitanium implant surfaces.

These initial reports of nanoscale topography implants provide insight into potential advantages for dental implant therapy. High implant survival rates have been reported. The high survival in effectiveness trials involving the HF-modified $TiO_2$ grit blasted surface implant and in challenging clinical examinations may reflect greater control of initial bone formation due to the rapid differentiation of osteoblastic cells observed in laboratory studies. The potential impact of bone bonding measured in preclinical studies requires further study; however, the possible advantages of bone-bonding behavior at a titanium surface could have clinical merit. How nanoscale topography and nanotechnology may be used to enhance the tissue–abutment interface remains largely unexplored. It should be noted that the currently available implants differ in their micron-level topography, in their design and in their bulk material composition. It may be difficult to derive specific conclusions from the aggregate data regarding nanoscale surface topography alone. However, for each example of current nanoscale implant surfaces of available implants, cell culture, histological, and clinical data suggest that nanoscale surfaces offer incremental advantages to clinical problems where rapid bone accrual at the implant surface provides solutions.

## 9. Conclusions

Nanoscale modification can alter the chemistry and/or topography of the implant surface. Different methods have been described to modify or to embellish titanium substrates with nanoscale features. Such changes alter the implant surface interaction with ions, biomolecules and cells. These interactions can favorably influence molecular and cellular activities and alter the process of osseointegration. Cell culture studies reveal that there exists a range of nanoscale topography that promotes the osteoinductive molecular program for adherent osteoprogenitor cells. Additionally, nanoscale alterations may promote bone-bonding behavior at the titanium–bone interface. Nanoscale modification of titanium endosseous implant surfaces enhances interfacial bone formation measured as bone-to-implant contact. At this moment, both a hydrofluoric acid modified titanium endosseous implant with nanoscale features and two calcium phosphate nanofeature-modified titanium implants are available for clinical use. The potential risks and benefits of manipulating biomaterial interfaces at the nanoscale will be defined by long-term clinical evaluation of such endosseous devices.

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