Chapter

Surface Modification of Titanium Orthodontic Implants

Abdulqadir Rampurawala and Amol Patil

Abstract

Orthodontic miniscrews have had a considerable impact on modern orthodontic treatment, not only by providing a new source of anchors for anchorage-demanding cases, but also for force management and control. Whilst miniscrews need to be mechanically stable during treatment to provide sufficient anchorage and predictable force control, as temporary anchorage devices they need also be easy to remove after orthodontic treatment. These requirements differentiate orthodontic miniscrews from dental implants - which once placed, are not to be removed - and dictate the approach as to how their clinical performance can be optimized. Over the past decade, various titanium surface modifications and improvements in implant surface topography have shown to enhance osseointegration of endosseous dental implants. Some of these techniques have helped provide a similar enhancement of the biomechanical potential of orthodontic miniscrews as well. In this perspective, we present a brief discussion on all such reported techniques followed by a detailed account of the most recently proposed ultraviolet photofunctionalization technique - a novel chair-side surface modification method.

Keywords: anchorage, stability, surface modification, osseointegration, biomechanical potential, photofunctionalization, miniscrews

1. Introduction

Anchorage control plays an important role in orthodontic treatment. Nevertheless, in clinical practice, this was a typically difficult and unpredictable challenge for many years. In the 1990s, temporary anchorage devices (TADs) called mini-implants were the first implants used to provide absolute and compliance-free intraoral anchorage [1]. Subsequently, these implants became smaller in size and are today used as 'orthodontic miniscrews' (**Figure 1**). They have the advantages of low cost, simple surgical placement, and ease of removal. Miniscrews have, therefore, found applications in the treatment of a variety of malocclusions. However, as with any other implanted material in the human body, the stability of orthodontic miniscrews is paramount to their clinical acceptability. The clinical stability of miniscrews has proven to be exceptionally high (**Table 1**). A few studies have reported success rates higher than 90% [2, 3], while others have reported slightly lower success rates [4, 5]. Notwithstanding such a high rate of clinical success, various surface modification techniques have been

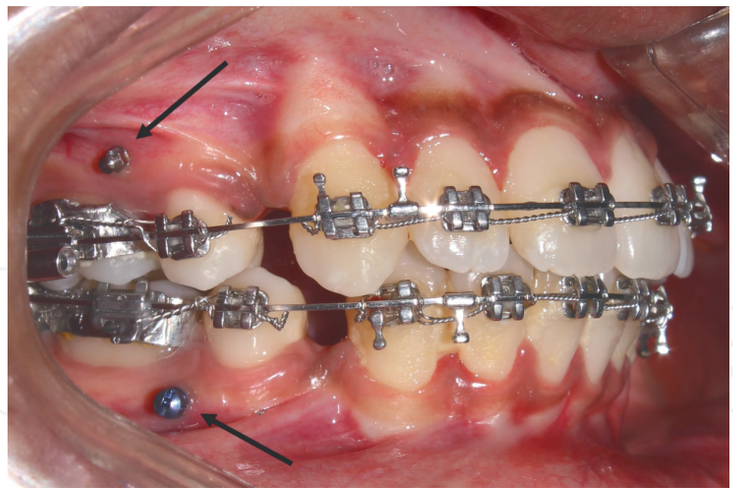

Figure 1.
Miniscrews used as temporary anchorage devices (TADs) in fixed orthodontic treatment of malocclusions (black arrows).

Study	Result
Antoszewska et al. (2009) [2]	Success rate of 93.43%
Park et al. (2006) [3]	Success rate of 91.6%
Papageorgiou et al. (2012) [4]	Failure rate of 13.5%
Alharbi et al. (2018) [5]	Failure rate of was 13.5%

Table 1.
Clinical stability of orthodontic miniscrews.

proposed to further enhance the stability of miniscrews, thereby allowing the orthodontist to optimize and expand its clinical use.

2. Surface modification of orthodontic miniscrews

The use of commercially pure titanium or titanium alloy (Ti-6Al-4 V) as an implant material has made it possible to predictably secure miniscrews into the maxilla and/or mandible by facilitating direct bone apposition to the implant surface and creating a unique bone-implant interface. This process is termed as "osseointegration" [6]. It is this intimate relationship between living bone and the titanium miniscrew surface that is responsible for its high degree of stability. Various surface treatments of titanium implants have been known to modify both the surface composition as well as its topography, thereby increasing the implant surface roughness and area, which might lead to enhanced bone-screw contact (BSC) [7–12]. Surface modification also enhances the interactions with biological fluids and cells, and thereby accelerates peri-implant bone healing as well as improves osseointegration at sites that lack sufficient quantity and/or quality of bone [7, 11–14]. Evaluation of BSC and removal torque (RT) can, therefore, be used as reliable measures of osseointegration of implants [4]. The improved osseointegration by surface modification is a characteristic exhibited by all titanium surfaces and hence, it applies equally to titanium orthodontic miniscrews [15].

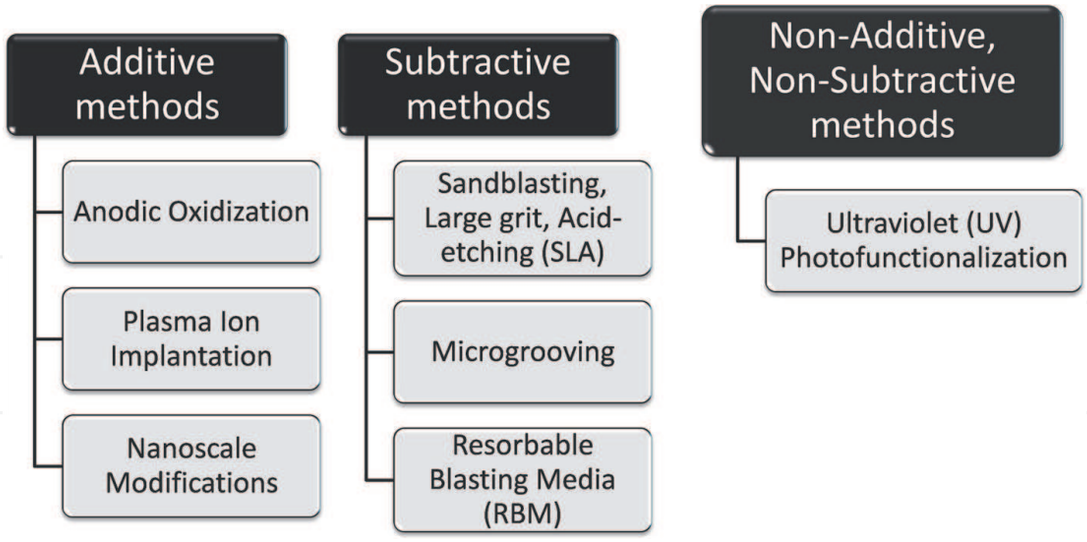

Figure 2.
Different types of surface modification techniques available for orthodontic miniscrews.

Since the advent of titanium dental implants as prosthetic tooth replacements in the 1990s and titanium mini-plates and miniscrews as skeletal anchorage devices later in the same decade, a considerable amount of research has been done on surface treatments and modifications of these titanium devices. Broadly, these surface modifications can be categorized as either subtractive or additive methods (**Figure 2**). The subtractive methods are machining/turning, sandblasting, acid-etching, sandblasting (large-grit) combined with acid-etching (SLA), dual acid-etching and laser treatment. The additive methods are anodization (also known as anodic oxidization), fluoride surface treatment, plasma spraying (titanium or hydroxyapatite), sol–gel coating, sputter deposition, electrophoretic deposition, biomimetic precipitation (Ca-P) and most recently, nanoscale modifications with or without drug incorporation [16, 17]. Many of these techniques have been used to augment the biomechanical potential of orthodontic miniscrews and have proven to be experimentally as well as clinically effective. Following is an account of all the surface modification techniques that have been used to enhance the biomechanical potential of orthodontic miniscrews.

2.1 Sandblasting, large-grit, acid-etching

One of the earliest methods for surface treatment that was introduced, and one that has stood the test of time, is sandblasting with or without acid-etching. In this technique, alumina (Al_2O_3) particles at high pressures are blasted onto the implant surface, after which it may be treated with acidic solutions. The alumina particles are essentially large-grit particles with sizes ranging from approximately 250–500 μm, and the solutions used are highly concentrated acids like hydrochloric acid (HCl), nitric acid (HNO_3) and sulfuric acid (H_2SO_4). This process creates the desired roughness on the implant surface. The application of sandblasting using large-grit alumina particles followed by acid-etching is collective known as the SLA method (**Figure 3**). Wehrbein et al. was one of the first to study the effects of SLA surface treatment on orthodontic implants in humans. Histomorphometric findings revealed that the SLA technique was able to achieve up to 70–80% of BSC, which was remarkably high [18].

Animal studies have routinely been carried out in this regard and have shown successful results. Various experimental studies conducted in rabbit tibiae and

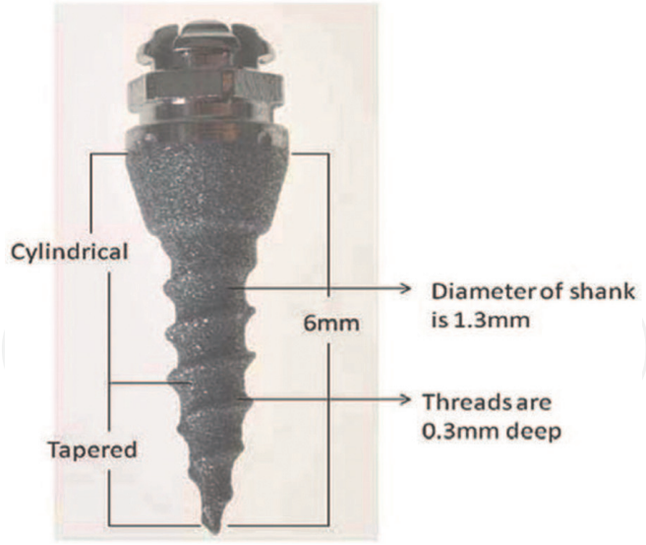

Figure 3.
Miniscrew surface modified with large-grit sand-blasting and acid-etching (SLA) (Taken from: Yadav et al. [20].)

femurs that have compared smooth (machined or untreated) and SLA miniscrews have reported greater RT values and BSC in the surface treated miniscrews [19–22]. These results are suggestive of higher miniscrew stability especially in the early stages of healing thereby allowing immediate/early loading, and of an enhanced biological response due to increased osseointegration potential. Chang *et al.* compared conventional smooth miniscrews with SLA as well as alkaline-etched (SL/NaOH) miniscrews in rabbit tibiae and found that both SLA and SL/NaOH groups had greater RT and BSC values than the conventional group [15]. However, as per a scanning electron microscope (SEM) analysis, the SLA surface showed roughness at two levels: (i) small micro-pits produced by the acid-etching procedure and (ii) microscopic pits superimposed on a sandblasted macro-rough texture, whereas the SL/NaOH surface showed only macroscopic surface properties. This indicates that alkaline-etching might not be as effective as acid-etching for surface treatment of miniscrews. Sirisa-Ard et al. reported that despite an increase in BSC values of SLA miniscrews over 8 weeks of healing in New Zealand rabbits, there was no significant increase of RT values as compared to machined miniscrews over a similar period, suggesting that SLA surface preparation did not have any added benefit in enhancing miniscrew stability [23].

Similar comparative studies between SLA and machined miniscrews have been carried out in other animals such as beagle, foxhound and mongrel dogs. Histomorphometric and micro-computed tomographic (micro-CT) analyses from those studies have revealed greater BSC values with SLA miniscrews indicating their increased osseointegration potential [24, 25]. Some studies have also reported variable torque values for SLA miniscrews at both insertion and removal, essentially indicating equal or improved stability when compared to machined miniscrews [25, 26]. Kim et al. used a digital device to measure the total energy at removal of miniscrews and found that the SLA group had greater values, thus indicating an enhanced biomechanical potential [26]. On the contrary, a similar torque analysis by Vilani et al.

concluded that since there was no significant difference between mobility and insertion torque (IT) or RT of the SLA and machined miniscrew groups, their stability was nearly comparable [27].

The aforementioned positive effects of SLA surface treatment have been validated by a few *in vivo* studies on humans as well. Schätzle et al. compared the stability of standard SLA treated palatal implants with those modified by rinsing under nitride (N_2) protection following SLA treatment to enhance their wettability [28]. Resonance frequency analysis (RFA) at various time points over a period of 12 weeks showed that the implant stability quotient (ISQ) for both groups was similar at the beginning but gradually increased significantly for the experimental group by the end of the study period. This suggests that chemical modification of SLA miniscrews can positively influence their biologic potential and decrease healing time. While most of the research has been focused on evaluating BSC and individual implant stability, some authors have also reported the effect of SLA surface modification on the anchorage ability of miniscrews under orthodontic loads. Calderón et al. used a method of angular measurements on occlusal radiographs for evaluation of positional mini-implant stability and subsequently confirmed those readings on a cone-beam computed tomography (CBCT) occlusal view of just one patient from the study group [29]. As per their calculations, 65% mini-implants showed a $\leq$ 1degree shift, whereas 35% mini-implants showed a $\geq$ 2 degree shift. Kim et al. conducted a comprehensive 3-dimensional CBCT analysis of SLA treated mini-implants inserted in the posterior maxillary buccal alveolar region and found that there was no significant change in implant position over 9 months of en-masse retraction [30]. Both of these studies indicate that SLA modification of miniscrews may provide stable and stationary anchorage for orthodontic considerations. However, a couple of studies have reported that despite their relatively greater success rates and better IT values, SLA miniscrews do not have any significant advantage over conventional machined miniscrews in terms of initial stability or overall success [31, 32].

Results from clinical studies hold greater value if they are supplemented by similar proofs from experiments carried out at cellular and/or molecular levels, and vice-versa. In an *in vitro* study, Proff et al. compared three groups: airflow treated, SLA treated and machined miniscrews, incubated in a fibroblast cell culture [33]. Using the AlamarBlue assay and fluorescence microscopy, they reported a slight reduction in metabolic cell activity after 24 hours in the airflow group but fibroblast survival and rate of cell proliferation were identical in all the three groups. In an *ex vivo* study of the peri-implant tissue surrounding SLA miniscrews obtained from beagle dogs after 1 and 4 weeks of healing, Nahm et al. carried out gene profiling analyses to reveal that genes encoding extracellular matrix (ECM) constituents were upregulated at the early stage of healing and that genes associated with bone mineralization, ossification, stem-cell fate regulation were upregulated at the later stage of healing [34]. Kim et al. attempted to study the chemical integration mechanism between human bone and titanium miniscrew surfaces at a nanoscale level [35]. A single SLA treated miniscrew was analyzed after 2 months of healing. High-resolution transmission electron microscopy (TEM) and energy dispersive X-ray spectroscopy (EDS) showed evidence of crystalline hydroxyapatite and intermixing of bone with the oxide layer of the miniscrew surface. Scanning TEM (STEM) and electron energy loss spectroscopy (EELS) revealed that carbon existed in polysaccharides, calcium and phosphorus existed as tricalcium phosphate (TCP), and titanium existed in its oxidized form, all rather interesting results. Additionally, the oxygen energy loss near edge structures (ELNESs) showed a possibility of the presence of $CaTiO_3$. The possible existence of the osseohybridization area and the form of the carbon suggests that osseointegration is not purely a mechanical bone-implant interaction and therefore, reconsideration of the standard definition of osseointegration is necessary. In a most recent study on this

topic, Kim et al. studied the molecular surface interaction of a titanium mini-implant (SLA treated) retrieved from a patient after 2 months of healing [36]. Layer profiling using atom probe tomography (APT) showed high concentrations of calcium (Ca) and phosphorus (P) in the bone, titanium oxide (TiO) in the interface, and titanium (Ti) in the implant. Such a nanoscale resolution showing atom-sharing zones at the implant-bone interface provides valuable insight into the process of osseointegration.

It is evident by now that SLA modification of the orthodontic miniscrew surface has some kind of positive biomechanical advantage over conventional machined miniscrews. One would think that this intimate bone-implant relationship comes at a cost of tissue damage to the surrounding bone while retrieval of miniscrews at the end of the treatment period. Studies have shown that despite SLA treated miniscrews having greater BSC and RT values on removal, there was no reported bone fracture or tissue destruction during unscrewing [30, 46]. Kim et al. recommended a non-loading period of fewer than 6 months before removal for optimal bone health and post-operative healing [37].

2.2 Microgrooving

Machining/turning is one of the most basic and simplest forms of implant surface treatment. In actuality, it is an essential part of the manufacturing process that gives shape to the cutting surface and determines the pitch of the screw, which in turn affects the cutting capacity and biomechanical properties of the implant (**Figure 4**). Kim et al. extended this concept of surface turning to a micro-scale level and prepared miniscrews with microgrooves (50 μm pitch, 10 μm depth) on 300 μm of the upper cutting surface [38]. This experimental group (MG) was compared against conventional non-microgroove (NMG) miniscrews in beagle dogs after 16 weeks of orthodontic loading. Histomorphometry revealed higher BSC values on the pressure side of the MG group. Further histological analysis showed that gingival connective tissue

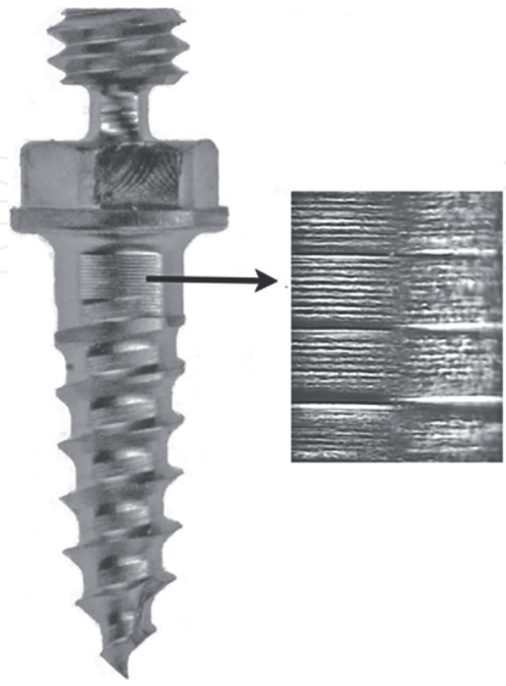

Figure 4.
Microgrooving technique of surface modification. The microgroove shown here is 50 μm pitch and 10 μm depth in 300 μm on the surface. (Taken from: Kim et al. [38].)

fibers (GCTF) in the MG group were oriented perpendicular to the miniscrew surface whereas in the NMG group they were parallel. Additionally, fluorescent microscopy showed more bone remodeling on the pressure sides in both groups as compared to the tension sides. This suggests that addition of microgrooves could exert some positive effects on the soft tissue adaptation and bone healing around orthodontic miniscrews.

2.3 Anodic oxidization

Another type of surface treatment reported in the past is anodic oxidization of titanium implants [39]. It is an electrochemical process wherein an oxide film is produced on a metallic substrate. Anodic oxidization of titanium orthodontic miniscrews produces a titanium dioxide (TiO_2) layer on the implant surface with a thickness ranging from 10 to 25 μm increasing from the neck of the implant to the apex (**Figure 5**). Ivanoff et al. conducted some of the first clinical studies to evaluate the effects of anodic oxidization on micro-implant osseointegration [40, 41]. With the help of an optical confocal laser profilometer and histomorphometric analysis, they showed that anodized micro-implants had an increased surface roughness and BSC value as compared to machined micro-implants. Omar et al. investigated the gene expression and cellular reaction around machined and anodized miniscrews in rabbit tibiae at 1, 3 and 6 days [42]. The quantitative polymerase chain reaction (qPCR) and immunohistochemistry results concluded that (i) the rapid recruitment of mesenchymal cells, (ii) the rapid triggering of gene expression crucial for bone remodeling and (iii) the transient nature of inflammation, probably constitute the biological mechanisms for osseointegration and high implant stability associated with anodically oxidized miniscrews. Karmarker et al. reported higher RT values for anodized miniscrews indicating their improved stability [43]. Choi et al. carefully studied the changes in surface roughness and characteristics of anodically oxidized miniscrews [44, 45]. Atomic force microscopy (AFM) revealed that anodized miniscrews had nanotubular open pores and increased roughness on the middle thread edges. Nonetheless, there were no differences in IT or RT

Figure 5.
Surface modification by anodic oxidization. (A) Machined surface miniscrew; (B) Anodic oxidized miniscrew. (Taken from: Choi et al. [44].)

values as well as BSC values of anodized miniscrews when compared to machined miniscrews. Conflicting results from the aforementioned studies suggest that the role of anodic oxidization in enhancing the biomechanical stability of orthodontic miniscrews might yet be questionable.

2.4 Plasma ion implantation

Attempts by some researchers to improve the corrosion and wear resistance of titanium implants have led to the development of a surface modification technique known as plasma ion implantation. In this technique, the surface of orthodontic miniscrews is coated with a thin film of titanium nitride (TiN) and/or zirconium nitride (ZrN) which acts as a protective layer (**Figure 6**). Kim et al. studied the mechanical and electrochemical changes on the surface of plasma ion implanted miniscrews [46]. Field emission SEM (FE-SEM) and EDS analysis showed that when compared to non-coated miniscrews, the TiN and ZrN coated miniscrews had a smoother surface owing to a decrease in the number of machined defects. Electrochemical tests revealed that coated miniscrews had a reduced corrosion current density. Later, on comparing the biologic stability of plasma ion implanted and SLA miniscrews in beagle dogs after a loading period of 3 and 12 weeks, Cho et al. concluded that since there was no difference in BSC, bone volume ratio or the number of osteoblasts around the miniscrews in both groups, they had similar biologic characteristics [47].

2.5 Resorbable blasting media

The previously described method of SLA surface modification of miniscrews consisted of sandblasting with alumina (Al_2O_3) particles. These particles do not resorb *in vivo* and therefore, are non-resorbable blasting media. However, sandblasting of implant surfaces with resorbable blasting media (RBM) such as hydroxyapatite or calcium phosphate particles has also been reported recently [48]. In an *in vitro* comparative evaluation of the physical characteristics of machined, acid-etched, RBM treated and hybrid (machined + acid-etched) orthodontic mini-implants, Kim et al. reported

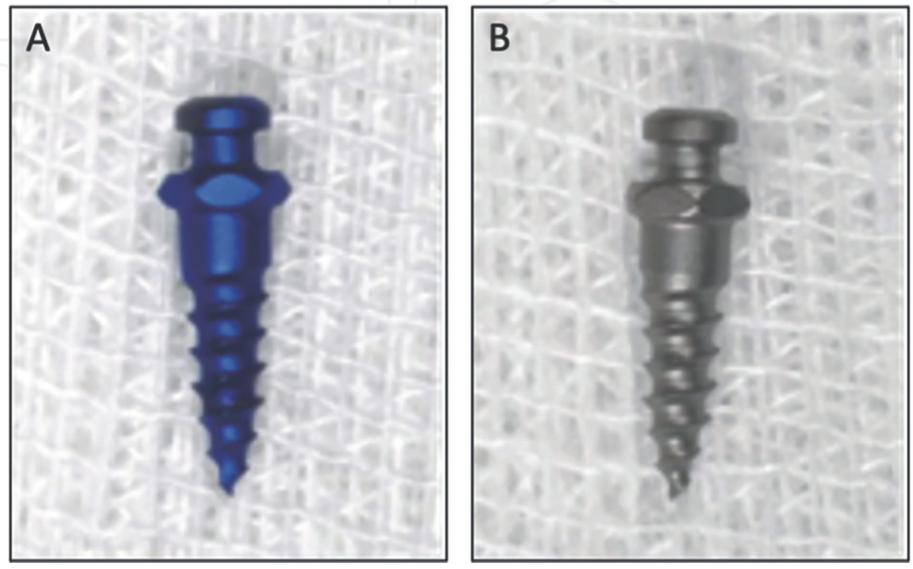

Figure 6.
Surface modification with plasma ion-implantation (A) and SLA treated miniscrew (B). (Taken from: Cho et al. [47].)

that all the surface treated groups had higher IT values, and the RBM and hybrid groups showed significantly higher surface roughness values [49]. *In vivo* studies on rabbit tibiae have also shown effective results. Gansukh et al. verified previous findings by reporting that after 4 weeks of healing, there was no difference in the IT, RT, and BSC values of machined and RBM treated mini-implants [50]. However, histomorphometric analysis showed an increased bone-area (BA) in the RBM group. In a similar study by Kim et al., the hybrid group consisted of partially RBM treated mini-implants i.e. lower 1/3rd of the cutting edge was left untreated [51]. Out of the four groups, the hybrid group showed the least reduction in bone cutting capacity, highest RT values at 4 and 8 weeks of healing, and the highest amount of tissue remnants on the mini-implant surface. Analysis by EDS showed that calcium and phosphorus were present only on the surface of the hybrid group implants, suggesting that partial RBM surface treatment was perhaps the most clinically effective one. All of these studies conclude that surface treatment of orthodontic mini-implants with RBM may provide good initial stability and has the potential to enhance osseointegration without negatively affecting their bone cutting capacity.

2.6 Nanoscale modifications

One of the latest techniques for surface modification of dental alloys and implants is their nanoscale modification. This involves the formation of nanotubular arrays mainly by anodization of the surface under specific voltages in various electrochemical solutions (**Figure 7**). Oh et al. combined multiple methods of surface treatment and studied its effect on the stability and osseointegration potential of orthodontic miniscrews in rat tibia [52]. This unique method involved anodization (TiO_2 nanotubular arrays) and cyclic pre-calcification (biomimetic Ca-P coating) of miniscrews followed by heat treatment. This method was called APH treatment. Results from mechanical torque testing and histological and SEM/EDS analysis showed that APH treated miniscrews had higher RT and BSC values after both 3 and 6 weeks of healing. Early deposition of densely mineralized bone around APH treated miniscrews was observed, implying good bonding to the treated surface. Jang et al. closely studied the effects of isolated nanoscale modifications on miniscrew biomechanical properties in rabbits [53]. Nanotubular arrays of TiO_2 (70 nm diameter, 5 μm length) were produced using a two-step anodization process. When compared to machined miniscrews, the experimental group showed higher BSC and bone-volume-ratio (BVR) values on histomorphometric and micro-CT analysis. Nanotubular arrays have also been used as drug-delivery systems to enhance the biologic potential of miniscrews. In a similar evaluation, Cha et al. used tunnel miniscrews with and without recombinant human bone morphogenetic protein – 2 (rhBMP-2) loaded

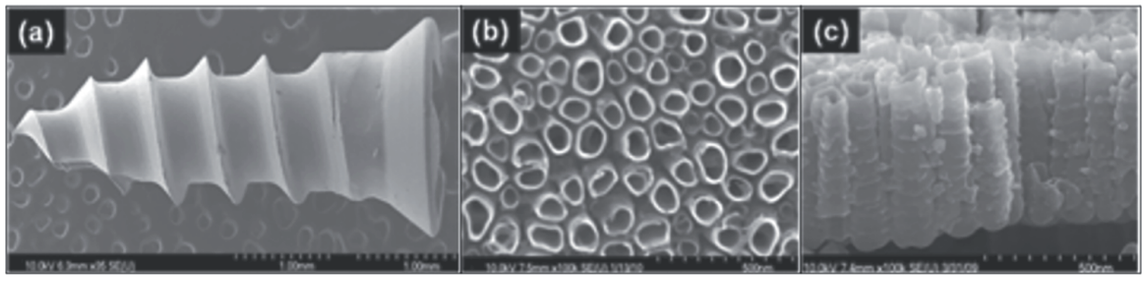

Figure 7.
SEM images of Ti_6Al_4V miniscrews: (A) untreated, and (B,C) nanotubes formed on the surface; (B) top and (C) cross-sectional views. (Taken from: Oh et al. [52].)

onto them and compared them against conventional machined miniscrews [54]. After 8 weeks of healing, BSC, BVR and bone-surface-ratio (BSR) values of tunnel miniscrews with nanotube arrays were considerably higher than machined miniscrews. The rhBMP-2-loaded miniscrews showed a slightly greater osseointegration potential than the non-loaded miniscrews. Jang et al. further studied the effects of drug-loaded nanotube arrays by comparing rhBMP-2-loaded and Ibuprofen-loaded miniscrews along with a machined and non-loaded nanotube array miniscrew group [55]. After 8 weeks of healing, the highest BSC values were recorded for the Ibuprofen-loaded miniscrews followed by the non-loaded, machined and rhBMP-2-loaded groups. In spite of their limited scope, these studies clearly suggest that nanoscale surface modifications of orthodontic miniscrews increase their biologic potential and the same nanotubular structures can also be used as drug-delivery systems to further enhance their osseointegration potential.

3. Ultraviolet photofunctionalization

Ultraviolet (UV) - mediated photofunctionalization is a method of surface modification for titanium that alters its physiochemical properties and enhances its biologic capability. It is characterized by remarkable efficacy, unique mechanisms, and a simple delivery method [56]. The effectiveness of UV treatment has been proven for all surface topographies tested. One of its unique features that set it apart from previously discussed surface modification techniques is that it does not alter the existing topography, roughness, or other morphologic features of miniscrews and is therefore categorized as neither an additive nor a subtractive method.

3.1 Physiochemical properties

For a very long time, it was assumed that the biologic properties of implant surfaces remained stable over time. It was later noted that over time, these surfaces underwent biologic degradation even when kept sterilized under optimal storage conditions. This is known as the time-dependent biologic degradation or biological aging of implant surfaces [57]. UV photofunctionalization affects these physiochemical changes via three key surface properties: i) the generation of superhydrophilicity; ii) a significant reduction of surface carbon, which unavoidably and unexceptionally accumulates on titanium surfaces; and iii) electrostatic conversion of surface charge from negative to positive.

3.1.1 Hydrophilic conversion

Titanium surfaces that have been sufficiently aged (i.e., more than 1 month after surface preparation) are hydrophobic; that is, the contact angle of water is greater than 60 degrees and close to or above 90 degrees on most surface types. Such a hydrophobic nature is common to all surface topographies of titanium and has been reported extensively [58, 59]. Water dropped on these surfaces does not spread and stays in a hemispherical form. Very intriguingly, after treatment with UV light, these titanium surfaces become remarkably wettable to water, with a contact angle of 0 degrees, which is referred to as being superhydrophilic (**Figures 8** and **9**) [56, 58, 59–63]. The superhydrophilic surfaces were obtained after UV treatment at

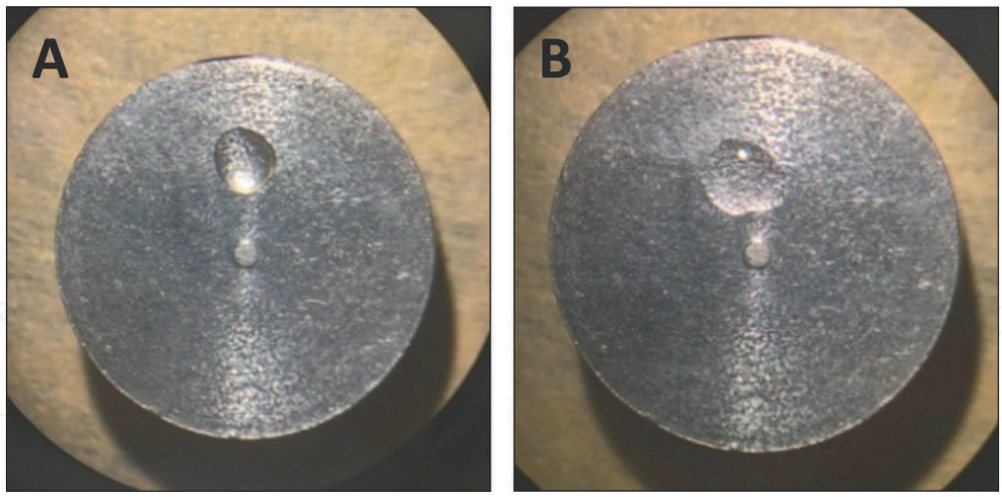

Figure 8.
(A) Untreated titanium surface showing lack of droplet spread. (B) UV-treated titanium surface showing complete spread of water droplet. (Taken from: Rampurawala et al. [105].)

Figure 9.
Hydrophilic conversion by photofunctionalization: (A) miniscrew; (B) untreated miniscrew with 2 drops (1 μL each); (C) photofunctionalized miniscrew with 2 drops (Taken from: Tabuchi et al. [103].)

an intensity of 0.1 mW/cm2 (λ = 360 ± 20 nm) and 2 mW/cm2 (λ = 250 ± 20 nm) for varying durations of time ranging from as little as 20 minutes to as much as 48 hours.

3.1.2 Carbon reduction

Another notable change affected by UV modification is seen in the chemical composition of implant materials. Titanium surfaces, which become titanium dioxide surfaces as soon as they are exposed to the atmosphere, are covered by carbon-containing molecules to a significant degree because of the unavoidable constant accumulation of carbonyl moiety, particularly hydrocarbons, from the atmosphere and surrounding environment during surface preparation and storage [56, 57]. Similarly, presently used titanium implants are also contaminated with hydrocarbons. The amount of carbon varies depending upon the age of the surface. X-ray photoelectron spectroscopy (XPS) studies have revealed that the atomic percentage of carbon increases from 20% up to 60% after 4 weeks of aging. UV photofunctionalization of these surfaces reduces the atomic carbon percentage to 20–35% depending on the wavelength of UV light used [58]. Thus, photofunctionalization of titanium has proven to be effective in reducing the atomic percentage of carbon, thereby cleaning such carbon-contaminated surfaces [56, 57, 60–62, 64–66].

3.1.3 Electrostatic conversion

At an ionic level, ordinary titanium surfaces, viz. titanium surfaces without UV treatment, require inorganic bridges for protein adsorption and cell surface interaction, thus making titanium a bioinert material. In contrast, UV-treated titanium enables a direct cell-surface protein-titanium interaction without the aid of any inorganic bridges, thereby converting it into a bioactive surface (**Figure 10**). Albumin adsorption examined under different electrostatic environments revealed that adsorption on UV-treated surfaces at pH 7.0 was considerably greater than that on untreated surfaces (6-fold after 3 hrs of incubation and 2.5-fold after 24 hrs). Albumin adsorption on untreated control titanium surfaces increased after treating these surfaces with divalent cations but not after treating them with monovalent cations [66]. These findings suggest that the distinctly induced electropositive charge on UV-photofunctionalized titanium surfaces was responsible for the substantially increased efficiency of and capacity for protein adsorption on these titanium surfaces. Conversely, UV-enhanced cell adhesion was eliminated when the UV-treated titanium surfaces were electrostatically neutralized by either removing the electric charge or masking with monovalent anions, while the surfaces maintained their superhydrophilicity [67]. This unique electrostatic status of UV-treated titanium surfaces serves as a chemo-attractant for proteins, superseding the effect of the hydrophilic status, and may, therefore, be a critical regulatory factor in determining its subsequent bioactivity.

3.2 *In vitro* effects

The *in vitro* effects of UV-treated titanium have been studied extensively. A majority of these studies have been aimed at the discovery and explanation of the interaction between living cells and implant material after UV treatment. The key findings of these studies are that UV photofunctionalization leads to: i) increased protein adsorption, ii) increased osteogenic cell attachment and facilitated cell spread, iii) increased retention of cells, iv) increased cell proliferation, and v) enhanced osteoblastic differentiation.

The affinity between biomaterials and cells is determined initially by the interaction between cells as well as proteins adsorbed on material surfaces. Protein adsorption to titanium implant surfaces plays a crucial role in cell attachment and subsequently regulates the spread, proliferation, and other cell functions [56, 60, 63, 66, 68–70]. UV-mediated enhancement of protein adsorption has been reported with different surface topographies of titanium as well as with different proteins. The amount of albumin and fibronectin adsorbed to titanium surfaces after 3 to 6 hrs of incubation was 6-fold greater for UV-treated surfaces in the initial few hours and remained up to 3-fold greater after 24 hrs [56, 66]. Iwasa et al. reported that the protein adsorption levels on the UV-treated 4-week-old titanium surface were equivalent to that on the new surfaces after 3 and 24 hrs of incubation [63]. Qin *et al.* reported that UV photofunctionalization increased adsorption of fibrinogen along with albumin but had no influence on competition between the two proteins [68]. Even though most studies have reported increased protein adsorption following UV treatment, Areid et al. found no qualitative differences in protein adsorption between UV and non-UV treated surfaces, but found that platelet adhesion was increased after UV treatment and that might suggest UV-enhanced thrombogenicity of nanostructured titanium [70].

Various behaviors and responses of osteogenic/osteoblastic cells have been compared in cultures on UV-treated and untreated titanium surfaces. Osteogenic cell

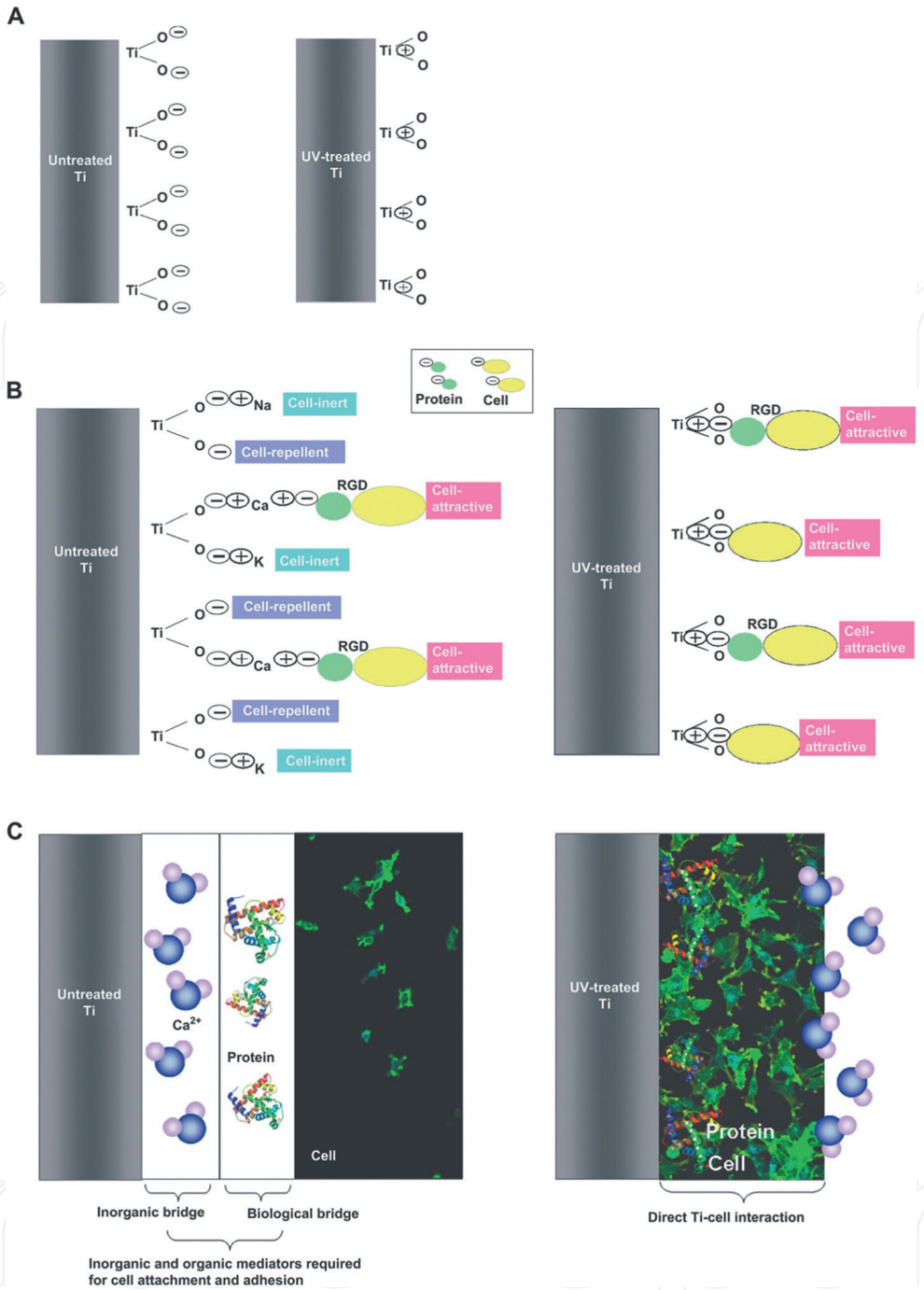

Figure 10.
Schematic description of the proposed mechanism of electrostatic interactions underlying the UV-photofunctionalization of titanium dioxide surfaces: UV-mediated conversion of titanium surfaces from bioinert to bioactive. (A) Hypothetical electric status of untreated and UV-treated TiO2 surfaces. As known and understood, ordinary TiO2 surfaces are electronegative, whereas UV-treated TiO2 surfaces are electropositively charged because of exited electrons from valence bands to conduction bands. (B) Electrostatic interaction of TiO2 surfaces with ions, proteins and cells. The untreated titanium surface (left) largely involves cell-inert terminals consisting of competitive binding of monovalent cations to negatively charged TiO2 surface. When cations are insufficient, this titanium surface remains electronegative and protein- and cell-repellent. The surface attracts proteins and cells only with an aid of divalent cations, such as Ca^{2+}. In contrast, the UV-treated titanium surface (right) is full of cell-attracting terminals consisting of the RGD sequence of proteins or positively charged TiO2 surface, which serve as direct chemo-attractants to cells without divalent cations such as Ca^{2+}. Proteins, that are negatively charged, adsorb directly to the positively charged the TiO2 surface. Cells, that are negatively charged, also attach directly to the positively charged the TiO2 surface. (C) A distinct interfacial layer formation at UV-photofunctionalized titanium surfaces. Based on the mechanisms in panel B, UV-induced bioactive titanium surfaces enable direct titanium–cell interaction, as opposed to untreated titanium surfaces that are bioinert and require inorganic and biological bridges for cell attachment and adhesion. (Taken from: Iwasa et al. [67].)

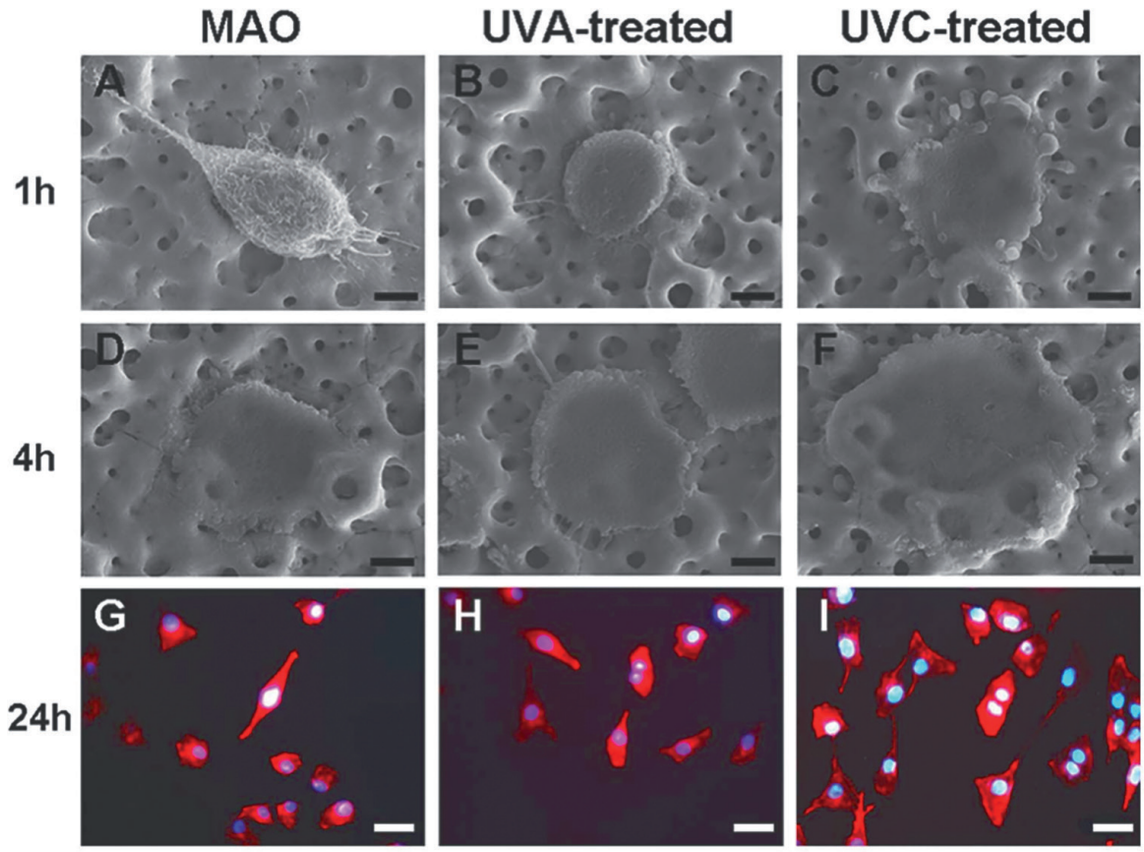

Figure 11.
Initial morphologies of the MG-63 osteoblasts on the titanium surface. (3000X, bar = 10 mm) SEM images of cells on the micro-arc oxidized (MAO), UVA-treated and UVC-treated surfaces after (A–C) 1 h and (D–F) 4 h incubation; (400X, bar = 50 mm) Fluorescence microscopy images of cells on the MAO, UVA-treated and UVC-treated surfaces after (G–I) 24 h incubation. (Taken from: Gao et al. [60].)

attachment and spread is one such behavior that may indicate the responsiveness of implant materials towards UV pre-treatment. Different surface topographies, including but not limited to acid-etched, sandblasted, machined, and nano-featured surfaces, have been investigated [56, 57, 59, 60, 63, 67, 69, 71–76]. The number of osteoblasts attached to UV-treated surfaces was reported to be 3 to 5-fold higher after 3 hrs of incubation, and 2 to 3-fold higher after 24 hrs of incubation [56, 67, 74]. It is evident from these studies that UV photofunctionalization increases the capacity of osteoblastic cells to attach to and spread along titanium surfaces (**Figure 11**).

The degree and nature of osteogenic cell settlement on implant surfaces is important. For instance, lack of adequate attachment and spread of osteogenic cells fails to induce their functional phenotypes or even their differentiation [69, 71]. Further, considering that implant materials are subjected to functional loading which causes mechanical stress and friction at the interface, the initial settlement and retention of osteogenic cells is crucial. Iwasa et al. studied the retentive capacity of osteoblasts cultured on titanium surfaces for 3 and 24 hrs [67]. Cell detachment was attempted mechanically by vibrational force and enzymatically by trypsin treatment. Retention of the cells, as evaluated by the percentage of cells remaining after the detachment procedures, was substantially enhanced on UV-treated titanium surfaces compared to untreated surfaces (110–120% greater for cells incubated for 3 hrs and 50–60% greater for cells incubated for 24 hrs). Miyauchi et al. and Yamada et al. used a special biomechanical setup monitored under phase-contrast microscopy to assess the retention capacity of cultured osteoblasts [73, 77]. Their results showed that after incubation

of 3 hrs, the mean critical shear force required to initiate detachment of a single osteoblast and the total energy required to complete the detachment was much greater for UV-treated TiO_2 surfaces as compared to untreated surfaces. Such substantial increases in single-cell adhesion were also observed for osteoblasts cultured for 24 hrs.

Cell retention and adhesion can also be assessed by studying the cytoskeletal structure and proteins on the osteoblasts. It was observed by Iwasa et al. that during the initial stage of cell culture, osteoblasts on UV-treated surfaces were larger, with elongated cytoplasmic projections (filopodia and lamellipodia) and increased formation of cytoskeleton [67]. Vinculin, a focal adhesion protein involved in cell linkage serving a key role in initiating and establishing cell adhesion, has also been used to evaluate cell retention capacity. Studies using image-based densitometry as well as western blot test revealed that the extent of vinculin expression in an individual osteoblast was substantially higher on UV-treated surfaces than on untreated surfaces after incubation with rat-derived osteoblasts (up to 5-fold higher at 3 hrs and 2.5-fold higher at 24 hrs). However, the increased vinculin expression was observed only when standardized with the total protein and not when standardized with the cell area [63, 67, 69, 73, 77]. Iwasa et al. found that expression of other focal adhesion proteins such as paxillin and phosphorylated paxillin was higher on UV-treated surfaces [63]. Thus, the increased retention of the cells may be caused by the expedited and efficient settlement as well as reinforced adhesion of cells on UV-treated titanium surfaces.

The proliferation and differentiation of osteogenic cells determine the amount and speed of bone formation, respectively. The rate of proliferation of osteoblasts evaluated by BrdU incorporation assay, which targets the S phase of the cell cycle, has been reported to increase by up to 50–80% after UV-treatment of titanium [71]. The rate of osteogenic differentiation can be examined using multiple assays for various biologic markers. Alkaline phosphatase activity, calcium ion deposition, expression of collagen I, osteopontin, osteocalcin, and expression of other osteoblastic genes are some parameters which have been consistently evaluated on UV-treated titanium surfaces [67, 71, 72, 77]. Cell mineralization assays have reported increased alkaline phosphatase activity as well as increased calcium ion deposition for all UV-treated surfaces with different topographies. Studies with RT-PCR analysis showed an upregulation of the expression of collagen I, osteopontin and osteocalcin by up to 70%. As much as adhesion behavior varies with surface properties of implant materials, it is also regulated by the Rho-family GTPase enzymes. These enzymes are controlled by the Rac, Rho and Cdc42 genes. Gene expression analysis by Iwasa et al. revealed that for UV-treated titanium surfaces cultured with rat-derived osteoblasts, expression of Rac was upregulated by 1.5-fold after 3 hrs and 1.7-fold after 24 hrs of incubation, expression of Cdc42 was upregulated by 2-fold after 3 hrs and 1.5-fold after 24 hrs, but expression of Rho was not altered significantly [63]. Harder et al. studied the changes in pro-inflammatory gene expression in human whole blood after initial contact with UV-conditioned implant surfaces and found that there was suppression of IL-1β expression whereas there was no change in TNF-α expression [78]. All of the above *in vitro* studies have been confirmed with both animal and human-derived osteoblasts, as well as periosteum-derived osteogenic cells [63, 67, 68].

Microbial attachment on implant surfaces, especially at the implant-tissue interface is the primary cause of peri-implant inflammation and subsequent implant failure. UV photofunctionalization has been shown to have a considerable effect on bacterial accumulation around implants. The UV-induced physiochemical changes in titanium surfaces were reported to be responsible for the reduced bacterial attachment and biofilm formation. Yamada et al. reported via fluorescence microscopic

quantification that attachment of bacterial pathogens such as *Staphylococcus aureus* or *Streptococcus pyogenes* on titanium surfaces (irrespective of their topography) was reduced following UV treatment [61]. Denaturing gradient gel-electrophoresis (DGGE) and DNA sequencing analyses by de Avila et al. revealed that while bacterial community profiles appeared different between UV-treated and untreated titanium in the initial attachment phase, this difference vanished as biofilm formation progressed [79]. Jain et al. reported that despite the reductive effect of UV pre-irradiation on bacterial attachment, cell viability was not affected adversely as 50% of bacterial killing capacity was maintained [80]. This suggests that UV-photofunctionalization of titanium has a strong potential to improve the outcome of implant placement by creating and maintaining antimicrobial surfaces.

A few authors sought to explain the effect of implant photofunctionalization from a technical perspective. Ohyama et al. carried out finite element analyses to understand how the photofunctionalization-led increase in BSC affected the peri-implant mechanical stress distribution. They reported that the simulated increase in BSC from 53–98% improved distribution and diffusion of peri-implant stress more effectively than using longer implants [81]. Another such study by Ohyama et al. concluded that under vertical loading, photofunctionalization had a greater effect than increased implant diameter on stress reduction [82]. Thus, UV treatment of implants may potentially reduce peri-implant stress and counteract the stress-induced marginal bone loss.

3.3 *In vivo* effects

It is important to correlate the results from *in vitro* studies with the results of *in vivo* studies to help understand and validate the biologic processes and mechanisms behind them. *In vivo* establishment of implant fixation in bone is a pertinent variable that reflects the clinical capacity of implants to bear loading. There has been extensive documentation regarding the strength of osseointegration and implant stability as determined by the histomorphometric assessment of BSC, biomechanical testing, and ISQ measurements.

Photofunctionalization substantially increases the strength of bone-implant integration by enabling near-complete coverage of bone around the implant. Various studies have reported the degree of osseointegration as evaluated by micro-CT, SEM and EDS analyses to be considerably higher when implants were pre-treated with UV light [56, 64, 71, 72, 83–85]. Pyo et al. evaluated the bone-implant interface of UV-treated implants using static and dynamic histological techniques, and when compared to UV-untreated implants, they reported an intensive mineralized layer in marginal bone which improved marginal bone seal and support, and expedited robust interfacial bone deposition (**Figure 12**) [83]. Studies have also shown that new bone formation occurs extensively around UV-treated implants, with little intervention by soft tissue (less than 1%), while the bone tissues around untreated implants are fragmentary and localized with intervening soft tissue (up to 21%) [71]. Yamazaki et al. reported increased peri-implant bone volume (1.5–2 fold) after UV treatment at the early and late stages without deterioration of bone mineral density [84]. In addition to bone volume studies, Hirota et al. used EDS mapping to determine the mineral content of new bone. Their results showed elemental peaks of calcium and phosphorus on various parts of UV-treated implants but the treated, as well as untreated implants, comprised the same Ca/P ratio, indicating bone tissue. However, the Ca/Ti ratios of the UV-treated implant surfaces were approximately 20 times greater than those of the control group (**Figure 13**) [72]. It is noteworthy that UV photofunctionalization maintains its advantage during later stages of healing, unlike other surface modification

techniques which are effective only initially, indicating that UV photofunctionalization does not merely accelerate the process of osseointegration but also increases the level/degree of osseointegration [71].

RT values for UV-treated implants were reported to be 50–60% than those of untreated implants [83]. The osseointegration speed index (OSI) calculated as the difference between two ISQ readings at different intervals was reported to be 2–3 times higher for UV-treated implants [86–89]. The biomechanical push-in values assessed for UV-treated implants using a rat model were 2.5–3 times greater than those of untreated implants [63, 64, 71, 90]. In most of the studies the level of osseointegration seen at week 2 around UV-treated implants was equivalent to that seen around the untreated implants at week 8, indicating that UV treatment may have the potential to accelerate the process of osseointegration 4-fold [71]. These results suggest that UV photofunctionalization may be effective in enhancing the anchoring capability of titanium implants.

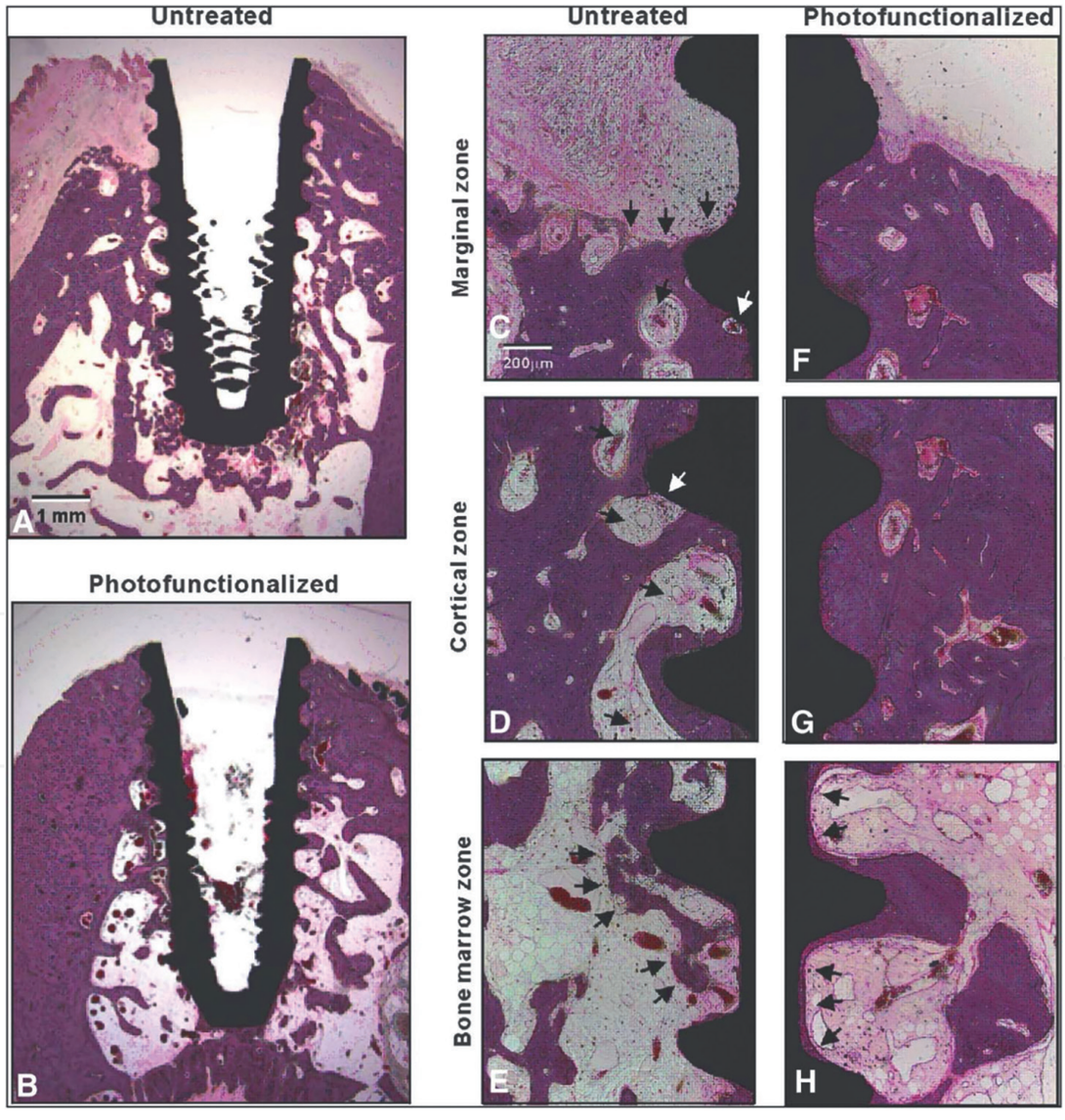

Figure 12.
Peri-implant bone morphogenesis enhanced by photofunctionalization. Low magnification microscopic images of peri-implant tissues around untreated implants (A) and photofunctionalized implants (B). High magnification images of untreated implants (C–E) and photofunctionalized implants (F–H), zooming up the portions in (A) and (B) in each of marginal, cortical, and bone marrow zones. (Taken from: Pyo et al. [83].)

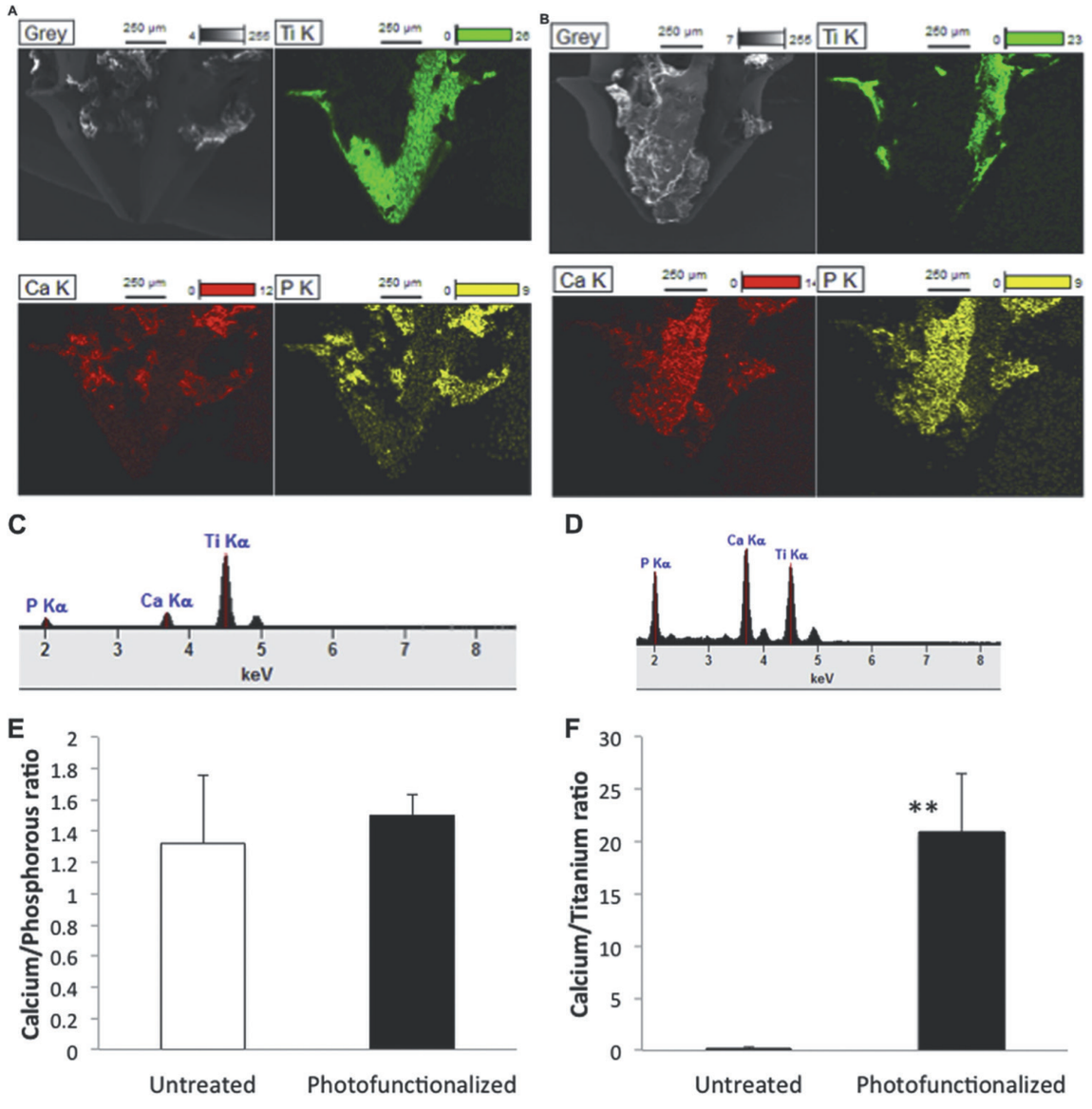

Figure 13.
*Scanning electron microscopy images showing energy dispersive x-ray spectroscopy (EDX) mapping (A,B) and EDX spectrum (C,D) of the apical part of the screw at 4 weeks. The Ca/P ratio shows that the mineralized tissue attached to the surface on the screw is bone. Titanium (Ti) was mainly detected in the mapping of the untreated group (A). However, much more bone tissue had attached to the screws in the photofunctionalized group, and mapping showed more Ca and P than Ti, indicating that the surface was more greatly covered by bone tissue than in the untreated group (B). Ca/P ratio (E) and Ca/Ti ratio (F) of the surface of the apical part of the screw at 4 weeks. Both Ca/P ratios were equal and consistent with bone tissue. The Ca/Ti ratio in the photofunctionalized group was extraordinarily greater compared with that of the untreated group, indicating dense and rich bone tissue covering the screw surface (**P < .01). (Taken from: Hirota et al. [72])*

The effects of UV photofunctionalization of implants have been studied in challenging host conditions for osseointegration to simulate clinical situations [64, 65, 66, 69, 91–94]. Ueno et al. reported greater strength of osseointegration in a rat model at both early and late healing stages for UV-treated shorter implants as compared to untreated regular length implants [91]. This suggests that UV photofunctionalization may overcome the loss of anchoring capacity due to reduced length of implants and may allow the use of shorter implants in certain clinical situations. Kim et al. reported enhanced osseointegration in UV-treated implants placed near critical one-wall defects in beagle dogs [85]. Kitajima et al. reported that photofunctionalized implants placed with low, extremely low, or even absent primary stability showed a high success rate eventually

[92]. Kim et al. and Lee et al., through their studies in rabbit calvarial defects, showed that UV-treatment promoted *de novo* osteogenesis as well as enhanced bone regeneration in critical rabbit calvarial defects [93, 94]. Thus, there is enough evidence to suggest that UV photofunctionalization may play a major role in mitigating challenging/compromised host conditions and aid in enhanced implant integration.

However, of all the studies which have reported the effects of photofunctionalization, only Mehl et al. reported this surface modification technique to be ineffective in enhancement of implant biologic activity [95]. Their *in vivo* study in edentulous minipig jaws revealed that the BSC value for UV-treated implants after 9 months of healing was about 64% only, which is similar to what many studies have reported for conventional UV-untreated implants, suggesting that photofunctionalization had no significant effect in enhancing osseointegration.

3.4 Effects on other implant materials

A majority of published literature on UV photofunctionalization is based on titanium as the implant material as it is most commonly used. However, there are some studies which have reported the effect of UV treatment on other implant materials as well. *In vitro* analyses of zirconia disks showed that their UV pre-treatment resulted in a physiochemical alteration of surface properties similar to those seen in UV-treated titanium surfaces [96, 97]. Brezavšček et al. showed that osteoconductive capacity of zirconia-based implant materials in a rat model was enhanced by their UV pre-treatment [98]. Shahramian et al. reported that UV treatment of zirconia disks ($_{TiO2}$-coated and non-coated) promoted platelet activation and thereby hastened blood coagulation [99]. This suggests that UV treatment has the potential to expedite wound healing around plain as well as coated zirconia implants.

Decco et al. reported that UV treatment of sandblasted chromium-cobalt-molybdenum (Cr-Co-Mo) alloy disks resulted in physiochemical alteration of surface properties similar to that of UV-treated titanium [100]. A recent study by Elkhidir et al. on rat-derived mesenchymal stem cells (MSCs) showed that UV treatment of gold nanoparticles increased its osteogenic capabilities by enhancing cell functions as well as osteogenic gene expression (Col-1, osteoprotegerin, osteocalcin) and mineralization [101]. All of these studies suggest that photofunctionalization of non-titanium implant materials also enhances their bioactivity and can have varied applications in the future.

3.5 Effects on orthodontic miniscrews

Despite this technique having been proven effective for all sizes and topographies of titanium implants, its clinical use with orthodontic miniscrews has not yet been investigated thoroughly. An *in vivo* study by Tabuchi et al. in rat femurs evaluated the osseointegration potential of photofunctionalized orthodontic miniscrews [102]. Via biomechanical push-in tests, it was found that displacement of untreated screws was 1.5–1.7 times greater than that of UV-functionalized screws (**Figure 14**). Surface evaluation showed robust bone formation around UV-treated screws with strong elemental peaks of calcium and phosphorus, whereas the tissue around untreated miniscrews appeared thin and showed no clear peak of calcium. In a similar comparative study, the maximum IT and RT values were measured. While the IT values were similar for both groups, the RT values were considerably higher for UV-treated miniscrews. This implied that implant strength at insertion was similar whereas, at removal, the strength of UV-treated miniscrews was much greater. SEM analysis

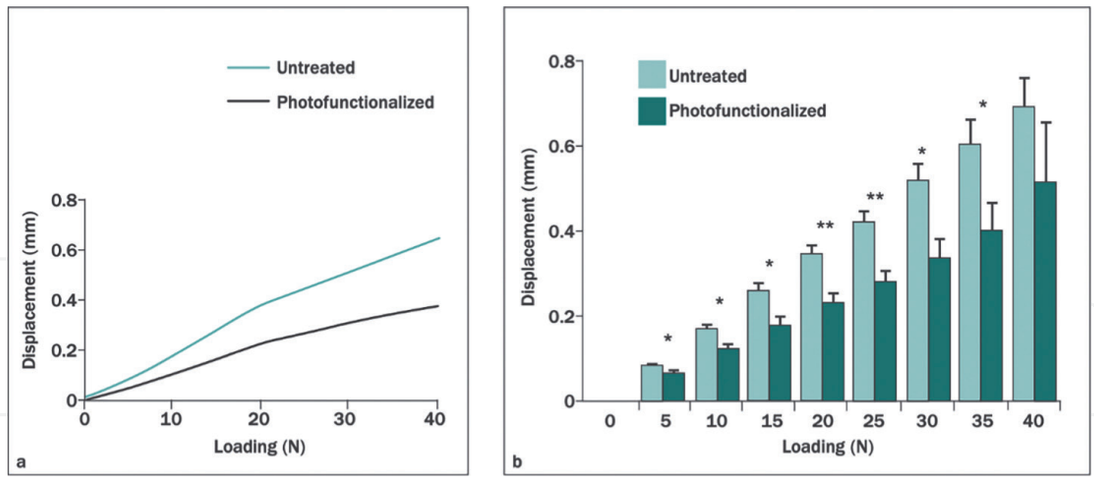

Figure 14.
*The anchorage strength of orthodontic miniscrews with and without photofunctionalization. (a) Representative load–displacement curves for untreated and photofunctionalized miniscrews subjected to a lateral tipping load. (b) The amount of miniscrew horizontal displacement under various levels of load; *P < .05; **P < .01. (Taken from: Tabuchi et al. [102].)*

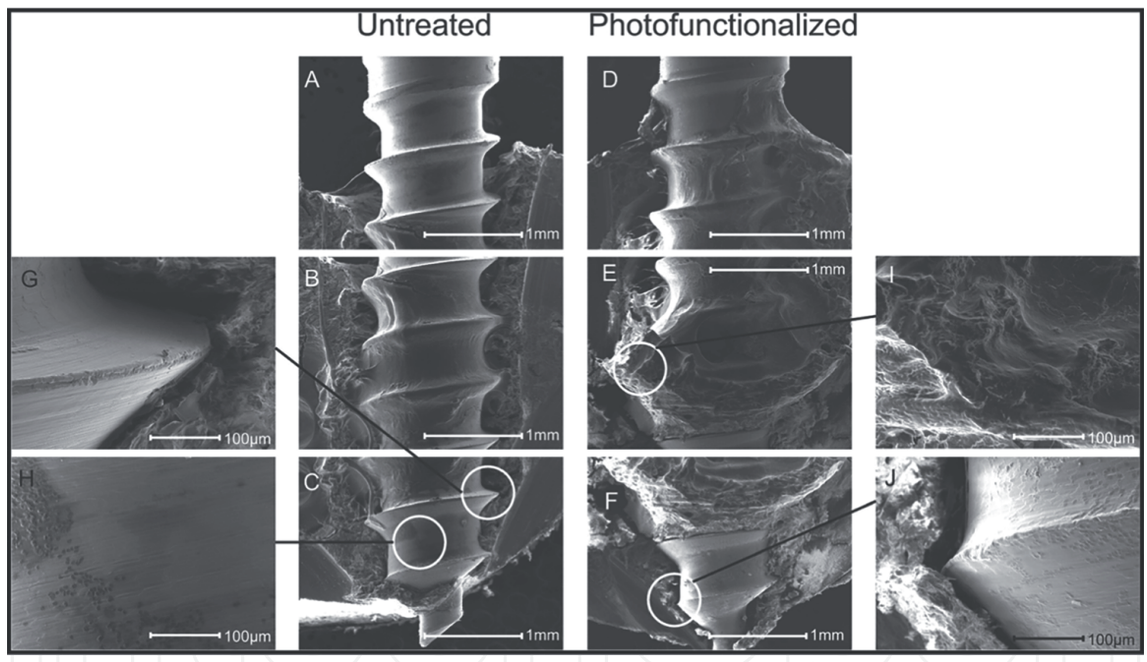

Figure 15.
Scanning electron micrograms of the miniscrews at week 3: (A-J) miniscrews with and without photofunctiolization were compared. (Taken from: Tabuchi et al. [103].)

revealed that regenerated bone tissue was more intact and contiguous around the UV-treated miniscrews than around the untreated ones, and the miniscrew-bone complex seemed to produce interface failure, and not cohesive fracture (**Figure 15**) [103]. Takahashi et al. studied the stability of UV-functionalized orthodontic miniscrews under immediate loading in growing rats [104]. A significantly less (almost 1/2) screw mobility was observed with the UV-treated miniscrews in both, the unloaded as well as immediately loaded groups. Once again SEM analysis revealed an increased BSC (1.8 times) in the UV-treated miniscrew groups.

Recently, the authors conducted a split-mouth *in vivo* human study for the first time using photofunctionalized miniscrews [105]. They studied the effect of UV

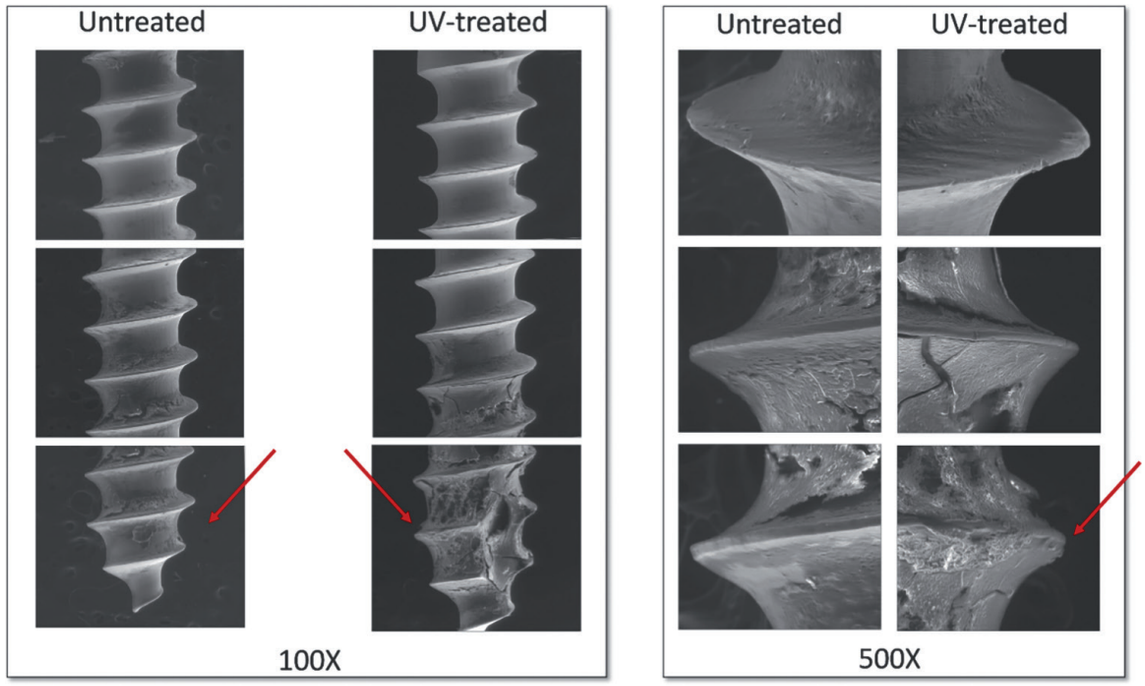

Figure 16.
Representative SEM images of untreated and UV-treated groups from upper, middle and lower regions of miniscrews: **A**, *images taken at 100X magnification,* **B**, *images taken at 500X magnification. (Taken from: Rampurawala et al. [105].)*

Comparison	M_1-M_2	sd	t-value	p-value	Inference
Ca/Ti Ratio					
Upper region of untreated v/s UV-treated group	0.08	0.4199	0.70	0.75619	NS
Middle region of untreated v/s UV-treated group	-0.05	0.2683	-0.701	0.24853	NS
Lower region of untreated v/s UV-treated group	-0.75	2.4915	-0.998	0.16978	NS
Ca/P Ratio					
Upper region of untreated v/s UV-treated group	-0.03	0.8025	-0.153	0.4415	NS
Middle region of untreated v/s UV-treated group	-0.07	0.7978	-0.393	0.34946	NS
Lower region of untreated v/s UV-treated group	0.19	0.8616	0.912	0.81202	NS

Table 2.
Comparison of Ca/Ti and Ca/P ratios between surfaces of untreated and UV-treated miniscrews in the upper, middle and lower regions.

photofunctionalization on orthodontic miniscrews using SEM to evaluate the BSC and EDS to evaluate surface element deposition. It was observed that there was increased BSC in lower regions of miniscrews in the photofunctionalized group

(**Figure 16**), but this was not statistically significant. There was also no significant difference between the Ca/Ti and Ca/P ratios of UV-treated and untreated miniscrews (**Table 2**). The results of this study were in agreement with only one previous study that reported a lack of improvement in the biomechanical potential of implants [95].

4. Conclusion

Surface modification of orthodontic miniscrews can serve to be an effective method for enhancement of the biologic potential of implant surfaces that could lead to better adaptation with the surrounding bone, as well as for the improvement of their mechanical capabilities thereby allowing better anchorage in more difficult intraoral sites. The SLA, microgrooving, anodization, plasma ion implantation, RBM and nanoscale modifications are techniques meant to be incorporated in the manufacturing process, whereas the UV photofunctionalization technique can be used as a chair-side method for surface treatment of miniscrews. All the aforementioned methods have shown to be effective in both experimental as well as clinical scenarios. The UV photofunctionalization technique is yet to be tested in a clinical situation with orthodontic miniscrews, and it may take a few more years of research before any or some of these techniques can be substantiated to become a standard operating procedure.

Conflict of interest

The authors declare no conflict of interest.

Author details

Abdulqadir Rampurawala[1*] and Amol Patil[2]

1 Private Practice, Mumbai, India

2 Bharati Vidyapeeth Deemed to be University Dental College and Hospital, Pune, India

*Address all correspondence to: aqrampura@gmail.com

References

[1] Kanomi R. Mini-implant for orthodontic anchorage. J Clin Orthod. 1997;31(11):763-767.

[2] Antoszewska J, Papadopoulos MA, Park HS, Ludwig B. Five-year experience with orthodontic miniscrew implants: A retrospective investigation of factors influencing success rates. Am J Orthod Dentofac Orthop. 2009;136(2):158.e1-10.

[3] Park HS, Jeong SH, Kwon OW. Factors affecting the clinical success of screw implants used as orthodontic anchorage. Am J Orthod Dentofac Orthop. 2006;130(1):18-25.

[4] Papageorgiou SN, Zogakis IP, Papadopoulos MA. Failure rates and associated risk factors of orthodontic miniscrew implants: A meta-analysis. Am J Orthod Dentofac Orthop. 2012;142(5):577-595.

[5] Alharbi F, Almuzian M, Bearn D. Miniscrews failure rate in orthodontics: systematic review and meta-analysis. *Eur J Orthod.* 2018;40(5):519-530.

[6] Brånemark PI, Hansson BO, Adell R, Breine U, Lindström J, Hallén O, Ohman A. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. Scand J Plast Reconstr Surg Suppl. 1977;16:1-132.

[7] Buser D, Schenk RK, Steinemann S, Fiorellini JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. J Biomed Mater Res. 1991;25(7):889-902.

[8] Buser D, Broggini N, Wieland M, Schenk RK, Denzer AJ, Cochran DL, Hoffmann B, Lussi A, Steinemann SG. Enhanced bone apposition to a chemically modified SLA titanium surface. J Dent Res. 2004;83(7):529-533.

[9] Giavaresi G, Fini M, Cigada A, Chiesa R, Rondelli G, Rimondini L, Aldini NN, Martini L, Giardino R. Histomorphometric and microhardness assessments of sheep cortical bone surrounding titanium implants with different surface treatments. J Biomed Mater Res A. 2003;67(1):112-120.

[10] Bagno A, Di Bello C. Surface treatments and roughness properties of Ti-based biomaterials. J Mater Sci Mater Med. 2004;15(9):935-949.

[11] Germanier Y, Tosatti S, Broggini N, Textor M, Buser D. Enhanced bone apposition around biofunctionalized sandblasted and acid-etched titanium implant surfaces. A histomorphometric study in miniature pigs. Clin Oral Implants Res. 2006;17(3):251-257.

[12] Tavares MG, de Oliveira PT, Nanci A, Hawthorne AC, Rosa AL, Xavier SP. Treatment of a commercial, machined surface titanium implant with H2SO4/H2O2 enhances contact osteogenesis. Clin Oral Implants Res. 2007;18(4):452-458.

[13] Ogawa T, Nishimura I. Different bone integration profiles of turned and acid-etched implants associated with modulated expression of extracellular matrix genes. Int J Oral Maxillofac Implants. 2003;18(2):200-210.

[14] Ogawa T, Ozawa S, Shih JH, Ryu KH, Sukotjo C, Yang JM, Nishimura I. Biomechanical evaluation of osseous implants having different surface topographies in rats. J Dent Res. 2000;79(11):1857-1863.

[15] Chang CS, Lee TM, Chang CH, Liu JK. The effect of microrough surface treatment on miniscrews used as orthodontic anchors. Clin Oral Implants Res. 2009;20(10):1178-1184.

[16] Fouziya B, Uthappa MA, Amara D, Tom N, Byrappa S, Sunny K. Surface modifications of titanium implants - The new, the old, and the never heard of options. J Adv Clin Res Insights. 2016;3:215-219.

[17] Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dent Mater. 2007;23(7):844-854.

[18] Wehrbein H, Merz BR, Hammerle CH, Lang NP. Bone-to-implant contact of orthodontic implants in humans subjected to horizontal loading. Clin Oral Implants Res. 1998;9(5):348-353.

[19] Jeon MS, Kang YG, Mo SS, Lee KH, Kook YA, Kim SH. Effects of surface treatment on the osseointegration potential of orthodontic mini-implant. Korean J Orthod. 2008;38(5):328-336.

[20] Yadav S, Upadhyay M, Roberts WE. Biomechanical and histomorphometric properties of four different mini-implant surfaces. Eur J Orthod. 2015;37(6):627-635.

[21] Espinar-Escalona E, Bravo-Gonzalez LA, Pegueroles M, Gil FJ. Roughness and wettability effect on histological and mechanical response of self-drilling orthodontic mini-implants. Clin Oral Investig. 2016;20(5):1115-1120.

[22] Maino BG, Di Blasio A, Spadoni D, Ravanetti F, Galli C, Cacchioli A, Katsaros C, Gandolfini M. The integration of orthodontic miniscrews under mechanical loading: a pre-clinical study in rabbit. Eur J Orthod. 2017;39(5):519-527.

[23] Sirisa-Ard A, Woodroffe Michael SN, Ahmed K, Dunstan CR, Pearce SG, Bilgin AA, Dalci O, Darendeliler MA. Histomorphological and torque removal comparison of 6mm orthodontic miniscrews with and without surface treatment in New Zealand rabbits. Eur J Orthod. 2015;37(6):578-583.

[24] Park SH, Kim SH, Ryu JH, Kang YG, Chung KR, Kook YA. Bone-implant contact and mobility of surface-treated orthodontic micro-implants in dogs. Korean J Orthod. 2008; 38(6):416-426.

[25] Ikeda H, Rossouw PE, Campbell PM, Kontogiorgos E, Buschang PH. Three-dimensional analysis of peri-bone-implant contact of rough-surface miniscrew implants. Am J Orthod Dentofac Orthop. 2011;139(2):e153-163.

[26] Kim SH, Lee SJ, Cho IS, Kim SK, Kim TW. Rotational resistance of surface-treated mini-implants. Angle Orthod. 2009;79(5):899-907.

[27] Vilani GNL, Ruellas AC deO, Elias CN, Mattos CT. Stability of smooth and rough mini-implants: clinical and biomechanical evaluation - an in vivo study. Dent Press J Orthod. 2015;20(5):35-42.

[28] Schätzle M, Männchen R, Balbach U, Hämmerle CHF, Toutenburg H, Jung RE. Stability change of chemically modified sandblasted/acid-etched titanium palatal implants: a randomized-controlled clinical trial. Clin Oral Implants Res. 2009;20(5),489-495.

[29] Calderón JH, Valencia RM, Casasa AA, Sánchez MA, Espinosa R, Ceja I. Biomechanical anchorage

evaluation of mini-implants treated with sandblasting and acid etching in orthodontics. Implant Dent. 2011;20(4):273-279.

[30] Kim SH, Choi JH, Chung KR, Nelson G. Do sand blasted with large grit and acid etched surface treated mini-implants remain stationary under orthodontic forces? Angle Orthod. 2012;82(2):304-312.

[31] Chaddad K, Ferreira AF, Geurs N, Reddy MS. Influence of surface characteristics on survival rates of mini-implants. Angle Orthod. 2008;78(1):107-113.

[32] Park HJ, Choi SH, Choi YJ, Park YB, Kim KM, Yu HS. A prospective, split-mouth, clinical study of orthodontic titanium miniscrews with machined and acid-etched surfaces. Angle Orthod. 2018;89(3):411-417.

[33] Proff P, Kauschke E, Rumpel E, Bayerlein T, Dietze S, Fanghänel J, Gedrange T. The survival and proliferation of fibroblasts on orthodontic miniscrews with different surface treatment: an in vitro study. Folia Morphol (Warsz). 2006;65(1):78-80.

[34] Nahm KY, Heo JS, Lee JH, Lee DY, Chung KR, Ahn HW, Kim SH. Gene profiling of bone around orthodontic mini-implants by RNA-sequencing analysis. Biomed Res Int. 2015;2015:538080.

[35] Kim JS, Kang SM, Seo KW, Nahm KY, Chung KR, Kim SH, Ahn JP. Nanoscale bonding between human bone and titanium surfaces: osseohybridization. Biomed Res Int. 2015:960410.

[36] Kim JS, Ahn JP, Kim YH, Seo KW, Zadeh H, Kim SH. Atomic layout of an orthodontic titanium mini-implant in human tissue: Insights into the possible mechanisms during osseointegration. Angle Orthod. 2019;89(2):292-298.

[37] Kim SH, Cho JH, Chung KR, Kook YA, Nelson G. Removal torque values of surface-treated mini-implants after loading. Am J Orthod Dentofac Orthop. 2008;134(1):36-43.

[38] Kim TW, Baek SH, Kim JW, Chang YI. Effects of microgrooves on the success rate and soft tissue adaptation of orthodontic miniscrews. Angle Orthod. 2008;78(6):1057-1064.

[39] Hall J, Lausmaa J. Properties of a new porous oxide surface on titanium implants. Appl Osseointegration Res. 2000;1:5-8.

[40] Ivanoff CJ, Hallgren C, Widmark G, Sennerby L, Wennerberg A. Histologic evaluation of the bone integration of TiO_2-blasted and turned titanium microimplants in humans. Clin Oral Implants Res. 2001;12(2):128-134.

[41] Ivanoff CJ, 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(3):341-348.

[42] Omar O, Svensson S, Zoric N, Lennerås M, Suska F, Wigren S, Hall J, Nannmark U, Thomsen P. In vivo gene expression in response to anodically oxidized versus machined titanium implants. J Biomed Mater Res A. 2010;92(4):1552-1566.

[43] Karmarker S, Yu W, Kyung HM. Effect of surface anodization on stability of orthodontic microimplant. Korean J Orthod. 2012;42(1):4-10.

[44] Choi SH, Cha JY, Joo UH, Hwang CJ. Surface changes of anodic oxidized orthodontic titanium

miniscrew. Angle Orthod. 2012;82(3): 522-528.

[45] Choi SH, Jang SH, Cha JY, Hwang CJ. Evaluation of the surface characteristics of anodic oxidized miniscrews and their impact on biomechanical stability: an experimental study in beagle dogs. Am J Orthod Dentofac Orthop. 2016;149(1):31-38.

[46] Kim SJ, Moon YP, Park GH, Jo HH, Kim WG, Son MK, Choe HC. Surface characteristics and electrochemical behaviors of TiN and ZrN coated orthodontic miniscrew. J Korean Inst Surf Eng. 2008;41(5):232-239.

[47] Cho YC, Cha JY, Hwang CJ, Park YC, Jung HS, Yu HS. Biologic stability of plasma ion-implanted miniscrews. Korean J Orthod. 2013;43(3):120-126.

[48] Coelho PG, Granjeiro JM, Romanos GE, Suzuki M, Silva NR, Cardaropoli G, Thompson VP, Lemons JE. Basic research methods and current trends of dental implant surfaces. J Biomed Mater Res B Appl Biomater. 2009;88(2):579-596.

[49] Kim SC, Kim HY, Lee SJ, Kim CM. Influence of surface treatment on the insertion pattern of self-drilling orthodontic mini-implants. Korean J Orthod. 2011;41(4):268-279.

[50] Gansukh O, Jeong JW, Kim JW, Lee JH, Kim TW. Mechanical and histological effects of resorbable blasting media surface treatment on the initial stability of orthodontic mini-implants. Biomed Res Int. 2016;2016:7520959.

[51] Kim HY, Kim SC. Bone cutting capacity and osseointegration of surface-treated orthodontic mini-implants. Korean J Orthod. 2016;46(6):386-394.

[52] Oh EJ, Nguyen TDT, Lee SY, Jeon YM, Bae TS, Kim JG. Enhanced compatibility and initial stability of Ti6Al4V alloy orthodontic miniscrews subjected to anodization, cyclic precalcification, and heat treatment. Korean J Orthod. 2014;44(5):246-253.

[53] Jang I, Shim SC, Choi DS, Cha BK, Lee JK, Choe BH, Choi WY. Effect of TiO_2 nanotubes arrays on osseointegration of orthodontic miniscrew. Biomed Microdevices. 2015;17(4):76.

[54] Cha BK, Choi DS, Jang I, Choe BH, Choi WY. Orthodontic tunnel miniscrews with and without TiO_2 nanotube arrays as a drug-delivery system: in vivo study. Biomed Mater Eng. 2016;27(4):375-387.

[55] Jang I, Choi DS, Lee JK, Kim WT, Cha BK, Choi WY. Effect of drug-loaded TiO_2 nanotube arrays on osseointegration in an orthodontic miniscrew: an in-vivo pilot study. Biomed Microdevices. 2017;19(4):94.

[56] Aita H, Hori N, Takeuchi M, Suzuki T, Yamada M, Anpo M, Ogawa T. The effect of ultraviolet functionalization of titanium on integration with bone. Biomaterials. 2009;30(6):1015-1025.

[57] Att W, Ogawa T. Biological aging of implant surfaces and their restoration with ultraviolet light treatment: a novel understanding of osseointegration. Int J Oral Maxillofac Implants. 2012;27(4):753-761.

[58] Att W, Hori N, Iwasa F, Yamada M, Ueno T, Ogawa T. The effect of UV-photofunctionalization on the time-related bioactivity of titanium and chromium-cobalt alloys. Biomaterials. 2009;30(26):4268-4276.

[59] Aita H, Att W, Ueno T, Yamada M, Hori N, Iwasa F, Tsukimura N, Ogawa T. Ultraviolet light-mediated

photofunctionalization of titanium to promote human mesenchymal stem cell migration, attachment, proliferation and differentiation. Acta Biomater. 2009;5(8):3247-3257.

[60] Gao Y, Liu Y, Zhou L, Guo Z, Rong M, Liu X, Lai C, Ding X. The effects of different wavelength UV photofunctionalization on micro-arc oxidized titanium. PLoS One. 2013;8(7):e68086.

[61] Yamada Y, Yamada M, Ueda T, Sakurai K. Reduction of biofilm formation on titanium surface with ultraviolet-C pre-irradiation. J Biomater Appl. 2014;29(2):161-171.

[62] Roy M, Pompella A, Kubacki J, Szade J, Roy RA, Hedzelek W. Photofunctionalization of titanium: an alternative explanation of its chemical-physical mechanism. PLoS One. 2016;11(6):e0157481.

[63] Iwasa F, Baba K, Ogawa T. Enhanced intracellular signaling pathway in osteoblasts on ultraviolet light treated hydrophilic titanium. Biomed Res. 2016;37(1):1-11.

[64] Hirota M, Ikeda T, Tabuchi M, Ozawa T, Tohnai I, Ogawa T. Effects of ultraviolet photofunctionalization on bone augmentation and integration capabilities of titanium mesh and implants. Int J Oral Maxillofac Implants. 2017;32(1):52-62.

[65] Shen J, Liu J, Chen X, Wang X, He F, Wang H. The in vivo bone response of ultraviolet-irradiated titanium implants modified with spontaneously formed nanostructures: an experimental study in rabbits. Int J Oral Maxillofac Implants. 2016;31(4):776-84.

[66] Hori N, Ueno T, Minamikawa H, Iwasa F, Yoshino F, Kimoto K, Lee MC, Ogawa T. Electrostatic control of protein adsorption on UV-photofunctionalized titanium. Acta Biomater. 2010;6(10):4175-4180.

[67] Iwasa F, Hori N, Ueno T, Minamikawa H, Yamada M, Ogawa T. Enhancement of osteoblast adhesion to UV-photofunctionalized titanium via an electrostatic mechanism. Biomaterials. 2010;31(10):2717-2727.

[68] Qin Z, Teng W. Effect of ultraviolet-photofunctionalization of titanium on protein adsorption and competition. Zhonghua Kou Qiang Yi Xue Za Zhi. 2015;50(7):428-432.

[69] Ishijima M, Hirota M, Park W, Honda MJ, Tsukimura N, Isokawa K, Ishigami T, Ogawa T. Osteogenic cell sheets reinforced with photofunctionalized micro-thin titanium. J Biomater Appl. 2015;29(10):1372-1384.

[70] Areid N, Kangasniemi I, Söderling E, Närhi TO. Ultraviolet photofunctionalization of nanostructured titanium surfaces enhances thrombogenicity and platelet response. J Mater Sci Mater Med. 2018;29(5):56.

[71] Ishijima M, Ghassemi A, Soltanzadeh P, Tanaka M, Nakhaei K, Park W, Hirota M, Tsukimura N, Ogawa T. Effect of UV photofunctionalization on osseointegration in aged rats. Implant Dent. 2016;25(6):744-750.

[72] Hirota M, Tanaka M, Ishijima M, Iwasaki C, Park W, Ogawa T. Effect of photofunctionalization on Ti6Al4V screw stability placed in segmental bone defects in rat femurs. J Oral Maxillofac Surg. 2016;74(4):861.e1-16.

[73] Miyauchi T, Yamada M, Yamamoto A, Iwasa F, Suzawa T, Kamijo R, Baba K,

Ogawa T. The enhanced characteristics of osteoblast adhesion to photofunctionalized nanoscale TiO_2 layers on biomaterials surfaces. Biomaterials. 2010;31(14):3827-3839.

[74] Tsukimura N, Yamada M, Iwasa F, Minamikawa H, Att W, Ueno T, Saruwatari L, Aita H, Chiou WA, Ogawa T. Synergistic effects of UV photofunctionalization and micro-nano hybrid topography on the biological properties of titanium. Biomaterials. 2011;32(19):4358-4368.

[75] Kim HS, Lee JI, Yang SS, Kim BS, Kim BC, Lee J. The effect of alendronate soaking and ultraviolet treatment on bone-implant interface. Clin Oral Implants Res. 2016;28(9):1164-1172.

[76] Henningsen A, Smeets R, Hartjen P, Heinrich O, Heuberger R, Heiland M, Precht C, Cacaci C. Photofunctionalization and non-thermal plasma activation of titanium surfaces. Clin Oral Investig. 2017;22(2):1045-1054.

[77] Yamada M, Miyauchi T, Yamamoto A, Iwasa F, Takeuchi M, Anpo M, Sakurai K, Baba K, Ogawa T. Enhancement of adhesion strength and cellular stiffness of osteoblasts on mirror-polished titanium surface by UV-photofunctionalization. Acta Biomater. 2010;6(12);4578-4588.

[78] Harder S, Quabius ES, Meinke F, Mehl C, Kern M. Changes in proinflammatory gene expression in human whole blood after contact with UV-conditioned implant surfaces. Clin Oral Investig 2019.

[79] de Avila ED, Lima BP, Sekiya T, Torii Y, Ogawa T, Shi W, Lux R. Effect of UV-photofunctionalization on oral bacterial attachment and biofilm formation to titanium implant material. Biomaterials. 2015;67:84-92.

[80] Jain S, Williamson RS, Marquart M, Janorkar AV, Griggs JA, Roach MD. Photofunctionalization of anodized titanium surfaces using UVA or UVC light and its effects against *Streptococcus sanguinis*. J Biomed Mater Res B Appl Biomater. 2017;106(6):2284-2294.

[81] Ohyama T, Uchida T, Shibuya N, Nakabayashi S, Ishigami T, Ogawa T. High bone-implant contact achieved by photofunctionalization to reduce periimplant stress: a three-dimensional finite element analysis. Implant Dent. 2013;22(1):102-108.

[82] Ohyama T, Yasuda H, Shibuya N, Tadokoro S, Nakabayashi S, Namaki S, Hara Y, Ogawa T, Ishigami T. Three-dimensional finite element analysis of the effects of implant diameter and photofunctionalization on peri-implant stress. J Oral Sci. 2017;59(2):272-278.

[83] Pyo SW, Park YB, Moon HS, Lee JH, Ogawa T. Photofunctionalization enhances bone-implant contact, dynamics of interfacial osteogenesis, marginal bone seal, and removal torque value of implants: a dog jawbone study. Implant Dent. 2013;22(6):666-675.

[84] Yamazaki M, Yamada M, Ishizaki K, Sakurai K. Ultraviolet-C irradiation to titanium implants increases peri-implant bone formation without impeding mineralization in a rabbit femur model. Acta Odontol Scand. 2015;73(4):302-311.

[85] Kim MY, Choi H, Lee JH, Kim JH, Jung HS, Kim JH, Park YB, Moon HS. UV photofunctionalization effect on bone graft in critical one-wall defect around implant: a pilot study in beagle dogs. Biomed Res Int. 2016;2016:4385279.

[86] Funato A, Ogawa T. Photofunctionalized dental implants: a case series in compromised bone. Int J

Oral Maxillofac Implants. 2013;28(6):1589-1601.

[87] Funato A, Yamada M, Ogawa T. Success rate, healing time, and implant stability of photofunctionalized dental implants. Int J Oral Maxillofac Implants. 2013;28(5):1261-1271.

[88] Suzuki S, Kobayashi H, Ogawa T. Implant stability change and osseointegration speed of immediately loaded photofunctionalized implants. Implant Dent. 2013;22(5):481-490.

[89] Hirota M, Ozawa T, Iwai T, Ogawa T, Tohnai I. Implant stability development of photofunctionalized implants placed in regular and complex cases: a case-control study. Int J Oral Maxillofac Implants. 2016;31(3):676-86.

[90] Soltanzadeh P, Ghassemi A, Ishijima M, Tanaka M, Park W, Iwasaki C, Hirota M, Ogawa T. Success rate and strength of osseointegration of immediately loaded UV-photofunctionalized implants in a rat model. J Prosthet Dent. 2017;118(3):357-362.

[91] Ueno T, Yamada M, Hori N, Suzuki T, Ogawa T. Effect of ultraviolet photoactivation of titanium on osseointegration in a rat model. Int J Oral Maxillofac Implants. 2010;25:287-294.

[92] Kitajima H, Ogawa T. The use of photofunctionalized implants for low or extremely low primary stability cases. Int J Oral Maxillofac Implants. 2016;31(2):439-447.

[93] Kim SY, Bark CW, Van Quy H, Seo SJ, Lim JH, Lee JM, Suh JY, Lee Y, Um HS, Kim YG. Photofunctionalizing effects of hydroxyapatite combined with TiO_2 on bone regeneration in rabbit calvarial defects. J Biomed Mater Res B Appl Biomater. 2019;107(6):1953-1959.

[94] Lee JE, Bark CW, Quy HV, Seo SJ, Lim JH, Kang SA, Lee Y, Lee JM, Suh JY, Kim YG. Effects of enhanced hydrophilic titanium dioxide-coated hydroxyapatite on bone regeneration in rabbit calvarial defects. Int J Mol Sci. 2018;19(11):e3640.

[95] Mehl C, Kern M, Neumann F, Bähr T, Wiltfang J, Gassling V. Effect of ultraviolet photofunctionalization of dental titanium implants on osseointegration. J Zhejiang Univ Sci B. 2018;19(7):525-534.

[96] Tuna T, Wein M, Swain M, Fischer J, Att W. Influence of ultraviolet photofunctionalization on the surface characteristics of zirconia-based dental implant materials. Dent Mater. 2015;31(2):e14-24.

[97] Roy M, Pompella A, Kubacki J, Piosik A, Psiuk B, Klimontko J, Szade J, Roy RA, Hedzelek W. Photofunctionalization of dental zirconia oxide: Surface modification to improve bio-integration preserving crystal stability. Colloids Surf B Biointerfaces. 2017;156:194-202.

[98] Brezavšček M, Fawzy A, Bächle M, Tuna T, Fischer J, Att W. The effect of UV treatment on the osteoconductive capacity of zirconia-based materials. Materials (Basel). 2016;9(12):e958.

[99] Shahramian K, Abdulmajeed A, Kangasniemi I, Söderling E, Närhi T. TiO_2 coating and UV photofunctionalization enhance blood coagulation on zirconia surfaces. Biomed Res Int. 2019;8078230.

[100] Decco O, Zuchuat J, Farkas N. Improvement of Cr-Co-Mo membrane surface used as barrier for bone regeneration through UV photofunctionalization: an in vitro study. Materials (Basel). 2017;10(7):e825.

[101] Elkhidir Y, Lai R, Feng Z. The impact of photofunctionalized gold nanoparticles on osseointegration. Heliyon. 2018;4(7):e00662.

[102] Tabuchi M, Ikeda T, Hirota M, Nakagawa K, Park W, Miyazawa K, Goto S, Ogawa T. Effect of UV photofunctionalization on biologic and anchoring capability of orthodontic miniscrews. Int J Oral Maxillofac Implants. 2015;30(4):868-879.

[103] Tabuchi M, Ikeda T, Nakagawa K, Hirota M, Park W, Miyazawa K, Goto S, Ogawa T. Ultraviolet photofunctionalization increases removal torque values and horizontal stability of orthodontic miniscrews. Am J Orthod Dentofac Orthop. 2015;148(2):274-282.

[104] Takahashi M, Motoyoshi M, Inaba M, Hagiwara Y, Shimizu N. Enhancement of orthodontic anchor screw stability under immediate loading by ultraviolet photofunctionalization technology. Int J Oral Maxillofac Implants. 2016;31(6):1320-1326.

[105] Rampurawala AH, Patil AS, Bhosale VI. Bone-miniscrew contact and surface element deposition on orthodontic miniscrews after ultraviolet photofunctionalization. Int J Oral Maxillofac Implants 2020;35(6):1090-1097.