# Review
# Basic Research Methods and Current Trends of Dental Implant Surfaces

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**Abstract: Among dental implant design alterations, surface modifications have been by far the most investigated topic. Regarding implant surface research, the lack of hierarchical approaches relating *in vitro*, *in vivo*, clinical trials, and *ex vivo* analyses has hindered biomaterials scientists with clear informed rationale guidelines for implant surface design. This manuscript provides a critical hierarchical overview of the *in vitro*, laboratory *in vivo*, clinical, and *ex vivo* methodologies used to investigate the performance of novel biomaterials aiming to allow dental professionals to better evaluate the past, present, and future dental implant surface research. This manuscript also contains an overview of the commercially available surface texture and chemistry modifications including novel nanotechnology-based fabrication processes. Over the last decade, surface texturing has been the most utilized parameter for increasing the host-to-implant response. Recently, dental implant surfaces utilizing reduced length scale physico/chemical features (atomic and nanometric) have shown the potential to synergistically use both texture and the inclusion of bioactive ceramic components on the surface. Although surface modifications have been shown to enhance osseointegration at early implantation times, information concerning its long-term benefit to peri-implant tissues is lacking due to the reduced number of controlled clinical trials. Given the various implants/surfaces under study, the clinician should ask, founded on the basic hierarchical approach described for the *in vitro*, laboratory *in vivo* data, as well as the results of clinical studies to effectiveness before use of any dental implant.** © 2008 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 88B: 579–596, 2009

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## INTRODUCTION

Following the definition of "osseointegration" as the close contact between bone and titanium and its alloys at the light microscope level,[1,2] substantial manufacturing, laboratory, and clinical research resulted in enhanced dental treatment modalities and expanded application of the dental implants. During the early 80's, one treatment modality focused on very controlled surgical placement of biocompatible titanium screws in bone. The principles established by the Swedish group[3] with respect to the time of osseointegration and the necessity of isolation of the implant from mechanical loading required a latency period of several months for bone healing to establish device osseointegration.[3] Throughout this healing period, the implants were not submitted to intraoral functional load, and during a second surgical procedure the implant osseointegration was verified and a series of clinical and laboratorial steps fol-

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lowed until re-establishment of the patient's form, function, and esthetics.[4–6]

Since then, documentation of over two thousand scientific publications along with its application in thousands of patients during the last 40 years has been a key factor to make implant dentistry one of the most successful treatment modalities in medicine and dentistry. Treatment success rates often reported higher than 90% in controlled clinical trials although and agreed upon definition of success remains elusive.[3–5,7–9]

Despite early research reports showing that failure of dental implants were mainly associated with the time allowed for bone healing around the implants, and also possibly encouraged by the good results of the original two staged protocol, practitioners have pushed for decreased treatment times for therapy completion.[8,6,10–22]

Specific to early loading of endosseous implants, where the prosthetic component is installed and loaded shortly after the surgical procedure, it has been speculated that design alterations in both surgical and restorative procedures, as well as in implant design may significantly affect the treatment short and long-term outcomes. From an implant design perspective, two approaches including the fields of biomaterials and/or biomechanics have been most utilized; implant body design and surface modifications.

Despite contradictory research results and protocol opinion concerning immediate/early loading of endosseous implants,[4,6,11–16,20–22] it is apparent that instead of being based upon well-designed *in vitro*, laboratory *in vivo*, and clinical research results, the main driving force for implant design has been rationalization driven by implant therapy protocol alteration towards diminishing the period allowed for bone healing after implant placement. However, little to no implant bulk designs and biomaterials' variations (especially new surface treatments) have been fully characterized before commercialization.[1,2] Limitations in previous implant designs have been rarely investigated to allow an informed design rationale for their successors, resulting in empirical guidelines for the great majority of implant modifications.

Although the implant surface is the first component to interact with the host, surface modifications have been extensively investigated in an attempt to increase the rate of bone healing and thereby allowing practitioners immediate/early loading of dental implants. Increasing the surface biocompatibility and osseoconductive properties may promote enhanced bone healing and apposition that lead to rapid biological fixation of implants to bone.[23] According to the literature, postmachining surface texturization though a variety of techniques or the incorporation of bioactive ceramic as surface coatings favor both bone anchoring/biomechanical stability.[1,2,24]

This manuscript provides a critical overview of the most common *in vitro*, laboratory *in vivo*, clinical, and *ex vivo* methodologies used to investigate the performance of novel biomaterials/implant surfaces. Then, an overview of the current commercially available and ongoing development of implant surfaces obtained through a variety of processes is provided.

## IMPLANT SURFACES

Immediately following the implant placement, a series of events occur between the host and the surface of endosseous implants.[23] This sequence of events includes the initial interaction between blood and the implant surface, where proteins and ligands are dynamically adsorbed onto and released from the implant surface, through an inflammatory process, which is followed by initial bone formation around the implant (modeling), and through several remodeling cycles, where bone surrounding the implant achieves its highest degree of organization and mechanical properties.[23] Because of the dynamic nature of the bone-biomaterial interface as a function of implantation time, endosseous dental implant biomaterials must have short- and long-term biocompatible and biofunctional properties.[25]

From the point of view of physics, a surface may be defined as the sudden interruption of the atomic arrangement.[26] This sudden interruption results in differences between surface and bulk electronic properties, leading to different physico/chemical behavior between the two regions of the material. Therefore, from a theoretical standpoint, different modification methods utilized for implant surface engineering may lead to different and unique surface properties.[26] These different physico/chemical properties can potentially lead to changes in the host-to-implant response. New surface treatments should be tested as new biomaterials. As examples, the alteration of surface topography or the incorporation of bioactive ceramics as coatings have been investigated and utilized on a large scale by implant dentistry practitioners with no or limited surface characterization.[1,2,23,24,27–31]

Despite the extensive literature accumulated over the past decades concerning the host/biomaterial response, several considerations should be taken into account concerning the complex effects of endosseous dental implants surface modifications during and after the process of osseointegration. Biological considerations, such as biocompatibility and osseoconductivity of the implant should be addressed. In addition, specific surface effects on initial bone healing kinetics and mechanical properties evolution as implantation time elapses *in vivo*, as well as the *in vivo* stability of the surface (often regarded as one of the leading factors of long-term osseointegration) should be hierarchically investigated to more fully evaluate implant therapy surgical and/or prosthetic protocol modifications.

A hierarchical approach, where *in vitro* testing followed by laboratory animal research leading to subsequent controlled prospective and/or retrospective clinical trials, is often neglected before new biomaterials are commercially introduced. Therefore, treatment protocol changes, such as a decrease in the time allowed for osseointegration of

immediately/early loaded dental implants have often followed the empirical rationales.

### Biocompatibility of Biomaterials

Before clinical trials, new biomaterials (including surface modifications) should undergo *in vitro* and *in vivo* evaluation. This type of evaluation typically follows a hierarchical approach, where *in vitro* testing evolves to *in vivo* laboratory experiments, and then to clinical trials in humans.[23] The hierarchical testing approach is useful in cases where surface modifications are compared with previous surfaces that have successfully been in function for several years. In a simplistic fashion, if the new surface or biomaterial does not have at least equivalent performance when tested in *in vitro* and *in vivo* laboratory models, time consuming complex clinical research protocols may be avoided.

***In Vitro* Testing.** *In vitro* laboratory models often consist of evaluating the effects of novel surfaces versus control surfaces (in the case of dental implant surfaces, machined or surface-modified c.p. Ti or Titanium alloys) on cell cultures.[32]

Cell culture studies attempt to track cell morphology, adhesion, migration, proliferation, or death as a function of potentially toxic agents derived from the biomaterial.[23] Although *in vitro* cell culture evaluations have been shown to be useful for preliminary evaluation of novel biomaterials biocompatibility related to safety, results obtained in cell cultures have not yet been fully correlated to *in vivo* performance.[32] Specific to evaluating cellular behavior associated with implant surfaces, cell cultures by no means represent the dynamic *in vivo* bone/biomaterial environment, and multiple conclusions concerning the potential *in vivo* behavior based on *in vitro* cell testing should be taken as speculation. Validation must be based on animal models and subsequent clinical trials. Nonetheless, cell culture has been useful as a first assessment of biocompatibility related to the safety of novel biomaterial designs.[32]

Implant surface modifications through chemical process may lead to production of leachable products potentially toxic to cells.[33–35] Direct contact, agar diffusion, and extract dilution are the primary cytocompatibility assays, where standardized procedures enable comparisons and minimize bias. The inclusion of positive and negative controls and the use of established cell lines and standardized protocols published by the U.S. Pharmacopeia, the American Society for Testing and Materials (ASTM), the British Standards Institute (BSI), and International Standards Organization (ISO) rationalize the screening for cytocompatible biomaterials.[36] It's worthwhile to mention that Health organizations in the United States (Food and Drug Administration), Brazil (National Agency of Sanitary Vigilance), Europe, and other countries legally require Pharmacopeial assays for regulatory and commercialization of biomaterials and medical devices.[37,38] What remains to be fully explored are cell functions such as adhesion, migration, proliferation, synthesis, and deposition of extracellular matrix chemical compounds using mammalian cells of the tissue/organ relevant to specific applications.[39,40]

Considering new biomaterials, an understanding of biomaterial-induced cell signaling molecules is strategic for devices design. For instance, the role of monocytes/macrophages in foreign body reaction has become evident,[37,38] and specific information concerning the osteoblast[41] and osteoclast responses[42] to wear particles and surface topography can be screened in specific *in vitro* assays of cell signaling molecules. Thus, currently available *in vitro* assays have increasingly gained popularity in biomedical device designing regarding materials safety.

On the other hand, although biomaterials safety is currently tested in *in vitro* assays, regulatory and scientific governmental agencies such as the National Institutes of Health in the United States have expressed interest in developing more complex laboratory-based testing methods. The intent is to develop models that are more representative and predictive of *in vivo* behavior such as organ cultures presenting similar cellular content and architecture as the host tissue.

The development of bone organ cultures require the maintenance of three dimensional bone explants and their cellular and extracellular content in the laboratory setting.[43] In addition to the biological content maintenance *in vitro*, the physiologic-like maintenance of bone organ cultures has been challenged by difficulties in appropriately reproducing physiologic loading conditions *in vitro*.[43] Such difficulties have resulted in limited use of bone organ culture studies of hard tissue integration, which requires establishment and maintenance of cultures for long periods of time. However, bone organ cultures have been utilized in other research areas such as the effects of wear particle composition and size in bone inflammatory response.[44]

It is acknowledged that despite the current difficulties and limitations provided by *in vitro* cell and organ cultures, developments will soon result in cell and organ cultures that are more representative of *in vivo* scenarios. Such developments will expand the *in vitro* evaluation of biomaterials beyond safety issues, mimicking *in vivo* testing conditions decreasing the time, cost, and regulatory issues concerning animal research protocols.

***In Vivo* Testing.** Following *in vitro* laboratory testing for the general safety of new biomaterials' surfaces, laboratory *in vivo* models are the next step in biocompatibility testing complexity.

Various animal models and surgical protocols have been utilized to evaluate the host response to endosseous implants.[1,24,45–53] Despite the development of an extensive literature in the field, variations in wound healing and the kinetics of bone healing due to local physiologic properties of different surgical sites and animal species have not been sufficiently characterized to enable direct one-to-one com-

parisons between animal models or data extrapolation to human clinical scenarios.[48] Nonetheless, animal models are of vital importance when novel biomaterial design is compared with previously investigated designs of known clinical performance.

The most frequently used animals for dental implant research are rats, rabbits, sheep, dogs, pigs, and nonhuman primates. Among the attributes taken into consideration to determine which animal model is most appropriate for a particular research protocol are site similarity to humans under physiologic and pathologic conditions as well as availability of large numbers of specimens over time.[54,55] Other considerations include acceptability to the society, cost, availability, age, size (multiple implant placement for comparison), tolerance to surgery and captivity, housing, and different countries animal protection act.[56] Specific to studies considering the bone-implant interface, bone macrostructure, microstructure, and modeling/remodeling kinetics should be considered while extrapolating the results to humans.[56]

Because of its relatively low cost, ease of handling, and a substantial number of previously published data, the rabbit model has been the most utilized for dental implant bone-implant interface studies. The amount of published work is then followed by research protocols utilizing dogs.[54] Detailed information regarding other animal models utilized in bone-implant interface studies can be found elsewhere.[54–56]

Despite its extensive use in dental implant research, the rabbit model major drawback includes its size when compared with larger animals such as dogs and sheep when a number of control and experimental implants are recommended per animal (ISO 10993-6[36]). In addition, the commonly utilized rabbit bones such as tibia and femur are one of the least similar animal models when compared with human. Significantly different bone macrostructure (especially when comparing the amount of trabecular bone between human alveolar bone to rabbit long bones), microstructure, kinetics, and cell content are found between rabbit and human.[57] Thus, the extrapolation of results obtained in rabbit studies relative to humans is a challenge and should be carefully performed.

The second most utilized model in musculoskeletal and dental implant research is the canine model.[58] When compared with the rabbit model, the canine model is remarkably larger and different sites with relatively different bone macromorphology and micromorphology are available.

Considering the canine intra oral site, extraction of the four premolars followed by a healing period before implant placement has been commonly used.[59–61] Alternative to the intra oral site, the femur[62,63] and tibia[64,65] have also been utilized. Although the intra oral site provides a bone microstructure that is morphologically similar to human mandible with respect to cortical to trabecular ratio,[66–68] the tibia and femur sites provide a model where high amounts of trabecular bone are present. The elimination of potential complications involved in tooth extraction makes the tibia and femur attractive relative to the dog intra oral sites. In addition, the presence of high amounts of trabecular bone in these long bones is attractive for testing dental implant properties because highly osteoconductive materials are desirable for regions of low cortical-to-trabecular bone ratios. Specific to dental implant surface research, where most protocols comprise the temporal placement of implants for comparison in physiologically loaded implants, relative differences in osseointegration and biomechanical assessment can be tracked in both mandible[66] and long bones like the femur and tibia.[64,65]

Its has been previously shown that dog along with pig bones are the most similar to human bone composition among the animal models utilized for musculoskeletal research.[69] However, data extrapolation between these large animals and humans is still challenged by the different mineral apposition rates encountered at different bones.[69] Another drawback related to larger animal models is the ethical issue of their utilization in medical research, especially concerning the number of animals and operable sites/times per animal.

There are many different animal models, surgical sites, times *in vivo*, and the lack of a standard control biomaterial (i.e. a standard implant surface) among the many *in vivo* studies reported in the dental literature. Therefore, direct comparison between previously published results is practically impossible with respect to which implant surface has the best physico/chemical configuration to increase early wound healing kinetics.

Irrespective of differences in species and site, it is acknowledged that valuable information may be retrieved from properly designed animal studies. Specific to comparison between different implant surfaces, power analysis should be performed relative to the parameter to be evaluated as this dictates the number of animals to be utilized. Because implant surfaces are expected to increase the host-to-implant response, it is recommended that several implantation times be utilized in order to establish temporal evolution of the analyzed variables between the implant surfaces. The implantation times should be determined from the literature pertinent to each species and site, or from pilot investigations. Regardless of animal model, it is acknowledged that extrapolation of results to human scenarios is a challenge. However, controlled animal studies evaluating temporal changes in the bone-implant interface provide valuable relative comparisons between different implant surfaces.

Measurable indicators of the host/implant response have been utilized in cases where two different surface designs are compared. However, to decrease the degree of speculation with respect to the most critical mechanisms of the host/implant response between different surface designs, the largest possible number of biological response indicators (static and dynamic histomorphometric parameters, plus biomechanical testing) should be evaluated to the establishing correlations.

Substantial data have been published concerning the temporal evolution of various bone-biomaterial interfaces. Yet, whether the increased mechanical stability of different surfaces is due to an increased mechanical locking of tissue within the surface roughness, increased bone-implant contact, increased surrounding bone density, biologically modified bone bonding, or the interplay between such variables is still controversial or unknown.[23,70] Often a combination of factors exists.

*In vivo* comparisons between different implant surface designs typically have a histomorphometric and/or a biomechanical component. The histomorphometric part of the study typically evaluates static parameters such as the amount of bone-to-implant contact (BIC), bone density, amount, and type of cellular content, among others. Less often reported but not less valuable than the static measurements, dynamic histomorphometric parameters such as mineral apposition rate (MAR) have also been utilized. The biomechanical testing component usually evaluates the push-out force,[71] pull-out force,[72] or torque to interface failure[1,73] of implants in bone.

It has been established general tissue response to implants, biocompatibility, and osseoconductivity information may be obtained through static histomorphometric measurements. However, any of the previously mentioned parameters alone do not address the tissue healing events that led to the measured parameters evaluated at a given time period *in vivo*.[74] For example, if a given surface results in higher BIC percentage relative to another at early implantation times, it is impossible to determine the relevance of such observation unless extreme differences in BIC values were observed or a series of other supporting histomorphometric and biomechanical parameters were also measured. From a structural perspective, the BIC amount may be overwhelmed by the quality of the structural support, and implants surrounded by less bone with higher magnitude mechanical properties may be more desirable than an implant surrounded by more bone presenting lower magnitude mechanical properties. This concept should be taken into account especially as bone has the ability to model and remodel under microstrain thresholds (bone deformation under a given load),[75,76] and bone regions of high stress concentrations in the proximity of the implant may be unfavorable if low magnitude bone mechanical properties exist.

Because BIC has been the most often measured parameter *in vivo* investigations, meticulous histomorphologic and biomechanical testing (preferentially nanoindentation along and away from the implant surface) should also be performed to decrease the degree of speculation concerning the benefit of increased BIC for one surface relative to another. In this case, dynamic measurements such as mineral apposition rate (MAR) would be desirable to temporally evaluate bone modeling/remodeling kinetics around different implant surfaces. This would provide insight on how different histomorphologic, histomorphometric, and bone mechanical properties evolved as a function of implantation time.

Studies concerning the effect of different surfaces in bone healing kinetics have been successful in indicating relationships between MAR and static parameters like density.[77,33,34] Unfortunately, the literature concerning bone healing dynamics around different implant surfaces is not only sparse but also contradictory.[77–79] Also, comprehensive studies utilizing both static and dynamic histomorphometric parameters along with biomechanical testing are desirable for better characterizing the evolution of the bone-biomaterial interface around different implant surfaces. This information would decrease the degree of speculation concerning the mechanisms leading to differences in the results.

*Ex vivo* standard biomechanical tests (torque, pull-out, push-out)[1,27,53,71–73,80] usually measure the amount of force or torque to failure of the bone-biomaterial interface surrounding different implant surfaces. Although information concerning the relative degree of biomechanical fixation is obtained, these tests do not provide detailed microscopic information about inherent mechanical properties of the bone-biomaterial interface. In addition, these test methods tend to favor rough implant surfaces, making it a challenge to evaluate different implant surfaces effects on the evolution of bone healing/mechanical properties.

Recently, nanoindentation studies have successfully evaluated the effect of different surface textures in bone mechanical properties as a function of implantation time.[46] Although inherent mechanical property measurements made as a function of time may be assessed through nanoindentation, the value of relative changes in modulus and hardness as a function of healing time around implants is still subjective. For example, it is not possible to predict by simple mechanical property assessment that over a given loading range, if stress patterns or microstrain threshold for bone maintenance or loss[75,76] would significantly affect the overall biomechanical response as a function of implant surface and implantation time. Thus, biomechanical experimental designs that take into consideration both the bone mechanical properties and the geometry around the implant (through 3D imaging tools) are desirable for future designing of improved dental implant systems.

Several factors that influence the phenomena of osseointegration remain under active investigation (i.e. implant/biofluid interactions, the elemental chemistry and structure of surfaces, and the overall mechanisms and kinetics of bone response to implants). Therefore, what is needed is the careful interpretation of the literature along with the definitive characterization of bone physiology and kinetics of healing (MAR, bone mechanical properties) around implants with different surfaces. The evaluation of the highest possible number of host/implant response parameters should be taken into account in future research. This approach would allow a better understanding of bone healing kinetics associated with different implant surfaces,

providing an informed design rationale for future implant systems that would deliver reduced eosseointegration time frames and minimize failures of immediately/early loaded implants.

**Clinical Evaluation of Implant Surfaces.** Clinical evaluation comprises the most complex type of device testing especially the factors associated with the biomaterial *per se*. Although clinical data collection may illustrate the interaction between human tissues and different implant surfaces, from a statistical standpoint, any data collected from clinical trials should be interpreted with caution. Clinical evaluation of different implant surfaces may be a challenge, as large numbers of subjects must be analyzed in a previously determined statistically validated model, and any deviation from the established protocol may lead to results with low credibility.[81,82] Both prospective and retrospective studies must be carefully designed with rigorous number of subjects, inclusion, and exclusion criteria.[81,82] Because the description of prospective and retrospective studies is beyond the scope of this review, the reader may refer to articles where this type of study is critically evaluated.[2,81–84]

Despite the specific points concerning clinical evaluation of implants, it is important to highlight the need for double-blind studies and for registration of trials in order to mitigate against publication bias, to prevent study duplication, and to evidence gaps in the knowledge base favoring international collaboration.[85] To date, there are only three published randomized controlled double blinded studies of implant surface treatments.[86–88] Given that endosseous implants have been in clinical practice for several decades studies, it is surprising that effectiveness studies in the general practice setting have not been reported. The vast majority of clinical studies are based upon the outcomes from specialists and medical and university centers.

**Implant Retrieval Analysis.** The retrieval of previously functional endosseous implants is one of the valuable tools for characterizing short- and long-term host-to-implant interactions as well potential failure mechanisms.[23]

The relative value of implant retrieval analysis is directly related to the amount of information available from patient, clinician, implant therapy modality, and implant system (i.e. lot number). Nonetheless, a lack of knowledge of any of these variables does not limit specific information that can be acquired from retrieved specimens even though limitation of critical information could ultimately lead to erroneous conclusions. For instance, if data concerning the patient medical history and functional habits is not available, it is difficult to relate specific failure mechanisms obtained from retrieval analysis to associated risk factors.

Therefore, careful protocol design must be performed before establishing a retrieval program. If appropriately designed, implant retrieval analysis can be useful in the reverse engineering of biomaterial and biomechanical designs, as investigators are going to learn from both success and failures.[23] For instance, evaluation of implants retrieved from deceased individuals would provide valuable information about successful implant treatment and also be valuable for future implant design. Unfortunately, ethical issues concerning retrieving implants from deceased individuals, the limited number of currently active retrieval programs where multidisciplinary expertise is available, and the decreasing number of reports on failure from both practitioners and implant manufacturers has resulted in a decrease in the number of implant retrieval reports.

## SURFACE MODIFICATION OF ENDOSSEOUS DENTAL IMPLANTS

The primary intention of further processing endosseous implants' surfaces following the primary manufacturing of a device is to positively modulate the host/implant tissue response. For this purpose, numerous surface engineering methods have been utilized to change endosseous dental implant surface topography and chemistry.

For description purposes, surface modification methods will be separated into two categories. The first category comprises primarily topographic surface changes, despite subtle to moderate topographic, and chemical composition differences between different designs,. The second category includes bioactive ceramic incorporation on the implant surface as coatings.

### Topographic/Chemical Surface Modifications

To describe some of the surface modifications currently used in large scale in implant dentistry, it is important to establish the starting point of implant surface design. In early implant dentistry, following machining (turning) of the implant bulk, the implant surface was cleaned and packaged/sterilized before surgical placement. In general, after machining, the implant surface presents periodic grooves that vary based upon machining equipments, such as machining tool type and cutting angle with respect to the implant substrate (Figure 1). This procedure typically results in the implantation of a clean, minimally rough surface ($R_a$ typically ranging from 0.4 to 0.8 $\mu$m), which according to classic protocols requires several months for osseointegration. The machined implant surface was considered the gold standard of implant surface design for decades, and to date is the only surface design properly addressed in the dental implant literature from a statistical standpoint.[89,90] Thus, it is natural that most novel designs are compared with machined implant surfaces in *in vitro*, laboratory *in vivo*, and clinical investigations.[91]

Despite the successful utilization of machined/sterilized implant surfaces (Figure 1) for several decades, several studies have demonstrated that modification on the topographic pattern of the surface (especially if $R_a$ values range from 0.5 to 2 $\mu$m) tends to not only increase the bone-

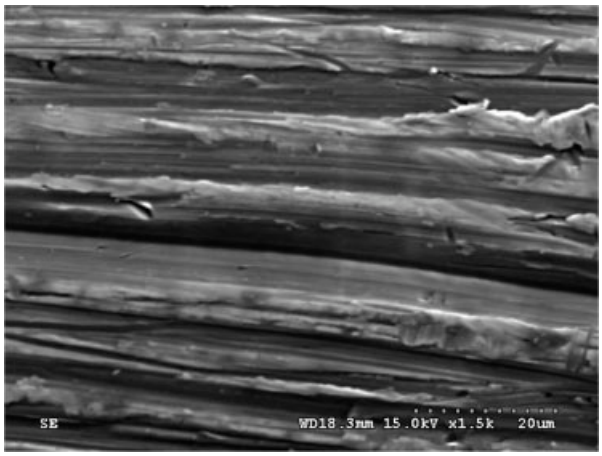


**Figure 1.** Scanning electron micrograph of a machined implant surface. Note the periodic grooves originated from the implant machining.

implant contact but also the biomechanical interaction of the interface between them at early implantation times (comparable values are obtained between rough and as-machined surfaces after several weeks *in vivo*).[1] It should be noted that the majority of current commercial implant systems present $R_a$ ranging from 1 $\mu$m to 2 $\mu$m,[1,27] and that the effects of such characteristics on the osseoconductivity and bone apposition on the implant surface are still under investigation.

If further increases in surface roughness profiles are desired, titanium plasma spraying (TPS, Figure 2) processing of the surface has been one of the methods commonly utilized for obtaining $R_a$ values higher than 2 $\mu$m. This processing results in a substantial surface area increase when compared with other commercially available surfaces.[92–94] Based on that, TPS implants have been often recommended for regions with low bone density (Figure 2).[25]

The TPS processing may increase the surface area of dental implants up to approximately six times the initial surface area.[95] Such increase in surface area is dependent on implant geometry and processing variables, such as initial powder size, plasma temperature, and distance between the nozzle output and target.[25] However, this significant increase in total area does necessarily represent an effective increase in osseointegration area, because spaces greater than 50 $\mu$m are typically required for bone formation and subsequent maintenance.[96] Consequently, the real effective increase in functional area becomes 1.5 to 2 times the initial surface area.[97] Also, increase of six times of the original surface area may not only be a scenario favorable for bone growth and apposition but also becomes a factor when there is an exposure of the implant surface to the oral fluids and bacteria. In addition, intercommunication between porous regions facilitates migration of pathogens to inner bone areas, potentially compromising the success of the implant therapy due to difficulties in controlling periimplantitis.[98] Bacterial contamination could synergistically result in autocatalytic chemical degradation and cause loss of metallic substrate and bone attachment.[97]

Several *in vivo* studies have shown the importance of the surface roughness on osseointegration improvement and acceleration. Rough surfaces, such as obtained by TPS and grit-blasted/acid-etched have shown torque to failure values significantly higher than implants with machined profiles.[1,2,21,24,46,94,97,99–102]

Over the last 5 to 10 years, implant surface texture has been increased through a variety of methods in an attempt to increase surface area, cleanliness, and chemistry.[1,2] One of the earliest methods that was commercially available was surface acid-etching (Figure 3) and grit-blasting/acid-etching (Figures 4 to 8). The majority of commercially available grit-blasted implant surfaces are subsequently acid-etched. The acid-etching procedure aims to further enhance the topographic profile of the surface and remove processing byproducts (this surface treatment may also be applied without previous grit-blasting resulting smoother profiles compared to grit-blasted/acid-etched surfaces, shown in Figure 3). The grit-blasting procedure is generally performed via propulsion towards the metallic substrate of

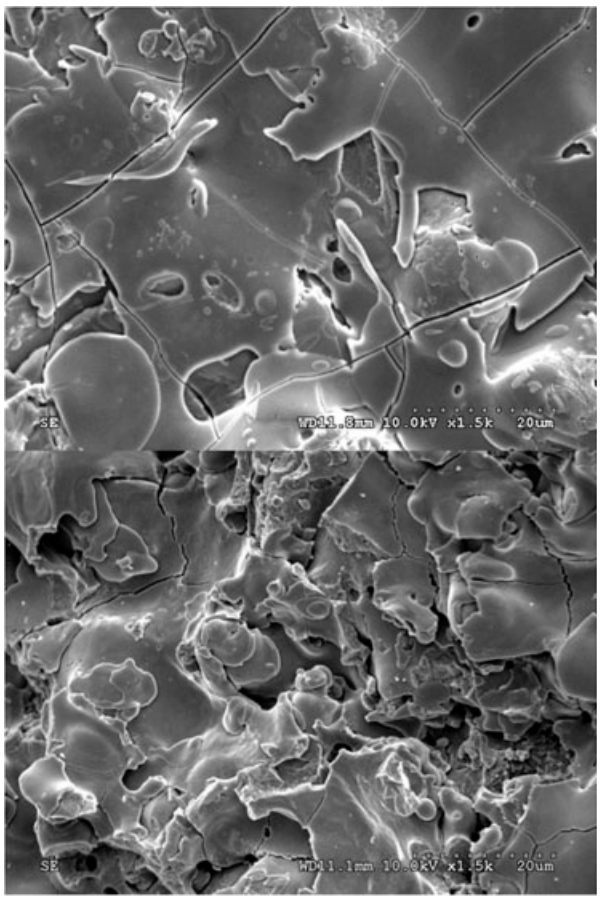


**Figure 2.** Scanning electron micrographs of TPS processed implant surfaces (top: Bicon, LLC USA; bottom: Straumann, Basel, Switzerland). These micrographs also depict the cracks inherent to TPS processing due to rapid cooling.

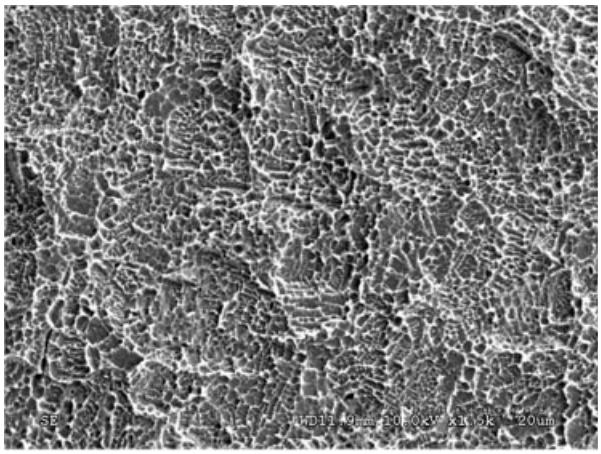

**Figure 3.** Scanning electron micrograph of an implant surface processed through a dual acid-etching procedure (Biomet-3i, Palm Beach Gardens, USA).

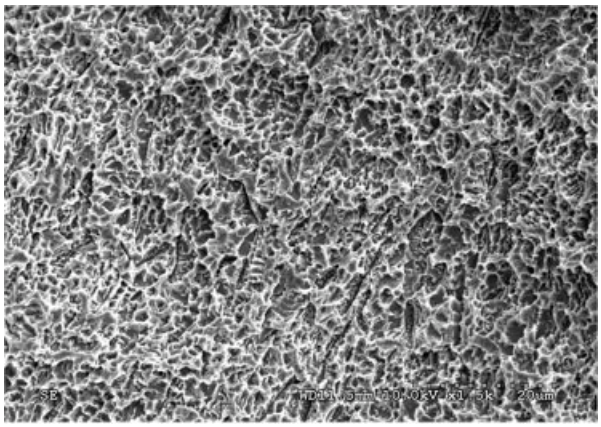

**Figure 5.** Scanning electron micrograph of a sandblasted/large grit/acid-etched (SLA) implant surface (Straumann, Basel, Switzerland).

particles of silica (sand) (Figures 4 and 5), resorbable bioceramic (Resorbable Blast Media—RBM) (Figure 6), alumina (Figure 7), or titanium dioxide (Figure 7) of different particle sizes.[25]

Following grit-blasting, the most commonly utilized acid etching agents are hydrofluoric, nitric, sulfuric, or a combination of different acid solutions.[103] The advantages of this method include an increase in the total surface area of the implant, achieved due to the selective removal resulting from electrochemical differences in the surface topography.[104] However, this process should be carried out under controlled conditions, as over-etching the surface decreases surface topography and mechanical properties and may be detrimental to osseointegration. In addition, it is important that the etching procedures following grit-blasting removes any particle remnants (especially in the case of alumina or silica), because chemical analyses of failed implants have shown evidence that the presence of such particles interferes with titanium osseoconductivity regardless of the established biocompatibility profiles of the biomaterial.[25] Alternatively, grit-blasting the surface with bioceramic particles (RBM process) or titanium dioxide particles would not result in detrimental osseointegration kinetics, because embedded (RBM) bioceramic particles are theoretically resorbed/dissolved after implantation, and titanium dioxide particles embedded in the surface are biocompatible.[25] However, it is acknowledged that irrespective of blasting media, release of particles of varied size from the surface may result in an inflammatory response detrimental to hard tissue integration.[41]

Observations of the dual acid-etched and grit-blasted/acid-etched surfaces showed that different roughness patterns can be obtained depending on the processing condition. Also, the increased surface area is obtained when compared with machined surfaces.[103] It is also evident that different types of particles used for grit-blasting result in surfaces with qualitatively different topographies. Based on the surface roughness ($R_a$), these different types of surface treatments typically result in $R_a$ between 0.5 and 2 $\mu$m,

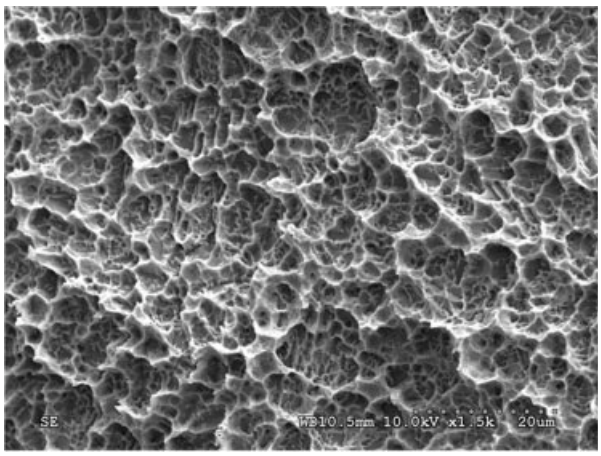

**Figure 4.** Scanning electron micrograph of a sandblasted/acid-etched implant surface (Ankylos, Mannheim, Germany).

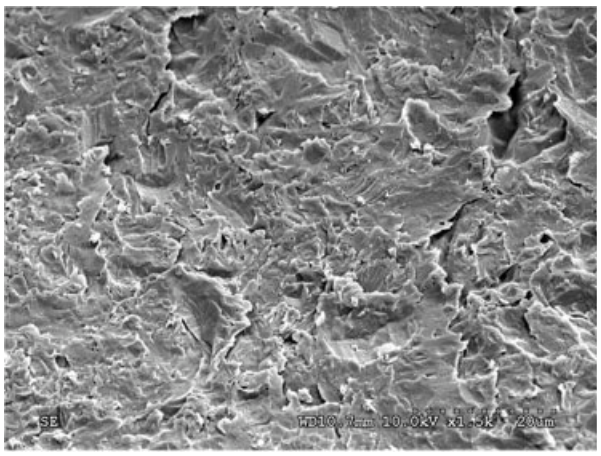

**Figure 6.** Scanning electron micrograph of a RBM-treated implant surface (Biolok-Biohorizons, Birmingham, USA).

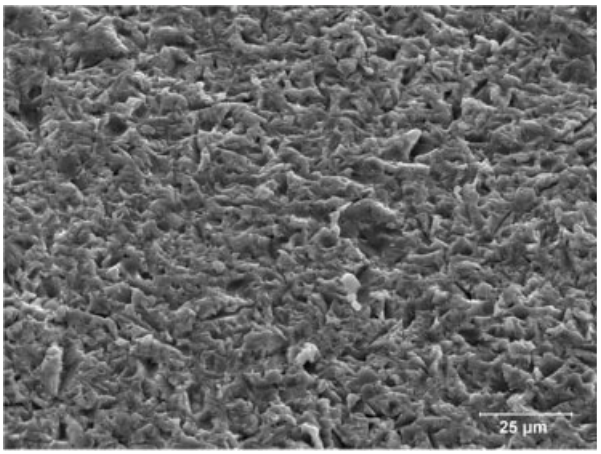


**Figure 7.** Scanning electron micrograph of an alumina-blasted/acid-etched implant surface (Bicon LLC, Boston USA).

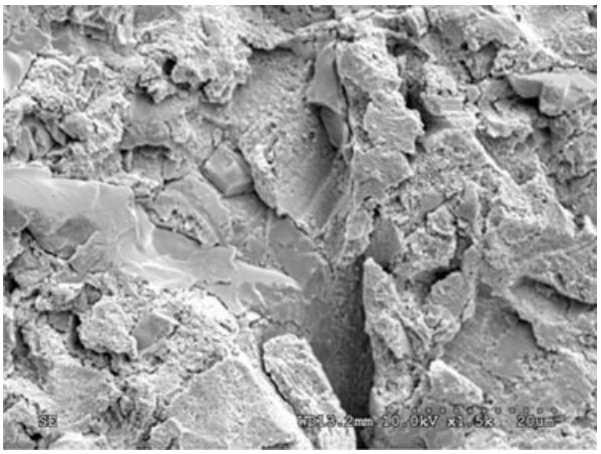

**Figure 9.** Scanning electron micrograph of an Osseospeed® surface (Astra, Mölndal, Sweden).

which are values associated with an increased host-to-implant response at early implantation times.[1,2]

A recent surface modifications presented to the market refer to chemical changes of grit-blasted and acid-etched surfaces. One modification comprises grit-blasting and acid-etching the surface with formulations that result in fluorideon the surface (Figure 9). The final fluoride content in the titanium oxide surface results from the high affinity between titanium and fluoride, resulting in a combination of species with varied stoichiometries within the surface oxide layer. The rationale for such modification is to benefit from both surface topography and chemical composition.[100] Fluoridated surfaces have been shown to enhance gene expression in cell arrays[105] and also enhanced the host-to-implant response at early implantation times.[100,106] However, the mechanism of the bone formation and its mechanical maturity around the implant due to this surface modification remains under investigation.

Another suface modification, named "SLActive" (Straumann, Basel, Switzerland) (Figure 10), involves the modification of the sterilization and storage method of the original SLA (Straumann, Basel, Switzerland) sand-blasted/acid-etched surfaces, in which the implants are provided submerged in saline solution.[24] This surface treatment is based on the hydroxylation of titanium oxides, where metallic surfaces are rendered hydrophilic for water adsorption (hydration).[107]

This surface presents the same roughness pattern when compared with the previous "SLA" (Figure 5).[108] However, physico/chemical characterization of the SLActive surface showed that despite the proprietary processing conditions to obtain the hydroxylated/hydrated surface, its oxide layer thickness was comparable to titanium alloys. Such surface characteristic has resulted in high surface wetability when compared with the SLA surface,[108] which is an at-

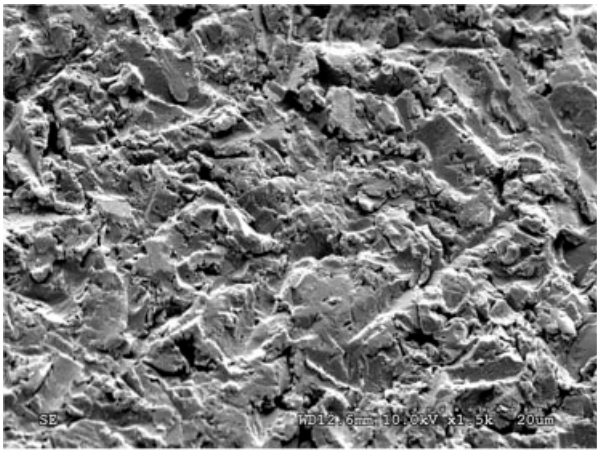

**Figure 8.** Scanning electron micrograph of a titanium oxide blasted /acid-etched implant surface, TiOblast (Astra, Mölndal, Sweden).

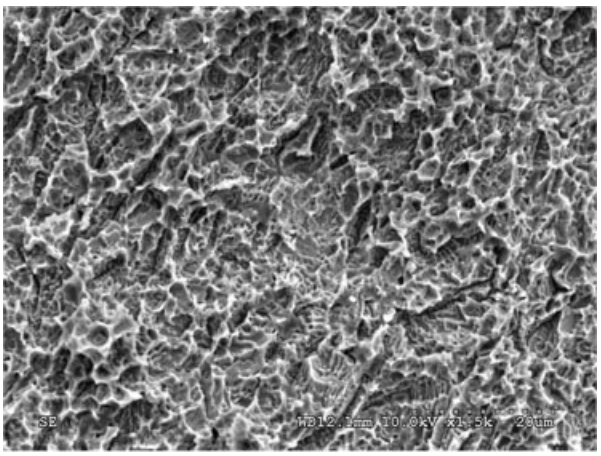

**Figure 10.** Scanning electron micrograph of an SLActive® implant surface (Straumann, Basel, Switzerland). Note the similar surface topography compared to the standard SLA surface (Figure 5). This implant was removed from the package solution and allowed to dry before imaging.

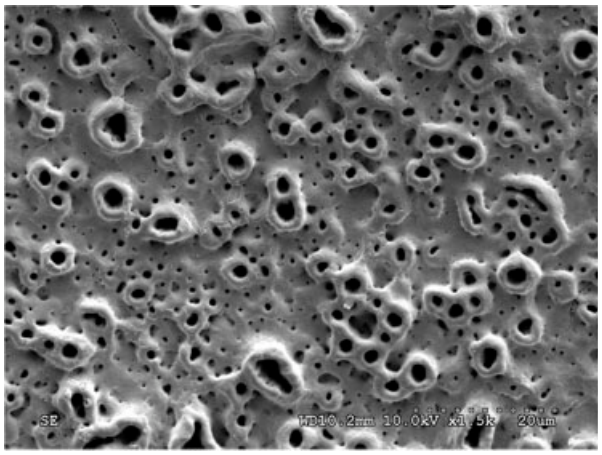


**Figure 11.** Scanning electron micrograph of an anodized (TiUnite®) surface (Nobel Biocare, Sweden).

tribute when implant surfaces-body fluids interact after implant placement.[109]

Animal experiments have shown that the hydrophilic nature of the SLActive surface significantly increased the wound healing kinetics when compared with the previous SLA surface.[24,110,111] However, studies considering the commercially available implant design with the SLActive surface are desirable, because studies using healing chamber models tend to favor an intramembranous-like bone formation instead of appositional bone (commonly observed in screw root form implants).[45] Also, the effect of surface hydrophylicity may not be as evident in screw-type implants when compared with existing studies using healing chamber models.

For a better evaluation of the effects of such chemical modifications onto rough substrates to the osseointegration process, more basic studies considering full surface characterization of experimental and control implants are desirable to elucidate the mechanisms which these subtle surface chemistry changes increase the host to implant initial response leading to its faster biomechanical fixation.

Another postmachining surface modification that has been shown to increase the surface microtexture plus surface chemistry changes/additions during processing is electrochemical anodization (Figure 11). Implant surface topography and chemistry modification is typically achieved by the combination of galvanostatic or potentiostatic anodization of titanium alloys at high current density and when submerged in strong acid solutions of controlled chemistry. This procedure results in thickening of the titanium oxide layer by several orders of magnitude when compared with passivated surfaces. During this process, interaction between forming and dissolving regions of the oxide layer results in a porous microstructure (Figure 11) with varied oxide stoichiometries.[112] Several animal and clinical studies have shown that this surface modification increase the host/implant response at early implantation times relative to other surfaces.[91,113–115]

In general, rough surfaces such as those obtained through grit-blasting with or without subsequent acid-etching, anodization, or through other acid-etching procedures' have demonstrated higher torque values at earlier implantation times when compared with machined surfaces. However, it should be noted that mechanical testing by means of torque-out, pull-out, or push-out tends to favor implants with rougher surface profiles due to mechanical interlocking between bone and implant surface.[1] Thus, whether rougher surface profiles maximally increase the host/implant response and bone mechanical properties at earlier implantation times, or mechanical interlocking between rougher surfaces and bone *per se* is the responsible for increased mechanical testing values, needs further investigation. As previously mentioned, an increase in bone mechanical properties around a dual acid-etched surface (Figure 3) compared with as-machined surface has been demonstrated in a rat model,[46] and the validation of this increase in more complex animal models and humans through retrieval analysis is highly desirable.

Suzuki et al.[77] compared various histomorphometric parameters between machined and titanium plasma sprayed implants in rabbit's tibiae at 6, 16, and 42 weeks. The histomorphometric results showed higher BIC for the rougher surfaces, and no differences in MAR were detected throughout the experiment. Another investigation by Grizon et al.[79] also compared histomorphometric parameters between machined and rough c.p.Ti implant surfaces in a goat model. The authors reported increased bone volume and BIC around implants with rough implant surfaces.[79] However, despite trends observed between the biological response of machined and rough implant surfaces, the mechanism resulting in increased bone response to rough surface is yet to be elucidated.

Studies comparing different implant surfaces are numerous, and it seems to be general consensus that rough implant surfaces with $R_a$[79] values between 0.5 and 2 $\mu$m enhance the host/implant response.[1,2] However, once again we note that direct comparison between different surgical sites, animal models, and the time periods of implantation makes limits evaluation concerning which rough surface better influences the host response to implants.

### Bioactive Ceramic Coating of Dental Implants

Among all engineering based surface modifications for dental and orthopedic implants, the addition of calcium- and phosphorous-based materials as coatings have received significant attention.[25,31,53,70,80,92,97] This interest is in part, because these elements are the same basic components of natural bone and coatings can be applied along the implant surfaces by various industrial processing methods.[25,31]

Most commercially available bio-ceramic coatings are processed as a 20–50 $\mu$m thick Plasma Sprayed Hydroxyapatite (PSHA) coatings (Figure 12).[25,30,31,53,92,97] PSHA coatings normally rely on mechanical interlocking between

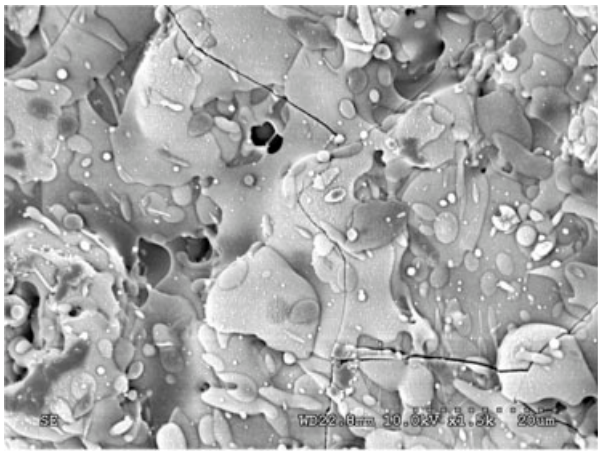

**Figure 12.** Scanning electron micrograph of a PSHA-coated surface (Bicon LLC, Boston, USA). Note the resulting irregular surface due to HA particle propulsion towards the implant surface at high temperatures, and the cooling cracks, which results from rapid cooling.

a grit-blasted or etched metallic surfaces and the ceramic-like PSHA biomaterial for physical integrity during implant placement and function.[25] Substantially enhanced *in vivo* bone-to-bioceramic bonding (bioactivity), and bone-to-implant contact magnitudes have been observed at early implantation times for PSHA-coated implants.[25,30,31,53,70,92,97] However, this type of implant has fallen out of favor in dental practice as studies have shown that coatings do not uniformly dissolve/degrade after long periods in function.[53,70,92,97] Also noted were compromised coating and bone-coating interface mechanical properties.[53,70,92,97]

Retrieval analyses of PSHA-coated implants have shown that translational interfaces between the bulk metal, metal oxide, and bio-ceramic coating may be regarded as weak links (Figure 13), where adhesive failure has been reported.[25,30,31]

Also, uniform coating composition and uniformity of crystallinity have not always been achieved through the PS process, and the overall literature database is controversial with respect to coating composition and crystalline content in relation to *in vivo* performance.[53,116] Therefore, alterations of calcium to phosphorous atomic ratios throughout the coating surface and differences in relative thickness have been shown to alter coating dissolution/degradation rates *in vivo*.[53,80,92,97] In addition to process-inherent issues and the variable dissolution behavior of PSHA *in vivo*, the transmucosal zone represents a challenge for PSHA coatings.[53,116] These factors have contributed to the decreased use of PSHA-coated implants in clinical dental practice. Despite limitations, which may lead to implant failure, it has been well documented[23,31,49,50,53,80,92,97,102,117,118] that PSHA-coated implants have higher osseoconductive properties when compared with uncoated implants. The higher osseoconductive property of bioactive ceramic coated implants may be a significant factor in implant survival especially in areas where the quantity and quality of bone is compromised and generation of additional bone attachment is needed.

**Current Developments on Bioactive Ceramic Surface Modifications–Incorporation of Submicroscopic Structured Bioactive Ceramics on Implant Surfaces (The 'Nano' Surfaces).** Evolution of engineering based manufacturing processes has led to the controlled production of submicroscopic structures of condensed matter domains. The production of reduced domains (nanostructures) may strongly affect the electronic configuration of materials, supporting opportunities for a variety of applications through biomedical engineering. In the case of biomaterials, the production of small domains appears to strongly influence the host response at both cellular and tissue levels.[28]

Tissue engineering through nanobiomaterials is under active investigation. However, the benefits of their use when compared with their "bulk" counterparts has not yet been fully characterized at either cellular or tissue levels. On the other hand, manufacturing processes utilized for controlling material structure dimensions has been useful in overcoming limitations in biomedical device production, particularly in the case of coating dental and orthopedic implants with bioactive ceramics.[119]

In an attempt to improve on the PSHA coating process limitations, thin-film nanostructured bioceramic coatings have been developed for implant surfaces through processes such as sol-gel deposition,[25] pulsed laser deposition (PLD),[116] sputtering coating techniques,[49,50] ion beam-assisted deposition (IBAD),[28,53,80,92] and electrophoretic deposition.[25] These techniques are often applied to achiever substantially thinner coating thicknesses when compared with PSHA, typically ranging from 1 to 5 $\mu$m. As an alternative to continuous thin coatings, discrete crystalline depositions (DCD)[109,120,121] and the combination of the RBM with modification in acid etching techniques (RBM +MAE) have also been developed for the incorporation of Ca and P onto and into implant surfaces. The following sections describe the available surfaces utilizing small scale fabrication/utilization of bioactive ceramics.

**Ion Beam Assisted Deposition (IBAD) of Nanothickness Bioceramic Coatings.** In an attempt increase surface osseoconductivity while avoiding the limitations presented by the standard (ASTM F1609-08[122]) PSHA coating process, substantially thinner coatings (ranging in the nanometer to the micrometer thickness) have been applied on implant surfaces.[49,50,80,123] Desirable features of thin-film coatings include coating controlled composition and thickness plus enhanced adhesion to the metallic substrate (40 MPa versus <20 MPa for PSHA-coated implants).[25,28,53,80,92,97] Controlled composition and thickness also have been shown to influence coating dissolution *in vivo*,[53] thereby potentially increasing osseoconductivity at early implantation times. However, rapid dissolution of thin films may result in the exposure of the metallic sub-

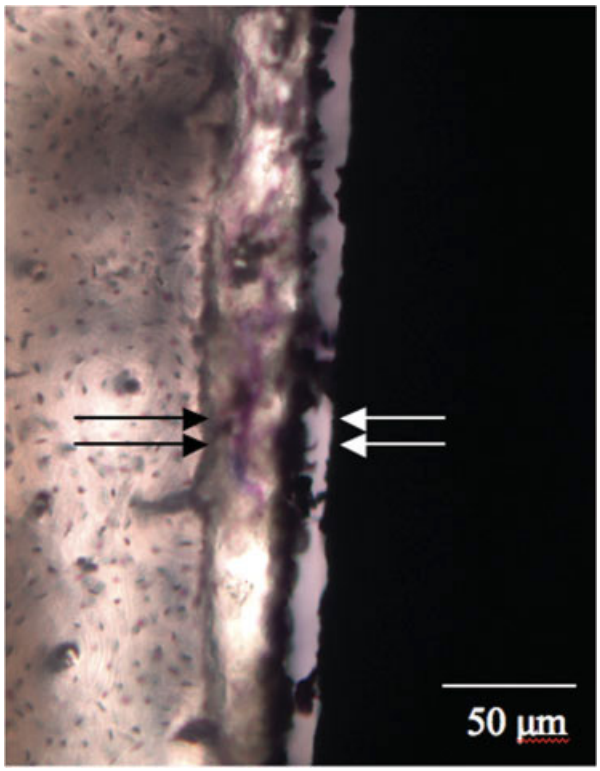


**Figure 13.** Representative optical micrograph showing a metallocer-amic interface disruption after mechanical loading of a PSHA-coated implant retrieved after a 5 week period in beagle dog tibia. The fracture presented shows that the bone-bioceramic interface (black arrows) has increased the mechanical properties when compared with the bioceramic-metallic substrate (white arrows) interface characterizing the weak link observed after osseointegration establishment of PSHA-coated implants at longer terms *in vivo*. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

strate some time soon after surgical placement. Therefore, the possibility of having close bone contact to the implant metallic substrate at the optical microscopy level after coating dissolution may be an attractive feature of thin-films. This close contact would avoid an interphase between bone, bioceramic, surface oxides, and implant metallic substrate, possibly supporting favorable conditions for implant device long-term anchorage.[53,80,97]

Animal studies at early implantation times including sputtering-coated[49,50] and IBAD-coated[28,64,65,80,123] Ca- and P-based thin-films on titanium implants have demonstrated higher biomechanical fixation,[49,50,80,123] bioactivity,[123] and BIC[49,50,80] when compared with noncoated implants. Also, investigations comparing PSHA-coated implants to sputtering-coated and IBAD-coated implants have shown favorable mechanical fixation after 12 weeks implantation time in dog femurs.[118]

A potential drawback of the novel processing techniques for thin-film deposition is its relatively high cost for large scale production. Therefore, to decrease processing time to make thin-coatings manufacturing commercially viable, it is desirable to process the thinnest coating that would significantly increase the biological response. Recent studies[64,65,119] at early implantation times have shown that a coating thickness of 300–500 nm resulted in increased biological response when compared with a 20–50 nm coating thickness at early implantation times. The same study showed that the *in vivo* performance of the 300–500 nm thickness coating was somewhat comparable to PSHA.[119] Figure 14 shows a commercially available Ion Beam Assisted bioceramic thin coating deposition that presents a partially crystalline microstructure.

**Calcium Phosphate Discrete Crystalline Deposition Method.** Another engineering-based approach to incorporate Ca- and P-based components onto implant surfaces is the discrete crystalline deposition (DCD) method. This process incorporates nanometer-size crystals of CaP onto a previously treated surface (dual acid-etch) (Figure 15).[121] The DCD method yields a surface which is different in

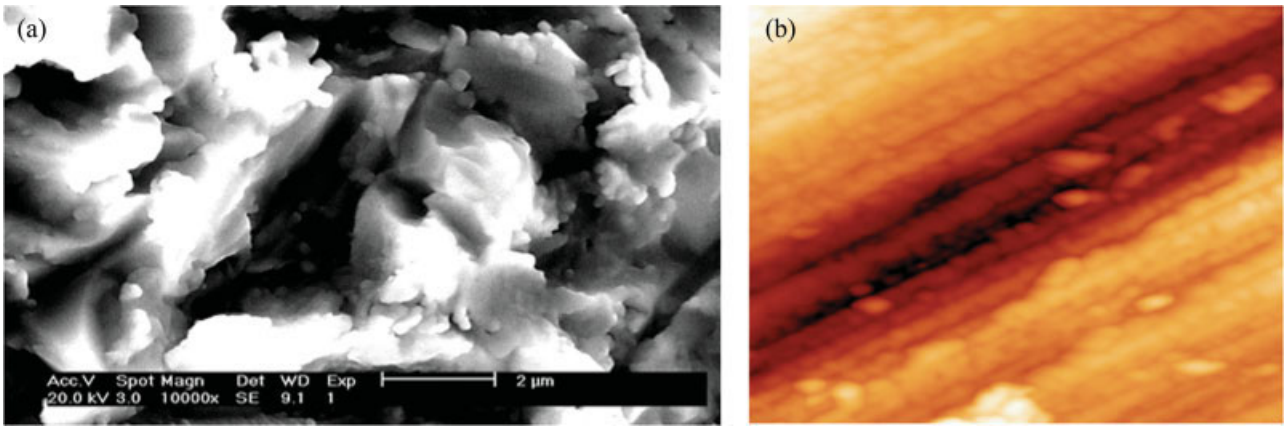


**Figure 14.** (a) FESEM of a high energy ion-beam bioceramic deposition in a cylindrical implant surface. (b) AFM of coating deposited in the machined flat substrate depicting the time-of-flight deposition of crystalline bioceramic nanoparticles within the amorphous Caand P-based matrix. (Bicon LLC, Boston USA). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

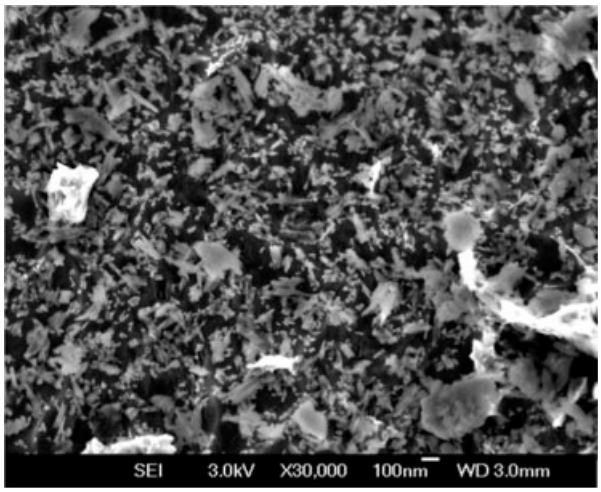


**Figure 15.** Field emission scanning electron micrograph of a DCD implant surface. Note the nanometer range particles deposited in a dual acid-etched surface. (Courtesy of Biomet-3i, Palm Beach Gardens, FL).

morphology and microstructure than IBAD and other thin-coating deposition methods. The rationale for such surface treatment represents another attempt to provide an increased osseoconductive component to the surface while avoiding potential long-term limitations of PSHA coatings.

Studies in rat models have shown that the surface chemistry and topography of the DCD treatment was beneficial when compared with a dual acid-etched surface.[109,124] Limitation of the studies on the DCD surface include the measurement of bone bonding by pullout force assessment in specimens of irregular shape,[109] and the utilization of implant shapes that are not representative of the endosseous implant in which the DCD surface is commercially available.[123] Nonetheless, the DCD surface has shown promising results in a study in humans, where higher BIC was found after 2 months *in vivo*.[121]

**Other Techniques for Incorporation of Calcium and Phosphorous at the Nanometer Scale.** Other alternatives to commercially available IBAD and DCD surface treatments have been explored with the objective of chemically modifying implant surfaces to provide elemental Ca and P on rough implant surfaces.

The technique comprises a combination of surface treatments used to increase implant surface roughness. This modification of grit-blasting the surface with biocompatible bioceramics (RBM) added to a selective cleaning procedures (modified acid-etching procedures, MAE) leading to a moderately rough surface with Ca and P remnants in the surface (Figure 16).

From a theoretical standpoint, all "nano" surfaces presented may be a benefit from both surface roughness and chemistry viewpoints. They have shown enhancement of the host response to implants. Although promising results have been obtained in preliminary studies and short-term clinical trials, more laboratory *in vivo* and controlled clinical trials should be performed to better characterize the performance of these surfaces at short- and long-term implantation times.

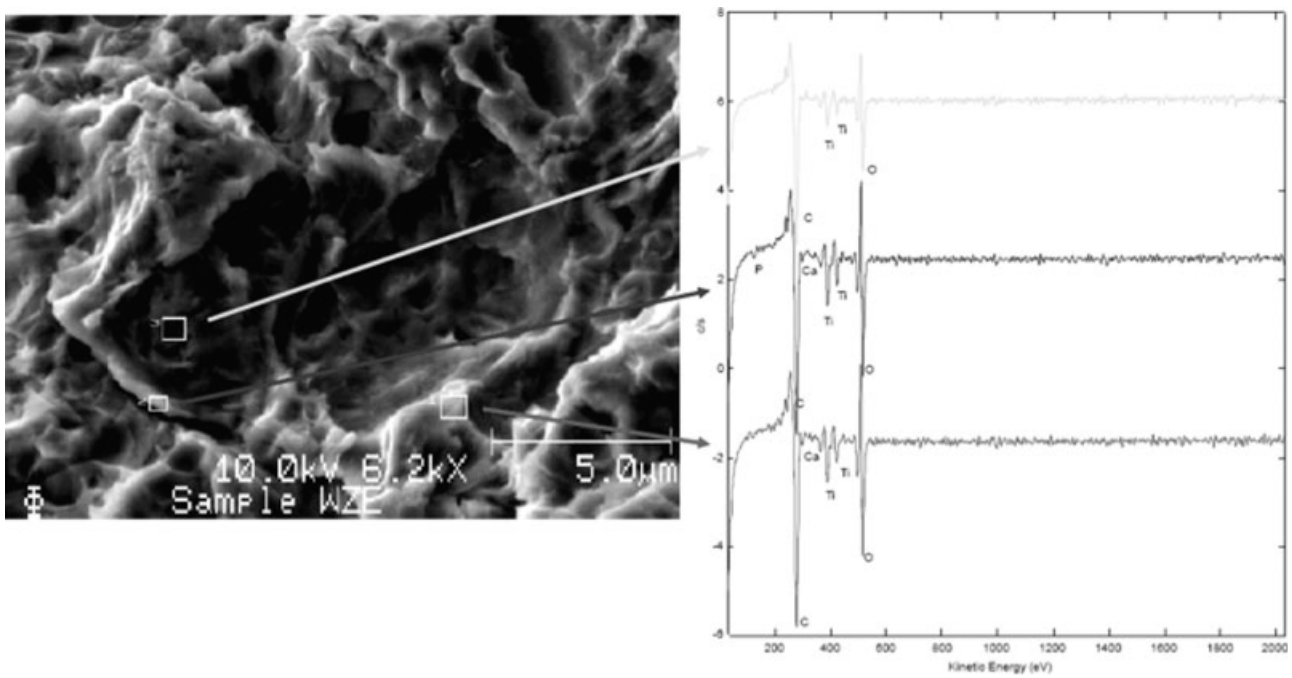


**Figure 16.** A scanning electron micrograph of the OsseanTM surface (Intra-Lock international, Boca Raton, USA), along with each spot's Auger electron spectrum showing the presence of Ca and P on the surface chemistry.

It is acknowledged that other research areas are showing promising results and may soon be commercially available. The incorporation of functionally graded surface structures for improvement of surface physical and chemical properties and better interphaseal interaction between bone and implant has been under development showing promising results.[125] Another promising field relates to the incorporation of biological factors to implant surfaces.[126] It is expected that future improvements in implant surface engineering will present a synergistic combination between surface roughness, chemistry, and incorporated biological factors that will further enhance the host-to-implant response. Current limiting factors for such technology remains its large-scale fabrication, shelf life, and the lack of regulatory standards.

## FINAL REMARKS

One of the main purposes for modifying dental implant surfaces is to decrease the healing period time for osseointegration. This is desirable for both the implant dentistry clinicians and patients. Along with implant macrodesign evolution surface treatment appears to be another step towards minimizing healing period times before implant restoration.

Because the surface is the first part of the implant to encounter the host, it is natural that surface engineering has become an extensively investigated area. Unfortunately, despite the extensive literature developed over the last decades, the lack of a hierarchical approach, as described in this manuscript, has led to difficulties in isolating the topographic and chemical parameters that provide the optimum bone healing around the dental implants. It is recognized that literature inconsistencies with respect to the mechanistic effect of surface modifications in short- and long-term of immediately loaded dental implants exist. However, laboratory *in vivo* and various clinical studies have demonstrated that increases in surface texture through a variety of techniques favors wound healing and appear to be potentially advantageous at early implantation times despite little evidence of its long-term beneficial effect. In fact, a systematic review has shown that bone loss due after long periods under functional loading due to periimplantitis is smaller for implants with smoother surfaces when compared with rougher surfaces.[127] Thus, more accurate clinical studies should be performed considering different implant surfaces' effect on periimplantitis incidence.[128]

The emerging technology comprising bioceramic coatings at nanoscale dimensions appears to benefit from surface topographies and chemistries to increase surface osseoconductivity. This technology is under active basic and clinical investigation to determine what the prevailing properties (surface chemistry or subnanometer level texturing) may lead to the most favorable results.

The clinician is faced with a wide range of competing products with many different surface treatments. Many small manufacturing firms have entered the market with FDA acceptance based upon similarity to what is currently available. The actual nature of the surfaces on these implants and their manufacturing control is of concern. Given the number of products and surface treatments under study the clinician should ask, based upon what has been presented above, for the *in vitro*, laboratory *in vivo* data as well as the results of clinical studies as to effectiveness before use of any dental implant.

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