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Implant Surfaces

David A. Puleo, PhD[a,*], Mark V. Thomas, DMD[b]

[a]*Center for Biomedical Engineering, 209 Wenner-Gren Laboratory, University of Kentucky, Lexington, KY 40506-0070, USA*
[b]*College of Dentistry, D444 Dental Science Building, University of Kentucky, Lexington, KY 40536-0297, USA*

The use of implants in the oral and maxillofacial skeleton continues to expand. In the United States alone, an estimated 300,000 dental implants are placed each year [1]. Implants are used to replace missing teeth, rebuild the craniofacial skeleton, provide anchorage during orthodontic treatments, and even to help form new bone in the process of distraction osteogenesis.

Although oral implants have improved the lives of millions of patients, fundamental information relating implant characteristics and clinical performance is often lacking. More than 220 implant brands, produced by 80 different manufacturers, have been identified [2]. Considering the variety of materials, surface treatments, shapes, lengths, and widths available, clinicians can choose from more than 2000 implants during treatment planning. This wide range of options is good. However, it complicates the clinician's task of selecting the correct device based on sound evidence. In many instances, new companies have entered the dental implant market using a "copycat" strategy of simply mimicking or making minor, incremental changes to a competitor's products. By seeking only 510(k) approval in the United States or CE marking in Europe, a company can easily demonstrate "substantial equivalence," often without extensive preclinical and clinical testing. Even without documentation of significantly better performance of new implants, existing systems may be abandoned in favor of devices that have not been thoroughly tested. As stated by Jokstad and colleagues [2], "A substantial number of claims made by different manufacturers on alleged superiority due to design characteristics are not based on sound and long-term clinical scientific research." Although many longitudinal studies of

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* Corresponding author.
E-mail address: puleo@uky.edu (D.A. Puleo).

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implant survival have been published, only a few have employed formal statistical methodology, and those few have not compared implant surfaces [3,4]. Thus, there is little rigorous evidence to guide the clinician in selecting the optimal surface for a given situation.

With so many variables affecting oral implants, it is sometimes difficult to reliably predict the chances for an implant's success. In light of the continuing development of new dental implants, this article focuses primarily on important surface characteristics and their potential effects on the performance of dental implants.

The tissue–implant interface

A goal of implantology research is to design devices that induce controlled, guided, and rapid integration into surrounding tissues. Events leading to integration of an implant, and ultimately to success or failure of the device, take place largely at the tissue–implant interface. Development of this interface is complex and involves numerous factors. These include not only implant-related factors, such as material, shape, topography, and surface chemistry, but also mechanical loading, surgical technique, and patient variables, such as bone quantity and quality. In contrast to orthopedic prostheses, which are designed to interact with only bone, dental implants also must interact with epithelium and submucosal soft connective tissue. Certain basic events, however, are common to all tissue–biomaterial interactions.

Following implantation, events take place both on the biological side and on the materials side. According to the "interface scenario" of Kasemo and Lausmaa [5], primary molecular events lead to secondary events that ultimately result in particular cell and tissue responses. On the implant side, studies indicate that electrochemical events take place on the surface of the implant and cause the oxide to double or triple in thickness [6–8]. The electrochemical reactions also lead to the incorporation of biological ions, such as calcium, phosphorus, and sulfur ions [6,7]. During these events, metal ions are released [9]. Reports about metal released from dental implants are sparse compared with reports related to orthopedic devices. The orthopedic literature indicates significantly elevated metal content both in periprosthetic tissues [10,11] and in serum and urine [12–14]. In one report, analysis of tissues around dental implants showed titanium at levels up to tens of ppm immediately adjacent to devices, but background levels were found within 0.4 mm [15]. Long-term effects of the metal remain unknown. Even though trace metals are essential for health, they can be toxic [16] or cause hypersensitivity reactions [17].

On the biological side, water molecules and hydrated ions associate with the implant surface within nanoseconds [18]. The presence of the substrate locally alters the organization of water molecules, and this may subsequently affect adsorption of biomolecules, which occurs within milliseconds. Hundreds

of biomolecules are available in body fluids to interact with the surface. A complex, time-dependent cascade of events involving adsorption, displacement, and exchange then takes place, during which smaller, lower-affinity molecules can be replaced with larger species having greater affinity for the biomaterial. Interaction with the surface may also alter the orientation and conformation of the biomolecules [19]. A further level of complexity is added in that inhomogeneities in "real" implant surfaces will likely result in a distribution of biomolecules and their properties on the surface. With time, cells encounter an implant surface that has been preconditioned with a variety of biomolecules. Cells do not interact with a "bare" biomaterial surface.

As mentioned, the success of dental implants depends on the interaction with both soft and hard tissues. Formation of a peri-implant soft tissue barrier is important for protecting the bone-implant interface from microbiological challenge. Lack of a perimucosal seal also can lead to apical migration of epithelium and possibly to encapsulation of the root of the implant. Successful implants exhibit a peri-implant mucosa that forms a cuff-like barrier and adheres to the implant [20,21]. Between the epithelium and bone is a collagenous connective tissue. The fibers of this tissue are aligned parallel to the implant surface. This interaction between the implant and soft tissue is analogous to the epithelial and supra-alveolar connective tissue attachment that exists between the tooth and the periodontal tissues. Hermann and colleagues have determined that the total dimension of the sulcus depth, epithelial attachment, and connective tissue dimension remains stable over time, although the individual components may change slightly [22].

Apically, the successful implant will be surrounded by bone. Bone can be formed on the adjacent bone surfaces in a phenomenon called distance osteogenesis, or on the implant surface itself in a phenomenon called contact osteogenesis [23,24]. In the case of distance osteogenesis, osteogenesis occurs from the bone toward the implant as the bone surfaces provide a population of osteogenic cells that deposit a new matrix that approaches the implant. In the case of contact osteogenesis, osteogenesis occurs in a direction away from the implant as osteogenic cells are recruited to the implant surface and begin secreting bone matrix. While both these processes are likely to occur with implants, their relative significance may depend on the specific type of implant and its surface characteristics.

Osseointegration versus osseocoalescence

The term *osseointegration* is commonly used in conjunction with dental implants. Unfortunately, investigators frequently use the term differently. The term stems from Brånemark's work with titanium bone chambers for intravital microscopy in the 1950s [25]. Observations of good interaction between bone and metal led to the crafting of dental implants using titanium. Osseointegration was originally defined as a relationship where "bone is in direct contact with the implant, without any intermediate

connective tissue'' [26]. A revised definition describes the interaction as a ''direct structural and functional connection between ordered living bone and the surface of a load-carrying implant'' [27]. In effect, osseointegration means that there is no relative movement between the implant and the surrounding bone.

Although some investigators believe there is chemical interaction between bone and the surface of titanium implants, osseointegration largely refers to the physical integration or mechanical fixation of an implant in bone. By having bone intimately apposed to the surface, whether macroscopically at the level of screw threads or microscopically at the level of machine marks and surface defects, the interlocking provides mechanical resistance to mechanical forces, such as shear experienced in ''pull-out'' and ''torque-out'' testing (Fig. 1). With purely physical interaction, however, the interface would not be able to withstand even moderate tensile forces (see Fig. 1).

The term *osseocoalescence* has been proposed to refer specifically to chemical integration of implants in bone tissue [28]. The term applies to surface reactive materials, such as calcium phosphates and bioactive glasses, which undergo reactions that lead to chemical bonding between bone and biomaterial. With these materials, the tissues effectively coalesce with the implant. An example of qualitative evidence for chemical bonding is when fracture lines propagate through either the implant or the tissue but not along the interface. With respect to Fig. 1, osseocoalesced implants would exhibit resistance to both shear and tensile loads. Unfortunately, the term has not found widespread use, and osseointegration still is often used when describing interactions between bioactive materials and bone.

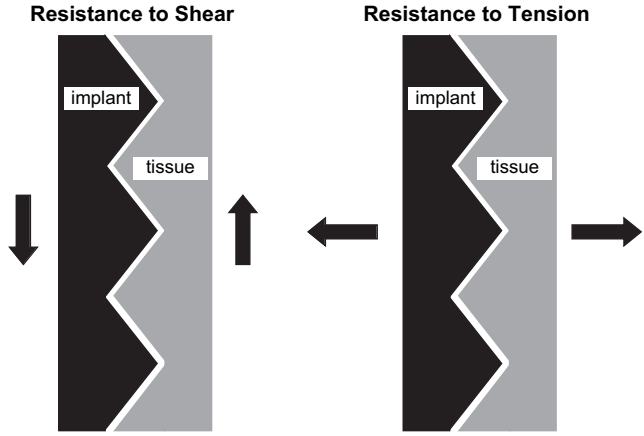

Fig. 1. Mechanical integration (ie, osseointegration) of an implant in bone provides good resistance to shear forces but poor resistance to tension. Chemical integration (ie, osseocoalescence) provides good resistance to both shear and tensile forces. Arrows indicate direction of force. (*From* Kasemo B, Gold J. Implant surfaces and interface processes. Adv Dent Res 1999; 13:11; with permission.)

Important surface characteristics

Two categories of surface characteristics commonly are cited as being important for determining tissue responses. One category includes the topographic or morphological characteristics. The other category includes the chemical properties. As will be discussed, independent study of topographic and chemical properties is confounded because methods used to alter surface morphology frequently lead to changes in surface chemistry. Some investigators include surface mechanical properties as being important. This differs from interfacial mechanics, which are known to affect integration of dental implants. For example, the adverse effect of excessive micromotion is understood [29]. However, the role of mechanical properties of the implant's surface is largely unknown. Poor wear resistance may generate particulate debris and high residual stresses may cause metal ion release. Both can affect cell and tissue behavior.

In the search for methods for altering surface characteristics to improve implant performance, much attention has been focused on changes in surface roughness and chemistry. Such changes can, for example, improve interaction with hard and soft tissues and strengthen characteristics for bearing loads. As indicated, mechanical interaction between bone and surfaces with texture can lead to osseointegration, and chemical interactions can lead to osseocoalescence. Macroscopic mechanical interlocking can provide initial fixation of the implant, allowing time for surface reactions that lead to chemical bonding.

Surface topography

Simply describing surfaces as "rough" or "smooth" is not sufficient. Quantitative evaluation is important for comparing surfaces prepared using different methods. As reviewed by Wennerberg and Albrektsson [30], several methods are available for measuring surface roughness, and more than 150 parameters can be calculated to characterize surface topography. The parameters may reflect vertical height of surface features, horizontal space between features, or a combination of height and spatial information (ie, hybrid parameters). Many reports provide only one quantitative parameter [30]. The most commonly reported parameter is R_a, the arithmetic mean of deviations in the roughness profile from the mean line. Other parameters that can be found with some frequency are R_q, which is the root mean square average, and R_{max} (or R_y), which is the maximum peak-to-valley height encountered during a scan. Three-dimensional parameters can also be calculated. For example, S_a represents the arithmetic mean of deviations in roughness from the mean plane of analysis. The three-dimensional nature of implants yields another difficulty in evaluating topography; many profilometric techniques were developed for planar surfaces, but not for threaded dental implants. Wennerberg and Albrektsson recommend evaluation at the

tops, valleys, and flanks of threads [30]. Reporting only one parameter following examination of only one region of an implant is unlikely to adequately characterize the device.

The scale of surface features also should be considered. The common, threaded root-form implant serves as a good example. The thread pitch may be on the order of 1000 μm, and the thread depth on the order of 300 μm. Cells, however, are 1 to 100 μm, and proteins are around 0.001 to 0.01 μm. These differences in scale are illustrated in Fig. 2. Because relevant surface features span six orders of magnitude in size, from the macro-, to micro-, to nano-scales, comprehensive assessment of the topography requires different methods, ranging from optical light microscopy to scanning probe techniques. The literature contains abundant evidence for the effects of macro- and micro-scale surface features on cells and tissues [31–33]. For example, microtopography causes osteoblastic cells to secrete factors that enhance differentiation and alters their responses to osteogenic factors, while decreasing osteoclast formation and activity [34,35]. Even though in vitro studies show that nanomaterials can affect cell responses [36,37], the influence of nanostructured materials on tissue behavior in vivo remains unknown.

Terms such as *contact guidance* and *rugophilia* have been used to describe the interaction of cells and tissues with textured surfaces. The former refers to the directional guidance provided by a substrate [31]. This phenomenon has been extensively studied in cell cultures by exposing cells to microfabricated substrata having grooves of various dimensions, but it also has practical, clinical implications. The best example is placement of circumferential grooves on a dental implant to prevent epithelial downgrowth. *Rugophilia* literally means "rough-loving." Whereas some types of cells will accumulate on smooth surfaces, others, such as macrophages, prefer roughened surfaces [38].

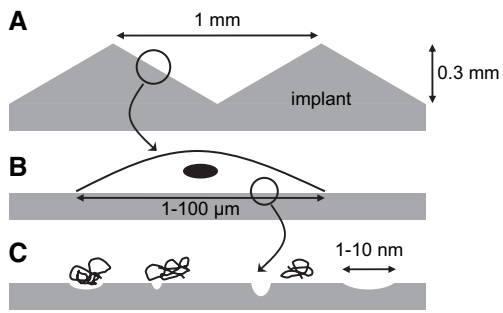

Fig. 2. Size and scale of surface features relevant to the tissue–implant interface. Screw threads (*A*) are on the macro-level; cells and surface topography (*B*) are on the micro-level; and proteins and surface defects (*C*) are on the nano-level. (*Adapted from* Kasemo B, Gold J. Implant surfaces and interface processes. Adv Dent Res 1999;13:11; with permission.)

Porous materials are examples of extreme surface roughness. Such materials have been used to allow growth of tissues into implants to enhance integration, particularly in orthopedics for total joint replacements. Early work with bioinert ceramics showed that pore sizes greater than 100 μm were needed for ingrowth of mineralized tissue [39]. Pores in the range of 40 to 100 μm allowed formation of osteoid, and only fibrous tissue was present in 5 to 15 μm pores. The importance of pores exceeding 100 μm was also shown for metallic implants [40]. More recent work with bioactive materials indicates that bone may grow into smaller pores and that the size and volume density of interconnections is important because of the need for blood circulation and extracellular liquid exchange [41]. Interconnections measuring 20 μm supported cell ingrowth and formation of chondroid tissue, but bone formed when interconnections were greater than 50 μm. A recent electron microscopic examination of implants retrieved from humans appears to show bone in small surface pores having diameters of around 2 μm [42]. These apparent discrepancies confirm the complex, multifactorial nature of tissue–implant interactions.

Surface chemistry

Commercially pure titanium (cpTi) and Ti-6Al-4V alloy are the most commonly used dental implant materials, although new alloys containing niobium, iron, molybdenum, manganese, and zirconium are being developed [43,44]. These materials dominate because of their combination of mechanical properties and biocompatibility. Biocompatibility is attributed to the stable oxide layer, primarily titanium dioxide (TiO_2), that spontaneously forms when titanium is exposed to oxygen. This reaction converts the base metal into a ceramic material that electrically and chemically passivates the implant. Manufacturers may also immerse implants in acidic solutions to enhance formation of the passivating oxide film. Depending on the method of preparation and sterilization, cpTi implants have an oxide thickness of 2 to 6 nm [45]. As described earlier, this biomaterial surface interacts with water, ions, and numerous biomolecules after implantation. The nature of these interactions, such as hydroxylation of the oxide surface by dissociative adsorption of water, formation of an electrical double layer, and protein adsorption and denaturation, determine how cells and tissue respond to the implant.

Surface energy, surface charge, and surface composition are among the physicochemical characteristics that can be manipulated to affect the interaction of implants with cells and tissues. Glow discharge treatment is a process in which materials are exposed to ionized inert gas, such as argon. During collisions with the substrate, high-energy species ''scrub'' contaminants from the surface, thereby unsaturating surface bonds and increasing surface energy. This higher surface energy will then influence adsorption of biomolecules, which in turn affects subsequent cell and tissue behavior. Some

speculate that high-energy surfaces increase tissue adhesion [46]. However improved interactions with bone have not been demonstrated [47,48].

Considering the role of electrostatic interactions in many biological events, charged surfaces have been proposed as being conducive to tissue integration. Conflicting findings have been reported, however, as both positively [49] and negatively [50] charged surfaces were found to facilitate bone formation. Calcium phosphate coatings have been extensively investigated because of their chemical similarity to bone mineral [51]. While their popularity has increased, their use has remained controversial. Concerns have arisen because of instances of such problems as dissolution and cracking of coatings as well as separation of coatings from metallic substrates, a phenomenon referred to as delamination [52,53].

Common implant systems

Implants with smooth surfaces (ie, $S_a < 0.2$ μm) are not used mainly because such implants show poor interaction with tissues, both soft and hard. Smooth, polished surfaces show poor mechanical integration with bone because, without surface irregularities, such surfaces provide no resistance to mechanical forces at the bone-implant interface (see Fig. 1). Furthermore, very smooth surfaces can allow epithelial downgrowth and are associated with deeper peri-implant pockets [54].

Machine-finished (ie, turned) implants, such as the Brånemark System implants (Nobel Biocare, Zurich, Switzerland), have a substantial history of use in the clinic. Whereas they may appear macroscopically smooth, the implants have a low roughness, in the range of 0.5 to 1 μm [30]. With careful selection of patients and anatomical sites, meticulous surgical technique, and delayed loading, this system has shown excellent survival rates [55,56]. In the mandible, success at 5 to 8 years exceeded 99% and was approximately 85% in the maxilla.

Even though Brånemark implants have been documented to perform well in humans, implants with different surface characteristics continue to be developed in attempts to increase the degree and rate of osseointegration, to allow early and immediate loading, and to promote integration in anatomic sites with poor bone quality or insufficient bone quantity for conventional implants. Because of experimental and clinical evidence of better integration with tissues, implants having rougher surfaces now receive the most attention. ''Moderately rough'' surfaces are described as having S_a between 1 and 2 μm, while ''rough'' surfaces have an S_a greater than 2 μm [30]. The methods used to increase roughness, however, frequently tend to change the surface chemistry as well as texture.

Roughened surfaces are associated with increased interfacial strength as measured, for example, by reverse (or removal) torque testing [57–59]. Experiments have also indicated a faster rate and higher degree of bone

formation for rougher implants than for implants with turned surfaces [60]. Rougher surfaces, however, are not necessarily better. This applies to both hard and soft tissue responses. Surfaces with intermediate roughness (ie, $S_a \sim 1.5$ μm) have higher bone–implant contact indices [58,61,62]. Furthermore, rough surfaces favor accumulation of plaque, which can lead to peri-implantitis and implant failure if that portion of the implant surface becomes exposed to the oral environment [63].

Methods for altering surface texture can be classified as either ablative or additive. Ablative methods remove material from the surface. Common methods for ablating dental implant surfaces include grit blasting, acid etching, and grit blasting followed by acid etching. The primary method used to deposit material on implant surfaces is plasma-spraying.

The TiUnite (Nobel Biocare, Zurich, Switzerland) surface is formed by anodically oxidizing titanium in a proprietary electrolytic solution. Treatment results in an increased thickness of the oxide layer and a porous surface topography [64]. In the coronal region, the oxide grows to 1 to 2 μm, whereas it approaches 10 μm in the apical region. In conjunction with oxide growth, surface roughness continuously increases from top to bottom, with an average R_a of 1.2 μm. The apical end also has numerous 1 to 2 μm pores. Although the composition of the electrolyte is not published, studies on anodic oxidation have shown that use of sulfuric or phosphoric acid in the bath results in incorporation of sulfur or phosphorus ions, respectively, in the oxide [65]. Furthermore, crystal structure of the oxide film can be altered during electrochemical oxidation [66]. Thus, there is the possibility for roughness-related as well as chemistry-related effects on integration of the implant [67]. A recent publication reported essentially 100% success of TiUnite implants at 18 months, even with early or immediate loading [68]. Four-year results indicate 97% success in an immediate loading protocol, even when implants were placed in soft bone [69].

Dual acid-etching (DAE) of titanium in a solution of hydrochloric acid and sulfuric acid results in microrough surfaces. This technique is used with the Osseotite Implant System (Implant Innovations, Inc. (3i), Palm Beach Gardens, Florida). However, the texture is not uniform over the entire screw surface. S_a is about 1.8 to 2 μm at the tops of the threads, but roughness decreases to 0.5 to 0.7 μm in the valleys and on the flanks [30,70]. Animal studies have demonstrated improved removal torque values, presumably because of greater mechanical interlocking [71,72]. Compared with machined implants, DAE surfaces showed significantly greater bone–implant contact, even in sites of poor bone quality [73]. The apparently accelerated integration of the implants enables loading to begin at 1 month instead of after 2 months of healing [74]. Davies describes de novo bone formation, a key part of contact osteogenesis, on acid-etched surfaces [24]. In clinical use, cumulative success rates approach 97% at 5 [75] and 6 [76] years. Even with immediate occlusal loading, excellent success rates are observed, 99% at a mean follow-up of 28 months [77].

The sandblasted (large grit) and acid-etched (SLA) surface of implants from Institut Straumann (Basel, Switzerland) has also received significant attention. Implants are blasted with 250 to 500 μm corundum grit followed by acid etching in a hot solution of hydrochloric acid and sulfuric acid. Sandblasting produces macroroughness onto which acid etching superimposes microroughness [78]. The S_a for SLA surfaces is around 1.8 μm [30,70]. The increased roughness compared with turned implants combined with possible microstructural changes in the oxide resulting from the acid treatment produces good cell and tissue responses, such as greater bone–implant contact [78] and increased removal torque values [79]. In clinical studies, SLA implants were loaded after 6 weeks when in class I, II, or III bone or after 12 weeks if in class IV bone [80]. At both 1- and 2-year follow-up, 99% of the implants were successful. An identical success rate (ie, 99%), was also reported at 3 years [81].

More recently, Salvi and colleagues [82] conducted a study using SLA implants in the mandible. A split-mouth design was employed, with the one side serving as the test site and the contralateral serving as the control. Control implants had abutments connected at 5 weeks followed by crown cementation (post-implant placement) at 6 weeks. The test implants received abutments at 1 week and crowns at 2 weeks. At 1 year, implant survival was 100% for both arms of the study, and no significant differences were noted between the arms. Even though these implants were placed in bone of good quality, this study underscores the affinity of osteoblasts for this surface.

Some of the roughest dental implant surfaces are titanium plasma-sprayed (TPS). The S_a depends on the manufacturer, but can be up to 6 μm [70]. To prepare these surfaces, titanium particles are heated to a nearly molten state and sprayed at the substrate via an inert gas plasma. The softened particles "splat" on the surface and rapidly solidify. The resultant surface is quite irregular and rough. This increased surface texture, with relatively greater void volume into which bone can grow, results in higher removal torque values [83,84]. Several studies, however, have shown cause for concern with TPS implants. For example, titanium particles have been detected in peri-implant tissues [85]. The authors speculate that friction during surgical insertion may have sheared off the particles. TPS surfaces have also been associated with increased mobility and higher incidence of peri-implant inflammation and recession [86,87].

By coating implants with hydroxyapatite (HA), such as by plasma spraying, both the roughness and surface chemistry are altered. The roughness increases to $S_a \sim 5.8$ μm [70], and the surface chemistry is dramatically changed from TiO_2 to a bone-like ceramic with the potential for chemically bonding to bone. Unfortunately, the properties of commercial coatings can be quite variable. During plasma spraying, HA can be transformed to other forms of calcium phosphate, with different crystalline structures, such as β-tricalcium phosphate. Because the chemical properties depend on the microstructure [88], dissolution characteristics may be quite different for various

coated implant preparations. However, reports documenting clinical use of dental implants coated with calcium phosphate show good success of the prostheses. Periodontal measurements were comparable for HA-coated and uncoated implants through 3 years [89], and survival rates were 95% to 99% at up to 7 years [90–92].

Other studies have observed "late" failures with HA-coated implants. Wheeler reported the results of an 8-year retrospective study that compared implant survival of TPS implants versus HA-coated implants [93]. A total of 1202 press-fit cylindrical implants were placed in 479 patients. Of these, 889 had TPS surfaces, and 313 were HA-coated. Cumulative survival rates based on life table analysis were 92.7% and 77.8% for TPS and HA-coated systems, respectively. Many of the HA-coated implants were lost after being in service for some years, and their failure was often accompanied by a good deal of bone loss.

Summary

Dental implants are valuable devices for restoring lost teeth. Implants are available in many shapes, sizes, and lengths, using a variety of materials with different surface properties. Among the most desired characteristics of an implant are those that ensure that the tissue-implant interface will be established quickly and then will be firmly maintained. Because many variables affect oral implants, it is sometimes difficult to reliably predict the likelihood of an implant's success. It is especially difficult to assess whether the various modifications in the latest implants deliver improved performance. Thus far, metanalysis of randomized clinical trials finds no evidence of any particular type of implant having better long-term success [94]. There is limited evidence, however, for decreased incidence of peri-implantitis around smooth (ie, machined) implants compared to implants with rougher surfaces.

The continuing search for "osseoattractive" implants is leading to surface modifications involving biological molecules. By attaching or releasing powerful cytokines and growth factors [23], desired cell and tissue responses may be obtained. Using even a simple delivery system, introduction of bone morphogenetic protein at the tissue–implant interface was shown to enhance the rate of periprosthetic bone formation [95]. In the future, similar approaches may also be used to promote interaction of mucosal and submucosal tissues with dental implants.

References

[1] Dunlap J. Implants: implications for general dentists. Dent Econ 1988;78(10):101–12.
[2] Jokstad A, Braegger U, Brunski JB, et al. Quality of dental implants. Int Dent J 2003;53(6, suppl 2):409–43.
[3] Boioli LT, Penaud J, Miller N. A meta-analytic, quantitative assessment of osseointegration establishment and evolution of submerged and non-submerged endosseous titanium oral implants. Clin Oral Implants Res 2001;12(6):579–88.

[4] Lang NP, Pjetursson BE, Tan K, et al. A systematic review of the survival and complication rates of fixed partial dentures (FPDs) after an observation period of at least 5 years. II. Combined tooth–implant-supported FPDs. Clin Oral Implants Res 2004;15(6):643–53.
[5] Kasemo B, Lausmaa J. Surface science aspects on inorganic biomaterials. CRC Crit Rev Biocomp 1986;2:335–80.
[6] Lausmaa J, Kasemo B, Rolander U, et al. Preparation, surface spectroscopic and electron microscopic characterization of titanium implant materials. In: Ratner BD, editor. Surface characterization of biomaterials. Amsterdam: Elsevier; 1988. p. 161–74.
[7] Sundgren JE, Bodo P, Lundstrom I, et al. Auger electron spectroscopic studies of stainless-steel implants. J Biomed Mater Res 1985;19(6):663–71.
[8] Sundgren JE, Bodo P, Lundstrom I. Auger electron spectroscopic studies of the interface between human tissue and implants of titanium and stainless steel. J Colloid Interface Sci 1986;110:9–20.
[9] Williams DF. Tissue reaction to metallic corrosion products and wear particles in clinical orthopaedics. In: Williams DF, editor. Biocompatibility of orthopaedic implants, vol. I. Boca Raton (FL): CRC Press; 1982. p. 231–48.
[10] Hennig FF, Raithel HJ, Schaller KH, et al. Nickel-, chrom- and cobalt-concentrations in human tissue and body fluids of hip prosthesis patients. J Trace Elem Electrolytes Health Dis 1992;6(4):239–43.
[11] Dorr LD, Bloebaum R, Emmanual J, et al. Histologic, biochemical, and ion analysis of tissue and fluids retrieved during total hip arthroplasty. Clin Orthop 1990;261:82–95.
[12] Bartolozzi A, Black J. Chromium concentrations in serum, blood clot and urine from patients following total hip arthroplasty. Biomaterials 1985;6(1):2–8.
[13] Michel R, Nolte M, Reich M, et al. Systemic effects of implanted prostheses made of cobalt-chromium alloys. Arch Orthop Trauma Surg 1991;110(2):61–74.
[14] Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am 1998;80(10):1447–58.
[15] Wennerberg A, Ide-Ektessabi A, Hatkamata S, et al. Titanium release from implants prepared with different surface roughness. Clin Oral Implants Res 2004;15(5):505–12.
[16] Friberg L, Nordberg GF, Vouk VB. Handbook on the toxicology of metals. Amsterdam: Elsevier/North-Holland; 1979.
[17] Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. Clin Orthop 1996;329(Suppl):S233–43.
[18] Kasemo B, Gold J. Implant surfaces and interface processes. Adv Dent Res 1999;13:8–20.
[19] Horbett TA, Brash JL. Proteins at interfaces: current issues and future prospects. In: Brash JL, Horbett TA, editors. Proteins at interfaces: physiochemical and biochemical studies. Washington (DC): American Chemical Society; 1987. p. 1–33.
[20] Berglundh T, Lindhe J, Ericsson I, et al. The soft tissue barrier at implants and teeth. Clin Oral Implants Res 1991;2(2):81–90.
[21] Glauser R, Schupbach P, Gottlow J, et al. Periimplant soft tissue barrier at experimental one-piece mini-implants with different surface topography in humans: a light-microscopic overview and histometric analysis. Clin Implant Dent Relat Res 2005;7(Suppl 1):S44–51.
[22] Hermann JS, Buser D, Schenk RK, et al. Biologic width around titanium implants. A physiologically formed and stable dimension over time. Clin Oral Implants Res 2000;11(1):1–11.
[23] Puleo DA, Nanci A. Understanding and controlling the bone-implant interface. Biomaterials 1999;20(23–24):2311–21.
[24] Davies JE. Understanding peri-implant endosseous healing. J Dent Educ 2003;67(8):932–49.
[25] Brånemark PI, Harders H. Intravital analysis of microvascular form and function in man. Lancet 1963;41:1197–9.
[26] Brånemark PI, Hansson BO, Adell R, et al. 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.

[27] Brånemark PI, Zarb G, Albrektsson T. Tissue-integrated prostheses: osseointegration in clinical dentistry. Chicago: Quintessence Publishing Co.; 1985.
[28] Daculsi G, LeGeros RZ, Deudon C. Scanning and transmission electron microscopy, and electron probe analysis of the interface between implants and host bone: osseo-coalescence versus osseo-integration. Scanning Microsc 1990;4:309–14.
[29] Szmukler-Moncler S, Salama H, Reingewirtz Y, et al. Timing of loading and effect of micromotion on bone-dental implant interface: review of experimental literature. J Biomed Mater Res 1998;43(2):192–203.
[30] Wennerberg A, Albrektsson T. Suggested guidelines for the topographic evaluation of implant surfaces. Int J Oral Maxillofac Implants 2000;15(3):331–44.
[31] Brunette DM. The effects of implant surface topography on the behavior of cells. Int J Oral Maxillofac Implants 1988;3:231–46.
[32] Kieswetter K, Schwartz Z, Dean DD, et al. The role of implant surface characteristics in the healing of bone. Crit Rev Oral Biol Med 1996;7(4):329–45.
[33] Cooper LF. A role for surface topography in creating and maintaining bone at titanium endosseous implants. J Prosthet Dent 2000;84(5):522–34.
[34] Lohmann CH, Tandy EM, Sylvia VL, et al. Response of normal female human osteoblasts (NHOst) to 17beta-estradiol is modulated by implant surface morphology. J Biomed Mater Res 2002;62(2):204–13.
[35] Lossdorfer S, Schwartz Z, Wang L, et al. Microrough implant surface topographies increase osteogenesis by reducing osteoclast formation and activity. J Biomed Mater Res A 2004; 70(3):361–9.
[36] Webster TJ, Ergun C, Doremus RH, et al. Enhanced functions of osteoblasts on nanophase ceramics. Biomaterials 2000;21(17):1803–10.
[37] Popat KC, Leary Swan EE, Mukhatyar V, et al. Influence of nanoporous alumina membranes on long-term osteoblast response. Biomaterials 2005;26(22):4516–22.
[38] Salthouse TN. Some aspects of macrophage behavior at the implant interface. J Biomed Mater Res 1984;18(4):395–401.
[39] Hulbert SF, Morrison SJ, Klawitter JJ. Tissue reaction to three ceramics of porous and nonporous structures. J Biomed Mater Res 1972;6(5):347–74.
[40] Bobyn JD, Pilliar RM, Cameron HU, et al. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. Clin Orthop Relat Res 1980; 150:263–70.
[41] Lu JX, Flautre B, Anselme K, et al. Role of interconnections in porous bioceramics on bone recolonization in vitro and in vivo. J Mater Sci Mater Med 1999;10(2):111–20.
[42] Schupbach P, Glauser R, Rocci A, et al. The human bone-oxidized titanium implant interface: a light microscopic, scanning electron microscopic, back-scatter scanning electron microscopic, and energy-dispersive x-ray study of clinically retrieved dental implants. Clin Implant Dent Relat Res 2005;7(Suppl 1):S36–43.
[43] Lavos-Valereto IC, Costa I, Wolynec S. The electrochemical behavior of Ti-6Al-7Nb alloy with and without plasma-sprayed hydroxyapatite coating in Hank's solution. J Biomed Mater Res 2002;63(5):664–70.
[44] Yu SR, Zhang XP, He ZM, et al. Effects of Ce on the short-term biocompatibility of Ti-Fe-Mo-Mn-Nb-Zr alloy for dental materials. J Mater Sci Mater Med 2004;15(6): 687–91.
[45] Lausmaa J, Linder L. Surface spectroscopic characterization of titanium implants after separation from plastic-embedded tissue. Biomaterials 1988;9:277–80.
[46] Baier RE, Meyer AE. Implant surface preparation. Int J Oral Maxillofac Implants 1988;3: 9–20.
[47] Carlsson LV, Albrektsson T, Berman C. Bone response to plasma-cleaned titanium implants. Int J Oral Maxillofac Implants 1989;4(3):199–204.
[48] Wennerberg A, Bolind P, Albrektsson T. Glow-discharge pretreated implants combined with temporary bone tissue ischemia. Swed Dent J 1991;15(2):95–101.

[49] Hamamoto N, Hamamoto Y, Nakajima T, et al. Histological, histocytochemical and ultrastructural study on the effects of surface charge on bone formation in the rabbit mandible. Arch Oral Biol 1995;40:97–106.
[50] Krukowski M, Shively RA, Osdoby P, et al. Stimulation of craniofacial and intramedullary bone formation by negatively charged beads. J Oral Maxillofac Surg 1990;48(5):468–75.
[51] Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. Clin Orthop 1981;157: 259–78.
[52] Jarcho M. Retrospective analysis of hydroxyapatite development for oral implant applications. Dent Clin North Am 1992;36(1):19–26.
[53] Dhert WJ. Retrieval studies on calcium phosphate-coated implants. Med Prog Technol 1994;20(3–4):143–54.
[54] Bollen CM, Papaioanno W, Van Eldere J, et al. The influence of abutment surface roughness on plaque accumulation and peri-implant mucositis. Clin Oral Implants Res 1996;7(3):201–11.
[55] Albrektsson T, Dahl E, Enbom L, et al. Osseointegrated oral implants. A Swedish multicenter study of 8139 consecutively inserted Nobelpharma implants. J Periodontol 1988;59(5): 287–96.
[56] Eckert SE, Parein A, Myshin HL, et al. Validation of dental implant systems through a review of literature supplied by system manufacturers. J Prosthet Dent 1997;77(3):271–9.
[57] Gotfredsen K, Berglundh T, Lindhe J. Anchorage of titanium implants with different surface characteristics: an experimental study in rabbits. Clin Implant Dent Relat Res 2000;2(3): 120–8.
[58] Wennerberg A, Hallgren C, Johansson C, et al. A histomorphometric evaluation of screw-shaped implants each prepared with two surface roughnesses. Clin Oral Implants Res 1998;9(1):11–9.
[59] Piattelli A, Manzon L, Scarano A, et al. Histologic and histomorphometric analysis of the bone response to machined and sandblasted titanium implants: an experimental study in rabbits. Int J Oral Maxillofac Implants 1998;13(6):805–10.
[60] Abrahamsson I, Berglundh T, Linder E, et al. Early bone formation adjacent to rough and turned endosseous implant surfaces. An experimental study in the dog. Clin Oral Implants Res 2004;15(4):381–92.
[61] Wennerberg A, Albrektsson T, Andersson B, et al. A histomorphometric and removal torque study of screw-shaped titanium implants with three different surface topographies. Clin Oral Implants Res 1995;6(1):24–30.
[62] Wennerberg A, Ektessabi A, Albrektsson T, et al. A 1-year follow-up of implants of differing surface roughness placed in rabbit bone. Int J Oral Maxillofac Implants 1997;12(4):486–94.
[63] van Steenberghe D, Naert I, Jacobs R, et al. Influence of inflammatory reactions vs. occlusal loading on peri-implant marginal bone level. Adv Dent Res 1999;13:130–5.
[64] Hall J, Lausmaa J. Properties of a new porous oxide surface on titanium implants. Appl Osseointegration Res 2000;1:5–8.
[65] Sul YT, Johansson CB, Kang Y, et al. Bone reactions to oxidized titanium implants with electrochemical anion sulphuric acid and phosphoric acid incorporation. Clin Implant Dent Relat Res 2002;4(2):78–87.
[66] Sul YT, Johansson CB, Petronis S, et al. Characteristics of the surface oxides on turned and electrochemically oxidized pure titanium implants up to dielectric breakdown: the oxide thickness, micropore configurations, surface roughness, crystal structure and chemical composition. Biomaterials 2002;23(2):491–501.
[67] Ivanoff CJ, Widmark G, Johansson C, et al. Histologic evaluation of bone response to oxidized and turned titanium micro-implants in human jawbone. Int J Oral Maxillofac Implants 2003;18(3):341–8.
[68] Vanden Bogaerde L, Rangert B, Wendelhag I. Immediate/early function of Branemark System TiUnite implants in fresh extraction sockets in maxillae and posterior mandibles: an 18-month prospective clinical study. Clin Implant Dent Relat Res 2005;7(Suppl 1): S121–30.

[69] Glauser R, Ruhstaller P, Windisch S, et al. Immediate occlusal loading of Branemark System TiUnite implants placed predominantly in soft bone: 4-year results of a prospective clinical study. Clin Implant Dent Relat Res 2005;7(Suppl 1):S52–9.
[70] Al-Nawas B, Gotz H. Three-dimensional topographic and metrologic evaluation of dental implants by confocal laser scanning microscopy. Clin Implant Dent Relat Res 2003;5(3): 176–83.
[71] Klokkevold PR, Nishimura RD, Adachi M, et al. Osseointegration enhanced by chemical etching of the titanium surface. A torque removal study in the rabbit. Clin Oral Implants Res 1997;8(6):442–7.
[72] Cordioli G, Majzoub Z, Piattelli A, et al. Removal torque and histomorphometric investigation of 4 different titanium surfaces: an experimental study in the rabbit tibia. Int J Oral Maxillofac Implants 2000;15(5):668–74.
[73] Weng D, Hoffmeyer M, Hurzeler MB, et al. Osseotite vs. machined surface in poor bone quality. A study in dogs. Clin Oral Implants Res 2003;14(6):703–8.
[74] Vernino AR, Kohles SS, Holt RA Jr, et al. Dual-etched implants loaded after 1- and 2-month healing periods: a histologic comparison in baboons. Int J Periodontics Restorative Dent 2002;22(4):399–407.
[75] Davarpanah M, Martinez H, Etienne D, et al. A prospective multicenter evaluation of 1,583 3i implants: 1- to 5-year data. Int J Oral Maxillofac Implants 2002;17(6):820–8.
[76] Sullivan DY, Sherwood RL, Porter SS. Long-term performance of Osseotite implants: a 6-year clinical follow-up. Compend Contin Educ Dent 2001;22(4):326–328, 330, 332–324.
[77] Testori T, Meltzer A, Del Fabbro M, et al. Immediate occlusal loading of Osseotite implants in the lower edentulous jaw. A multicenter prospective study. Clin Oral Implants Res 2004; 15(3):278–84.
[78] Cochran DL, Schenk RK, Lussi A, et al. Bone response to unloaded and loaded titanium implants with a sandblasted and acid-etched surface: a histometric study in the canine mandible. J Biomed Mater Res 1998;40(1):1–11.
[79] Buser D, Nydegger T, Hirt HP, et al. Removal torque values of titanium implants in the maxilla of miniature pigs. Int J Oral Maxillofac Implants 1998;13(5):611–9.
[80] Cochran DL, Buser D, ten Bruggenkate CM, et al. The use of reduced healing times on ITI implants with a sandblasted and acid-etched (SLA) surface: early results from clinical trials on ITI SLA implants. Clin Oral Implants Res 2002;13(2):144–53.
[81] Bornstein MM, Lussi A, Schmid B, et al. Early loading of nonsubmerged titanium implants with a sandblasted and acid-etched (SLA) surface: 3-year results of a prospective study in partially edentulous patients. Int J Oral Maxillofac Implants 2003;18(5):659–66.
[82] Salvi GE, Gallini G, Lang NP. Early loading (2 or 6 weeks) of sandblasted and acid-etched (SLA) ITI implants in the posterior mandible. A 1-year randomized controlled clinical trial. Clin Oral Implants Res 2004;15(2):142–9.
[83] Klokkevold PR, Johnson P, Dadgostari S, et al. Early endosseous integration enhanced by dual acid etching of titanium: a torque removal study in the rabbit. Clin Oral Implants Res 2001;12(4):350–7.
[84] Bernard JP, Szmukler-Moncler S, Pessotto S, et al. The anchorage of Branemark and ITI implants of different lengths. I. An experimental study in the canine mandible. Clin Oral Implants Res 2003;14(5):593–600.
[85] Franchi M, Bacchelli B, Martini D, et al. Early detachment of titanium particles from various different surfaces of endosseous dental implants. Biomaterials 2004;25(12):2239–46.
[86] d'Hoedt B, Schulte W. A comparative study of results with various endosseous implant systems. Int J Oral Maxillofac Implants 1989;4(2):95–105.
[87] Mau J, Behneke A, Behneke N, et al. Randomized multicenter comparison of 2 IMZ and 4 TPS screw implants supporting bar-retained overdentures in 425 edentulous mandibles. Int J Oral Maxillofac Implants 2003;18(6):835–47.
[88] Kay JF. Calcium phosphate coatings for dental implants. Current status and future potential. Dent Clin North Am 1992;36(1):1–18.

[89] Morris HF, Ochi S, Spray JR, et al. Periodontal-type measurements associated with hydroxyapatite-coated and non-HA-coated implants: uncovering to 36 months. Ann Periodontol 2000;5(1):56–67.
[90] Morris HF, Ochi S. Survival and stability (PTVs) of six implant designs from placement to 36 months. Ann Periodontol 2000;5(1):15–21.
[91] Jeffcoat MK, McGlumphy EA, Reddy MS, et al. A comparison of hydroxyapatite (HA)-coated threaded, HA-coated cylindric, and titanium threaded endosseous dental implants. Int J Oral Maxillofac Implants 2003;18(3):406–10.
[92] McGlumphy EA, Peterson LJ, Larsen PE, et al. Prospective study of 429 hydroxyapatite-coated cylindric omniloc implants placed in 121 patients. Int J Oral Maxillofac Implants 2003;18(1):82–92.
[93] Wheeler SL. Eight-year clinical retrospective study of titanium plasma-sprayed and hydroxyapatite-coated cylinder implants. Int J Oral Maxillofac Implants 1996;11(3):340–50.
[94] Esposito M, Coulthard P, Thomsen P, et al. Interventions for replacing missing teeth: different types of dental implants. Cochrane Database Syst Rev 2005;(1):CD003815.
[95] Cochran DL, Schenk R, Buser D, et al. Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants. J Periodontol 1999;70(2):139–50.