

# Osseointegration of titanium, titanium alloy and zirconia dental implants: current knowledge and open questions

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Replacement of missing teeth with implants and implant-supported prostheses are currently routine procedures for the oral rehabilitation of partially or fully edentulous patients. The foundation of this achievement was laid in the late 1960s and early 1970s by experiments conducted by Brånemark and coworkers (15, 16) and by Schroeder and coworkers (78). These two pioneers in implant dentistry provided evidence for direct bone apposition on the surface of titanium, a phenomenon later termed 'osseointegration'. In a comprehensive way, osseointegration is defined as 'a direct structural and functional connection between ordered, living bone and the surface of a load-bearing implant' (59). Since this revolutionary breakthrough, bone-related research in implant dentistry has mainly centered around two important issues: how can the osseointegration process be improved; and how can dental implants be maintained well-integrated in bone in the long term.

It has become clear that the surface characteristics of a biomaterial, such as a dental implant made of titanium, exert a decisive influence on the speed of osseointegration. An implant that quickly osseointegrates may reduce the so-called stability dip (88) and this, in turn, may allow earlier implant loading, which is beneficial for the patient (11, 64). In the last few years, implants made of titanium alloys (7, 43) and zirconia (31, 47, 61, 81) have been studied in detail as alternative biomaterials for replacement of missing teeth. While titanium alloys such as titanium-6aluminum-4vanadium (Ti6Al4V) and titanium-zirconium (TiZr) possess better mechanical properties than commercially pure grade 4 titanium, zirconia or

compound ceramics have other advantages over titanium or titanium alloys (31, 74). Surface modifications of these more recently introduced biomaterials were found also to influence the osseointegration process (61).

Despite all these new developments and excellent long-term results in patients, there are still unanswered questions regarding the factors contributing to marginal bone loss around osseointegrated implants (3, 4, 94). The aims of this review were to describe the temporal sequence of osseointegration and the effects of implant surface modifications and chemical composition of the bulk biomaterial on osseointegration. Soft-tissue integration, although important for the long-term success of dental implants, will not be discussed. For more information about soft tissues around dental implants the readers are referred to recent reviews (9, 80, 95). For obvious reasons, mostly preclinical data, predominantly from animal experiments, will be included in this review. *In vitro* and clinical data will be discussed only where it seems necessary.

## Evaluation of osseointegration and mechanical stability

The early healing phase of a dental implant placed in bone is important for its long-term success. In particular, mechanical implant stability is regarded as a prerequisite for the short- and long-term clinical success of osseointegrated implants (6). Osseointegration is a dynamic process during which primary stability becomes substituted by secondary stability.

Immediately after implant installation, mechanical fixation of the implant is provided by the primary stability (i.e. the direct contact between the surface of the bony walls of the implant bed and the surface of the dental implant). The nature of this bonding is mechanical, not biological. The magnitude of the primary stability is determined by many factors, including: the macro-design of the implant (i.e. diameter, length, cylindrical vs. tapered, thread architecture) in relation to the implant bed preparation (i.e. press-fit); the vertical position of the implant relative to the bone crest (i.e. sink depth); the surface morphology or roughness of the implant (i.e. micro- and nanotopography); and the local bone quality (i.e. density of bone). As compact bone contributes more than trabecular bone to primary stability, the implant diameter may contribute more than implant length to primary stability. The building up of the secondary stability starts with the first apposition of new bone onto the implant surface. The nature of the bonding between new bone and the implant is biological. New bone apposition on the implant surface begins earlier in trabecular bone than in compact bone regions because the latter needs to be resorbed first. The sum of the primary stability, which decreases over time, and the secondary stability, which increases over time, accounts for the total stability. From a clinical point of view, it must be noted that a transient decrease in total implant stability is commonly observed 3–4 weeks after implant placement as a consequence of the loss of primary stability. For smooth development of total stability with a less-pronounced stability dip, a good balance between cortical and trabecular bone surrounding the freshly placed implant appears to be desirable.

The gold standard used to evaluate how much bone is in contact with an implant surface is histomorphometry. The bone-to-implant contact is expressed as the percentage of the implant surface covered by bone. Osseointegration, by definition, means living (newly formed) bone in contact with an implant. Unfortunately, there are numerous publications in which no information can be found on the type of bone (i.e. new, old or total) in contact with the implant. This can create great confusion. Particularly at early-healing phases, such a distinction makes a big difference, but this largely also depends on the implant model used (13). Regarding mechanical implant stability, the bone-to-implant contact may not necessarily be as informative as commonly believed (12). In trabecular regions or in studies where implants with a wound chamber design were used, the initial bony coating may be

very thin and may therefore not contribute greatly to mechanical implant stability. Stability of osseointegrated implants may depend on: the percentage of bone-to-implant contact; how the new bone deposited on the implant surface is connected to the surrounding bone; and the bone density (quality) of the surrounding bone. Nevertheless, the percentage of bone-to-implant contact can be used to evaluate differences in the speed of bone apposition onto the implant surface between materials and/or surface modifications. How relevant faster osseointegration in a clinical situation really is, is another issue. To determine mechanical implant stability, other tests must be applied.

Push-out or pull-out tests, or removal torque analysis experiments, are used to measure implant anchorage in bone. Simply speaking, the greater the forces required to remove an implant, the greater the strength of osseointegration. This technique is not applicable to patients. However, it may be used to correlate biomechanical interlocking with surface roughness (topography) and biomechanical interlocking with bone-to-implant contact values.

In patients, primary stability can be measured using insertion torque analysis, whereas implant stability at the time of abutment connection can be evaluated by applying reverse or unscrewing torque testing. A noninvasive and widely accepted technique is, however, resonance frequency analysis (82). This technique can provide clinically relevant information about the condition of the bone-to-implant interface at any time interval after implant placement. Longitudinal monitoring of the resonance frequency analysis values may allow optimal loading times to be determined and identification of implants at risk (46, 82, 85).

## Temporal sequence of wound healing and osseointegration

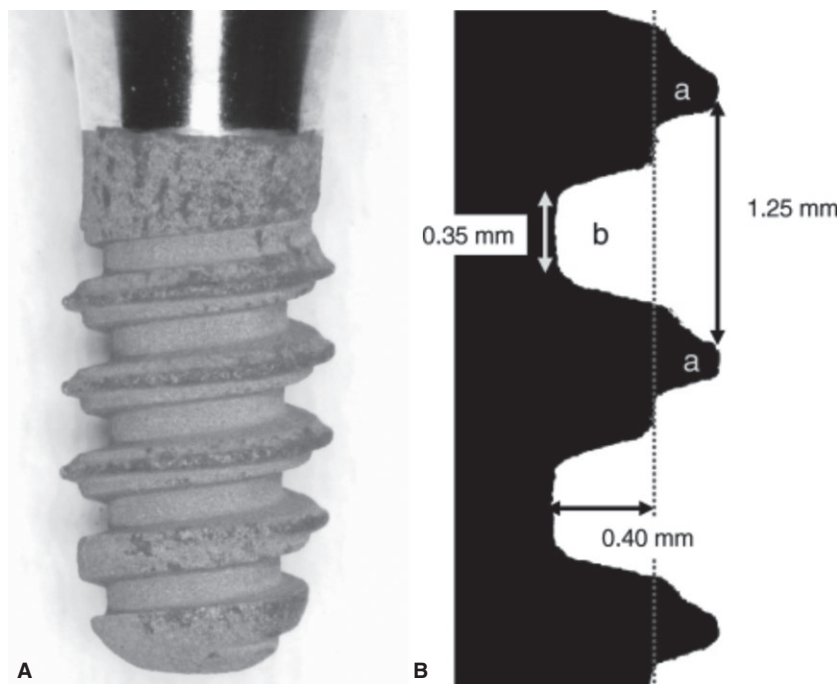
Osseointegration of dental implants has been studied in many animal models that vary in the following factors: species exhibiting different speeds of wound healing, bone formation and turnover; anatomic location; observation periods; implant bed preparation; implant design; loading conditions; implant bulk material and surface treatment; and implant–abutment interface configuration. Such a large degree of heterogeneity is a problem and makes comparisons between studies very difficult.

The drilling of an implant bed in the jaw bone creates a bleeding wound that in turn initiates the

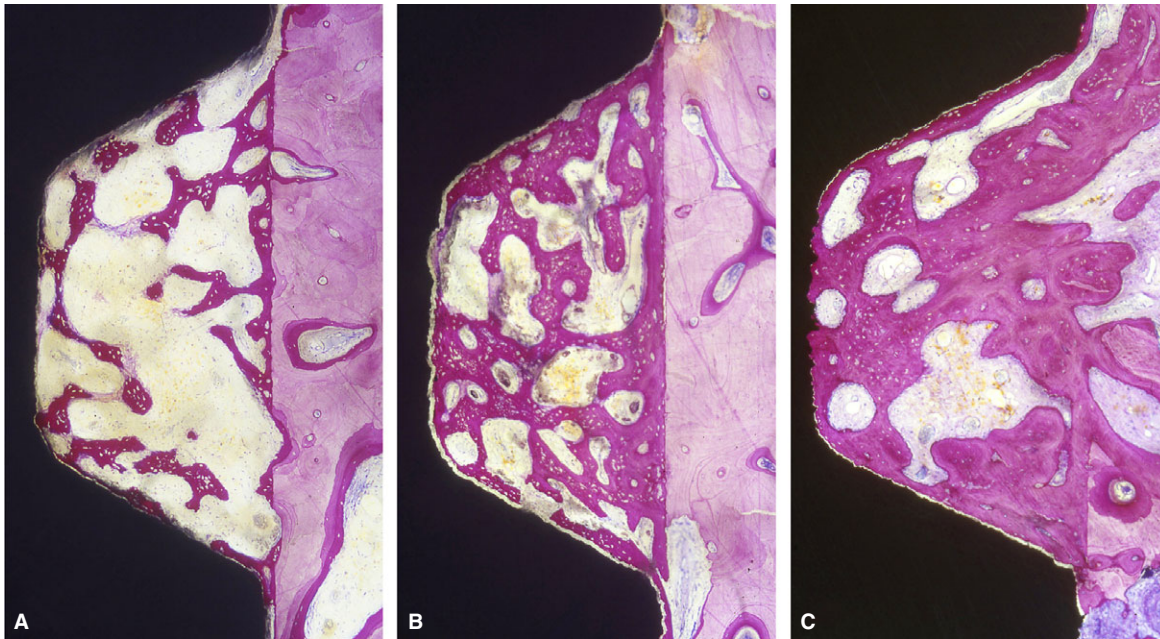
cascade of wound-healing steps. Wound healing and tissue regeneration is a coordinated process controlled by different cell types that communicate with each other via cytokines, growth factors and extracellular matrix molecules. Insertion of a biomaterial into wounded tissue interferes in some way with the healing process and also influences the apposition of bone onto this biomaterial. Osseointegration of a dental implant is based on the principle of bone regeneration and on the osteoconductivity of the biomaterial (5, 76). While a large number of studies have shown histologically that titanium implants become integrated in living bone in both animals and humans (76), few studies have investigated the temporal sequence leading to osseointegration of titanium implants (52, 83, 84). The very early events of healing and tissue formation were not shown until 2003 in an animal experiment (10). The sequential steps of healing and osseointegration have recently been reviewed (73, 89). It is important to understand that different wound- and bone-healing models exist. Berglundh and coworkers (10) used a specially designed implant design resulting in a geometrically well-defined wound compartment. Solid-screw implants made of commercially pure grade 4 titanium with a sandblasted and acid-etched surface were fabricated with an additional circumferential U-shaped trough between the implant threads (Fig. 1). This resulted in deeper and wider thread pitch functioning as a wound chamber, whereas the thread crests were

engaged in the wall of the prepared bone bed, providing the necessary primary stability. The observation periods ranged from 2 h to 12 weeks. This experimental chamber model was an elegant approach because it allowed analysis of the wound-healing sequence and early phases of bone formation in a standardized manner, eliminating variations in the timing of tissue modeling that occur close to the implant surface as a result of the presence or absence of old bone contacting the implant surface. The healing sequence in humans was described in a different implant design in which both parent bone matrix and bone marrow were in contact with the titanium implants (13, 56).

If wound healing proceeds without complications, the series of events leading to osseointegration can be summarized as follows: (i) hemostasis and formation of a coagulum; (ii) granulation tissue formation; (iii) bone formation; and (iv) bone remodeling. The process of bone formation starts during the first week and this is true for both animals and humans (10, 13, 56). The bone initially formed is woven bone that emerges from the surface of the cut bone bed and forms trabecular struts connecting the parent bone with the implant surface (Fig. 2A). Later, when a certain thickness of these woven bone trabeculae is reached, parallel-fibered (Fig. 2B) bone, followed by lamellar bone deposition (Fig. 2C), further increases the bone density until primary osteons



**Fig. 1.** Wound chamber model by Berglundh et al. (10). (A) Screw-shaped titanium implant, 4.1 mm in diameter and 10 mm in length, with a circumferential trough in the endosseous part. (B) Cross-section of the wound chamber: a, pitches engaging the bone tissue walls; and b, inner U-shaped wound chamber proper. The dotted line indicates the lateral wall of the chamber (i.e. the position of the cut bone surface). With permission.



**Fig. 2.** Bone formation in bone chambers and apposition to titanium implants with a sandblasted and acid-etched modified surface at (A) 2, (B) 4 and (C) 8 weeks. (A) At 2 weeks, bone is deposited on the bony wall of the tissue chamber and on the implant surface. A scaffold of tiny trabeculae, consisting of woven bone, connects the bone and implant surfaces. (B) At 4 weeks, the volume density of this scaffold has increased both by the formation of new trabeculae and by deposition of more mature, parallel-fibered bone onto the primary scaffold. Woven bone is mainly

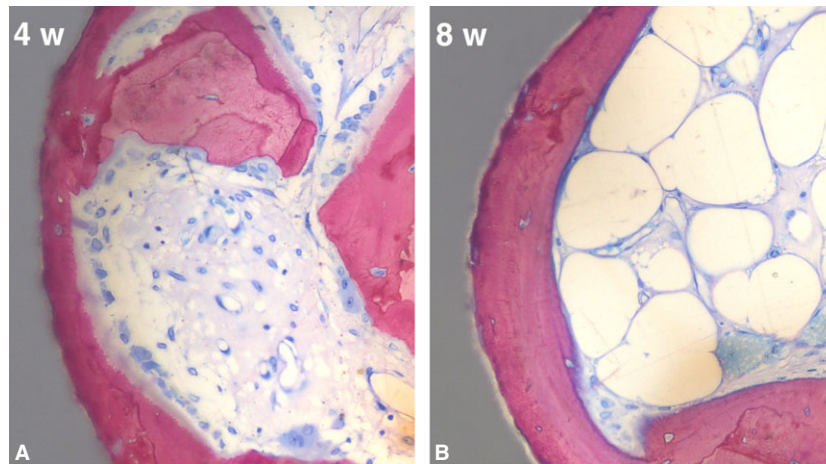
recognized by the numerous large osteocyte lacunae. The gap between bone and the implant surface is an artifact. (C) At 8 weeks, growth and reinforcement result in a further increase in bone density and an almost perfect coating of the implant surface with bone. Remodeling has started, replacing the primary bone with secondary osteons. The images show undecalcified ground sections surface-stained with toluidine blue and basic fuchsin. From Buser et al. (19). With permission.

are established. In trabecular bone regions, a cessation of bone formation and maturation of bone marrow can be observed after 8 weeks (Fig. 3). Between 1 and 2 weeks at sites with compact parent (old) bone in contact with the implant surface, the process of new-bone formation is delayed because the parent bone needs to be resorbed first (Fig. 4). While in animals this resorption process starts between 1 and 2 weeks (10), in humans bone resorption close to the implant surface is observed at 2 weeks (13). At later stages, starting at 6 weeks in animals, the presence of primary and secondary osteons in compact bone indicates bone remodeling. Depending on the anatomic location, the position of the implant within jaw bone and possibly also patient-specific factors, part of the implant surface will be covered by trabecular bone, while other regions are in contact with compact bone (Figs. 5 and 6). Bone remodeling continues for the rest of life. Importantly, bone remodeling (i.e. bone resorption followed by bone apposition) also involves the tissue-implant interface and therefore transiently exposes the formerly bone-covered implant surface to soft tissue present within bone (Fig. 7). If the

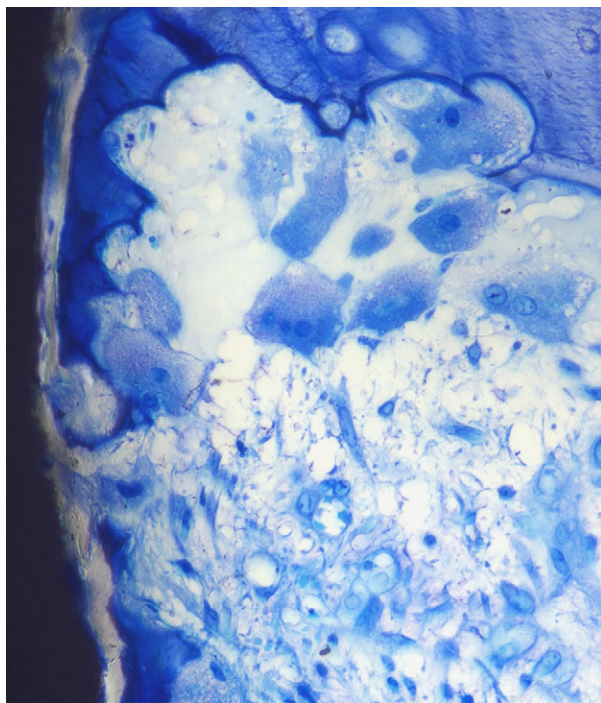
amount of newly formed bone does not match that of resorbed bone, this imbalance can, in the strict sense, not be regarded as remodeling. A continuous net loss of bone-to-implant contact will compromise osseointegration and eventually lead to implant loss. As bone remodeling can be regarded as a slow process, such destabilization will not immediately be recognized. Consequently, as animal experiments do not last long enough, experimental approaches to study loss of osseointegration are not available, except for ligature-induced peri-implant lesions, which are artificial models and do not mimic clinical reality.

The descriptive histology of osseointegration of titanium implants has been complemented by gene analysis (90). Wide genome-expression profiling of human peri-implant tissues (33, 50) shows that between 4 days and 2 weeks after implant insertion the gene-expression profile switches from one being associated with immuno-inflammatory processes and cell proliferation to one being related to angiogenesis, osteogenesis and neurogenesis. These studies show that a proinflammatory wound-healing phase precedes a regenerative phase in which down-regulation



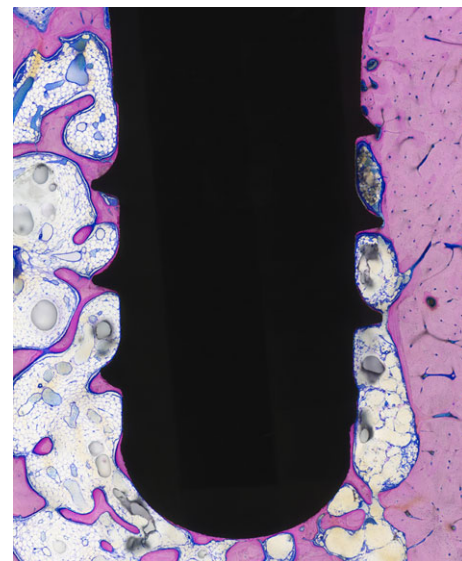


**Fig. 3.** Maturation of bone adjacent to zirconia implants placed in the maxilla of miniature pigs. (A) At 4 weeks, mineralized bone matrix is in direct contact with the implant surface. Osteoid and osteoblasts indicate ongoing bone formation, while osteoclasts and Howship's lacunae on old bone indicate resorption of pre-existing bone (light red). (B) At 8 weeks, bone formation has ceased, as indicated by the absence of both osteoid and osteoblasts. Bone marrow indicates maturation of bone. The images show undecalcified ground sections surface-stained with toluidine blue and basic fuchsin.



**Fig. 4.** Osteoclasts approaching a titanium implant surface (chemically activated and treated with sandblasting and acid etching) while resorbing old compact bone matrix in contact with the implant, 14 days after implant placement in the retromolar region of a human volunteer. The image shows an undecalcified ground section surface-stained with toluidine blue. From Bosshardt et al. (13). With permission.

of inflammation and up-regulation of osteogenesis-related genes occur during the early osseointegration process.

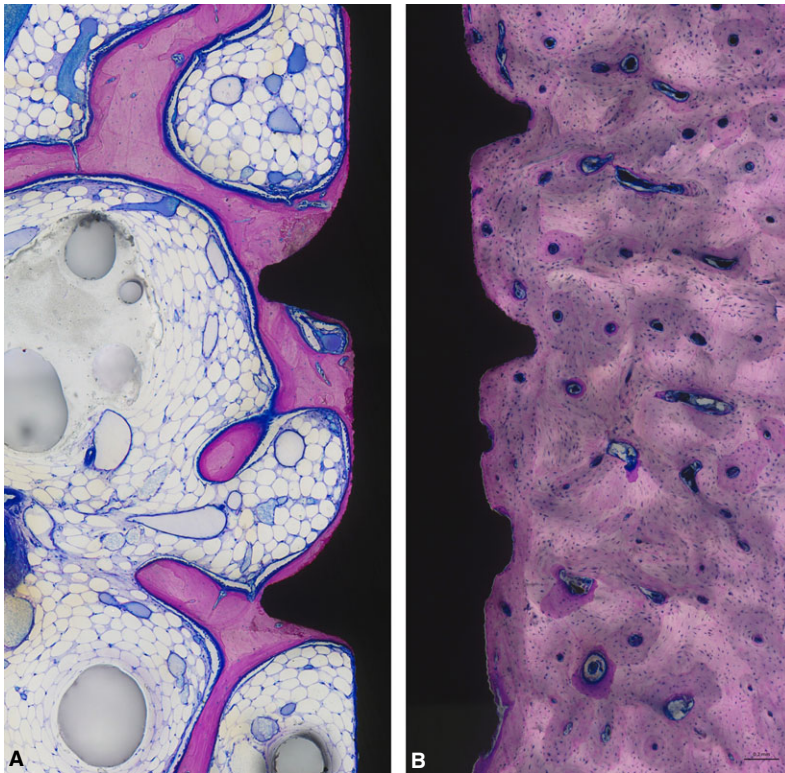


**Fig. 5.** Titanium implant placed in the canine mandible. At 22 weeks after implant placement, the bone on the lingual aspect is very trabecular, whereas the bone on the buccal side is more compact. The image shows an undecalcified ground section stained with toluidine blue and basic fuchsin.

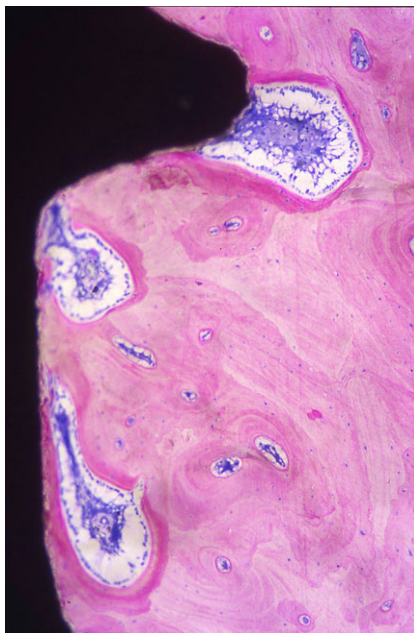
## Surface topography and chemical modification

### Titanium

Surface modifications have been a major focus of research in the last 25 years in implant dentistry. Numerous *in vivo* studies demonstrate the influence



**Fig. 6.** Titanium implants placed in the canine mandible (A) and retrieved from the mandible of a patient 5 years after placement because of fracture (B). The surface of an implant can be in contact with either (A) trabecular or (B) compact bone. Bony anchors have formed in the cancellous part of the implant site (A), whereas bone covers almost the entire implant surface where compact bone prevails. The images show undecalcified ground sections stained with toluidine blue and basic fuchsin.



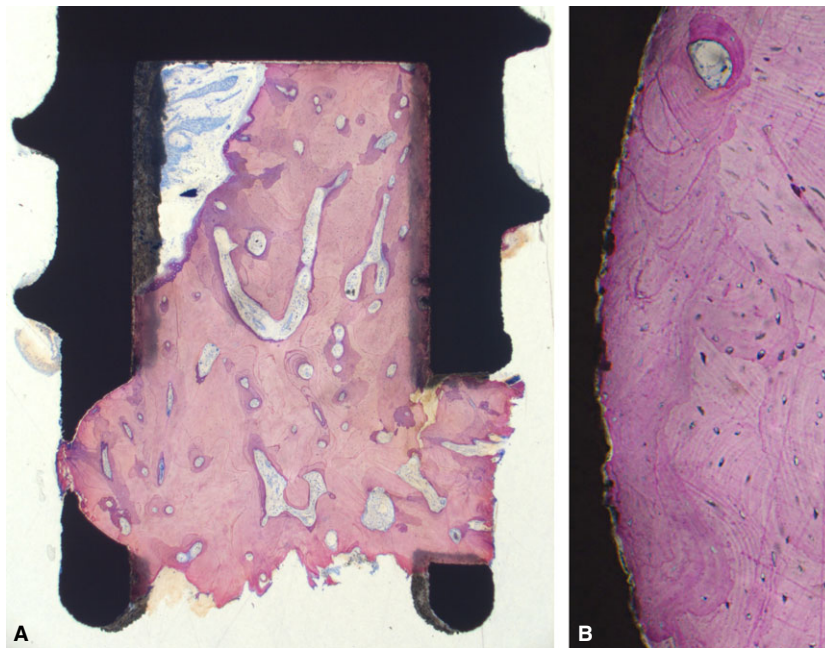
**Fig. 7.** Osseointegration of a micro-rough titanium implant demonstrating secondary bone-to-implant contact achieved by cortical bone remodeling. Three cortical bone-remodeling units have evolved in direct contact with the implant surface, which is sandblasted and acid-etched, 3 months unloaded. The image shows an undecalcified ground section stained with toluidine blue and basic fuchsin. From Schenk & Buser (76). With permission.

of implant surface characteristics on osseointegration of titanium implants, leading to significantly higher bone-to-implant contact percentages at earlier time

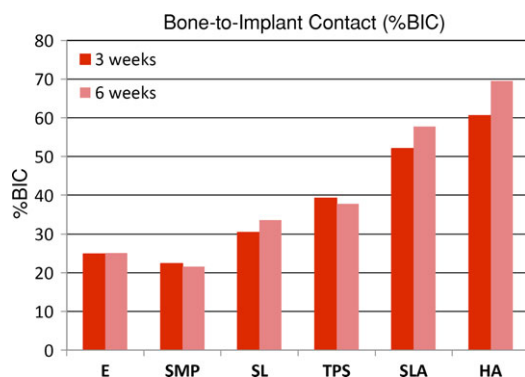
points following implant placement. In addition, a wealth of information from *in vitro* studies documents the influence of titanium surface modifications on osteoblastic cells (38–40).

The original Brånemark implant was a machined (turned) screw with a low average surface roughness value of 0.5–1.0  $\mu\text{m}$ . This implant was regarded as the gold standard for many years. Later experimental studies demonstrated a higher percentage of bone-to-implant contact for implants with a titanium plasma-sprayed surface (Fig. 8), an additive technique, than for titanium implants with a smooth surface (86). The next generation of implant surfaces were sandblasted with or without acid-etching, which are subtractive techniques. A study in long bones of miniature pigs demonstrated significant differences in bone-to-implant contact in cancellous bone (Fig. 9) (22). The highest bone-to-implant contact values were found for sandblasted and acid-etched surfaces and hydroxyapatite-coated implants. The hydroxyapatite-coated implants, however, consistently showed signs of resorption. Sandblasting was performed with alumina particles of large grit (0.25–0.50  $\mu\text{m}$ ) and acid treatment was performed with hydrogen chloride/sulfuric acid. This surface treatment was called sandblasting and acid-etching and a study in the canine mandible showed the superiority of sandblasting and acid-etching over titanium plasma-spraying in unloaded and loaded conditions

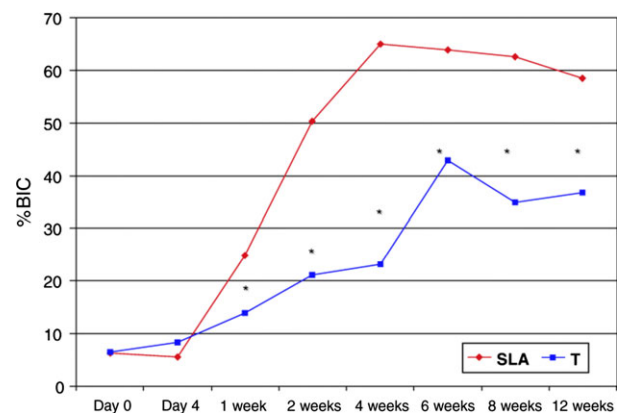




**Fig. 8.** Implant with a titanium plasma-sprayed surface retrieved from a patient because of peri-implantitis. (A) Note direct bone-to-implant contact in the interior of the hollow screw implant, except in the upper left corner. (B) Higher magnification showing direct bone-to-implant contact. The images show undecalcified ground sections stained with toluidine blue and basic fuchsin.



**Fig. 9.** Mean percentage of direct bone-to-implant contact (%BIC) of different implant surfaces at 3 and 6 weeks. E, electropolished; HA, hydroxyapatite-coated plasma sprayed; SL, sandblasted with large grit; SLA, sandblasted with large grit and acid-etched; SMP, sandblasted with medium grit and acid pickling; TPS, titanium plasma-sprayed. Modified from Buser et al. (22). With permission.

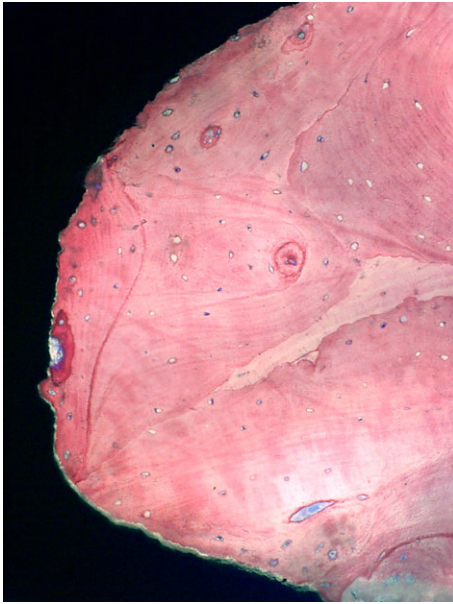


**Fig. 10.** Diagram showing the degree of osseointegration (presented as percentage of bone-to-implant contact [% BIC]) from day 0 to 12 weeks at sandblasted and acid etched (SLA) and turned (T) titanium implants. Osseointegration – BIC% (entire intraosseous portion). From Abrahamsson et al. (1). \* $p < 0.05$ . With permission.

(28). In another animal study, a significantly higher percentage of bone-to-implant contact was found on surfaces of titanium implants following treatment with sandblasting and acid-etching than on machined surfaces of titanium implants between 1 and 12 weeks after placement in canine mandibles (Fig. 10) (1). Another strategy used to modify the titanium surface is anodic oxidation, which results in growth of the native titanium oxide layer and a porous surface topography (57). Histologic analyses from animal studies (17, 57, 72, 87, 103) and from implants retrieved from humans (49, 71, 79) have

demonstrated a strong interlock between bone and the implant surface. The sandblasting and acid-etching treatment has become one of the standards for dental implants made of titanium. Figure 11 shows bone on a sandblasted and acid-etched-treated implant retrieved from a human patient. Other surface treatments resulting in micro-rough titanium surfaces also demonstrated higher percentages of bone-to-implant contact when compared with machined or polished titanium surfaces (41, 96).

The next step was to modify chemically these micro-rough implant surfaces in order to increase the



**Fig. 11.** Palatal implant with a titanium sandblasted and acid-etched surface retrieved from a patient. Compact bone is in direct contact with the implant. A bone-remodeling unit is present on the implant surface. The image shows an undecalcified ground section stained with toluidine blue and basic fuchsin.

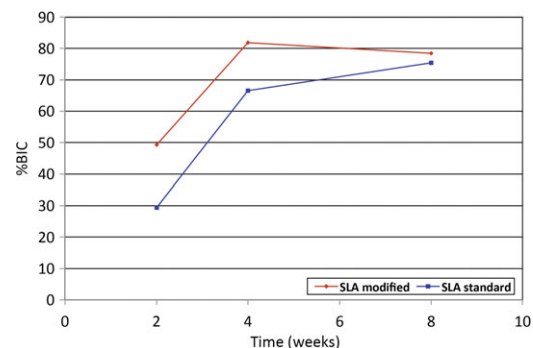
hydrophilicity and make them biologically more active. These chemically modified SLA surfaces (SLActive) were manufactured using the same sandblasting and acid-etching process as used for sandblasting and acid-etching of implants, but were rinsed under nitrogen protection and stored in an isotonic salt solution following the acid-etching procedure. Titanium implants with an activated sandblasted and acid-etched surface and a wound chamber design (Fig. 12), similar to the one originally used by Berglundh and coworkers (10), demonstrated significantly greater bone-to-implant contact compared with SLA implants at 2 and 4 weeks after placement in the maxilla of miniature pigs (Fig. 13) (19). Figure 14 illustrates bone apposition on the SLActive titanium surface at 8 weeks. In a human experimental study of SLA and SLActive micro-rough surfaces of solid titanium screw test devices, a significantly higher percentage of bone-to-implant contact was verified for the SLActive implants at an early healing phase (Figs. 15 and 16) (13, 56).

## Titanium alloys

For certain indications, diameter-reduced titanium alloy implants with improved mechanical strength are highly desirable. Titanium-6aluminum-4vanadium (Ti6Al4V) and titanium-zirconium (TiZr) are



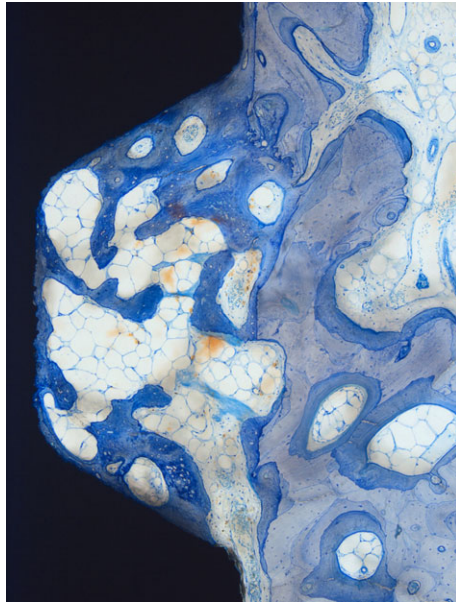
**Fig. 12.** Implant design with wound chambers by Buser et al. (19). Shown is a titanium implant measuring 6 mm in length with two rings forming two bone chambers with an inner diameter of 2.7 mm and an outer diameter of 4.2 mm. Each chamber has a depth of 0.75 mm and an outer vertical height of 1.8 mm.



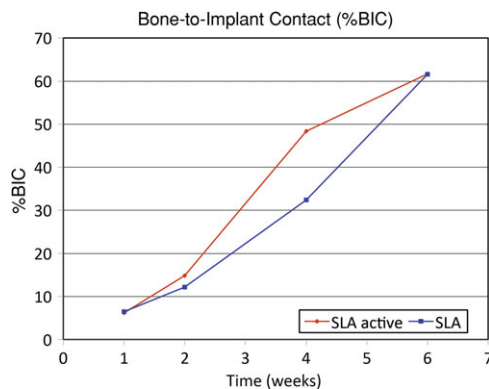
**Fig. 13.** Graph illustrating the effect of implant surface chemistry on the percentage of bone-to-implant contact (%BIC) over time. From Buser et al. (19). SLA modified, treated with sandblasting and acid etching followed by chemical activation. With permission.

such biomaterials. However, whether surface modifications of such alloys result in comparable bone-to-implant contact values was initially not known. Therefore, osseointegration was compared between Ti6Al4V and commercially pure titanium implants with machined (53) and titanium dioxide-blasted (45) surfaces. A difference in bone-to-implant contact between Ti6Al4V and commercially pure titanium was observed in both studies but did not reach statistical significance. Osseointegration of TiZr implants was studied in miniature pigs (43, 74, 91) and in dogs (91). No statistically significant differences in the



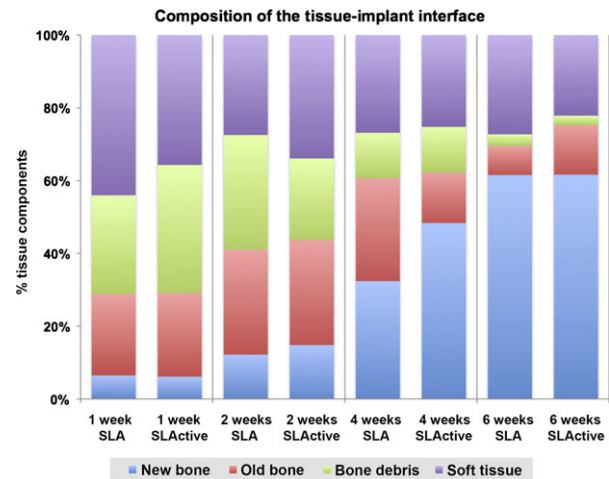


**Fig. 14.** Bone apposition on a titanium implant surface (chemically activated and treated with sandblasting and acid etching) after 8 weeks of healing in the maxilla of a miniature pig. The image shows an undecalcified ground section stained with toluidine blue. SLA modified, treated with sandblasting and acid etching followed by chemical activation. With permission.

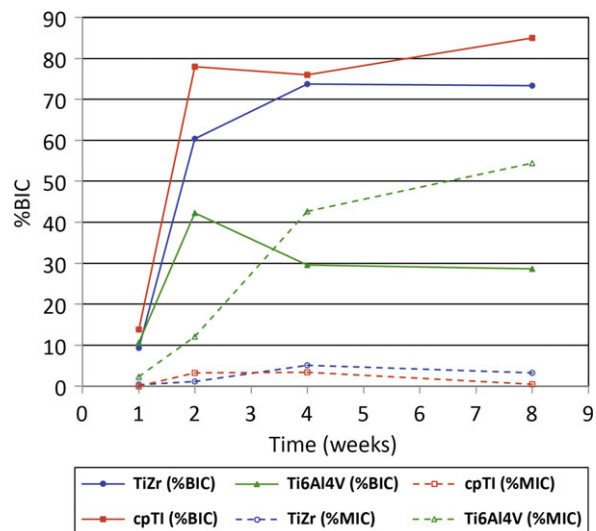


**Fig. 15.** Graph illustrating the effect of implant surface chemistry on the percentage of new bone-to-implant contact (%BIC) over time. From Lang et al. (56). SLA, sandblasted and acid etched; SLActive, chemically activated and treated with sandblasting and acid etching. SLA modified, treated with sandblasting and acid etching followed by chemical activation. With permission.

percentage of bone-to-implant contact were demonstrated between TiZr and commercially pure titanium implants. In one of these studies, osseointegration of TiZr and commercially pure grade 4 titanium implants with a modified sandblasted and acid-etched surface and implants made of Ti6Al4V alloy that was sandblasted with alumina and acid-washed with 65% nitric acid were compared with each other in a miniature pig model (74). All implants had an identical wound chamber design, which has been



**Fig. 16.** Histogram illustrating the effect of implant surface chemistry on the percentages of new bone, old bone, bone debris and soft tissue covering the implant surface after 1, 2, 4 and 6 weeks of healing (13). With permission.

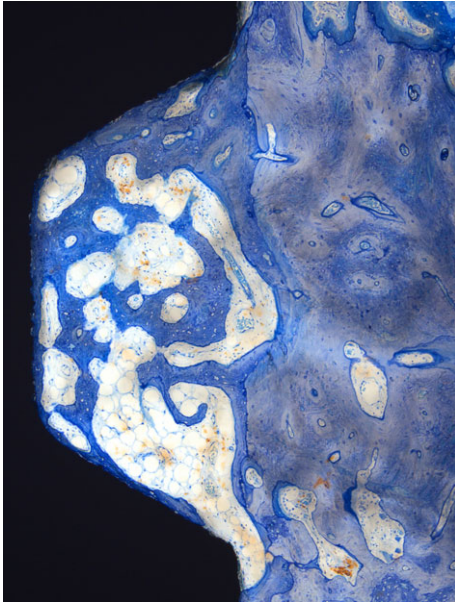


**Fig. 17.** Graph illustrating the effect of the implant materials on the percentage of bone-to-implant contact (%BIC) and the percentage of implant surface along the grooves covered with multinucleated giant cells (%MNGCs) over time. From Saulacic et al. (74). With permission.

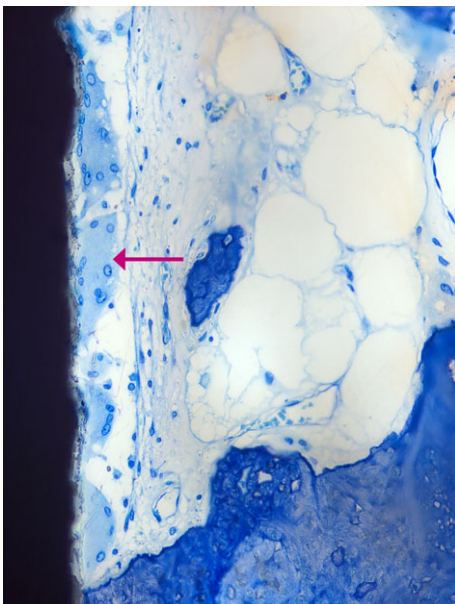
previously described (19). While the bone-to-implant contact was comparable between TiZr and commercially pure titanium implants and both of these implant types showed fast osseointegration, the bone-to-implant contact of the Ti6Al4V implants peaked at a significantly lower value and declined thereafter (Fig. 17). Figure 18 illustrates bone apposition on the TiZr implant. An interesting observation in this study was that significantly more surface was covered by multinucleated giant cells on Ti6Al4V implants than on TiZr and commercially pure titanium implants (Figs. 17 and 19).

## Zirconia and other ceramics

Zirconia has received great interest as a dental material. The mechanical stability of zirconia is increased by the addition of tetragonal polycrystals of yttrium. Because of improvements in mechanical stability, zirconia implants have recently been introduced to



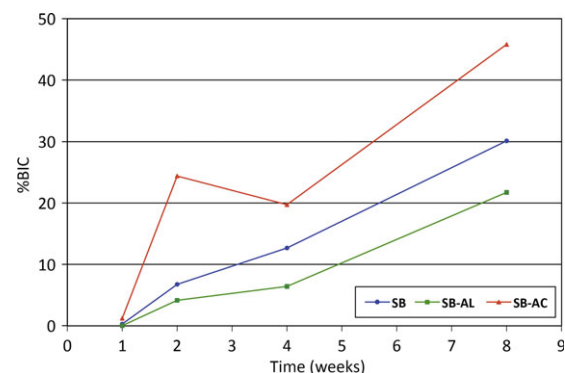
**Fig. 18.** Bone apposition on the surface of a TiZr implant, treated with sandblasting and acid etching followed by chemical activation after a healing period of 8 weeks in the maxilla of a miniature pig. The image shows an undecalcified ground section stained with toluidine blue. From Saulacic et al. (74).



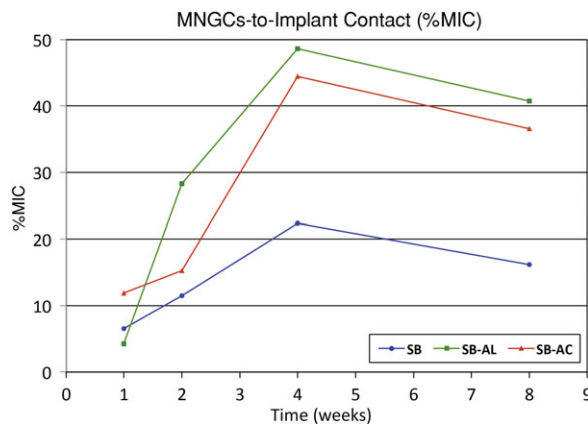
**Fig. 19.** Multinucleated giant cells (arrow) on a micro-rough Ti6Al4V implant surface. From Saulacic et al. (74). With permission.

implant dentistry and are increasingly used as fixtures to replace missing teeth. An advantage of zirconia over titanium is its ivory color. However, at the start of their clinical use, the impact of surface modifications of zirconia implants on osseointegration was not clear. Therefore, as with the titanium implants over the last 25 years, particular attention was paid to the effect of modification of zirconia surfaces on osseointegration in experimental animal studies. These preclinical studies have revealed bone apposition on zirconia implants with various surface modifications, including sandblasting (48, 77), etching (35, 36, 77), sintering and coating (58, 70, 81). Some of these studies showed that subtle changes of the zirconia surface had a high impact on bone apposition onto the implant surface. A recent study in miniature pigs demonstrated that acid-etching, but not alkaline-etching, of sandblasted zirconia implants caused more bone-to-implant contact than did sandblasting alone (Fig. 20) (75). Alkaline-etching resulted in lower bone-to-implant contact values compared with sandblasting alone. Interestingly, both acid-etching and alkaline-etching increased the presence of multinucleated giant cells on the implant surface (Figs. 21 and 22).

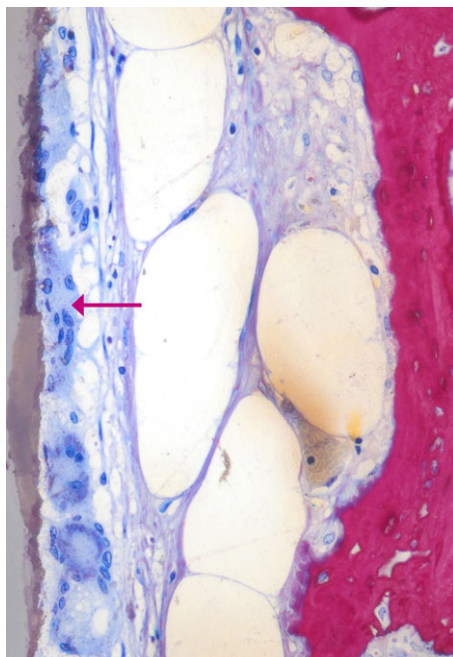
Yttria-stabilized zirconia can be toughened by adding alumina. In a further study in miniature pigs, the performance of alumina-toughened zirconia implants was compared with those of zirconia implants and titanium implants (25). The commercially pure grade 4 titanium implants were sandblasted with alumina and acid-etched with hydrogen chloride/sulfuric acid, whereas the two ceramic implants were treated with alumina followed by hypophosphorous acid. All implant types achieved osseointegration (Figs. 23 and 24) and showed high bone-to-implant contact values



**Fig. 20.** Graph illustrating the effect of implant surfaces on the percentage of bone-to-implant contact (%BIC) for sandblasted (SB), sandblasted and acid-etched (SB-AC), and sandblasted and alkaline-etched (SB-AL) zirconia implants. Modified from Saulacic et al. (75). With permission.



**Fig. 21.** Graph illustrating the effect of implant surfaces on the percentage of implant surface along the grooves covered with multinucleated giant cells (%MNGCs) for sandblasted (SB), sandblasted and acid-etched (SB-AC), and sandblasted and alkaline-etched (SB-AL) zirconia implants. Modified from Saulacic et al. (75). With permission.



**Fig. 22.** Multinucleated giant cells (arrow) on a micro-rough zirconia implant surface. The image shows an undecalcified ground sections stained with toluidine blue and basic fuchsin. From Saulacic et al. (75). With permission.

after 4 and 8 weeks, with greater percentages of bone-to-implant contact on the titanium implants (Fig. 25). Also in this study, the implant surface covered by multinucleated giant cells (Fig. 26) was quantified. These cells were found on the surface of the titanium implants and on the surfaces of both types of ceramic implants. However, less surface on the titanium implants was covered.

## Summary of surface modifications

It can be concluded that surface modifications of biomaterials made of commercially pure grade 4 titanium, titanium alloys (such as Ti6Al4V and TiZr) and ceramics (such as zirconia and alumina-toughened zirconia) have an effect on osseointegration (i.e. bone-to-implant contact) during the early wound-healing and tissue-integration phases in various animals. In addition, there is ample evidence that increased surface roughness results in higher removal torque values (20, 21, 25, 27, 41, 42, 45, 52, 54, 55, 92, 96–98, 101) and that in some of these studies this is linked to a higher percentage of bone-to-implant contact. While the clinical relevance of ultimate fast osseointegration is debatable, the maintenance of osseointegration over time is not.

Owing to favorable *in vivo* osseointegration and *in vitro* effects on osteoblastic cells, implants with a micro-rough surface currently dominate the market of dental implants. It should be noted that it is probably impossible to determine whether an effect on osseointegration is caused by surface chemistry or topography. Although surface characteristics, such as topography and chemistry, have often been discussed independently of each other, these characteristics are virtually inseparable (23). It is also important to point out that the surface analogy originally believed to occur between surfaces treated with sandblasting and acid-etching and with activation after sandblasting and acid-etching was found to be wrong as nanostructures superimposed to microstructures were identified on activated sandblasted and acid-etched implants but not on standard sandblasted and acid-etched implants (100). Thus, part of the bioactivity of activated sandblasting and acid-etching treatment may be attributable to nanostructures. It is clear that histologic and histomorphometric studies cannot unravel the biological mechanisms behind faster osseointegration. Most information on how surface modifications provoke a cellular response comes from *in vitro* studies. Several recent review articles focus on this topic (8, 40, 68). Our knowledge of the biologic response to surface modifications is increasing but still very incomplete; however, recent studies suggest a stimulating effect of certain surface modifications on cells involved in hard- and soft-tissue integration. Translating these stimulatory *in vitro* effects on osteoblastic cells to the *in vivo* situation could mean that bone apposition onto modified implant surfaces occurs faster because of enhanced osteoconductivity once bone has reached the implant surface from the surrounding resident bone (distance



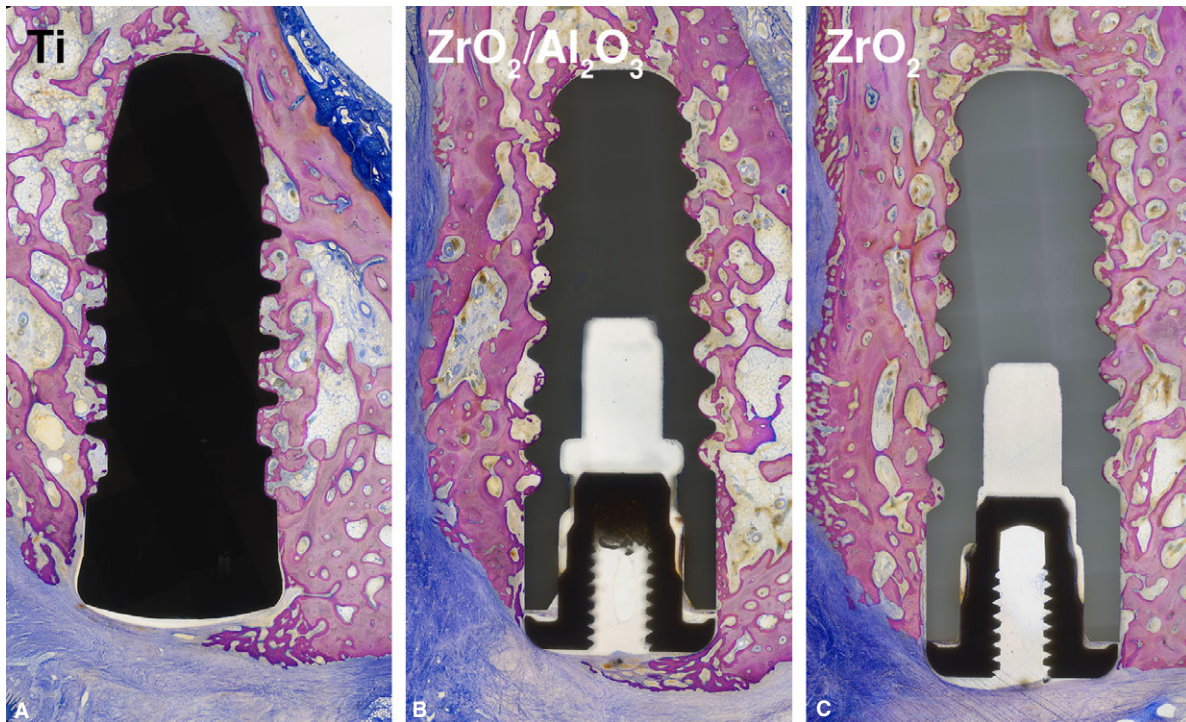


Fig. 23. Osseointegrated (A) titanium (Ti), (B) alumina-toughened zirconia ( $\text{ZrO}_2/\text{Al}_2\text{O}_3$ ) and (C) zirconia ( $\text{ZrO}_2$ ) implants after 4 weeks of healing and tissue integration in the maxilla of miniature pigs. The images show decalcified ground sections stained with toluidine blue and basic fuchsin. From Chappuis et al. (26). With permission.

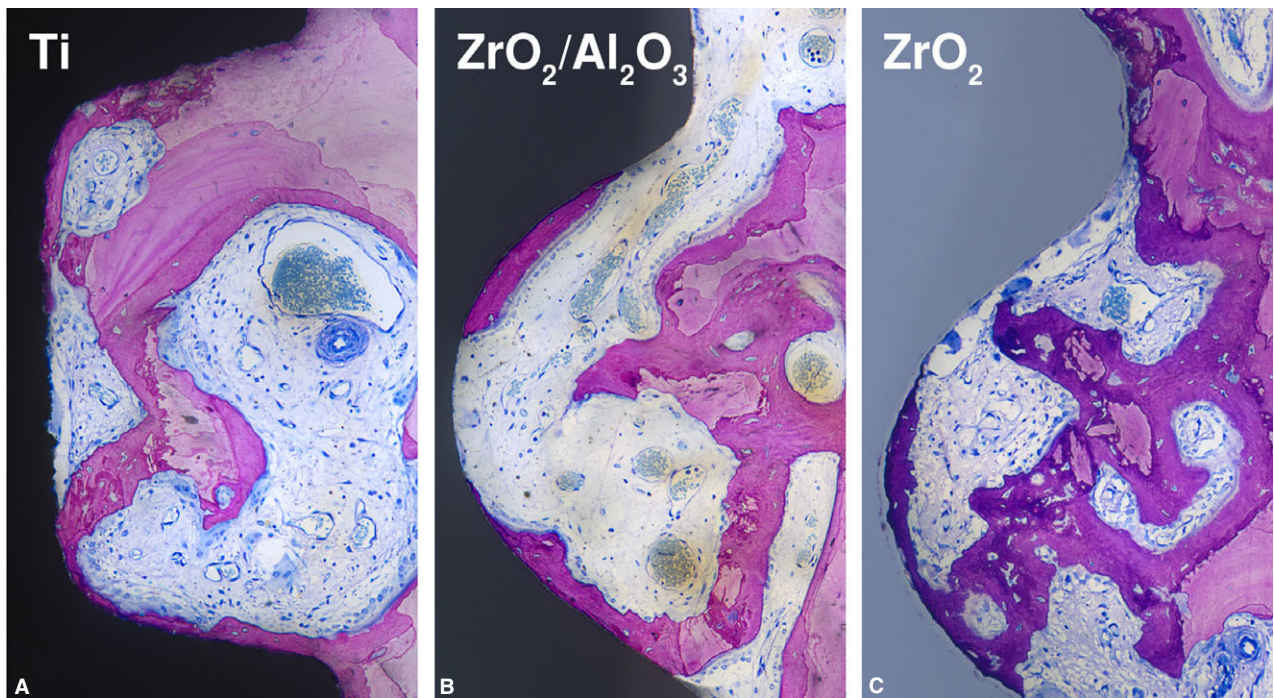
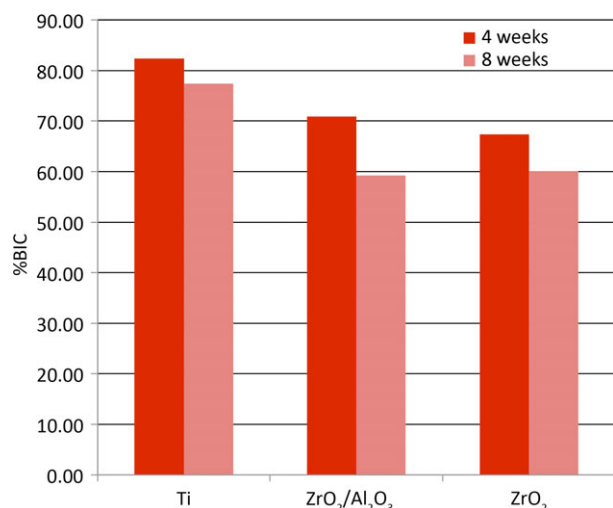


Fig. 24. Osseointegrated (A) titanium (Ti), (B) alumina-toughened zirconia ( $\text{ZrO}_2/\text{Al}_2\text{O}_3$ ) and (C) zirconia ( $\text{ZrO}_2$ ) implants after 4 weeks of healing and tissue integration in the maxilla of miniature pigs. Both new and old bone are present on and around the implants. The images show undecalcified ground sections stained with toluidine blue and basic fuchsin. From Chappuis et al. (26). With permission.



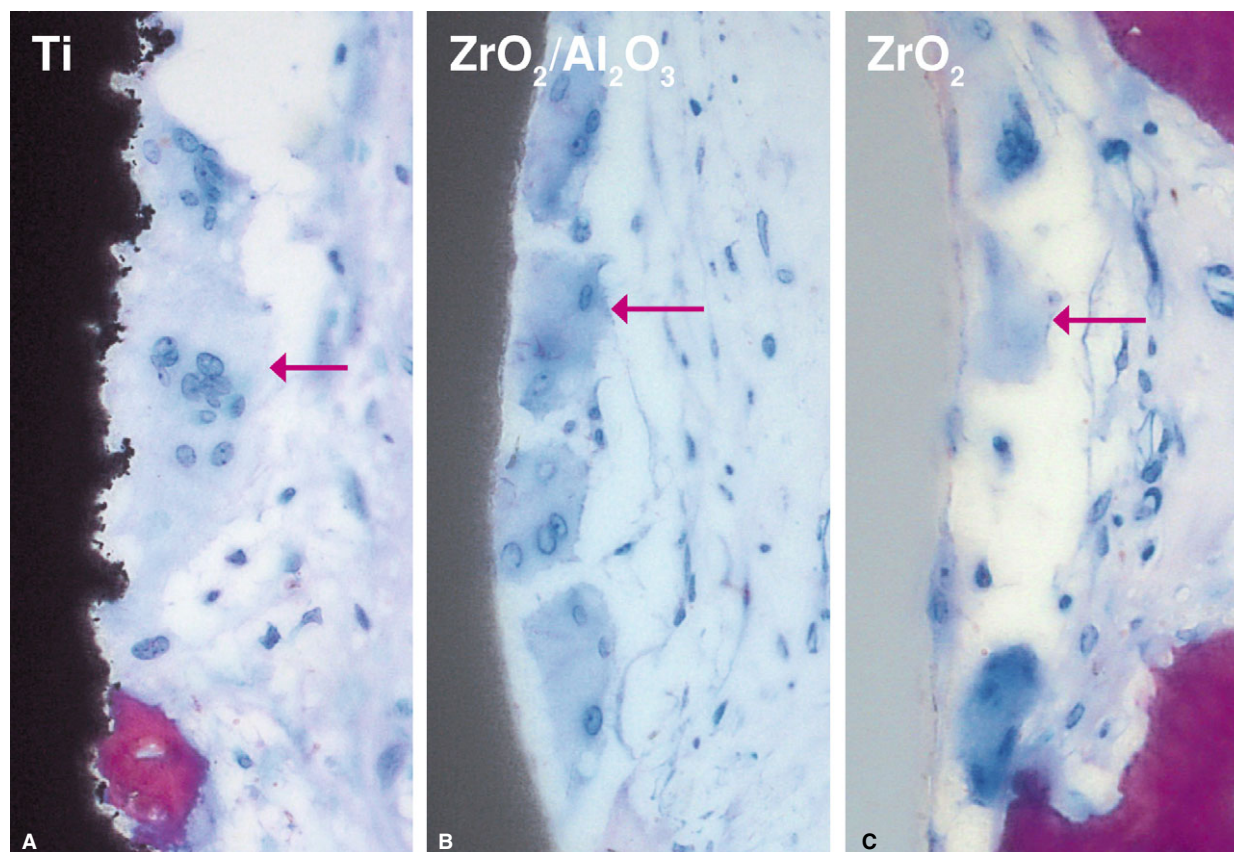
osteogenesis). In contrast to distance osteogenesis, contact osteogenesis means *de novo* bone formation by osteoblasts directly on the implant surface (29).



**Fig. 25.** Histogram illustrating the percentage of bone-to-implant contact (%BIC) for titanium (Ti), alumina-toughened zirconia (ZrO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>) and zirconia (ZrO<sub>2</sub>) implants after 4 and 8 weeks of healing. Modified from Chappuis et al. (26). With permission.

Signs of bone formation directly on the oxidized titanium implant surface have indeed been reported in a histological study (17). However, histology is always a snapshot in time and two-dimensional tissue sections cannot reveal the true three-dimensional connection between surrounding bone and the implant surface. Although signs of direct bone formation on the implant surface were described in a study using micro-computed tomography (18), it may be concluded that there is presently still only anecdotal evidence for the hypothesis of direct bone formation starting on the implant surface without connection to the pre-existing peri-implant bone.

Another aspect that must be borne in mind is that animal experiments only cover the wound-healing and early osseointegration phases and rarely exceed observation periods of 3 months. How the bone-to-implant contact values change over longer periods of time is unknown, as are possible consequences of the presence of multinucleated giant cells on implant surfaces in the long-term. Multinucleated giant cells on dental implants appear to be an integral part of the process of osseointegration. They were detected on titanium implants many years ago by Donath and



**Fig. 26.** Multinucleated giant cells (arrows) in contact with (A) titanium (Ti), (B) alumina-toughened zirconia (ZrO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>) and (C) zirconia (ZrO<sub>2</sub>) implants after 4 weeks of healing. The images show undecalcified ground sections stained with toluidine blue and basic fuchsin. From Chappuis et al. (26). With permission.

coworkers (32) and Sennerby and coworkers (83, 84) and were recently quantified on different implant materials and surfaces (26, 74, 75). Surprisingly few studies document these cells on dental implant surfaces, either because of poor histological quality or neglect. One possible explanation for their presence on dental implants during the wound-healing and osseointegration phases is that they may be derived from osteoclasts because these cells inevitably come into contact with the implant surface while resorbing pristine bone contacting the implant surface. The persistence of these cells on certain implant surfaces may indicate that some specific surface characteristics, such as chemistry and/or topography, are very attractive for these cells. Alternatively, they may be derived from macrophages after their fusion into larger cells. The presence and possible origin of these cells on dental implants made of commercially pure titanium have previously been discussed (83, 84).

The macrophage is one of the first types of cells to come in contact with any implanted biomaterial. Macrophages and multinucleated giant cells may have two origins: blood-derived monocytes and tissue-resident macrophages. The tissue-resident macrophages in bone are called OsteoMacs and appear to have an important function in bone homeostasis and remodeling, and their potentially important role in association with biomaterials is just about to be realized (63). Macrophages can polarize toward proinflammatory M1 cells and toward regenerative M2 cells. By releasing proinflammatory or regenerative cytokines, macrophages are capable of guiding the healing process in different directions (i.e. toward ongoing inflammation or tissue regeneration). Macrophages thus have a key function in wound healing and probably also in bone regeneration (14, 63, 65). During normal wound healing there is always an initial proinflammatory phase with M1 macrophages followed by a regenerative phase with M2 macrophages. Thus, it is important that a biomaterial does not induce an ongoing inflammation and that macrophages switch from the M1 phenotype to the M2 phenotype. A study with bone substitutes has demonstrated that fine tuning of the surface of beta-tricalcium phosphate determines the phenotype of monocytes. Depending on the surface topography, they differentiated either into osteoclasts or multinucleated giant cells (30). The same may apply to dental implants. However, much less is known for dental implant surfaces. Understanding the influence of modifications of the dental implant surface on wound-healing events is imperative because dental implant loss has been associated with a provoked

foreign-body reaction (3, 4, 94). The observations of multinucleated giant cells on implants (26, 74, 75) so far do not support such a theory as all implants osseointegrated, the bone area density adjacent to the implant surfaces was not affected by the percentage of implant surface covered by these cells and no signs of chronic inflammation and fibrous encapsulation, the hallmarks of a true foreign body reaction (62), were observed.

## Breakdown of osseointegration

An experimental animal model to study breakdown of osseointegration unrelated to ligature-induced peri-implantitis would be very advantageous. However, it is not realistic to obtain data on the long-term stability of osseointegration from animal experiments. Nevertheless, clinical data from humans documenting bone loss are available (3). These authors concluded the following: marginal bone loss during the first year after implant installation represents the effects of bone adaptation as a response to surgery in the great majority of cases; marginal bone loss caused by peri-implantitis occurs in 1–2% of implants at follow-up time points of 10 years or longer provided that clinicians are properly trained and use well-controlled implant systems; and complications leading to marginal bone loss after the first year include implant components, surgery, prosthodontics and/or compromised patient factors and are coupled to immunologic reactions. Thus, it may be concluded that marginal bone loss around dental implants is multifactorial in terms of causation, rendering preventive measures and targeted therapeutic interventions difficult.

The so-called aseptic loosening, originally described for orthopedic implants (69) may deserve particular attention also in the case of dental implants. Particle release as a result of increased surface roughness, and ion leakage as a result of corrosion have been suggested as factors contributing to bone loss and this topic has been discussed in the dental field for many years (45, 53). Regarding titanium plasma-sprayed implants, titanium granules of 3–60 µm were detected in the peri-implant tissue as a result of friction during surgical insertion (34). However, no correlation was found between increasing roughness and ion release after subtractive surface roughening, either *in vitro* or *in vivo* (99). Extracellular body fluids have been suggested to have corrosive properties and contain metal-binding proteins (51), and osteoclasts have been shown *in vitro* to corrode



titanium and stainless-steel surfaces directly and take up corresponding metal ions (24). There is experimental *in vivo* evidence that minimal load-bearing titanium implants can release titanium debris into the surrounding soft tissue (2). Metal ions and released particles are known to induce inflammatory reactions. As it has been shown that the response of macrophages to titanium particles is determined by macrophage polarization (67), it is conceivable that under the influence of bacteria, the response of M2 macrophages to titanium particles and/or ions is much stronger than for macrophages unexposed to biofilm.

Titanium is perceived to be biocompatible and corrosion resistant owing to the presence of a robust passive oxide film at its surface under physiological conditions (60). As the extent and clinical relevance of cell-induced corrosion of dental implants is not clear, more research is needed to find out what factors cause destruction of the protective titanium dioxide layer and thus lower the corrosion resistance. It is possible that some patients may be more susceptible to titanium particles and/or ions released from implants and this may fall under the term 'hypersensitivity'.

Another, probably underestimated, patient factor is medication, but even more so polymedication. Numerous medications interact with both the immune system and bone. Because of the intimate link between immunology and bone biology, known as osteoimmunology (44), this may have negative effects on tissues around biomaterials, such as dental implants. Antiresorptive and anti-angiogenic medications are available to treat both osteoporosis and certain forms of cancer. As angiogenesis and bone resorption are important in bone formation, modeling and remodeling, such medications may interfere with the longevity of osseointegration. As the peri-implant bone undergoes remodeling, particular attention should be paid to medications interfering with bone turnover. Some preliminary data suggest that bone turnover is 10-fold greater in the mandibular alveolar process of certain teeth than in the mid-shaft of the tibia in a canine model (93). Remodeling occurs also at the bone-implant interface and consequently exposes the implant surface. Higher turnover exposes more implant surface. Thus, the implant surface in contact with mandibular bone is particularly vulnerable to disturbances that shift the balance between bone resorption and apposition more toward resorption and thus result in a net loss of bone over time. This can be a very slow process and may remain undetected for a long period of time. Among the medications interfering with bone

formation and turnover are selective serotonin reuptake inhibitors. A recent study has shown that fluoxetine and venlafaxine, two selective serotonin reuptake inhibitors widely used for the treatment of depression, can positively or negatively influence bone loss in ligature-induced periodontitis (37) and that serotonin inhibits osteoblast differentiation and bone regeneration in rats (66). Preliminary data demonstrate an increased failure rate of osseointegrated implants in patients treated with selective serotonin reuptake inhibitors (102). As so many different prescription drugs interfere with both the immune system and bone metabolism, and some may compromise osseointegration, it seems wise to ask about the drug history not only before implant placement but also at follow-up visits.

## Conclusions

- Placement of dental implants has become routine for the oral rehabilitation of partially or fully edentulous patients.
- Bone healing around implants follows the pattern and sequence of intramembraneous osteogenesis starting with woven bone formation and followed later by formation of parallel-fibered bone and by lamellar bone. Bone remodeling also involves the bone-implant interface.
- Contemporary implants made of commercially pure grade 4 titanium, TiZr and zirconia with a micro-rough surface are biologically well tolerated and quickly osseointegrate, as shown in many animal and a few human experiments. Surface-modified Ti6Al4V implants may behave differently.
- Multinucleated giant cells appear to be an integral part of the normal osseointegration process. However, on certain dental-implant materials these cells are present in higher numbers.
- The presence of multinucleated giant cells during the osseointegration process cannot predict future implant loss.
- High success and survival rates for certain implant systems corroborate the safety and longevity of osseointegration.
- Implant loss unrelated to classical peri-implantitis requires further investigations. Patient factors, such as (poly)medication, interfere with the immune system as well as with bone cells and bone turnover and may, alone or in combination with other factors, contribute to bone loss of osseointegrated implants.

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