Tensile bond between bone and titanium

A reappraisal of osseointegration

Ralf Skripitz and Per Aspenberg

When Brånemark in the 1970s established the term osseointegration, this implied a direct chemical bond between a titanium implant and bone. However, ultrastructural studies seemed not to support this idea, and osseointegration came to be defined as the absence of interfering fibrous tissue. Titanium was therefore described as bioinert rather than bioactive. We now demonstrate mechanically a chemical bond between bone and titanium, using unloaded cp titanium plates, similar to those used in previous studies on prosthetic loosening. Tensile force can be transmitted only by chemical bonds. Bone-bonding was therefore evaluated by a detachment test. The plates were developed so that a flat titanium surface touched traumatized bone and the rest of the detachable part had no contact with surrounding tissue. The titanium plates were either polished and sterilized in an autoclave or treated in 4 M NaOH and then heated to 600 °C according to Yan et al. (1996). After 4 weeks, the plates were separated from the bone by a perpendicular traction force.

The detaching load of the untreated titanium plates never exceeded 0.03 MPa, whereas with treatment it increased to median 0.8 MPa, with bone remaining attached to parts of the plates after detachment. Our findings confirm that a chemical bond can be obtained within 4 weeks with the described pretreatment. It may occur also without treatment, after a longer implantation time.

Department of Orthopedics, Lund University Hospital, SE-221 85 Lund, Sweden. Tel +46 46-171510. Fax -130732.
E-mail: Per.Aspenberg@ort.lu.se Correspondence: Dr. P. Aspenberg
Submitted 97-06-07. Accepted 98-01-30

Commercially pure (cp) titanium is regarded as a bioinert material, which means that it is possible to achieve a direct contact with bone without intervening fibrous tissue. Generally it is not believed that there is a direct chemical bond between titanium and bone tissue, but when the term osseointegration was coined by Brånemark in the 1970s, a chemical bond may have been implied. Later, ultrastructural studies indicated an amorphous ground substance at the bone- implant interface, which appeared not to support the idea of a chemical bond (Thomas et al. 1987, Linder 1989a, b, Davies et al. 1990). Osseointegration then became defined as contact between implant and bone without an intervening fibrous tissue layer at the interface, on the light microscopic level (Carlsson et al. 1986).

A chemical bond between titanium and the mineral phase of bone is, however, theoretically plausible. In vivo, a titanium surface may become modified to a titania gel by oxidation. An oxide layer on the surface of the titanium implant grows slowly and a titania hydrogel is formed on the surface of the passive layer (Cook et al. 1987, Kitsugi et al. 1996). Titania gel has many properties in common with, e.g., a silica gel, which forms on bioactive glass and is known to induce epitaxial growth of hydroxyapatite (Bagambisa et al. 1993, Li et al. 1994).

To demonstrate a chemical bond between an implant and bone mechanically, a tensile test is necessary (Gross et al. 1981, Takatsuka et al. 1995). Most tests for implant fixation, however, measure shear strength, which is technically easier (Cook et al. 1987, Thomas et al. 1987). The roughness of any material surface will then cause mechanical interlock, which may obscure any direct chemical bond. The few tensile tests with titanium implants that have been reported do, indeed, show tensile strength of the titanium to bone interface, indicating a chemical bond. This tensile strength developed only after months in vivo (Steinmann et al. 1986, Takatsuka et al. 1995, Kitsugi et al. 1996).

Recently, Yan et al. (1996) demonstrated tensile bonding already after 4 weeks to a titanium surface which had been transformed to a titania gel by subjecting cp titanium to preoperative alkali- and heat-treatment. At the same time, no bonding of untreated cp titanium was found. To confirm their findings, we have now applied the same principle in a different model, using a newly developed "pull-away" plate in rats.

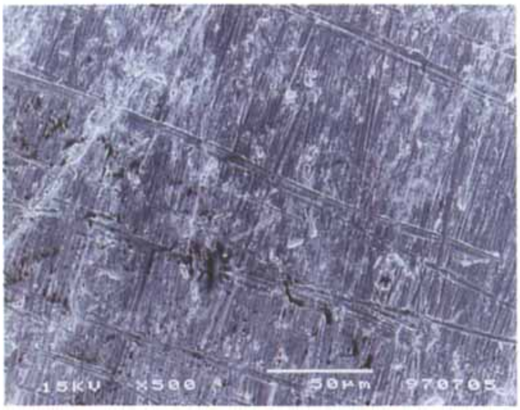

Figure 1. Untreated test surface of a pull-away plate after polishing.

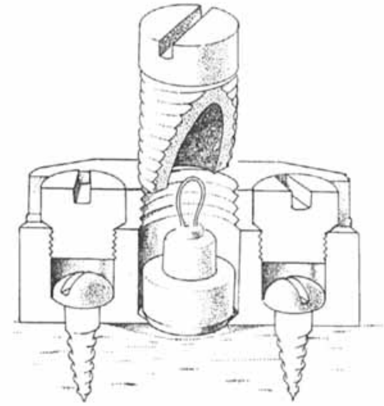

Figure 2. Pull-away plate in holder after implantation.

Material and methods

Material preparation

Two titanium implant surface conditions were evaluated: cp titanium and a gel-derived titania surface, which was obtained through alkali- and heat-treatment of cp titanium. The titanium surfaces were first polished with fine sandpaper (800 grains/cm^2) to give a surface roughness of average Ra 0.48 μm and a maximum R_{max} 3.1 μm, as examined by a needle surface-measuring instrument (Surfaceanalyser 402 Mitutoyo, Tokyo, Japan) (Figure 1).

After polishing of the surface, half of the cp titanium plates were put in a 4 M NaOH solution at 60 °C for 4 hours. Due to the alkali-treatment, we obtained a titanium gel on the surface, which allow an easier access to the abundant OH-groups, that are necessary for calcium and phosphate precipitation. The gel plates were then heated to 600 °C for 1 hour, to obtain the intended stable titania surface.

Implants

The purpose of the construction we used was to hold the pull-away plates and their contact area on the bone, without allowing tissue to grow along its sides, so that no shear strength could influence the results (Figure 2).

The cylindrical pull-away plates were machined from cp titanium. The contact area was circular and flat, with a diameter of 3.2 mm and a 0.4 mm wide bevel at the edge. Titanium holders kept the implants in place. The holders were also manufactured of cp titanium and consisted of a top and a bottom part. The bottom part, which contained a cylindrical space slightly larger than the pull-away plate, was to be fixed to the bone using two 1.5 mm cortical screws. Its purpose was to hold the pull-away plates in place and to prevent any tissue from growing at the side of the plates. At its lowest point, there was a lip fitting with the bevel of the pull-away plate. The lip functioned as a seal against tissue ingrowth along the sides of the plate. The upper part of the holder functioned as a hood, so that the plate was sealed from outer influences.

A top screw in the middle was inserted after assembling the holder to press the bevel of the pull-away plate against the lip of the holder in order to hinder any tissue ingrowth between the plate and the holder. A small hole in the holder allowed rinsing the interior of the system, so that the implant could be cleaned from blood after the system had been mounted. The hole was closed with a screw. Thus, the pull-away plate could have contact with the tissue only at its flat surface. The rest of it had contact with the lip, the top screw and the injected saline.

Animals

18 male Sprague-Dawley rats with a mean body weight of 386 (363–424) g were used. The observation time was 4 weeks in all cases. Each animal received a pull-away plate at the proximal tibial metaphysis of one leg.

6 animals were operated on each operating day, 3 with polished cp titanium, 3 with alkali- and heat-treated titanium, in varying order.

Surgery

The animals were operated on aseptically under general anesthesia. 12.5 mg of streptomycin was given intramuscularly before surgery. The medial aspect of one proximal tibia was exposed, using a longitudinal incision. The periosteum was reflected proximally up to the epiphysis.

At first, the bottom part of the holder was attached with a proximal cortical screw, which was brought in

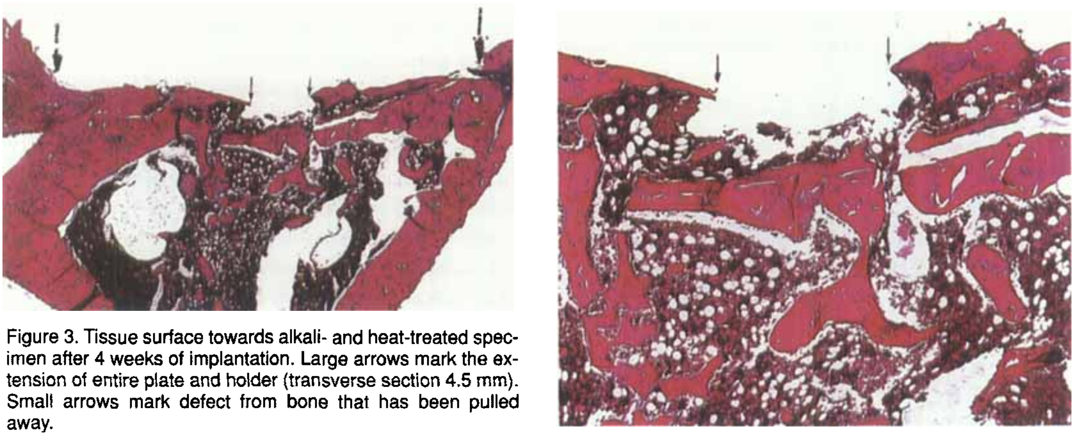

Figure 3. Tissue surface towards alkali- and heat-treated specimen after 4 weeks of implantation. Large arrows mark the extension of entire plate and holder (transverse section 4.5 mm). Small arrows mark defect from bone that has been pulled away.

using a cannula-drilled hole. A depression in the tibial cortex was milled out to correspond to the contact area of the pull-away plate. This was carried out without removing all the cortical bone, using slow rotating burrs, during irrigation with saline. After preparation of the depression, the second screw was attached and the plate was inserted. Now the rest of the implant system was assembled. Following this procedure, the implant was rinsed with saline through the small hole in the holder and the skin was sutured. The pull-away plates, after insertion, faced traumatized bone and hematoma. The bone was allowed to grow towards the test surface, until there was a fit.

Pull-away force measurement

After 4 weeks, the animals were killed with an overdose of pentobarbital and the whole tibia containing the implant was detached in the knee joint. The soft tissue surrounding the implants was removed, so that the fresh unfixed specimens could be used for tensile testing. This was done immediately after the animals were killed.

The top screw and the hood were removed from the implant, so that the wire loop of the pull-away plate could be reached. Traction through a metal hook attached to the loop was applied to the implant plate. The hook was connected to a transducer by a 4/0 ethylon suture thread, acting as a spring to gradually increase the force when the self-constructed tensile testing device was moving at a across-head speed of approximately 40 mm/min. The increase in the force pulling away the plate from the bone was according to a linear function approximately 0.4 N/sec. The detaching load was measured as the peak force, when the plate was loosened from the bone.

Histology

In all specimens, the tibial segments beneath the test surface were demineralized and prepared by standard histological techniques. Sections were produced at a right angle to the test surface, through the middle of the circular surface, and stained with hematoxylin and eosin (Figure 3). All specimens were examined by a computerized video system attached to the microscope (Videoplan TM Kontron Bildanalyse GmbH, Eschingen, Germany) and by drawing on a digital table with a screen magnification of ×40. We measured interface surface length and the length of each part of the interface surface, which consisted of fibrous tissue. Bone marrow and areas, where bone appeared to have been pulled away, were considered to be part of the bone fraction.

The total length of bony interface surface, divided by the total length of the interface constituted a bone-contact index (Figure 3). These measurements were made blindly, thus it was not known if a treated or an untreated specimen was evaluated.

Results

1 alkali- and heat-treated titanium plate showed clinical signs of infection, which were confirmed by histology, and therefore excluded from the study. All other implants were clinically stable, without discoloration or swelling around the implants. Macroscopically, 5 of the treated pull-away plates had some areas with bone attached to them after the test, meaning that failure had occurred through bone, not through the bone-titania interface. This was not seen with untreated cp titanium.

3 of the tested pull-away plates (untreated cp titanium plates) were detached from the bone as soon as the

Detaching load (MPa), bone-contact index and detaching load per bone-contact index of differently treated titanium plates; median (range)

	Untreated	Alkali- and heat-treated
Detaching load (MPa)	0.01 (0–0.027)	0.27 (0.025–0.78)
Bone-contact index	0.70 (0–0.90)	0.87 (0.41–1.00)
Detaching load/ bone-contact index	0.01 (0–0.32)	0.27 (0.033–0.78)

implant was opened. Therefore, the detaching load was defined as 0. Two untreated cp titanium plates which had no bone contact at all and they were excluded from the calculation of the bone contact index.

The detaching loads of the alkali- and heat-treated titanium samples were higher than those of the controls ($p = 0.0006$, Mann-Whitney U-test; Table). The bone-contact fraction of the treated and untreated plates, on the other hand, did not differ (Table). The detaching loads per bone-contact fraction differed between treated and untreated plates ($p = 0.002$, Mann-Whitney U-test; Table).

Discussion

Our study confirms the findings of Yan et al. (1996) that alkali- and heat-treatment leads to early chemical bonding of titanium to bone. It is one of the few studies for measuring the strength of the chemical bond between bone and a titanium implant. Mechanical evaluations concerning the fixation of titanium to bone have mainly measured shear strength (Cook et al. 1987, Thomas et al. 1987). This is dependent on surface characteristics, since the inevitable roughness of any surface will cause mechanical resistance to shear (Takatsuka et al. 1995). In contrast, pure tensile forces can be transmitted only by chemical bonds (Gross et al. 1981, Osborn 1989).

Our implants were placed in a fresh bone wound, and the bone that formed along its surface was newly regenerated. This is similar to the clinical situation after implantation of a joint replacement, although our implants did not bear weight. The similar bone-contact index in our 2 groups and the different detaching loads per bone contact indicate a qualitative difference in the bonding of bone to titanium. This bonding is unlikely to be the result of some kind of 'micro-interlock' of only the treated specimens, since the treated surfaces would resemble or be smoother than the untreated ones.

Our study relates to titanium, but fibrous tissue-free anchorage does not in itself refer to a specific implant material. Hicks as early as 1958 suggested, at a time when pure titanium was hardly ever used, that "zero reaction" (an interface without a membrane) was the normal response of bone to an inert material. In our study, the modification of the surface chemistry by using an alkali- and heat-treatment of cp titanium increased the bone-bonding ability of titanium in an early-term implantation, as compared to the untreated cp titanium. The mechanisms leading to formation of a chemical bone-implant bond are still obscure. Ionic activity has been found to contribute to the bond between an oxide layer and bone. The Ca-P-rich apatite layer formed on the surface of bioactive materials plays an essential role in chemical bonding between glass-ceramics and bone tissue (Neo et al. 1992). It is considered to mediate atomic continuity with the hydroxyapatite of bone epitaxially.

The composition and structural characteristics of this surface layer are common to those of bone apatite (Kokubo et al. 1990). The difference in the capacity to stimulate apatite formation between silica glass and silica gel indicated the importance of the gel state also for titanium (Li et al. 1994). Similarly to the difference between silica glass and silica gel, cp titanium and titania gel differ in the density and availability of OH^--groups. The gels are readily hydrolyzed and dissolve faster, leaving more OH^--groups on its surface (Li et al. 1994, Kitsugi et al. 1996).

The alkali-treatment of titanium might then produce a titania gel, which would allow an easier access to OH^--groups. A sufficient number of OH^--groups are thought to be required to trigger nucleation of hydroxyapatite (Kitsugi et al. 1996). With the heat treatment, we intended to obtain a stabilized titania, which is regarded as an inducer for early hydroxyapatite formation. Implants of hydroxyapatite-coated materials become integrated faster and require a less perfect fit than control implants of cp titanium (Linder 1992).

However, with titanium, ionic exchange between the cp titanium and the host tissue will, in time, increase the number of OH^--groups to such levels that they can induce apatite formation. Hanawa reported in 1991 the formation of a hydroxyapatite layer in vitro, using different electrolyte solutions. The calcium phosphate layer on Ti resembled hydroxyapatite and became thicker with time, being 5 nm at 1h and 8 nm at 30 days.

Titanium screw fixtures for dental reconstruction are left unloaded until they are osseointegrated and can then bear high loads with a remarkably low failure rate (Brånemark 1977). A similar concept has hardly been tried in orthopedics. Possibly, changes in the titanium surface structure can reduce the need for an unloading period, so that concepts similar to the dental fixtures can be used for, e.g., joint replacement. The loosening rate for osseointegrated dental fixtures decreases with time, whereas the loosening rate for joint implants increases (Linder et al. 1988). Clearly, a chemical bond between a joint replacement and sufficiently elastic cancellous bone could be expected to reduce the risk of loosening.

Acknowledgements

We thank Mats Christensson for help with design and manufacturing of the implants, Inger Mårtensson and Carina Forslund for technical assistance. This study was financially supported by the Swedish Medical Research Council (project 2031), the Medical Faculty of Lund University, the King Gustaf V Jubileumsfond, the Greta och Johan Kocks, Alfred Österlund, Trygg-Hansa and Tore Nilsson Foundations.

References

Bagambisa F B, Joos U, Schilli W. Mechanisms and structure of the bond between bone and hydroxyapatite ceramics. J Biomed Mater Res 1993; 27: 1047-55.

Brånemark P-I, Zarb G A, Albrektsson T. Tissue-integrated prostheses. Osseointegration in clinical dentistry. Quintessence Publishing 1985.

Carlson L, Rostlund T, Albrektsson B, Albrektsson T, Brånemark P-I. Osseointegration of titanium implants. Acta Orthop Scand 1986; 57: 285-9.

Cook S D, Kay J F, Thomas K A, Jarcho M. Interface mechanics and histology of titanium and hydroxylapatite-coated titanium for dental implant applications. Int J Oral Maxillofac Impl 1987; 2: 15-22.

Davies J E, Lowenberg B, Shiga A. The bone-titanium interface in vitro. J Biomed Mater Res 1990; 24: 1289-306.

Gross U, Brandes J, Strunz V, Bap I, Sela J. The ultrastructure of the interface between a glass ceramic and bone. J Biomed Mater Res 1981; 15: 291-305.

Hanawa T. Titanium and its oxide film: A substrate for formation of apatite. In: The bone material interface (ed. Davis J E). University of Toronto Press, 1991: 49-61.

Hicks L. Pathological effects from surgical metal (ed. Gilles L). Modern trends in surgical materials, London 1958: 29.

Kitsugi T, Nakamura T, Oka M, Yan W-Q, Goto T, Kokubo T, Miyaji S. Bone-bonding behavior of titanium and its alloys when coated with titanium oxide and titanium silicate. J Bone Joint Surg 1996; 32: 149-56.

Kokubo T, Kushitani H, Sakka S, Kitsugi T, Yamamuro T. Solutions able to reproduce in vivo surface-structure changed in bioactive glass-ceramic A.W. J Biomed Mater Res 1990; 24: 721-34.

Li P, Ohtsuki C, Kokubo T, Nakanishi K, Soga N, Groot K. The role of hydrated silica, titania and alumina in inducing apatite on implants. J Biomed Mater Res 1994;28: 7-15.

Linder L. Osseointegration of metallic implants. I. Light microscopy in the rabbit". Acta Orthop Scand 1989a; 602: 129-34.

Linder L. Osseointegration of metallic implants. II. Transmission electron microscopy in the rabbit. Acta Orthop Scand 1989b; 60 (2): 135-9.

Linder L. Ultrastructure of the bone-cement and the bone-metal interface. Clin Orthop 1992; 276: 147-56.

Linder L, Carlsson A, Marsal L, Bjursten L M, Brånemark P-I. Clinical aspects of osseointegration in joint replacement. J Bone Joint Surg (Br) 1988; 70: 550-5.

Neo M, Nakamura T, Yamamura T, Ohtsuki C, Kokubo T. Transmission electron microscopic study of apatite formation on bioactive ceramics in vivo. Bone-bonding biomaterials, Reed Healthcare Communications. 1992: 111-20.

Osborn J F. Bonding osteogenesis under loaded condition-the histological evaluation of a human autopsy specimen of a hydroxyapatite ceramic-coated stem of a titanium hip prosthesis. Bioceramics, Ishiyaku EuroAmerica, Inc., Japan 1989; 1: 388-400.

Steinmann S G, Eulenberger J, Maeusil P-A, Schroder A. Adhesion of bone to titanium. Biological and Biomechanical Performance of Biomaterials 1986: 409-14.

Takatsuka K, Yamamuro T, Nakamura T, Kokubo T. Bone-bonding behavior of titanium alloy evaluated mechanically with detaching failure load. J Biomed Mater Res 1995; 29: 157-63.

Thomas K A, Kay J F, Cook S D, Jarcho M. The effect of surface macrotexture and hydroxylapatite coating on the mechanical strengths and histological profiles of titanium implant materials. J Biomed Mater Res 1987; 21: 1395-414.

Yan W-Q, Nakamura T, Kobayashi M, Kawanabe K, Kokubo T, Kim H-M, Miyaji F. The effects of alkali and SBF treatment on the bone-bonding ability of titanium implants. Program of SIROT 7th World Congress 1996: 218.