The Early Remodeling Phases Around Titanium Implants: A Histomorphometric Assessment of Bone Quality in a 3- and 6-Month Study in Sheep

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The purpose of this study was to evaluate the quality of the bone matrix around commercially pure titanium implants at 3 and 6 months postplacement in sheep. Implants were placed in the corticotrabecular areas of both femurs in 6 animals. Each animal received 4 Euroteknika implants in the right femur and 4 Nobel Biocare implants in the left femur. Bone blocks containing the implants were studied undecalcified after being embedded in methylmethacrylate. Sections were stained with toluidine blue and basic fuchsin. The amount of bone around the implants, the contact interface between the implant and bone, and the mineral apposition rates were measured. The fractional amount of woven bone could be quantified because of its high glycosaminoglycan content. No differences could be observed between the 2 types of implants. Total bone volume did not increase around both types of implants between 3 and 6 months, indicating that ankylosis was rapidly achieved. In contrast, in the area in contact with the implant, the bone-titanium interface drastically increased and the mineral apposition rate decreased. The fractional volume of woven bone around implants was considerably reduced after 6 months. Bone quality around implants was improved at 6 months (volume of woven bone near zero), and true osteonic structures were observed in close contact with titanium. The remodeling process appeared to improve bone quality and increase the bone-titanium interface around implants, while the net bone quantity necessary to immobilize implants was achieved rapidly and remained unchanged.
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Key words: animal study, bone histomorphometry, bone quality, dental implant, woven bone

Several factors are known to influence the anchorage of an implant in bone: biocompatibility of the metal, design, surface structure, surgical technique, and biomechanical factors.[1] Excellent results have been obtained in recent decades with cylindric threaded implants made of commercially pure (cp) titanium.[2] Titanium implants are commonly used in a 2-stage procedure according to Brånemark's principles.[3] During the first stage, implants are placed in recipient holes drilled in bone; after a variable amount of time, they are secondarily loaded with a prosthesis. However, there is actually no consensus on the time interval that is necessary between these 2 stages. A 4- to 6-month delay in load-bearing is thought necessary to obtain an intimate bond between bone and the implant surface.[3] This period was found by clinical studies to be optimal for bone to adapt to the new biomechanical conditions created by both surgery and the presence of a titanium implant. Loading an implant too early would induce increased microstrains responsible for micromotions, which would lead to formation of a fibrous tissue at the

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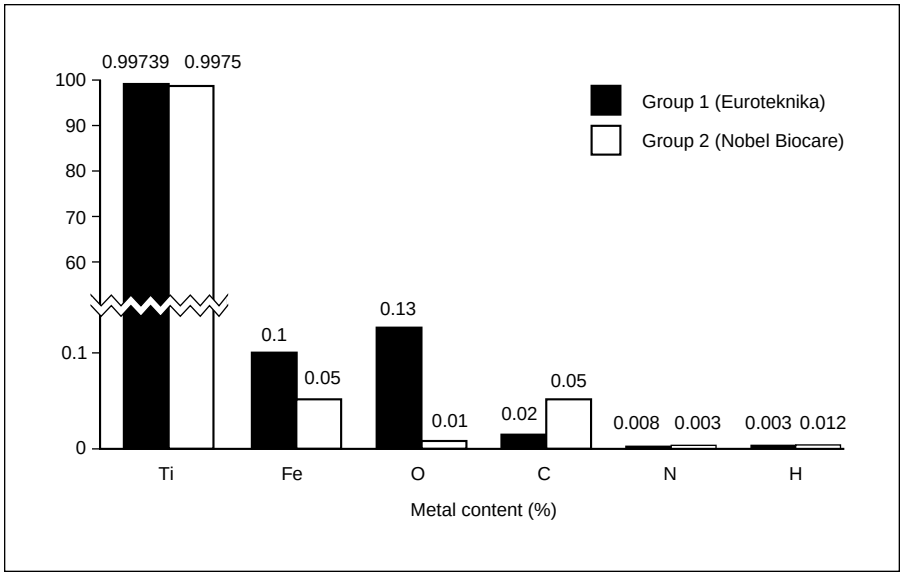

Fig 1 Metal characteristics of the 2 titanium implants as determined by Auger's microanalysis and x-ray dispersive energy microanalysis (data provided by J. Geller, Peabody, MA, USA).

interface.[4] Recently, several investigators have reported positive results with shorter intervals or even immediate loading.[5–7] However, factors other than the extent of bone-implant interface play a role in implant anchorage. The quality of the surrounding bone itself has received little attention.

Bone around the implant is modified by both modeling and remodeling processes. Actually, little is known about the dynamic of bone remodeling and time evolution of the mineralization level of bone surrounding implants. The aim of the present study was to evaluate, using histomorphometric methods, the remodeling process around titanium implants placed in corticotrabecular sites in sheep for 3 and 6 months.

Materials and Methods

Implants. Two different types of titanium implants were used in this study. They differed slightly in the shape of the thread, metal composition (Fig 1), surface treatment, and roughness, as previously reported.[8] Group 1 implants were treated with radiofrequency glow discharge and γ radiations (25,000 Gy) (Euroteknika, Paris, France). Group 2 implants were sterilized by dry heat after decontamination (Nobel Biocare, Göteborg, Sweden). Both types of implants are provided by manufacturers in titanium sealed vials, which were opened at the time of placement in bone.

Surgical Procedure. The experiment was conducted in a veterinary surgical center according to ethical principles of animal investigation. Six female Vendéean sheep 4 to 6 years old were used in the present study. Prior to surgery, animals were medicated with an intravenous injection of benzodiazepam, and the posterior limbs were prepared as for classical surgery. Natrium amoxicillin (500 mg) was given by intravenous injection as a preventive antibiotic. General anesthesia was induced with intravenous perfusion of ketamine and, after endotracheal intubation, maintained with halothane provided by an anesthetic apparatus. The femur was exposed by a classic lateral approach from great trochanter to distal epiphysis. One implant was placed at the base of the great trochanter and 3 others were placed in the femoral distal metaphysis.

The recipient sites were created with an electric rotary instrument (Medomotor High Torque Engine, Groof Company, Broenby, Denmark) at low speed (400 rpm), under physiologic saline as previously reported.[8] Titanium implants were placed at 10 rpm after the cavities had been flushed and cooled with sterile physiologic saline to remove bone debris. Each animal received 4 of the group 1 implants in the left femur and 4 group 2 implants in the right femur.

The incisions were closed by different layers with resorbable sutures. An additional injection of trihydrate amoxicillin (500 mg) was administered immediately after surgery and 2 and 4 days after implantation at the same dose.

A double tetracycline labeling was done with oxytetracycline chlorhydrate intramuscularly 20 mg/kg (Terramycine 100) according to the following schedule: 2 days on, 2 weeks off, 4 days on. An interval of 4 days off was respected before eutha-

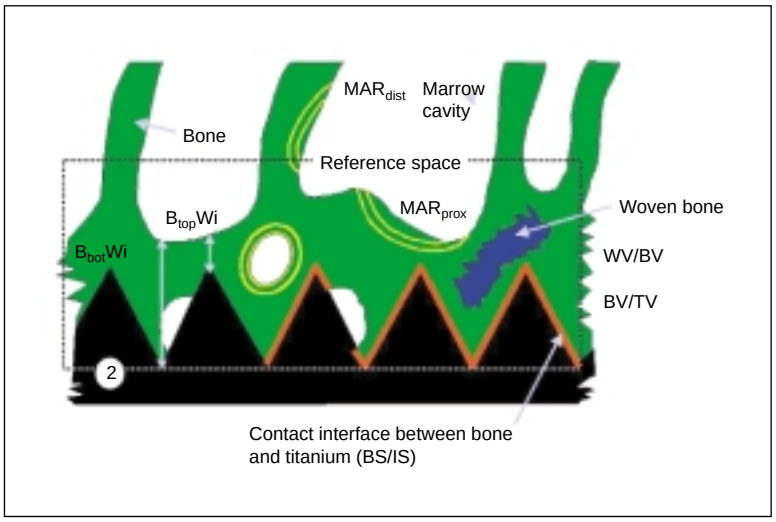

Fig 2 Diagram of histomorphometric methods used in the present study. The reference space (1400 µm in width) is illustrated. Mineral apposition rates are measured in bone inside the reference space (MAR_{prox}) or outside it (MAR_{dist}). Bone width is measured at the top and bottom of the threads, and the contact interface between bone and titanium (BS/IS) is measured on the best 3 threads. Blue = woven bone; green = calcified bone; yellow = tetracycline labeling; red = interface between titanium and bone.

nasia to avoid nonspecific labeling of eroded surfaces. Three sheep were sacrificed with an intravenous injection of natrium pentobarbital at 3 months and the remaining sheep were sacrificed 6 months after surgery. Contact radiographs of each femur were taken at the time of autopsy.

Specimen Preparation. Bones were immersed in 10% formalin for 7 days at 4°C. Blocks (containing 1 implant each) were prepared with an electric banding saw. They were then dehydrated in absolute acetone for 72 hours at 4°C (3 changes), defatted in chloroform, and embedded in purified methylmethacrylate. Specimens were processed undecalcified as previously reported.[9] Briefly, 2 longitudinal serial sections (300 µm thick) of the implant and surrounding bone were made parallel to the implant's axis on a low-speed saw equipped with a diamond blade (Struers Accutom, Copenhagen, Denmark). Slices were affixed onto translucent plastic slides with cyanoacrylic glue and were ground to a thickness of 20 µm on a bench top grinder with carborundum papers ranging from 400 to 2400 (Struers Accutom). One section was surface stained with toluidine blue (1% in sodium tetraborax) and basic fuchsin (1% aqueous) for histologic study and quantitative analysis. The other section was left unstained for histodynamic measurements with fluorescent microscopy.

Histomorphometric Analysis. Quantitative measurements were performed on a Quantimet Q570 (Leica, Rueil-Malmaison, France) coupled with a Sony 930P tri CCD camera (Sony, Tokyo, Japan). For each specimen, the following histomorphometric parameters were determined (the nomenclature used hereafter follows the recommendations of the Histomorphometric Committee of the American Society for Bone and Mineral Research).[10] Methods used for measurement are illustrated in Fig 2.

- Interface contact between bone and titanium implant (bone surface per implant surface [BS/IS], expressed as a percentage) was measured on the best 3 threads.
- Bone volume around the implant (bone volume per tissue volume [BV/TV], expressed as a percentage) was measured in a reference area 1400 µm in width from the bottom of the threads. This is a global measurement that takes into account woven bone and lamellar bone.
- The fractional volume of woven bone (woven bone volume per bone volume [WV/BV], expressed as a percentage) corresponded to the amount of nonlamellar bone inside the previously defined bony area.
- The thickness of bone interfacing with the implant was measured separately at the top and bottom of the threads ($B_{top}Wi$ and $B_{bot}Wi$, expressed in µm).
- The mineral apposition rate (MAR) was measured separately, both in the vicinity of the implant (ie, in the reference area) and at a distance from the implant (MAR_{prox} and MAR_{dist}, expressed in µm per day).

Results

The toluidine blue–fuchsin method used in this study offered the opportunity to accurately quantify woven bone. Woven bone appeared heavily stained in blue and could easily be observed in the

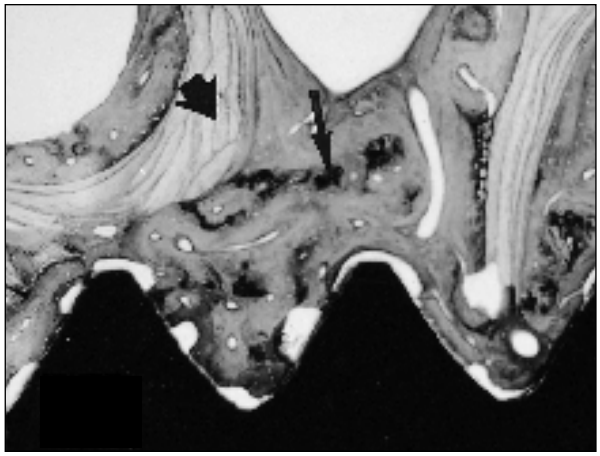

Fig 3 Group 1 (Euroteknika) implant placed in sheep bone for 3 months. The bone surrounding the implant is composed of trabecular remnants *(wide arrow)*, and woven bone, which appears heavily stained by toluidine blue *(long arrow)* is surrounded by lamellar bone (original magnification ×100).

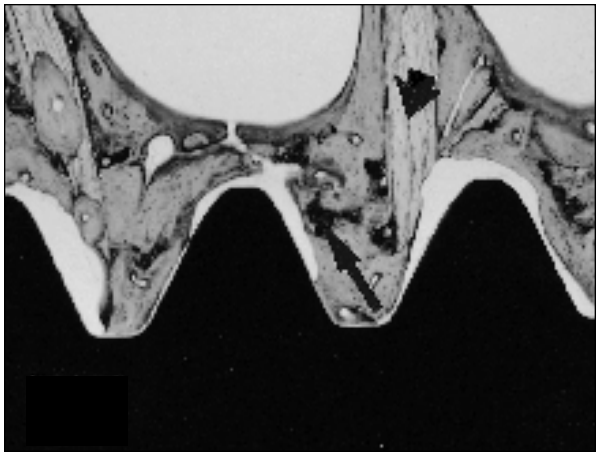

Fig 4 Group 2 (Nobel Biocare) implant placed in sheep bone for 3 months. Aspects similar to the group 1 implant are observed: bone surrounding the implant is composed of trabecular remnants *(wide arrow)*, and woven bone, which appears heavily stained by toluidine blue *(long arrow)*, is surrounded by lamellar bone (original magnification ×100).

Table 1 Histomorphometric Results for Both Types of Implants at 3 and 6 Months Postimplantation

	Group 1		Group 2		Pooled Groups	
	3 mo	6 mo	3 mo	6 mo	3 mo	6 mo
BV/TV (%)	43.5 ± 2.1	37.1 ± 2.6	37.6 ± 3.3	38.2 ± 2.3	37.6 ± 1.7	40.5 ± 0.2
WV/BV (%)	6.4 ± 1.0	0.7 ± 0.3	7.0 ± 1.5	0.6 ± 0.2	6.7 ± 0.9	0.7 ± 0.2
$B_{top}Wi$ (µm)	264 ± 25	266 ± 20	242 ± 27	261 ± 22	253 ± 18	263 ± 13
$B_{bot}Wi$ (µm)	572 ± 35	509 ± 26	473 ± 41	483 ± 40	523 ± 28	496 ± 23
BS/IS (%)	50.8 ± 2.6	85.5 ± 2.0	57.9 ± 3.37	82.0 ± 3.5	54.4 ± 2.2	83.8 ± 1.2
MAR_{dist} (µm/D)	0.97 ± 0.05	0.86 ± 0.04	0.99 ± 0.05	0.90 ± 0.05	0.98 ± 0.03	0.88 ± 0.03
MAR_{prox} (µm/D)	1.41 ± 0.04	1.17 ± 0.06	1.36 ± 0.04	1.19 ± 0.05	1.38 ± .04	1.18 ± .04

Results are expressed as mean ± SEM.
BV/TV = bone volume per tissue volume; WV/BV = woven bone per bone volume; $B_{top}Wi$ and $B_{bot}Wi$ = thickness of bone interfacing with the implant at the top and bottom of the threads, respectively; BS/IS = interface contact between bone and implant surface; MAR_{dist} and MAR_{prox} = mineral apposition rate in the vicinity and at a distance from the implant, respectively; D = day.

vicinity of both types of implants (Figs 3 and 4). On the contrary, the mature (ie, lamellar) bone was stained more lightly by toluidine blue because of its lower glycosaminoglycan content. Histomorphometry did not reveal differences between the 4 implantation sites, so data for all histomorphometric parameters were pooled. Similar results were observed in both types of implants. Once again, data from Euroteknika implants and Nobel Biocare implants were pooled, allowing for comparison of the effect of time on bone remodeling around implants (Table 1, Fig 5).

No effect was observed with regard to implant type (see Table 1) for any parameter during each period. All parameters reflecting the implant anchorage within bone (BV/TV, $B_{top}Wi$, and $B_{bot}Wi$) did not change between 3 and 6 months. Bone mass around the implants did not increase: BV/TV remained unchanged, and the thickness of bound bone remained constant at the top or at the bottom of the thread.

Obvious signs of adaptive remodeling were observed:

1. A net decrease in woven bone volume was evident (Figs 6 and 7). The amount of woven bone decreased considerably and only small remnants could be observed occasionally. This was associated with the development of Haversian canals around the implant, which were easily identified in polarized light and appeared interconnected with bone marrow spaces (Fig 8).

Fig 5 Histomorphometric results in Group 1 and Group 2 implants after 3 and 6 months.

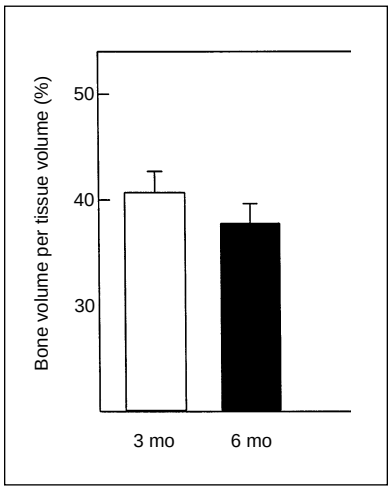

Fig 5a Bone volume around the implant, expressed as a percentage (bone volume per tissue volume).

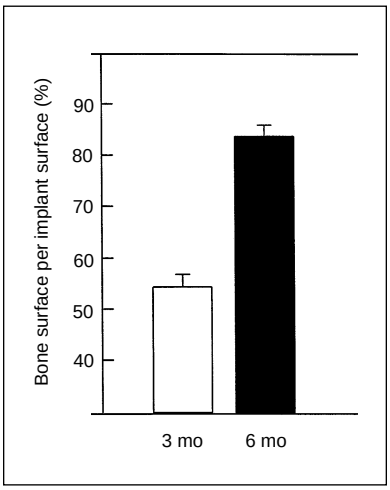

Fig 5b Interface contact between bone and implant (bone surface per implant surface), expressed as a percentage.

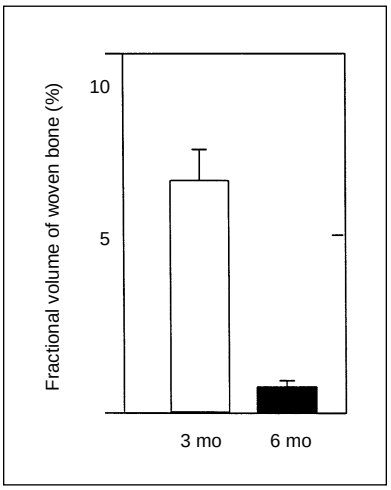

Fig 5c Fractional volume of woven bone, expressed as a percentage (woven bone volume per bone volume).

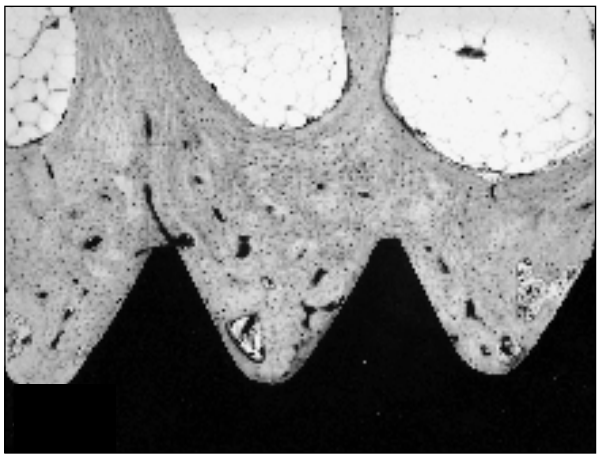

Fig 6 Group 1 (Euroteknika) implant placed in sheep bone for 6 months. The bone surrounding the implant is lamellar bone only. Compare with Fig 3 (original magnification ×100).

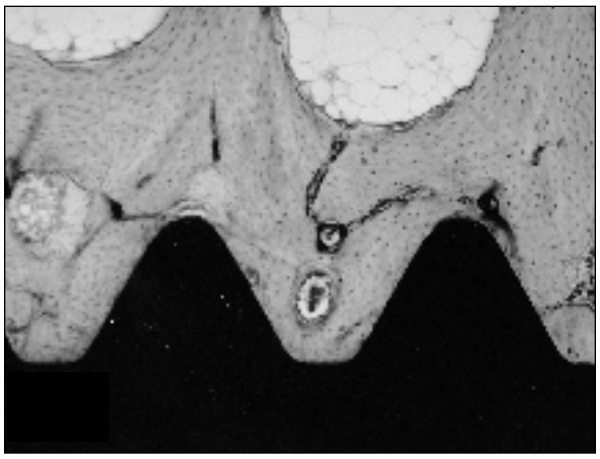

Fig 7 Group 2 (Nobel Biocare) implant placed in sheep bone for 6 months. The bone surrounding the implant is lamellar bone only. Compare with Fig 4 (original magnification ×100).

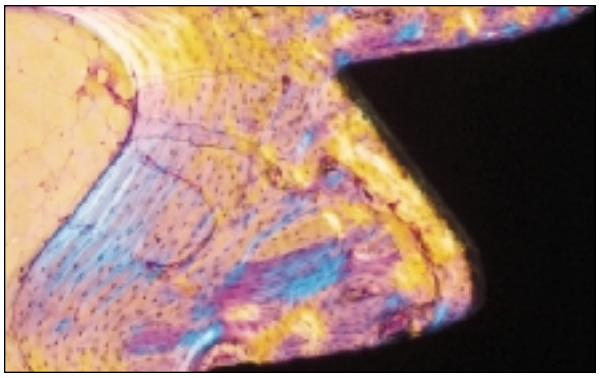

Fig 8 Group 1 (Euroteknika) implant placed in sheep bone for 6 months. The bone surrounding the implant is made only of lamellar bone. Note the extensive development of Haversian canals coming from the marrow areas (polarization microscopy; original magnification ×250).

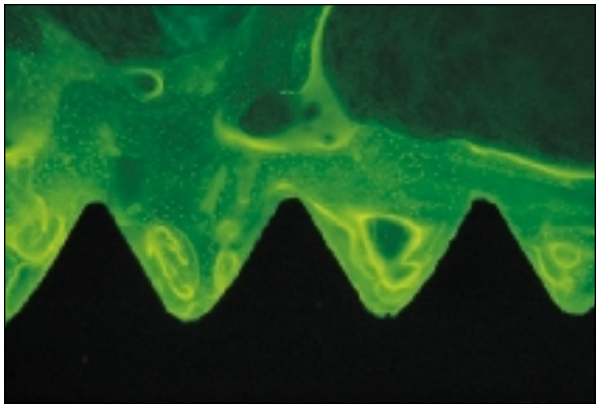

Fig 9 Group 1 (Euroteknika) implant placed in sheep bone for 3 months. Note the extensive tetracycline labeling around and at distance from the implant (fluorescence microscopy; original magnification ×100).

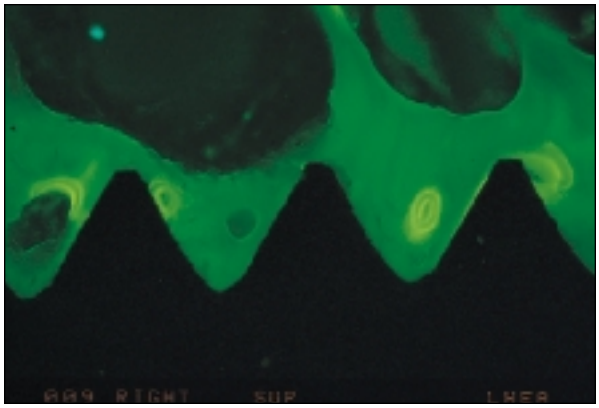

Fig 10 Group 1 (Euroteknika) implant placed in sheep bone for 6 months. The extent of tetracycline labeling is markedly reduced but still noticeable around the implant (fluorescence microscopy; original magnification ×100).

2. In both groups, BS/IS increased dramatically. These marked differences reflected the bone remodeling phenomenon and the progressive adaptation of bone to the implant.
3. The mineral apposition rate at distance from the implant (MAR_{dist}) did not change significantly during both time series. In contrast, the mineral apposition rate in bone areas close to the implant decreased between 3 and 6 months. However, MAR_{prox} always remained higher than MAR_{dist}. The apparent number of labeled bone surfaces also was markedly reduced in contact with the implant after the 6-month period, but no attempt was made to quantify the single- or double-labeled surfaces (Figs 9 and 10). Taken together, these observations serve as evidence that the number of active osteoblasts decreased between 3 and 6 months in the vicinity of the implant; this was associated with a decreased activity at the individual cell level.

Areas of bone resorption were still observed 6 months after implantation at the bone-implant interface, but no attempt was made to measure this parameter in the present study.

Discussion

Although the bone-implant interface has been studied extensively, a very small number of publications have been concerned with bone quality around implants. Johansson and Albrektsson were the first to study the interrelationships between the bone-titanium interface and the necessary removal forces for unscrewing an implant.[11] However, the method has now been used repeatedly to compare implants with various surface characteristics and was found to reflect the extent of the bone-implant contact interface.[12] The quality of bone is often referred to in the implant literature as the amount of cortical and trabecular bone bed in which the recipient socket is drilled.[13,14] However, this is relevant to bone volume and bone architecture and can be appreciated either by histomorphometry,[15] quantitative computed tomography studies,[16] or biomechanical testing.[17]

Other methods have been used, but they cannot properly differentiate the effects of volume and quality of bone as a material. Friberg et al used a cutting resistance technique to compare bone in various regions of arches in cadavers, but the method cannot be used when implants are placed.[18] The quality of the bony bed has been evaluated by the torque necessary to remove the implant. Clearly, several factors are known to affect bone quality. They have been recognized in metabolic bone disease and orthopedic literature, ie, the degree of mineralization of the bone structure units. Bone is known to be heterogeneous and can be quantified using microradiography[19] or backscattered electron techniques on a calibrated scanning electron microscope.[20] Hoshaw et al used backscattered electron imaging to evaluate the bone mineral changes around loaded implants in the dog, but did not focus on the postimplantation period.[21] The texture of the collagenous bone matrix of the bone structure units is also relevant.

Woven bone is formed rapidly on an implant (or in a fracture callus) to restore continuity.[22] Similar results have been described for dental implants by

several groups, but quantitative evaluation of woven bone is usually not provided.[23–25] Woven bone appears to restore the bone volume in a limited amount of time, but its mechanical competence is far lower than lamellar bone because of its random orientation of collagen fibers.[22,26] In addition, woven bone is less mineralized and contains more sulfated glycosaminoglycan than mature lamellar bone.[27,28] Woven bone is progressively remodeled and substituted by lamellar bone. In the present study, the high glycosaminoglycan content has been used to identify woven bone, using toluidine blue. The fractional volume of woven bone was noticeable after the 3-month period, but only remnants could be observed after 6 months. Lamellar bone deposition by osteoblasts was present at 3 months as indicated under polarized light and the presence of double tetracycline labeling in ultraviolet light. A 6-month period appeared necessary to obtain a fully lamellar bone bed with true osteons. The apposition of neocortical bone on the implant appeared to be achieved very quickly. In an experimental study in the rabbit, it was found that the amount of bone necessary to obtain primary ankylosis of a titanium rod was obtained after a 1-month period but did not increase afterward.[9] This was also found in the present study, as all histomorphometric parameters appreciating bone mass around the implants (BV/TV, $B_{top}Wi$, and $B_{bot}Wi$) remained unchanged between 3 and 6 months. These parameters do not increase with time, because the stress transfer is not modified.[29]

In contrast, the bone-titanium contact interface increased regularly and similarly in both groups of implants. This phenomenon corresponds to a slow adaptation of the bone to the titanium material itself and implies progressive and adaptive remodeling.[29]

Calculating the bone surface per implant surface provides a true estimate of the bonebonding mechanism, which is related mostly to the surface quality of the implant and the remodeling ability of the multicellular remodeling units to adapt bone. Of particular interest is the decrease in MAR_{prox}, which reflects the concept of the regional acceleratory phenomenon according to Frost.[30] A regional acceleratory phenomenon is characterized by a focal increase of the modeling and remodeling activities as a result of a definite stimulus (eg, a traumatic injury, a screw, etc). This is particularly well evidenced by the differential measure of MAR in contact and at distance from the implant. At 3 months, MAR_{prox} and MAR_{dist} differed markedly. After 6 months, MAR_{prox} was reduced, but the remodeling rate was higher than at a distance from the implant.

Conclusion

In this study, the bone surrounding 2 types of implants was found to have a mixed texture (woven and lamellar matrix) after a 3-month postimplantation period. The remodeling process produced a layer of nearly all lamellar bone after a 6-month period. In this study, MAR_{dist} (which reflects osteoblastic activity distant from the regional acceleratory phenomenon) was higher than in humans ($MAR = 0.72 \pm 0.12$ µm/D), meaning that more time would have been necessary to achieve the same results in humans. Although recent reports have emphasized the success of immediate placement techniques or short-term unloading periods, long-term results have not been presented. Loading of an implant should be done when bone has restored its biomechanical competence.[31]

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