Early Bone Tissue Responses to Turned and Oxidized Implants in the Rabbit Tibia

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ABSTRACT

Background: Previous studies have shown the formation of more bone contacts with a moderately rough and porous titanium surface, created by anodic oxidation, as compared with nonmodified turned titanium control surfaces. The mechanisms leading to a stronger bone response to oxidized titanium are not well understood.

Purpose: The aim of the study was to describe the early events of bone integration of titanium implants with oxidized and turned surfaces.

Materials and Methods: Nine adult New Zealand White rabbits and 18 implants were used in the study. One oxidized and one turned threaded titanium implants, which had been placed in the right tibial metaphysis, were analyzed in the present study. The implants were retrieved after 7, 14, and 28 days for light microscopic examination and histomorphometric measurements in ground sections.

Results: Integration of oxidized implants was seen to occur as direct bone formation on the surface, while the integration of turned implants was a result of bone ingrowth from preexisting bone and bone marrow. For oxidized implants, an almost acellular, darkly stained layer was seen after 7 to 14 days, which later became populated with osteoblasts. The presence of osteoid seams indicated appositional bone growth from the substrate toward the surrounding tissues. The bone contact values were higher for oxidized implants, and the bone area values were higher for turned implants.

Conclusions: The present study confirms the idea that implant surface modification alters the bone tissue response to titanium. The early bone formation following surgery occurs directly on the moderately rough oxidized surface, while turned titanium surfaces are integrated by the ingrowth of bone from the adjacent bone marrow and preexisting bone tissues.

KEY WORDS: anodic oxidation, bone formation, histology, titanium implant, turned surface

INTRODUCTION

Modification of the micro- and macrogeometry of biomaterials is well known to alter the biomolecular and cellular responses in vitro, as well as the soft and bone tissue responses in vivo.[1,2] Numerous studies have shown an increased affinity of osteoblasts and more rapid formation of direct bone contacts to surfaces with a moderate degree of roughness, in comparison with smoother surfaces.[3–6] In addition, biomechanical tests using pullout and removal torque measurements have demonstrated higher resistance to shear forces for rough implant surfaces,[7–8] which may be of importance for the clinical outcome. Anodic oxidation has been used to modify titanium surfaces.[10–12] This process results in a growth of the native titanium oxide layer and a porous surface topography. Histology from animal

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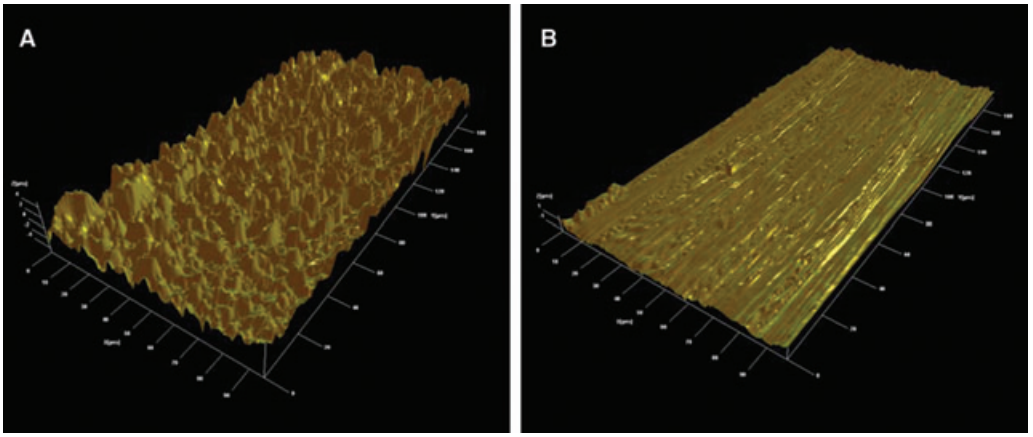

Figure 1 Three-dimensional presentations of the two surfaces examined. *A,* Oxidized implant, thread flank area. *B,* Turned implant, thread flank area.

experiments[10,12–14] and clinically retrieved implants[6,15,16] have demonstrated a strong bone tissue response to the oxidized surface and signs of bone formation directly on the implant surface. Scanning electron microscopy revealed an intimate contact between bone and clinically retrieved specimens and an ingrowth of bone to the pores.[16] Terms such as contact osteogenesis and distance osteogenesis have been coined to describe the different pathways of endosseous integration.[17,18] The former implies that bone is formed directly on the substrate, while the latter term indicates that bone is formed at a distance from the surface and that bone contacts are formed as a result of the ingrowth of bone toward the surface. However, few in vivo evidences of contact osteogenesis have been presented in the literature.

The aim of the present in vivo study was to histologically describe the early bone tissue responses to oxidized and turned titanium implants.

MATERIALS AND METHODS

Animals and Anesthesia

Nine female New Zealand White rabbits, at least 8 months old, were used in the study. The animals were kept free in a purpose-designed room and were fed *ad libitum* with water and standard laboratory animal diet and carrots. Prior to surgery, the animals were given general anesthesia by an intramuscular injection of fluanison and fentanyl (Hypnorm, Janssen Pharmaceutica, Brussels, Belgium) 0.2 mg/kg, and an intraperitoneal injection of diazepam (Stesolid, Dumex, Copenhagen, Denmark) 1.5 mg/kg body weight. Additional Hypnorm was added when needed. Local anesthesia was given using 1 mL of 2.0% lidocaine/epinephrine solution (AstraZeneca, Södertälje, Sweden). After surgery, the animals were kept in separate cages until their wounds healed (1–2 weeks) and then released to the purpose-designed room until termination. Postoperatively, the animals were given antibiotics (Intenpencillin 2.250.000 IE/5 mL, 0.1 ml/kg body weight, Leo, Helsingborg, Sweden) and analgesics (Temgesic 0.05 mg/kg, Reckitt and Colman, NJ, USA) as single intramuscular injections for 3 days. The study was approved by the local committee for animal research.

Implants

A total of 72 threaded titanium implants, 3.75 mm in diameter and 7-mm long (MKIII, Nobel Biocare AB, Göteborg, Sweden), were placed. The present study reports the histological results from 18 implants placed in the right tibial metaphysis. Nine test implants had been subjected to anodic oxidation (TiUnite™, Nobel Biocare AB), which resulted in a porous surface structure[11] (Figure 1A), and nine control implants were used with a turned surface (see Figure 1B). The results from the remaining implants have been reported elsewhere.[19]

Topographical analysis of one turned and one oxidized implant was performed using an optical interferometry (MicroXAM™, Phase-Shift, Tucson, AZ, USA) with a measurement area of $60 \times 190\ \mu m^2$ (50× objective, zoom factor 0.625), and the errors of form were removed with a digital Gaussian filter (size $50 \times 50\ \mu m^2$). Images from the thread top, valley, and inferior thread flank were obtained at three different levels of the implants: top, middle, and bottom (see

TABLE 1 Results from the Topographical Analysis of Test and Control Implants

	Oxidized implant				Turned implant			
	S_a (µm)	S_{ds} (µm^2)	S_{dr} (%)	S_{ci}	S_a (µm)	S_{ds} (µm^2)	S_{dr} (%)	S_{ci}
Top								
Mean	1.0	0.1	44.5	1.7	0.4	0.1	8.1	1.5
SD	0.1	0.0	5.7	0.1	0.1	0.0	2.3	0.4
Valley								
Mean	1.2	0.1	57.3	1.9	0.3	0.0	4.6	1.9
SD	0.2	0.0	7.9	0.1	0.1	0.0	1.1	0.3
Flank								
Mean	1.3	0.1	56.3	1.8	0.5	0.1	6.8	1.8
SD	0.0	0.0	2.4	0.1	0.1	0.0	0.5	0.1

S_a = arithmetic average height deviation from a mean plane; S_{ci} = core fluid retention index; S_{dr} = developed surface ratio; S_{ds} = density of the summits.

Figure 1, A and B). Thirty-six areas per specimen were analyzed, and the following three-dimensional parameters were calculated (Table 1): (1) S_a (µm), the arithmetic average height deviation from a mean plane; (2) S_{ds} (µm^2), the density of the summits; (3) S_{dr} (%), the developed surface ratio; and (4) S_{ci}, the core fluid retention index. The results from the topographical examination are presented in Table 1. In brief, the oxidized implant showed S_a values from 1.0 to 1.3 µm and S_{dr} values from 44.5 to 56.3% where the thread flank area showed the highest value. Corresponding S_a values for the turned implants were 0.4 to 0.5 µm and S_{dr} values were 4.6 to 6.8%.

The experimental area was exposed via a skin incision medial to the knee joint and separate incisions through the fascia and periosteum above each site. Holes

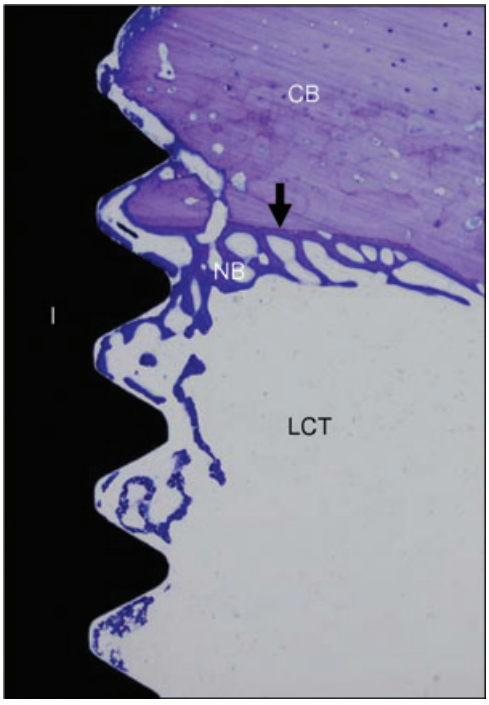

Figure 2 Light micrograph of turned implant after 14 days. The implant ("I") is protruding a dense cortical bone ("CB") and into a bone marrow cavity consisting of a loose connective tissue ("LCT") rich of fat cells, vessels, and cells. Formation of a new bone ("NB") is seen from the endosteal surface (*arrow*) and along the implant surface in the apical direction. Distance between two threads = 0.6 mm (toluidine blue stain).

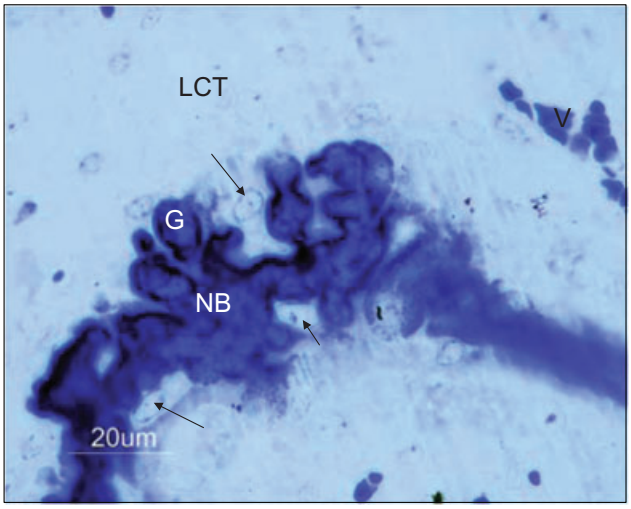

Figure 3 Light micrograph showing solitary bone formation in the loose connective tissue ("LCT") at a distance from the surface of a turned implant after 7 days. Globular aggregates ("G") of the granular material can be seen. *Arrows* are pointing to osteoblasts that became entrapped in the mineralized matrix (toluidine blue stain). (V = vessel).

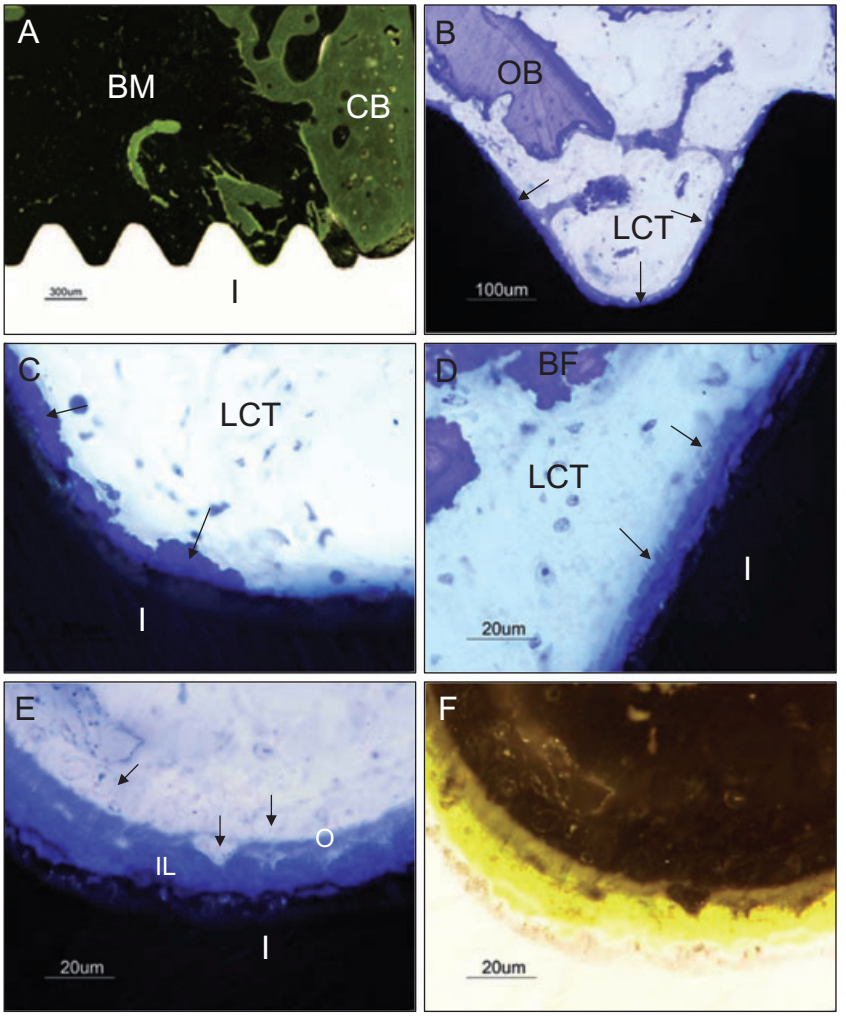

Figure 4 Light micrographs of oxidized implants after 7 days. *A,* Overview of one specimen in inverted colors. *B,* Showing the first thread below the endosteal surface. Bone formation is seen on the implant surface (*arrows*). *C,* Example of a darkly stained and acellular layer (*arrows*) frequently seen along the oxidized implant surface after 7 days. *D,* Showing a darkly stained layer on the oxidized surface with an osteoblast seam (*arrows*) facing the LCT. *E,* Showing a darkly stained IL on the oxidized surface with a globular appearance. Osteoblast (*arrows*) and osteoid ("O") are seen on top of the layer, indicating bone formation from the surface. *F,* Same area as in *E* in inverted colors (toluidine blue stain). (BM = bone marrow compartment; CB = cortical bone; I = implant; IL = interface layer; LCT = loose connective tissue; OB = old bone.)

were drilled in each tibial methaphysis using 1.8-, 2-, and 3-mm twist drills during generous cooling by saline. No countersink drill was used. One implant from each group were inserted in each right tibial metaphysis. The fascia-periosteal flap and the skin were closed in separate layers with resorbable sutures. Three animals each were killed after 7, 14, and 28 days by an overdose of pentobarbital (Mebumal®, ACO AB, Solna, Sweden).

Tissue Processing and Analyses

All implants and surrounding bone tissue were retrieved *en bloc* and fixed by immersion in 4% buffered formaldehyde. The implants from the left tibial methaphysis from each animal were used for micro-computerized tomography (micro-CT) as described further. The remaining specimens were dehydrated in graded series of ethanol and embedded in light-curing plastic resin (Technovit 7200 VCL, Kulzer, Friedrichsdorf, Germany). Sections were taken through the longitudinal axis of each implant by sawing and grinding (Exakt Apparatebau, Norderstedt, Germany). The sections, about 10-µm thick, were stained with toluidine blue and 1% pyronin-G. Examinations were performed with a Nikon Eclipse 80i microscope (Teknooptik AB, Huddinge, Sweden) equipped with an Easy Image 2000 system (Teknooptik AB) using ×1.8 to ×100 objectives for descriptive evaluation and morphometrical measurements. The qualitative analysis aimed at describing the

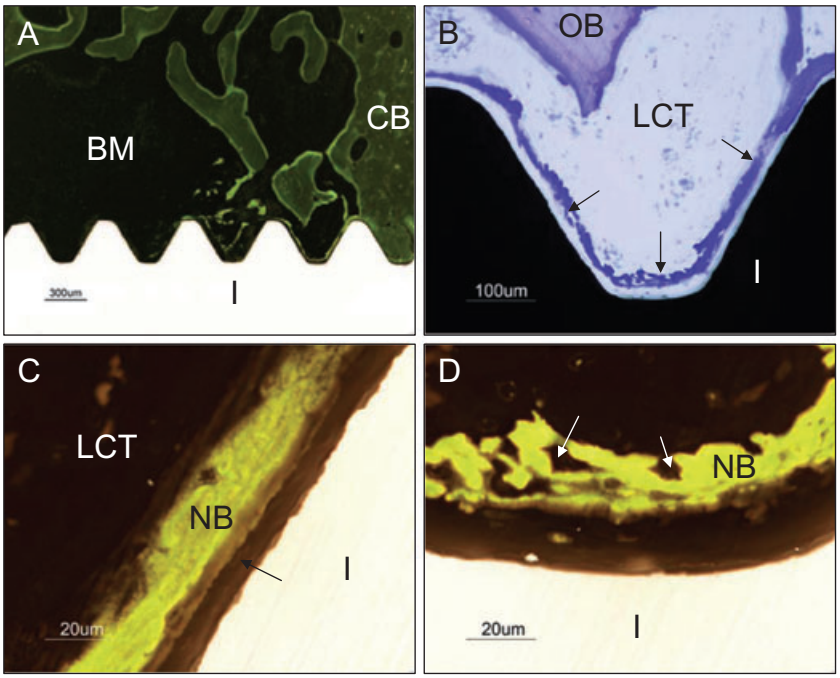

Figure 5 Light micrographs of turned implants after 7 days. *A,* Overview of one specimen in inverted colors. *B,* Showing the first thread below the endosteal surface. Bone formation is seen near the implant surface (*arrows*). *C,* Close up of *B* in inverted colors showing the presence of an osteoid at the surface of a newly formed bone ("NB") facing the interface gap (*arrow*). *D,* Close up of *B* in inverted colors. The new bone ("NB") contains large and scattered osteocyte lacunae (toluidine blue stain). (BM = bone marrow compartment; CB = cortical bone; I = implant; LCT = loose connective tissue; OB = old bone.)

early bone formation events at the oxidized and turned surfaces. The histomorphometrical evaluations comprised measurements of the degree of bone-implant contacts and the bone area occupying the implant threads. Data were presented as the mean value for each thread level and an implant mean based on the three specimens per time point and surface.

RESULTS

Light Microscopy

A typical specimen comprised the implant, which passed through a thin, about 1.5 mm, cortical layer and protruded into bone marrow tissue (Figure 2). Cancellous bone was generally not present.

Seven Days. Light microscopy of 7-day specimens showed a reorganized loose connective tissue with large vessels. Bone particles from the drilling procedure were seen, and the formation of bone was often seen in conjunction with these particles. Nonbone areas consisted of a loose connective tissue rich of vessels, fat cells, and hemopoetic cells, but few inflammatory cells such as macrophages could be seen (Figure 3). The periosteal and endosteal bone surfaces showed signs of bone formation by appositional growth, which sometimes reached the implant surface (see Figure 2). Solitary bone formation containing scattered osteoblasts/osteocytes surrounded by globular aggregates was observed in the bone marrow in close relation to blood vessels (see Figure 3).

For the oxidized implants, the tissue-implant interface seemed to be continuous (Figure 4), while the turned implants often showed a separation (Figure 5). Observation in high magnification revealed the presence of a darkly stained thin layer at the oxidized surface, seen as solitary spots or as continuous rims along several threads (see Figure 4, B–F). This material seemed to be acellular and had a globular appearance (see Figure 4, C and E). Osteoblasts were seen on top of this layer producing an osteoid toward the dark layer (see Figure 4, E and F). For the turned implants, bone formation was seen in the adjacent marrow tissue and was always separated from the implant surface (see Figure 5, B–D). The bone had a similar appearance as to that seen at the oxidized implants, but bone formation seemed to be more random with regard to direction (see Figure 5D). The gap between the newly formed bone and the

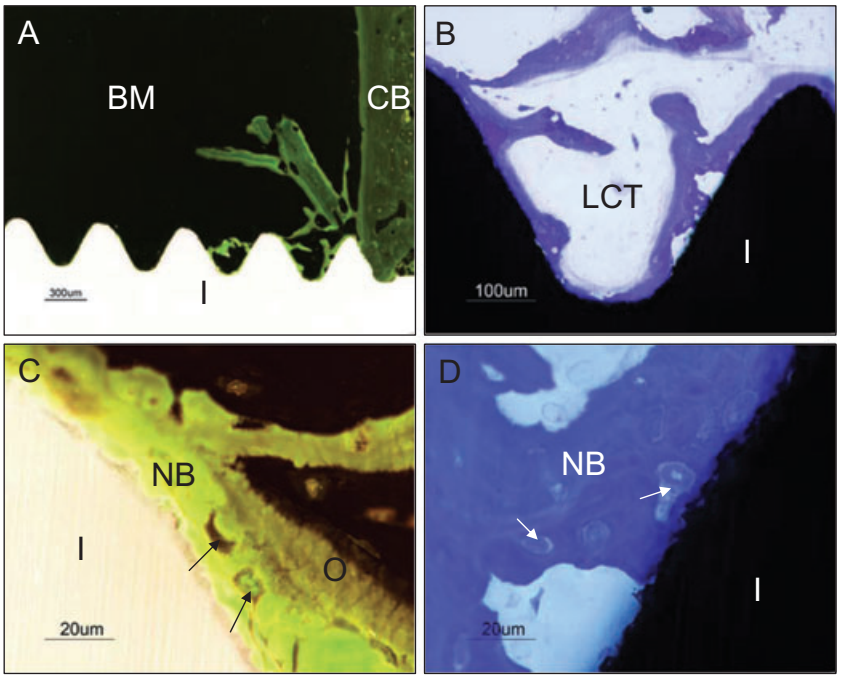

Figure 6 Light micrographs of an oxidized implant after 14 days. *A,* Overview. *B,* Showing the first thread with bone formation at the implant surface. *C,* Close up in inverted colors showing the new bone ("NB") in close contact with the surface and a layer of osteoid ("O") facing the bone marrow cavity. *Arrows* are pointing to osteocytes. *D,* Showing new bone ("NB") in contact with the oxidized surface. The innermost layer contains large osteocyte lacunae and is more darkly stained than the next layer of bone, as also seen in *B* (toluidine blue stain). (BM = bone marrow compartment; CB = cortical bone; I = implant; LCT = loose connective tissue.)

implant surface was occupied by nonmineralized tissue (see Figure 5).

Fourteen Days. At 14 days, more bone was contacting the oxidized implants (Figure 6) than the turned implants (Figure 7). Somewhat thicker bone rims were seen at the oxidized implant surface, compared with the 7-day specimens, and contained large, randomly scattered lacunae with osteoblasts (see Figure 6, B–D). Appositional bone formation toward the adjacent bone marrow was seen as the bone rims were lined with osteoid and osteoblast seams (see Figure 6C). A difference between the innermost interface layer and the overlying bone tissue could still be distinguished because of color differences (see Figure 6, C and D). In addition, for the turned implants, the amount of bone in the threads had increased, although not in contact with the surface to the same degree as for the oxidized implants (see Figure 7B).

Twenty-Eight Days. The 28-day specimens still showed more bone contacts for the oxidized implants, although the differences had diminished (Figure 8, A and B). The amount of bone in the threads was similar or higher for the turned implants (see Figure 8, C and D). Direct contacts seemed to be the result of primary contacts and ingrowth of bone toward the turned implant surface. The new bone showed signs of remodeling where woven bone had been replaced with lamellar bone for both types of implant surfaces.

Morphometrical Analyses. The morphometrical analyses showed higher bone contact values for the oxidized implants at all time points (Figure 9). The differences were especially evident in threads 3 and 4, which were situated in the bone marrow, where turned implants often showed no bone contacts at all. With regard to bone area in the threads, the turned implants showed higher values at all time points (Figure 10).

DISCUSSION

The purpose of the present animal study was to compare the early bone tissue responses to oxidized and turned titanium implants. Previous studies have demonstrated a stronger bone response to surface modified titanium implants as compared with turned control implants. Moreover, it has been suggested that the pathways of endosseous integration are different for smooth-

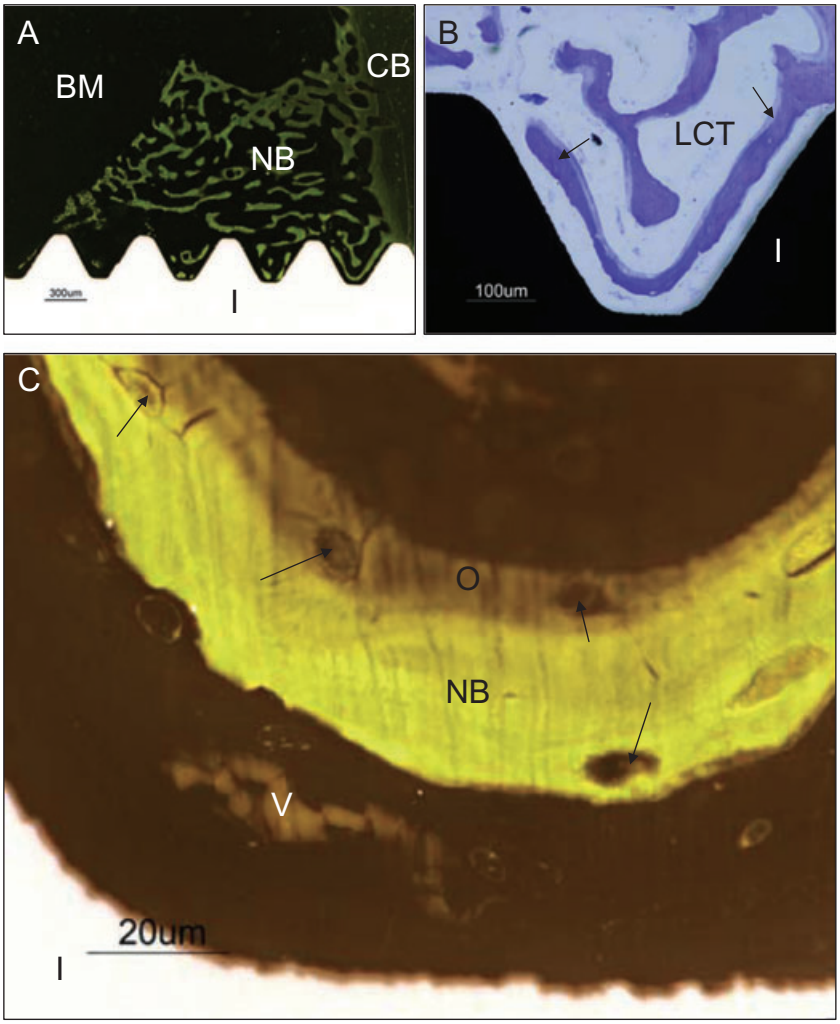

Figure 7 Light micrographs of a turned implant after 14 days of healing. *A,* Overview showing extensive formation of new bone ("NB") from the endosteal surface of the cortical bone ("CB"). *B,* Showing the first thread. Trabeculae of the new bone are seen in the thread not contacting the surface in this specimen. *C,* Close up of *B* in inverted colors showing the new bone ("NB") with an osteoid layer ("O") and osteocytes (*arrows*). A vessel ("V") is seen in the space between the bone and the implant surface (toluidine blue stain). (BM = bone marrow compartment; I = implant; LCT = loose connective tissue.)

surfaced implants and implants with a rough topography. The present study could confirm this because bone formation was seen to occur directly on the oxidized implants, while bone contacts to the turned implants were formed by bone growth from the adjacent tissues. Bone integration of the implant started with the formation of an about 10-μm thick layer with no or few cells. Thereafter, typical osteoblast and osteoid seams were seen to produce osteoids at this layer. The findings indicated that bone formation started on the surface and proceeded in the direction toward the surrounding tissues and along the implant surface. The anodic oxidation process results in a surface topography with interconnecting pores with a size of 2 μm or less.[11] It can be speculated that the pores may serve as a reservoir for bone-promoting factors from the blood clot. However, a similar bone response has been reported for other surface topographies,[18,20] which is in line with the implant-healing events as discussed by Davies and Hosseini.[21] According to these authors, the bone-forming process starts with de novo bone formation by newly differentiated osteogenic cells, which form a cement line directly on the substrate surface. The ground-sectioning technique, in combination with the irregular surface structures, makes it difficult to identify such thin layers, and ultrastructural techniques are needed for this purpose. However, it is possible that the darkly stained layer observed in the present study corresponds to the layer described by Davies and Hosseini.[21] Such a layer has been described by others,

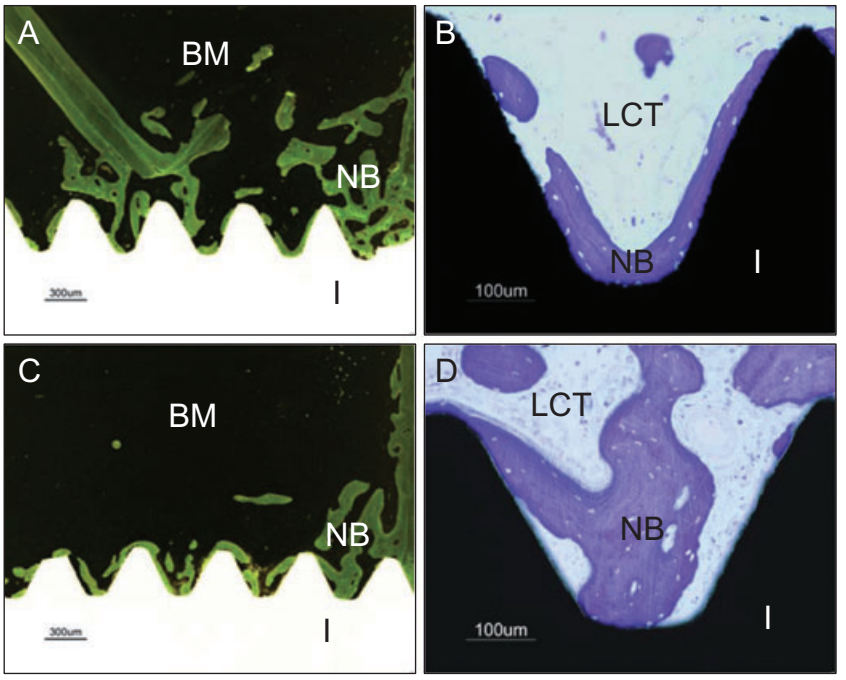

Figure 8 Light micrographs after 28 days. *A,* Oxidized surface. Overview showing an increased amount of bone compared with earlier observation times. *B,* Oxidized surface. The newly formed bone ("NB") contacting the oxidized surface has a lamellar appearance. *C,* Turned surface. Overview showing extensive bone formation along the implant surface. *D,* Turned surface. Newly formed lamellar bone is seen in contact with the implant surface (toluidine blue stain). (BM = bone marrow compartment; I = implant; LCT = loose connective tissue.)

but with a thickness of 500 nm up to 1 μm.[22] Thereafter, bone conduction leads to bone formation along the implant surface in parallel with an increased thickness of the bone by appositional growth. Our histology confirms this version. By using light and transmission electron microscopy (TEM), Sennerby and colleagues[23,24] described the early tissue responses to turned titanium implants using the same rabbit model. In these studies, bone was formed as a solitary islet in the matrix at a distance from the implant surface and never directly at the surface. Instead, they described the presence of multinuclear cells, which diminished with increased bone-implant contacts because of the ingrowth of bone toward the surface. A cement line-like "lamina limitans" layer was also observed where bone contacts had been established. The observations by Sennerby and colleagues and in the present study indicate different pathways of implant integration. This has been

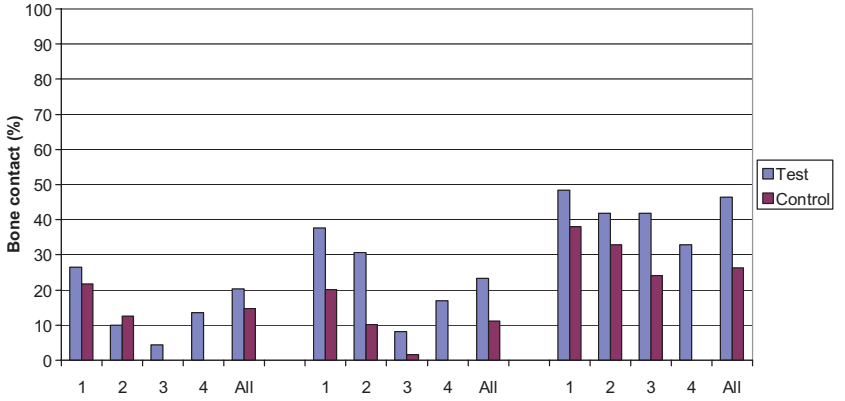

Figure 9 Graph showing the results from bone contact measurements at different thread levels and for all threads at the different time points.

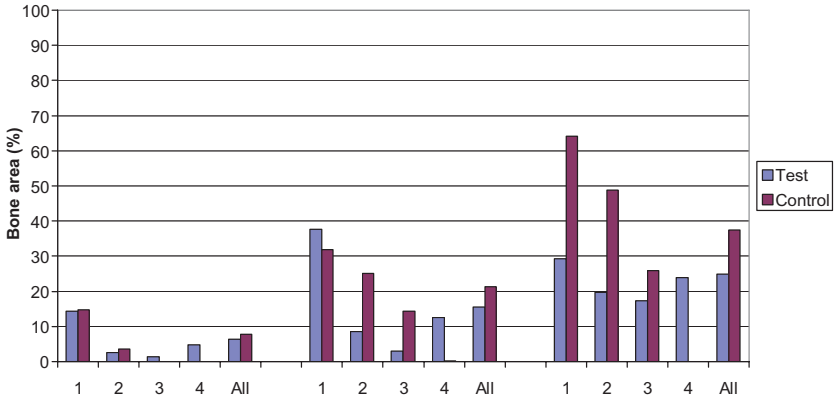

Figure 10 Graph showing the results from bone area measurements at different thread levels and for all threads at the different time points.

previously described as contact and distance osteogenesis.[17] However, comparative studies using ultrastructural techniques are needed to confirm this on a cellular level. It is possible that an electropolishing technique, as described elsewhere,[24] could be used for this purpose. With this technique, the bulk part of the titanium implants is electrochemically removed, leaving the surface oxide layer intact in the embedded tissue, which may enable the sectioning of the intact interface for TEM.

The mechanisms behind the different integration patterns are not fully known, but surface topography most certainly plays an important role, although other factors such as surface chemistry should not be underestimated. Davies and Hosseini[21] suggested that the initial blood clot and its retention on the implant surface is an essential prerequisite for the migration of osteogenic cells. The early blood contact and establishment of a fibrin matrix through which osteogenic cells can migrate to the surface is of importance.[18,25,26] An acid-etched titanium surface with rough topography has been shown to better retain a blood clot compared with a smoother turned titanium surface.[18] Moreover, a recent in vitro study demonstrated an increased trombocyte activation with increased surface roughness of calcium sulphate-coated surfaces.[26]

CONCLUSIONS

It is concluded that titanium implants with a turned or an oxidized surface are integrated with bone by following different paths. As observed at the light-microscopic level, bone formation occurs directly on the moderately rough oxidized surface, while turned titanium surfaces are integrated by the ingrowth of bone from the adjacent bone marrow and bone tissues. It is likely that the topographical differences play an important role for the bone tissue response.

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