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Titanium implants and BMP-7 in bone: an experimental model in the rabbit

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This study evaluates the effect of rhBMP-7/OP-1 on the osseointegration of commercially pure titanium implants in an experimental implant model in rabbits.

Threaded titanium implants with two transverse parallel canals were inserted in the femur and tibia of rabbits. The canals were filled with, 10 μg of BMP-7/collagen carrier, pure collagen carrier or were left empty as a control. The stiffness of the implant fixation was evaluated by Resonance Frequency Analysis (RFA) at baseline and four weeks postoperativly. Percentage of bone ingrowth in the canals was measured on microradiographs. Histomorphometry along the threaded part of the implants was performed on 15 μm thin sections.

The results from the RFA demonstrated a higher mean value for the BMP-7 treated implants in the tibia than the carrier treated implants but not compared to the control implants. The control implants in the tibia demonstrated more bone ingrowth in the upper canal than to the carrier or the BMP-7 treated implants. Apart from these differences there were no significant effects of BMP.

In this study BMP-7 did not contribute to any substantially improved bone anchorage of titanium implants.

1. Introduction

Success in treatment with commercially pure (c.p.) titanium implants in the dental clinic is dependent upon (1) implant material (2) implant macro-design (3) implant surface structure (4) status of the bone (5) surgical technique and (6) implant loading conditions [1].

In cases with poor quality or quantity of bone the use of growth factors (GF) [2–4] has been looked upon with high expectations. One of many groups of GFs is the Bone Morphogenetic Proteins (BMP) named by Urist *et al*. [5] and found to be a large group of related proteins [6–10].

The ability of BMPs to stimulate bone formation has been investigated by several authors. BMPs have been found to stimulate bone formation both in extra skeletal sites [11–13] and in large defect models [14–16] in different species. Cook *et al*. [17] tested implants with rhBMP-7 (also known as Osteogenic protein-1; OP-1) as an alternative to bone grafts for spinal fusion in a dog model. They found that implants with rhBMP-7/OP-1 demonstrated radiographic and histologic results of effective and stable posterior spinal fusion, resulting in bone with normal mechanical and histologic characteristics. BMP-2 has also been tested for effect in peri-implant bone regeneration around dental implants. Sigurdsson *et al*. [18] applied 0.43 mg/ml rhBMP-2 in a bovine collagen carrier around long implants installed in fresh extraction sites with drill-created peri-implant defects in dogs. Histologic evaluation demonstrated increased bone regeneration height and osseointegration in the defect in the rhBMP-2 treated implants. Jeppsson *et al*. [19] tested rhBMP-2 with a collagen sponge carrier in a titanium bone chamber study. An inhibitory effect was detected for two different concentrations (2.4 μg and 0.12 μg/mm^3) of rhBMP when evaluating bone ingrowth. In another study both rhBMP-2 and rhBMP-7/OP-1 were tested in similar bone harvest chamber models in rabbits with two different carriers and different concentrations but failed to stimulate bone ingrowth [20]. Hanisch *et al*. [21] used a titanium implant model in monkeys and evaluated 0.19 mg rhBMP-2 in a titanium dental implant model in monkeys with implants inserted in the maxillary sinus. The rhBMP-2 was applied on a collagen sponge and placed in a u-shaped defect in the sinus floor together with the screw-shaped titanium implant. A significant increase of the vertical bone height was found. However, bone density and bone-implant contact were not improved.

In another study, small differences in bone apposition

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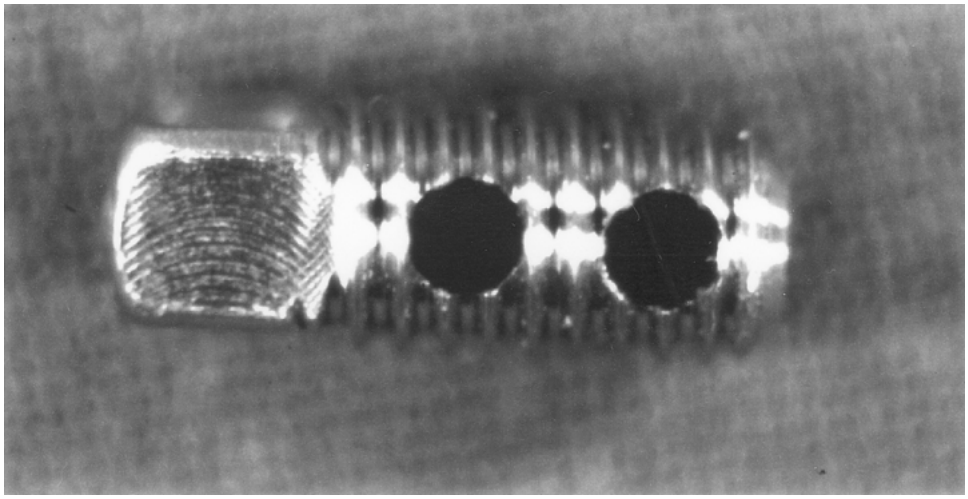

Figure 1 A survey picture of a threaded c.p. titanium implant with two parallel transverse canals.

to implant surfaces on implants treated with rhBMP-7/OP-1 and installed in fresh extraction sites were demonstrated [22]. Interestingly, extraction sites without implants in the same study demonstrated complete ''fill-out'' of bone tissue, with treatment by BMP-7/OP-1. With some exceptions the results from different studies indicate that BMP-7 may stimulate bone formation around implants. The aim of present the study was to evaluate weather two transverse canals filled with rhBMP-7/OP-1 could enhance the osseointegration of titanium implants and the bone ingrowth in the bone conductive canals, in a well documented experimental implant model in rabbit bone.

2. Materials and methods

2.1. Animals and anesthesia

Ten adult, female New Zealand White rabbits were used in this study, to a procedure approved by the animal ethical committee in Göteborg. They were kept uncaged in a large group enclosure.

The rabbits were anaesthetized with intramuscular injections of fentanyl and fluanison (Hypnorm Vet., Janssen Saunderton, England) at a dose of 0.5 ml/kg body wt and intraperitoneal injections of diazepam (Kabi Pharmacia, Helsingborg, Sverige) at a dose of 2.5 mg per animal. Local anaesthesia with 1.0 ml of 5% Xylocaine (Astra Zeneca, Södertälje, Sweden) was injected into the surgical area. Prior to surgery the shaved skin of the rabbits was carefully washed with a mixture of 2% iodine and 70% ethanol. After surgery all rabbits received analgesia of 0.05 ml Temgesic at a dose of 0.3 mg/ml (Reckitt and Coleman, Hull, England) subcutaneously. After four weeks healing time the animals were killed with 10 ml of Pentobarbital (100 mg/ml, Apoteksbolaget, Malmö, Sweden) intravenously.

2.2. Implants and surgical technique

The rhBMP-7/OP-1 was purchased from Stryker Biotech, Natick, Massachusetts, USA. Sixty screw-shaped implants were manufactured by turning of rods from commercially pure titanium (c.p.ti) grade 1 (Edstraco, Stockholm, Sweden). The implants had a total length of 7 mm (5 mm threaded and 2 mm non threaded top) and an outer diameter of 3.75 mm. The top of the implants was square headed and had an inner hole with a diameter of 2.0 mm designed to fit the screw that attached the Resonance frequency (RFA) transducer to the implants. The implants had two canals [23, 24] of 1.5 mm in diameter passing through the threaded part, separated by a distance of 1.2 mm (Fig. 1). These canals served as a site for bone ingrowth evaluation as well as a depot for the BMP-7/collagen carrier. The implants were ultrasonically degreased in trichlorethylene; and rinsed in absolute ethanol twice followed by autoclaving prior to insertion. Under aseptic conditions one implant was inserted in the distal femoral chondyle and two were inserted in the proximal tibial metaphysis. This procedure was performed in both legs. Implants in the tibia were allowed to penetrate the first cortical layer only. In one leg the femural and tibial implants were filled with BMP-7 and collagen carrier at a dose of approximately 10 μg BMP-7/canal before insertion into the bone bed. In the contralateral leg the canals in the femoral and one of the tibial implants were filled with a similar amount of the carrier (bovine collagen). The canals of the other tibial implant were left empty as a control (Fig. 2). Before the BMP-7 and collagen granules were inserted into the canals they were soaked with sterile saline according to the manufacturers instructions, to make the material managable. The animals were allowed full weight bearing immediately after surgery.

To test the effectiveness of BMP-7, a subcutaneous rat model was used [5]. Doses of 20 μg and 100 μg with the BMP-7/collagen carrier were implanted bilaterally in dorsal muscle pouches of two Sprague-Dawley rats. After three weeks *in situ* biopsies taken from the BMP-7 treated regions were processed to undecalcified histological sections followed by staining and analysis in a light microscope. The subcutaneous implants in rats were also evaluated by light microscopy. The biologic activity of the BMP-7 preparation was confirmed by bone formation in all four subcutaneous implants in rats (Fig. 3).

2.3. Resonance frequency analysis (RFA)

Immediately after implant insertion the resonance frequency was measured, i.e. baseline measurements on all implants were recorded. The RFA test is a non-

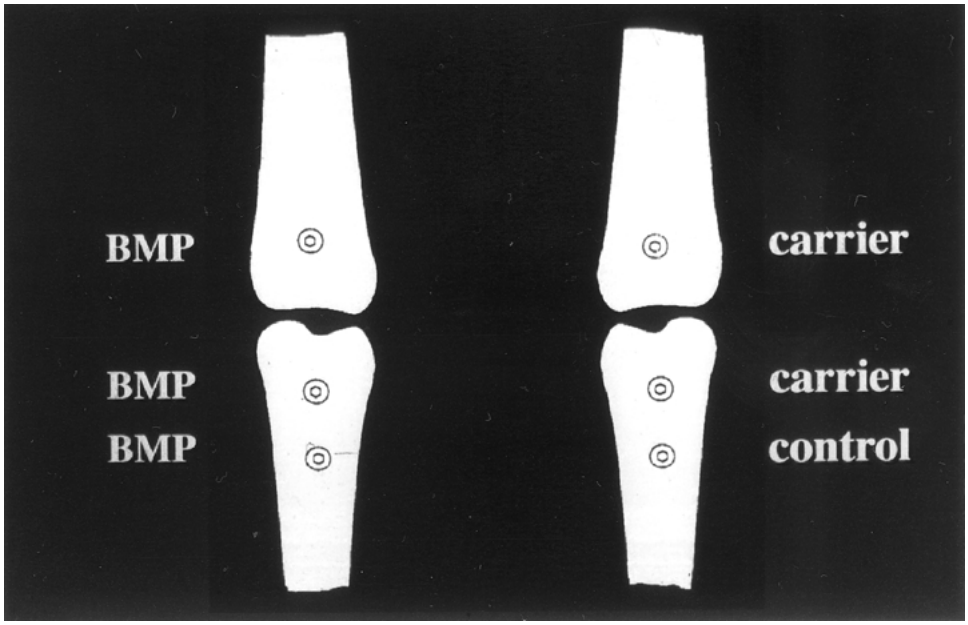

Figure 2 A schematic drawing of the distal femur and proximal tibia, implant placement and implant treatment.

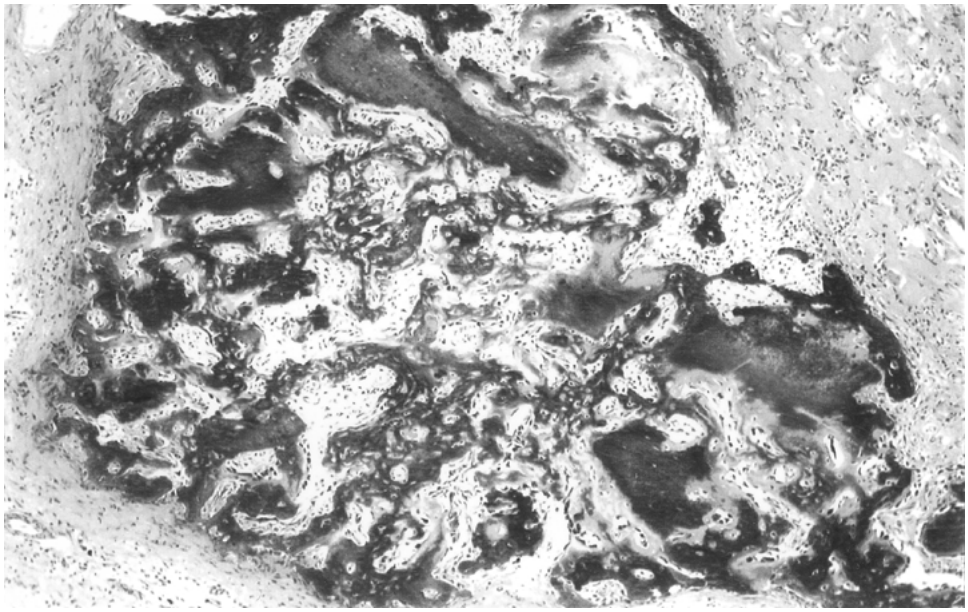

Figure 3 Survey picture of a histologic section from biopsy after subcutaneous implantation in rat. The 15 μm thick undecalcified cut and ground section has been stained with Tolouidine blue mixed with Pyronin G.

destructive method that enables measurements of the stiffness of the implant interface which, is related to the stability of the implant in the bone [25]. A specially designed transducer connected to a computer is attached to the implant with a small screw. The transducer is vibrated by exciting a piezoceramic element and the resonance frequency value, in Hertz (Hz), is recorded.

At the day of sacrifice, the rabbits were anaesthetized as described above. The skin and fascia were opened and the transducer was attached to the top of the implant and the resonance frequency was measured again. Resonance frequency value has been shown to have a positive correlation with the implant stability [25].

2.4. Specimen preparation, microradiographic and histomorphometric evaluations

All implants with surrounding tissue were removed en bloc, immersed in 4% neutral buffered formaldehyde and processed to be embedded in light curing resin (Technovit 7200 VLC, Kulzer Wehrheim, Germany). Undecalcified cut and ground sections were prepared with the Exakt saw machine and grinding equipment as described by Donath [26] for quantitative and qualitative light microscopic and quantitative computerbased analysis performed on microradiographed plates of the bone ingrowth into the canals.

Two sections were taken from each implant. The

central section was used for analysis of bone percentage in the canals and the second section was used for analysis of the tissue structures in the threads of the implants. Firstly, the central ground sections with a thickness of about 100 μm were microradiographed (OEG-50 Machlett X-ray tube) [27] with a 20 min exposure at 25 kV and 8 mA on Kodak High resolution film (Eastman Kodak, Rochester, N.Y). The exposed films were developed for 5 min at 20 °C, under constant agitation. Fixation of 10 min was followed by careful water rinsing for 15 min and air drying. The microradiographs of the implants visualising both canals were observed in a stereo microscope (Olympus SZH). With a high-resolution CCD video camera (3077 CCD, Hamamatsu) adapted to the microscope, the image was read into a PC-based image-analysis system (Compaq 386 with Matrox framegrabber, Image Access softwear developed by Micro Macro Bildanalys AB, Stockholm, Sweden). The image was digitized by division into 512×756 pixels with gray-values between 0 and 250 [27]. The area of interest was outlined by selecting a region of interest (ROI) and the proper intensity threshold was selected by the operator. From these instructions the system could calculate the area of bone and none-bone in the ROI. The optical threshold was set so that brighter pixels represented bone tissue and darker pixels represented non-bone tissue. The operator could adjust to ensure that all the bone tissue was calculated. The percentage of bone area in the ROI was calculated directly through the computer for each measured area. The upper and lower canals were calculated individually on each implant in both femur and tibia. The 100 μm sections were further ground to about 10 μm prior to histological staining followed by light microscopic quantitative and qualitative evaluation.

The non-central sections were further ground to about 10 μm and histologically stained with Toluidine blue mixed with pyronin G for quantitative investigations in a Leitz Aristoplan light microscope (Leitz, Wetzlar, Germany). Computerbased histomorphometry was performed by a Leitz Microvid equipment connected to a PC. These measurements were performed directly in the eyepiece of the light microscope using a 10X magnification objective and an zoom of 2.5X. Measurements of the percentage bone-to-metal contact and bone area in all threads and in the three best consecutive threads in the cortical region were calculated. ''Mirror image'' measurements of the percentage of bone in the outfolded thread area were also calculated in the three best consecutive threads. The three best consecutive threads around the entire implant in the femur and in the cortical region of the tibia were used for the mirror image measurements [28].

The entire bone length along the implant surface was measured on all implants in femora and in tibiae. This measurement was performed with a 1.6X magnification objective.

2.5. Statistics

Wilcoxon signed-rank test was used for paired comparisons within each animal. Calculations of mean difference between groups was performed and tested at the 95% level of significance.

3. Results

3.1. Surgical

There were no immediate post-operative complications. One rabbit had to be sacrificed after three weeks due to lung problems, and was excluded from the study. All other rabbits $(n = 9)$ completed the four weeks follow-up.

3.2. Resonance frequency analysis

In general, the resonance frequency after 4 weeks demonstrated a higher mean value for the carrier treated implants in femur. However, in tibia the BMP-7 treated implants demonstrated a higher mean value as compared to the carrier treated and control implants. None of the differences were statistically significant.

The mean value of difference in resonance frequency between baseline and 4 weeks demonstrated no significant differences for the implants inserted in the femur. The implants in the tibia, however, demonstrated a significantly higher mean value for the BMP-7 treated implants than the carrier treated group. Comparisons of test implants to the untreated control group demonstrated no significant difference (Table I).

3.3. Image analysis of bone area in the transverse canals on microradiographs

No effect of BMP-7 could be demonstrated in the upper or lower canal in the *femur*. The mean difference between BMP-treated implants and the carrier implants (upper and lower canals together) was − 8% (95% CI; − 20 to 2). When comparing the upper and lower canals separately a mean difference between the upper canals of the BMP-treated implants and the carrier implants was − 4% (95% CI: − 14 to 4) and − 12% (95% CI; − 21 to

TABLE I The results of the RFA measurements

Location/ treatment	RFA, day 0 to 4 weeks, kHz	Diff. Hz	95% CI Hz	RFA, 4 weeks, kHz	Diff. Hz	95% CI Hz
a. femur/BMP-7	1.2 ± 0.5 (0.3 to 2.0)			11.5 ± 0.7 (10.4 to 12.3)		
b. femur/carrier	1.3 ± 1.0 (0.4 to 3.5)	a. vs b. 287	a. vs b. − 208 to 781	11.6 ± 0.6 (10.7 to 12.5)	a. vs b. − 35	a. vs b. − 862 to 793
c. tibia/BMP-7	1.3 ± 0.4 (0.8 to 1.9)			11.2 ± 0.4 (10.8 to 11.9)		
d. tibia/carrier	1.1 ± 0.5 (0.2 to 1.8)	c. vs d.* 287	c. vs d. − 208 to 781	11.0 ± 0.4 (10.2 to 11.6)	c. vs d. 343	c. vs d. − 14 to 670
e. tibia/control	1.4 ± 1.1 (1.2 to 2.6)	c. vs e. − 22	c. vs e. − 869 to 825	11.0 ± 10.5 (8.9 to 12.2)	c. vs e. 225	c. vs e. − 493 to 943

* statistically significant; c. vs d. $p = 0.04$.

TABLE II Results of image analysis of the bone area ingrowth of the canals, presented as mean percentage of bone ingrowth (%), standard deviation and range

Location/treatment	Upper + lower canal	Upper canal	Lower canal
femur/BMP-7	17% ± 9 (6 to 40)	19% ± 11 (5 to 40)	14% ± 7 (6 to 20)
femur/carrier	21% ± 9 (8 to 42)	14% ± 7 (6 to 20)	18% ± 7 (8 to 29)
tibia/BMP-7	16% ± 8 (6 to 38)	18% ± 9 (to 38)	13% ± 5 (6 to 20)
tibia/carrier	16% ± 11 (0 to 41)	23% ± 11 (8 to 41)	8% ± 8 (0 to 17)
tibia/control	28% ± 22 (5 to 68)	44% ± 21 (13 to 68)*	12% ± 5 (5 to 18)

* statistically significant; tibia/control vs tibia/BMP-7 and tibia/carrier ($p = 0.02$).

− 2) for the lower canals. In *tibiae* the mean value of the upper and lower canals together did not demonstrate any difference between the test, carrier and control groups. The mean difference between the BMP-7 and carrier treated implant (upper and lower canals together) was 0.44% (95% CI; − 9 to 10) and 12% (95% CI; − 28 to 4) between the BMP implants and the control implants (upper and lower canals together). However, when comparing the upper canals in the tibia separately a significantly higher percentage of bone ingrowth in the control implants was demonstrated compared to the BMP-7 and carrier treated implants. The mean difference between the upper canals of the BMP-treated implants and the carrier implants in the tibia was − 4% (95% CI: − 15 to 7) and 5% (95% CI; − 1 to 11) for the lower canals. The mean difference between the upper canals of the BMP-treated implants and the control implants in the tibia was − 25% (95% CI: − 42 to − 8) and 1% (95% CI; − 4 to 7) for the lower canals (Table II).

3.4. Histomorphometrical evaluation of the threaded region of the implants

Irrespective of location (femur or tibia) the histomorphometrical quantifications did not demonstrate any statistically significant differences between the groups in any of the parameters evaluated (Table III).

4. Qualitative evaluation

Femur: The survey pictures in the light microscope of the cut and ground sections in the femur demonstrated implants with the upper and lower canal inserted in cancellous bone. Both the upper and lower canals demonstrated some bone ingrowth, in the BMP-7 and carrier treated implants (Fig. 4). The amount of bone appeared to vary between animals. At a higher magnification the bone in *the upper canal in the femur* both in the BMP-7 and carrier treated implants seemed to be of cancellous type, newly formed and undergoing remodeling. In general there were light blue stained remnants of the carrier (Fig. 5), occasionally with large amounts of multinucliated giantcells in close relation. The newly formed bone appeared sometimes as remineralized carrier or new formed islands of bone in close relation to the carrier. In general, the newly formed bone was located in the central part of the canal often in close contact to the implant surface. In the BMP-7 treated implants there appeared to be more areas with osteoid like tissue than in the carrier treated implants. *The lower canal in the femur* demonstrated less bone than the upper canal both in the BMP-7 and carrier treated implants.

Tibia: The survey picture of the implants in the tibia revealed monocortical insertion in the central part of the tibia. The upper canals in the tibia were situated in the old cortical region of the bone in all sections and the lower canals were located in the marrow region. Both the upper and lower canals demonstrated bone ingrowth, in

TABLE III Results from the histomorphometric evaluation (mean, standard deviation and range). Mean difference between groups and 95% confidence range

Parameter	1. femur/ BMP-7	2. femur/ carrier	3. tibia/ BMP-7	4. tibia/ carrier	5. tibia/ control	Diff.	95% CI
bone-to-metal contact, all threads,%	15% ± 12 (3 to 39)	22% ± 10 (7 to 38)	9% ± 4 (4 to 16)	13% ± 4 (8 to 19)	11% ± 11 (0 to 30)	1 vs 2: − 4 3 vs 4: − 3 3 vs 5: − 2	1 vs 2: − 14 to 7 3 vs 4: − 2 to − 10 3 vs 5: − 12 to 7
bone-to-metal contact, three best consecutive threads,%	21% ± 16 (6 to 54)	27% ± 14 (7 to 55)	15% ± 7 (5 to 26)	18% ± 4 (9 to 27)	18% ± 12 (5 to 38)	1 vs 2: − 6 3 vs 4: − 1 3 vs 5: − 1	1 vs 2: − 21 to 9 3 vs 4: − 6 to 7 3 vs 5: − 8 to 11
bone area, all threads,%	54% ± 14 (32 to 79)	55% ± 14 (30 to 76)	45% ± 7 (32 to 56)	48% ± 9 (30 to 62)	53% ± 8 (41 to 64)	1 vs 2: − 1 3 vs 4: − 4 3 vs 5: − 9	1 vs 2: − 13 to 11 3 vs 4: − 13 to 5 3 vs 5: − 18 to 1
bone area, three best consecutive threads,%	63% ± 12 (47 to 87)	70% ± 10 (47 to 78)	62% ± 10 (43 to 74)	69% ± 8 (52 to 77)	70% ± 8 (58 to 80)	1 vs 2: − 7 3 vs 4: 8 3 vs 5: − 9	1 vs 2: − 20 to 6 3 vs 4: − 1 to 17 3 vs 5: − 20 to 3
''mirror image'', %	60% ± 14 (45 to 86)	72% ± 11 (56 to 56)	68% ± 7 (52 to 75)	67% ± 8 (56 to 83)	74% ± 11 (57 to 85)	1 vs 2: − 13 3 vs 4: 1 3 vs 5: − 3	1 vs 2: 1 to − 27 3 vs 4: − 7 to 8 3 vs 5: − 7 to 8
bone length along the implant surface, mm	7.0 ± 1.2 (5.2 to 9.5)	6.1 ± 1.6 (3.8 to 8.9)	3.9 ± 0.5 (3.3 to 4.8)	3.9 ± 0.7 (3.0 to 4.9)	4.7 ± 1.5 (2.9 to 8.3)	1 vs 2: 0.9 3 vs 4: 0.1 3 vs 5: 0.6	1 vs 2: − 0.4 to 2.1 3 vs 4: − 0.6 to 0.7 3 vs 5: − 0.7 to 1.9

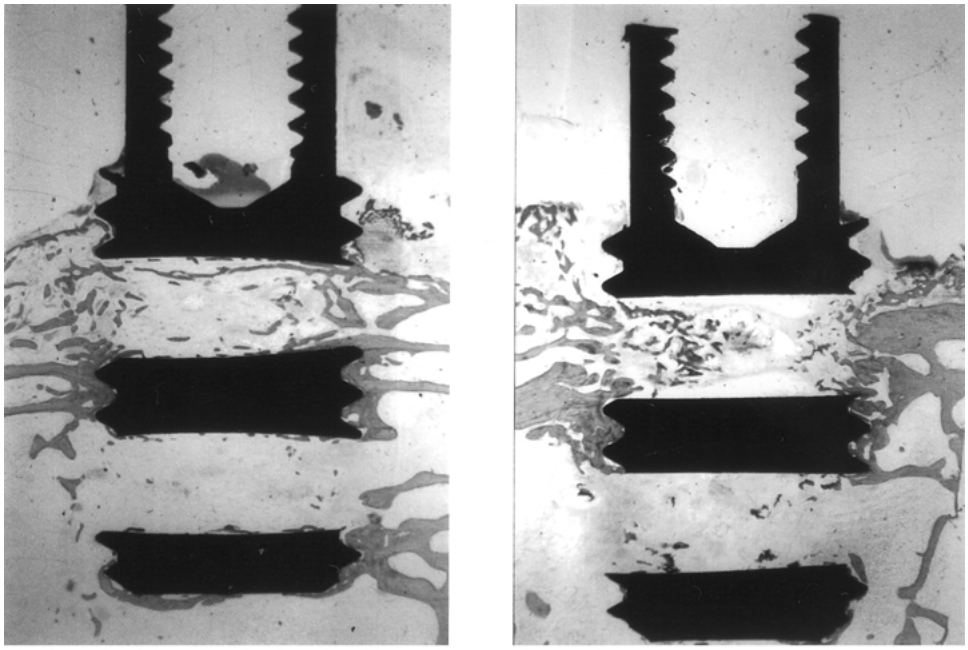

Figure 4 Histologic section of two different implants in the femur demonstrating location and bone ingrowth in the canal areas. The distance between the threads is 600 μm. A. BMP-7 treated implant. B. Carrier treated implant.

general with more bone in the upper canal. *The upper canals* contained newly formed bone, although the amount differed between the groups. The control implants (left empty) had a larger amount of bone ingrowth than the BMP and carrier treated canals in the tibia (Fig. 6). Osteoblasts and osteoclasts were observed in the canals in close relation to the newly formed bone. An inflammatory cell infiltrate could be seen inside the canals in all three implant groups, containing macrophages, plasma cells and multinucleated giant cells, appearing in a larger amounts in the BMP-7 and carrier treated implants. Remnants of the collagen in the test and carrier treated canals were observed. The periosteal part of the bone was undergoing extensive remodeling with resorptive areas immediately outside the canal in some specimens. This was not observed in the control implants. *In the lower canals in the tibia* a smaller amount of newly formed bone was observed mostly with a similar pattern to that in the upper canals.

The threaded region: In general, bone-to-implant contact was observed in the threads of the implants. In the femur there was bone in the threads around the entire implant. In the tibia a larger amount of bone was observed inside the threads in the old cortical region than in the threads in the marrow cavity. Cell activity appeared less prominent in the threads than in the canals.

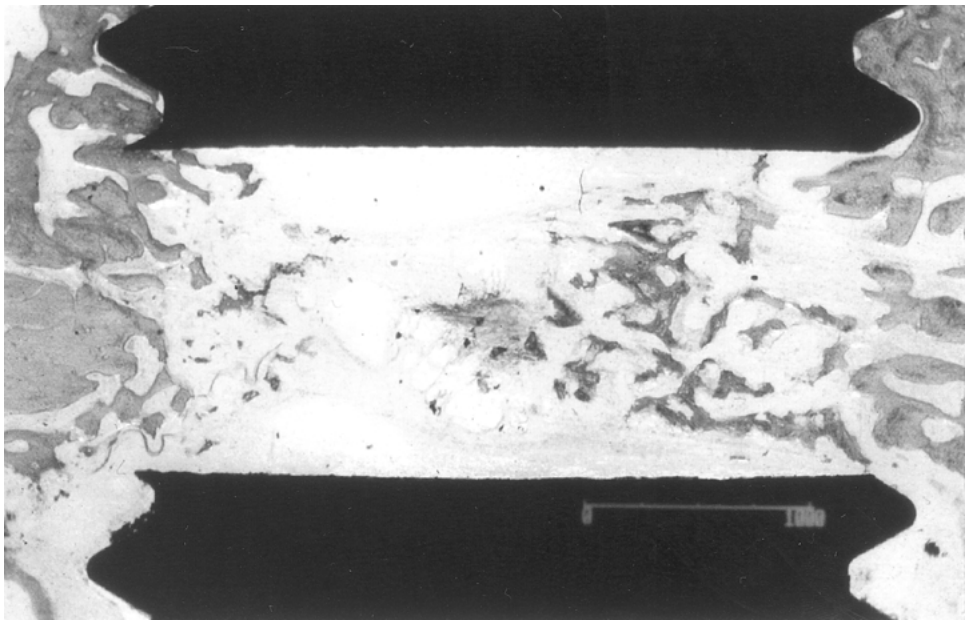

Figure 5 Histologic section of the canal area of a carrier treated femoral implant. New formed bone together with the remnants of the carrier (arrow) is observed in the middle of the canal. Bar = 1000 μm.

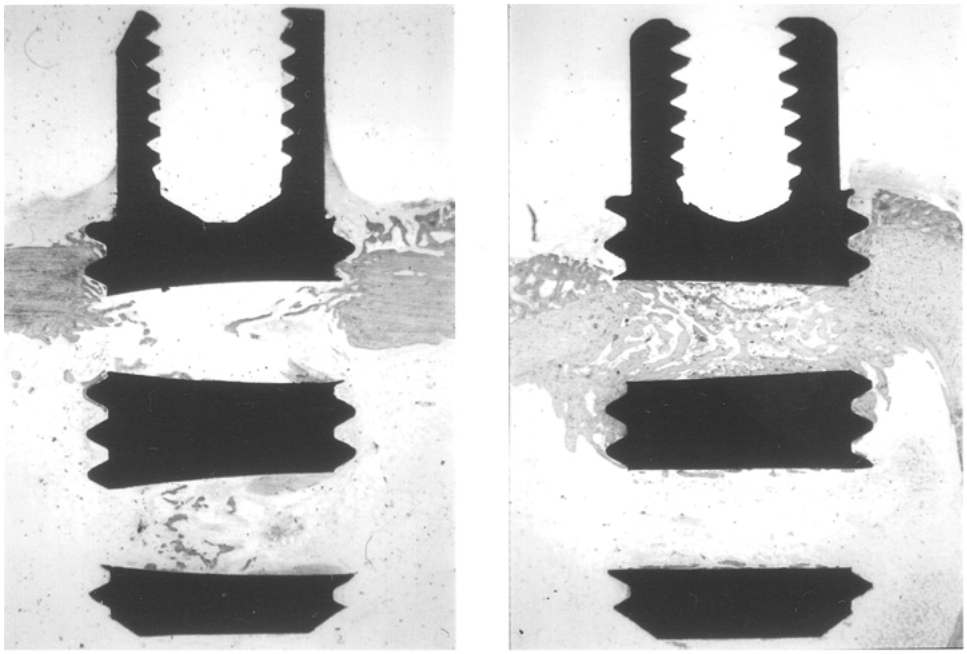

Figure 6 Histologic sections of two different implants demonstrating the bone ingrowth in the canal areas. (a) Canals of a BMP-7 treated implant. (b) Canals of a control implant. The diameter of the canals is 1500 μm.

5. Discussion

Several studies demonstrate beneficial effects of BMP in combination with titanium implants in different species and models [18, 21, 29, 30, 33–35]. The positive effect of BMP has been demonstrated by an increase in vertical bone height in periimplant defect models [18, 21, 35] and by increased bone density [22]. Bessho *et al.* [30] reported increased bone-implant contact in a dog study with purified bovine BMP compared to an untreated control. A few studies have also demonstrated an inhibitory effect from treatment with BMP-2 [19, 20] and BMP-7 [20] in combination with titanium bone chambers. Suggested cause to these contradictory results have been the concentration [19] of the BMP and also the degree of insertion trauma [20] caused in the model. Cook *et al.* [22] suggested their small effect was due to irregularities of implant sites in the extraction sockets, BMP dose and delivery technique. There is no doubt that the BMP-7 used in the present study was active since it was tested intramuscularly in a rat model with a positive response of bone formation (Fig. 3). The carrier used in this study was bovine collagen. The collagen carrier has been tested against another carrier together with BMP-2 by Cochran *et al.* [34]. They concluded that the collagen carrier was more effective than a polylactide/glycolide carrier. Histological examination in the present study demonstrated only small remnants of the carrier and a histologic section was made of some of the BMP and carrier material for light microscopic comparison. It is possible that initially the collagen carrier could have delayed bone ingrowth into the canals by its role as a spacer. However most of the carrier had been resorbed after four weeks. Another factor may be that the collagen carrier needs extensive exposure to macrophages and other cells to be completely degraded and to release the active substance in a proper way [36]. Possibly the canals could not provide sufficient contact with surrounding cells and tissue to enable optimal release of the BMP. The concentration of BMP-7 in the present study was approximately 10 μg/canal i.e. 20 μg/implant. This dose ought to have been sufficient since a study by Bostrom *et al.* [29], who applied a dosage of 0.6 μg, in a micromotion chamber in rabbits found more bone with BMP-2/collagen than with collagen only. That study, however, also demonstrated a negative effect with BMP-2 unless sufficient trauma was added to the model. In a non-union rabbit model Cook *et al.* [37] demonstrated that BMP-7 of different concentrations (3.13 μg, 6.25 μg, 12.5 μg, 25 μg, 50 μg, 100 μg, 200 μg, 400 μg) induced complete osseous union within 8 weeks except for the lowest dose. In several studies with positive results from both BMP-2 and BMP-7, considerable surgical trauma was used for the introduction of the BMP. In our study, minimal surgical trauma was used and this may be one explanation to the lack of effect. This explanation was also suggested by Jeppsson *et al.* [20] in similar study using a bone harvest chamber model. Trauma such as a fracture or an osteotomy will cause more extensive bleeding which will release endogenous factors that activate migration of inflammatory cells and cells of mesenchymal origin which can respond to the applied BMP and stimulate bone formation. We cannot exclude the possibility of an antibody formation to be responsible for the results. This possibility has not been discussed in the reference literature in conjunction with rhBMP in a rabbit model. Systemically administered human growth hormone has been shown to cause antibody formation in rabbits [38]. It should be investigated whether antibody formation may occur in the present situation to either rhBMP-7 or the collagen carrier.

The results from this study indicate that BMP-7 does not contribute to substantial differences in the osseointegration of titanium implants or to bone ingrowth in a bone conductive canal. However, BMP-7 and other

growth factors may be more useful in situations were a larger trauma is inevitable, or in cases with poor bone formation. Further studies are required to confirm this hypothesis and to understand the possible use of BMPs in the clinical implant field.

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