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Does sodium fluoride in bone cement affect implant fixation?

Part I: Bone tissue response, implant fixation and histology in nine rabbits

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The addition of sodium fluoride to poly (methyl-methacrylate) (PMMA) bone cement may theoretically improve the fixation of joint replacement. This hypothesis was tested in an animal model using nine mature healthy lop-eared rabbits. A femoral prosthesis was inserted in both knees to resurface the patellofemoral articulation. The same acrylic cement, with and without sodium fluoride, was randomised between the two sides for prosthetic fixation. Two screw shaped implants machined from cured rods of either cement were also inserted bilaterally into the proximal tibia.

Qualitative and quantitative histomorphometry of the bone tissue response surrounding the cement in the femur and the intact tibial implants revealed similar results regardless of sodium fluoride addition. Six weeks after surgery removal, torque did not significantly differ between the two sides. Our findings indicate that addition of sodium fluoride to PMMA has little effect on implant stability and bone remodeling in rabbits in the short-term.

Introduction

During 30–40 years of use in orthopaedics the constituents of acrylic bone cement have changed minimally. The most important improvement of cemented fixation has concerned the preparation of the bone bed and the application technique: pressure lavage, retrograde filling of the canal and cement pressurization. Magnan *et al*. [1] explored the possibility of enhancing bone formation around the cement to increase stability and reduce the subsequent risk of loosening by adding sodium fluoride. They used bone cement with a powder to liquid ratio of 3 : 1 and found greater bone formation on the surface of the fluoridated cement than on controls. The sodium fluoride molecules are inert during polymerization but are highly soluble if exposed to saline solution, where they release active fluoride ions.

Fluorine has an obvious effect on bone metabolism. Roholm [2] reported chronic intoxication of sodium fluoride by cryolite (Na_3AlF_6) dust inhalation in factory workers where cryolite was cleansed and ground. X-ray examination revealed osteosclerosis especially of the cancellous bone. Rich and Ensinck [3] performed the first clinical trial with sodium fluoride as oral treatment for one patient with Paget's disease of bone and six patients with osteoporosis. These authors found that oral treatment with sodium fluoride decreases the excretion rate of calcium. Since then knowledge of the optimal oral treatment regimen has advanced. In spite of this there is no consensus on the optimal model of oral treatment with sodium fluoride [4].

Sodium fluoride has two main effects on bone, the first is a direct stimulating effect on the proliferation of osteoblasts and bone matrix synthesis [5, 6]. Local administration of sodium fluoride acts by promoting deposition of new bone at the periosteal surface [7]. The second effect is a decreased rate of bone resorption [8]. The latter is probably an effect of ion exchange; hydroxyapatite being converted to fluorapatite [9]. This change makes the apatite crystal more resistant to osteoclastic resorption [4]. Because of the potential positive effect of fluoride on the local bone quality, sodium fluoride might improve the quality of the

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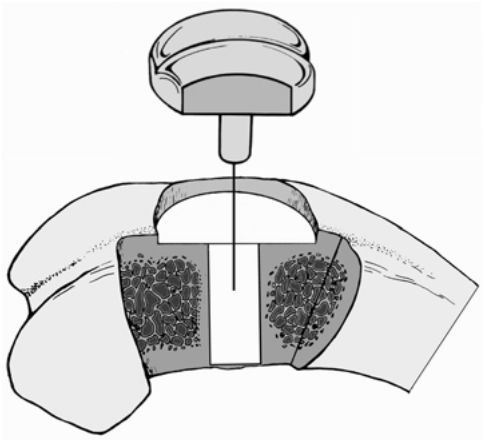

Figure 1 Drawing of knee prosthesis and the insertion in femur.

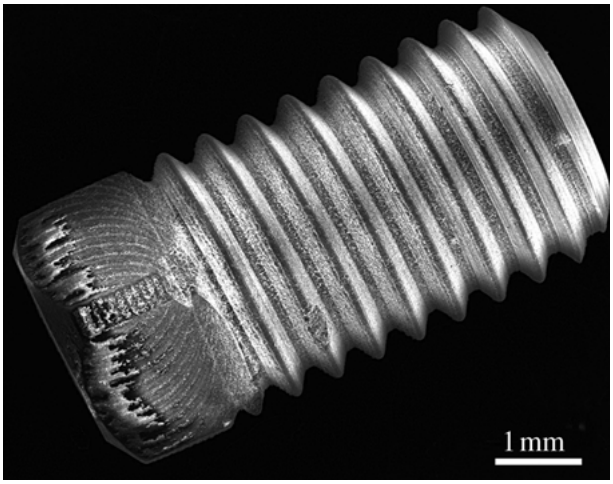

Figure 2 SEM of screw shaped implant made of Cemex® cement.

implant/bone interface and hence the fixation and/or make the interface more resistant to osteoclastic resorption. In this study we aimed to evaluate whether sodium fluoride added to bone cement improves the fixation and bone formation around implants in a rabbit model.

Methods

Bone cement

Commercially available bone cement (Cemex®, Tecres S.p.A., Italy) with a powder to liquid ratio of 3 : 1 was used. Cemex® is a room temperature mixed (cold-curing) cement with 13 wt % of barium sulfate added as a radiopacifier. In the fluoride cement a proportion of the barium sulfate was replaced by 6% sodium fluoride by weight.

Femoral implant

A hemiprosthesis designed for the patello-femoral joint in rabbits was used [10]. This implant resurfaces the femoral side of the articulation. It was machined from commercially pure (c.p.) titanium grade 1 (Fig. 1). The prostheses were degreased in trichlorethylene and rinsed in absolute ethanol in an ultrasonic bath and finally sterilized in an autoclave.

Tibial implant

Rods of cured bone cement with and without sodium fluoride were prepared from vacuum mixed cement (Optivac®, Scandi Med Implant AB, Sjöbo, Sweden). Screw shaped implants of an outer diameter of 3.7 mm and a total length of 8 mm were manufactured by manual machining (Fig. 2). The threads extended over a length of 6 mm. The top (height 2 mm) of the implant was square shaped. Prior to installation the cement implants were washed in 70% ethanol and sterilized using Glow discharge (Sterrad 100S® Sterilizer, Johnson & Johnson AB, Sollentuna, Sweden).

The microsurface structure of the bone cement implants was characterised with an optical profilometer (TopScan 3D, Heidelberg Instruments GmbH, Heidelberg) based on confocal laser scanning microscopy. Three screws, chosen at random, with and without sodium fluoride treatment were selected for topographical characterization. Each screw was measured on nine locations, three tops, three valleys, and three flanks. According to definition [11] waviness and errors of form must be subtracted from the original measurement before surface roughness parameters can be calculated. A Gaussian filter was used for this purpose on an area set to $50 \times 50\,\mu m$. Three different parameters were used to numerically characterize the roughness. Sa (arithmetic mean value) is the average height deviation from a mean plane, measured in μm, Scx (average wavelength) is the average wavelength, measured in μm, and Sdr (developed surface area) describes how much the surface area has increased from a totally flat reference area, measured in percent.

The implants were also examined in a scanning electron microscope (SEM) after washing in 70% ethanol and sterilization with Glow discharge (Fig. 2). The analysis of the the screw implants surface composition was performed by a JEOL JSM-5800® scanning electron microscope operated at 20 kV and equipped with a Link ISIS energy dispersive X-ray (EDX) system.

Animals, anesthesia and surgical technique

Nine mature (average 10 months old) lop-eared rabbits of both sexes were included in this study. The Local Animal Ethic Committee at the University of Göteborg approved the experiment.

During surgery the animals were anaesthetized with intramuscular injections of fentanyl and fluanison (Hypnorm Vet®, Janssen-Cilag, Ltd., Saunderton, England) at a dose of 0.5 ml per kg body weight and intraperitoneal injections of diazepam (Valium®, Roche, France) at a dose of 2.5 mg per animal. Prior to surgery the shaved skin of the hindlegs were carefully washed with a mixture of iodine and 70% ethanol. Local anesthesia with 1.0 ml of 5% lidocain (Xylocaine®, Astra-Zeneca, Sweden) was administered, at the medial part of the patello-femoral joint and in the region of the tibial tuberosity, where the incisions were planned. The skin and facial layers were opened and closed separately; commencing with a medial parapatellar incision and the patella was dislocated during the preparation of femur.

First, a hole was drilled at the center of the planned replacement of the patellofemoral articulation. Second, the cartilage was removed by a reamer to create a 12 mm diameter hole in the cartilage, exposing the subchondral cancellous bone and aiming to fit the articular surface of the implant flush to the surface of the cartilage. During all surgical drilling, drill speeds below 2000 rpm were used in conjunction with saline cooling. The bone cement was mixed using the Optivac® system (Scandi Med Implant AB, Sjöbo, Sweden) under vacuum conditions. Using the cement gun, the bone cement was injected into the femoral cavities. The implants were inserted and held in place with digital pressure until the cement had cured. Each animal received bone cement with sodium fluoride in one knee and cement without sodium fluoride in the other knee.

Following insertion of the femoral prosthesis the proximal-medial tibia was surgically prepared. The cortex was penetrated by a small burr followed by increasing diameter drills. The distance between the holes was reproduced by a template. The screw shaped implants of cured cement were inserted after tapping the drill-holes. Each screw were inserted to the same depth, i.e. two threads were visible. Two identical screws were inserted into each tibia: one for biomechanical testing and one for histomorphometrical analyses. Test and control sides were operated in the same manner by the same surgeon. Immediately after surgery the animals were allowed unrestricted weight bearing and received analgesics; 0.3 ml buprenorphin subcutaneously (Temgesic® 0.3 mg/ml, Schering-Plough, Stockholm, Sweden) postoperatively and twice a day the following three days. The animals were kept in separate cages during the follow-up time. Six weeks after surgery the animals were killed by intravenous injections of pentobarbital and ethanol (Pentobarbital® 100 mg/ml, Apoteksbolaget, Uppsala, Sweden).

Histomorphometrical analysis and mechanical testing

The proximal screw shaped implants with the surrounding tibia bone tissue were used for histological assessment, while the distal implants were used for assessment of the loosening torque; measured with a removal torque device [12]. The knee joint including the femoral and tibial implants were removed in one piece and immersed in 4% neutral buffered formaldehyde (pH 7.0). The implants with surrounding tissue were further processed and finally embedded in light-curing resin (Technovit 7200 VLC, Kulzer, Germany). The cured blocks with implants and bone were divided parallel to the long axis of the implants using a water-cooled band saw. Undecalcified ground sections were prepared with the Exakt® sawing and grinding equipment [13]. One central section was taken from both femoral and tibial specimens. Ground sections from femur of a thickness of 100 μm were first prepared and microradiographed. The same section was then ground to a final thickness of 10 μm prior to staining. Sections of tibia were ground to the final thickness of 10 μm. The sections were stained in 1% toluidine blue in 1% borax solution (mixed in a 4 : 1 proportion with 1% pyronin-G solution) prior to qualitative and quantitative histological assessment in the light microscope. Computer-based analysis was carried out on the femoral and tibial implants: the microradiographed plates of the femoral implants (100 μm sections) were quantified using an Image Access system® (MicroMacro Gothenburg/Stockholm, Sweden). The area of bone in a standard sized grid (83.3 mm^2) was calculated (Fig. 5). Means of three measurements/implants were calculated.

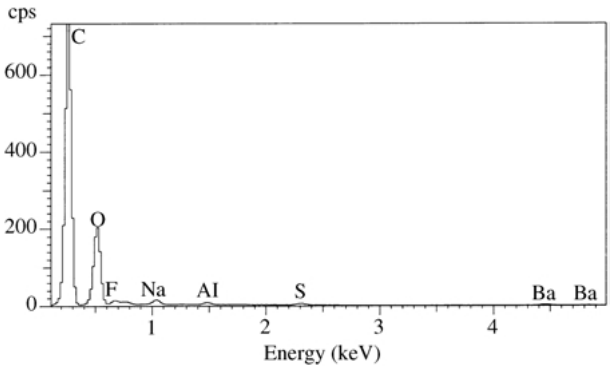

Figure 3 Analysis with a Link ISIS energy dispersive X-ray system of a screw implant with sodium fluoride.

On the tibial side the stained sections (about 10 μm) were histomorphometrically analyzed in a Leitz Aristoplan light microscope which is equipped with a Leitz Microvid unit, connected to a personal computer with a mouse. This permits the observer to perform quantifications ''directly in the eye-piece of the microscope'', using a 10 × objective and a zoom of 2.5 × [14].

Histomorphometrical investigations on the ground sections of the tibial implants involved quantification of the entire bone to implant contact, the bone area in all threads around each implant and the ''mirror area'' of the thread, i.e. the area immediately outside the inner thread.

The removal torque (RTQ) tested samples from the tibial implants were processed in the same manner. From the RTQ values a mean interfacial shear strength was calculated from the effective mean shear force and equivalent surface area based on the cylindrical area formed by the thread peaks. The calculation was performed using the formula: $T/\pi\, d\, l\, r_1$(%BMC), where T is the removal torque in Nmm, d is the mean diameter of the implant (3.45 mm), l is the length based on the entire length of bone surface in relation to the implant and r_1 is the lever arm (radius = 1.725 mm). Percent BMC is calculated bone to implant contact measurement obtained from the neighboring proximal implant in the same tibia [15].

Statistics

Wilcoxon signed rank tests were used for paired comparisons between test and control implants. The Mann-Whitney U test was used to compare shear strength. Students t-test was used to compare data describing the surface of the bone cement screws since this data was normally distributed.

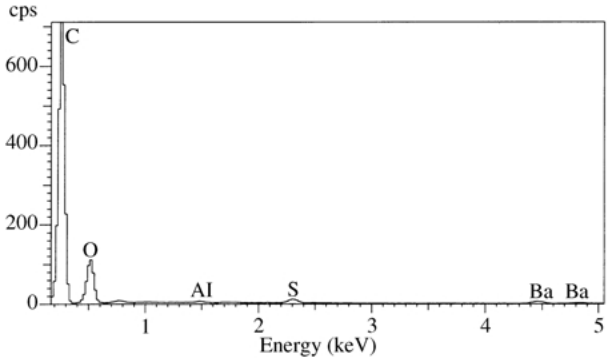

Figure 4 Analysis with a Link ISIS energy dispersive X-ray system of a screw implant without sodium fluoride.

Results

Quantitative investigation

The screws made of sodium fluoride cement were smoother than the control screws regardless of parameter used; Sa, Scx or Sdr (Table I).

The analysis of the screws with a Link ISIS energy dispersive X-ray system verified sodium fluoride at the test implant surface but not in the control (Figs. 3 and 4). The relative amount of bone tissue surrounding the femoral implants was not affected by the choice of cement (Table I).

The removal torque and shear strength recorded at extraction of the screws were not influenced by the choice of cement. Neither did the bone to implant contact, the bone area in the threads or the bone area in the mirror images outside the threads differ between the two groups.

Qualitative histomorphometry

Femoral implants (Fig. 5). Test and control specimens revealed similar observations. Typical fields demonstrated rather thin trabeculae in close relation to cement. More resorption than bone formation was observed close to the cement (Fig. 6). Less mineralized bone areas resembling osteoid rims could be observed on the bone facing both the cement and the marrow cavity. No osteoblasts were observed on these rims. The remodeling rate was low since the bone remodeling cavities were not frequent observed.

Under higher magnification a cellular layer was observed between cement and bone, consisting of macrophages and multi nucleated giant cells. The latter ones revealed internalized cement particles (Fig. 7).

Tibial implants. In general there was a cellular rich loose connective tissue capsule covering almost the entire implant (Fig. 8). Mostly macrophages and multinucleated giant cells (Fig. 9) as well as lymphocytes were observed in the capsule and in the interface. In some sections bone formation was observed in the vicinity of the periosteum and more seldom in the endosteal parts of the bone. More resorption than formation was noted in the cortical layer and there was low cellular activity of the bone close to the implant. There were fewer signs of remodeling in the test implants than in the controls. Less mineralized areas appearing as osteoid rims were observed in the interface in both test and control groups (Fig. 10). Elongated dark stained multinucleated giant cells were observed separating less mineralized areas from the cement surface. A greater foreign body reaction than an inflammatory reaction was observed.

Discussion

In Sweden fixation with cement is the most frequent method used in total hip and knee surgery [16, 17]. Compared with patients with arthrosis several studies have shown increased migration or increased risk of implant loosening in patients with rheumatoid arthritis and poor bone quality due to other reasons [18–22]. Therefore, there is a need to improve the bone cement properties to enhance the fixation of implants especially when the bone quality is poor. The potential advantage of using bone cement with small amount of monomer (3 : 1 ratio) is that the release of heat is lower than in conventional bone cements with lower powder to liquid ratio. In a randomized comparison between Cemex® and Palacos®, Nivbrant *et al*. [23] studied postoperative bone turnover and implant migration up to 5 years after total hip arthroplasty, but found no difference between the two groups. They noted similar curing temperatures for Cemex® used at room temperature and prechilled

TABLE I Histological analysis of bone tissue around the femoral and tibial implants, surface structure and fixation of the screws. Median, range and mean, SD (surface structure)

	Test (NaF)	Control	*p*-value
Surface structure			
Average height deviation (Sa) (μm)	0.8 ± 0.2	1.2 ± 0.5	0.002
Average wavelength (Scx) (μm)	10.8 ± 1.2	12.9 ± 2.7	0.0007
Mean surface enlargement (Sdr) (%)	23.8 ± 6.9	33.2 ± 15.1	0.005
Femoral prosthesis			
Bone formation			
Bone area in the grid (%)	17 (9–25)	13 (7–20)	0.11
Tibial screws			
Bone formation			
Bone to implant contact (%)	9 (5–36)	15 (0–33)	0.95
Area of bone in threads (%)	79 (66–86)	75 (57–87)	0.17
Area of bone in mirror images (%)	63 (43–87)	52 (28–70)	0.26
Fixation			
Removal torque (Ncm)	14 (12–20)	11 (8–25)	0.14
Shear strength (N/mm^2)	11 (3–30)	3 (0–28)	0.37

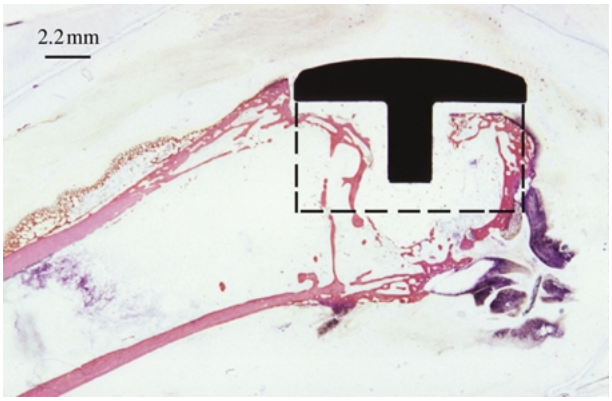

Figure 5 Undecalcified ground section (about 10 µm) of a knee prosthesis in rabbit femur after 6 weeks of insertion. Modified Van Gieson staining. Drawing of the grid around the implant used for the image analysis (dotted line). Bar 2.2 mm.

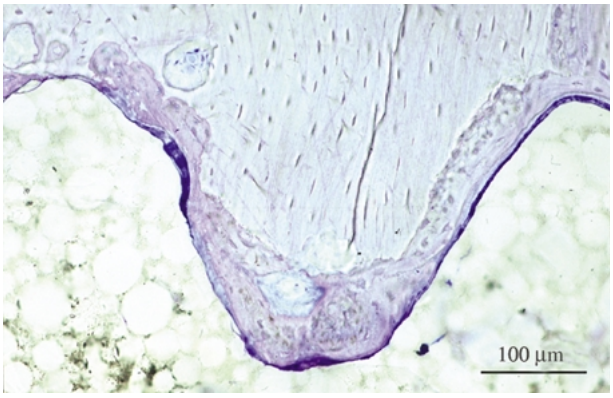

Figure 8 Undecalcified ground section (about 10 µm) demonstrating a cellular rich loose connective tissue capsule in the valley of a screw shaped implant made of Cemex® cement in the tibia of a rabbit. Toluidin blue staining. Bar 100 µm.

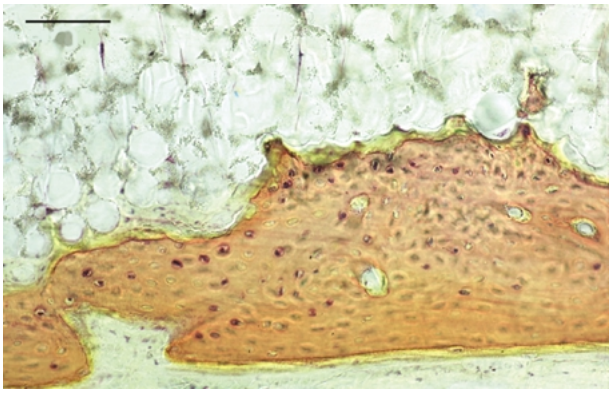

Figure 6 Undecalcified ground section (about 10 µm) of a rabbit knee with an implant fixated with Cemex® cement demonstrating resorption areas close to the cement. Modified Van Gieson staining. Bar 100 µm.

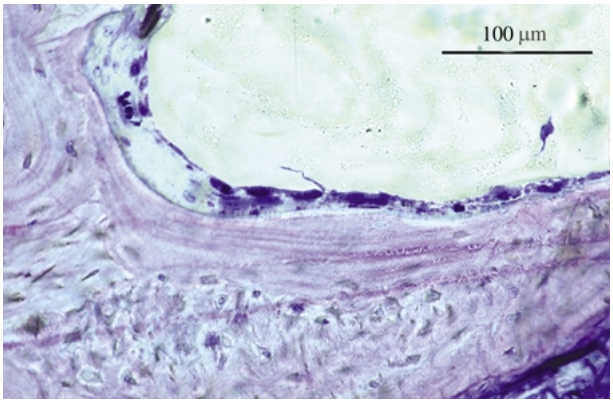

Figure 9 Macrophages and multinucleated giant cells observed in the capsule and in the interface in an undecalcified ground section (about 10 µm) of a screw shaped implant made of Cemex® cement in the tibia of a rabbit. Toluidin blue staining. Bar 100 µm.

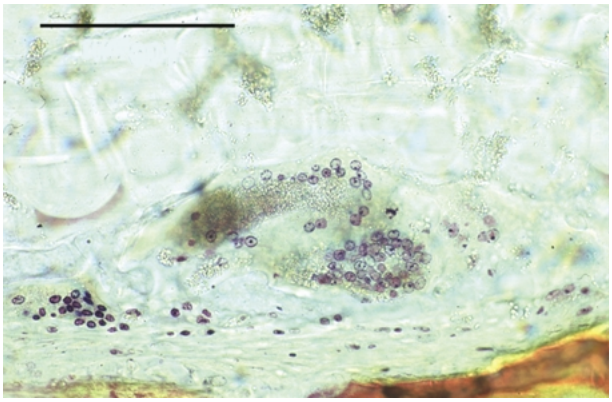

Figure 7 Cement particles internalized in a multinucleated giant cell in an undecalcified ground section (about 10 µm) from a rabbit knee. Modified Van Gieson staining. Bar 100 µm.

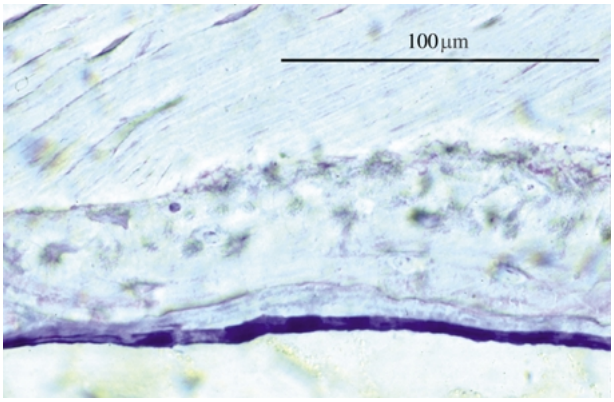

Figure 10 Less mineralized areas appearing as osteoid rims observed in the interface in an undecalcified ground section (about 10 µm) of a screw shaped implant made of Cemex® cement in the tibia of a rabbit. Toluidin blue staining. Bar 100 µm.

Palacos®, which at least partly might explain these observations. Thus, the properties of bone cement have to be related not only to its chemical and mechanical properties, but also to the way it is used in clinical practice. This factor also has to be considered regarding the use of acrylic cement containing fluoride. There are reasons to believe that the response to sodium fluoride differs between uninjured and traumatized bone and between cortical and cancellous bone. McCormack *et al*. [24] investigated bone healing capacity after local administration of sodium fluoride into defects in rabbit femur. They found that the defect healed better in the animals not exposed to sodium fluoride than in animals exposed to sodium fluoride. However, the authors discuss the possibility of local toxic levels of sodium fluoride as a reason since the local concentration could not be measured. According to Magnan *et al*. [1] the release

rate from Cemex® with 6% sodium fluoride is within the therapeutic range. Any systemic effects of sodium fluoride are most likely exceedingly small compared to the local effect since the released sodium fluoride concentration decreases rapidly [1]. Sodium fluoride has also been reported to increase spinal bone mass in a dose dependent manner [25, 26]. According to a review article by Kleerekoper [4], sodium fluoride increases bone mass by deposing newly formed bone on existing bone surfaces thus affecting cancellous bone more than cortical bone because of the small surface-to-volume ratio of cortical bone compared to cancellous bone. In the clinical situation mainly cancellous bone is exposed to the acrylic cement. This implies that any advantageous effect of the sodium fluoride cement used in our study should be noticed as improved femoral implant fixation because most of the implant surfaces contacted cancellous bone. In our rabbit model the addition of sodium fluoride to the cement did not, however, influence the outcome. The screws in the tibia did not affect cancellous bone as much as cortical bone. Cortical bone in the tibia was traumatized due to the surgery and the response to locally released sodium fluoride may be different compared to normal un-traumatized cortical bone. However, this effect is of minor relevance since the use of bone cement demands surgical trauma.

The period between insertion and killing of experimental animals was chosen on the basis of knowledge of osseointegration of titanium implants into bone [14, 27] and biological effects of bone cement [28].

The surfaces of the implants with sodium fluoride addition were smoother than the controls. This difference could have had a more significant influence on the bone apposition and implant fixation than sodium fluoride itself [12, 29]. However, our biomechanical results demonstrated similar implant stability for the two bone cements indicating a positive effect of sodium fluoride. It could be that the smoother surface on the sodium fluoride implants was partly compensated for by less remodeling of the bone as observed in the qualitative histologic studies. The locally released sodium fluoride most likely resulted in formation of fluoroapatite crystals close to the implant, with a higher resistance to osteoclastic resorption [4]. This might also have decreased the formation of new bone around the tibial implants in the present study. In our model the effect of fluoride on cancellous bone could mainly be studied on the femoral side. The area of bone close to the cement did not differ between test and control groups even if the tendency was in favor of the fluoride containing cement. It has been demonstrated in our laboratories that the methods of measuring bone to implant contact and RTQ have a high sensibility as an instrument of performing bio compatibility tests [12, 15, 29, 30].

Conclusions

Formation of fluorapatite might result in an interface which is more resistant to osteoclastic resorption in the long term. The detailed reaction of human bone to fluoride containing bone cement is however not known. So far, we have not been able to demonstrate any obviously advantageous effects on healthy rabbits of this type of bone cement.

Acknowledgments

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