Effect of submicron polyethylene particles on an osseointegrated implant

An experimental study with a rabbit patello-femoral prosthesis

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ABSTRACT – In a rabbit model of a weight bearing, articulating prosthetic joint we repeatedly injected submicron particles of Ultra-High-Molecular-Weight-Polyethylene (UHMWPE) produced in a hip simulator. The contralateral knee with the same prosthesis was injected with carrier (NaCl) without UHMWPE. Histomorphometrical studies on undecalcified cut and ground sections at 26 and 42 weeks involved quantifications of the entire bone to metal contact and the bone area around each implant. We found no statistically significant differences between test and control groups, and the UHMWPE debris did not induce any significant osteolysis, indicating that an osseointegrated implant with a sealed interface may not be affected by UHMWPE debris or progress to aseptic loosening.

The endpoint of a failed joint replacement is revision. Most revisions are due to aseptic loosening, which is usually caused by linear or focal osteolysis.

Osteolysis involves increased resorption of bone. The problems associated with osteolysis have been investigated in several studies (Anthony et al. 1990, Schmalzried et al. 1992, Harris 1994). There are many reasons for the imbalance of bone turnover leading to osteolysis or prosthetic loosening. Motion between bone and implant causes migration, loosening and osteolysis (Aspenberg et al. 1992, Kärrholm et al. 1994, Aspenberg and Herbertsson 1996). High pressure inside the joint capsule may induce osteolysis (Aspenberg and Van der Vis 1998a,b, Van der Vis et al. 1998). Particles from bone cement, metal and polyethylene (PE) induce an inflammatory process that starts with activation of macrophages (Haynes et al. 1997, Nivbrant et al. 1999) and may lead to osteolysis. An implant which is exposed to motion at the interface will not become stable (Aspenberg et al. 1992, Söballe et al. 1992, Goodman 1994) as the interface is transformed into a soft, fibrous tissue rather than to osseous tissue connected to the implant. Such an interface cannot withstand the various pressures to which it is exposed and seal against wear particles and synovial fluid. Several studies have shown that wear particles may trigger an inflammatory process and subsequently increased bone resorption will take place around the implant. Howie et al. (1988) demonstrated that PE particles injected in a rat knee joint with a plug of bone cement induced osteolysis, but they and others later reported problems in reproducing their results (Howie et al. 1993, Van Der Vis et al. 1997). Kim et al. (1998) showed that continuous infusion of high density polyethylene (HDPE) particles in rat knees with a K-wire implant caused osteolysis. However, Aspenberg and Van der Vis (1998a) suggested that high pressure and early migration are major causes of osteolysis and that the role of wear particles is mainly secondary. In the present study, we used a weight-bearing model of an osseointegrated hemiprosthesis in the rabbit patello-femoral joint and repeatedly injected ultra-high-molecular-

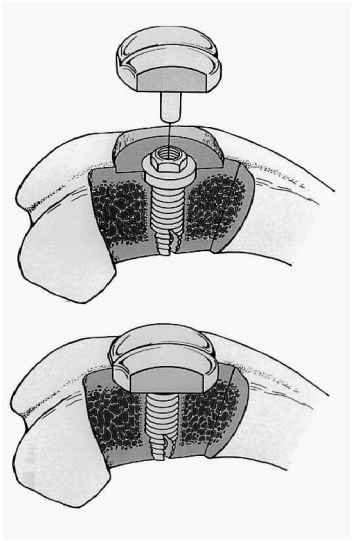

Figure 1. Drawing of knee prosthesis

weight-polyethylene (UHMWPE) particles of a comparable size and shape to clinically produced wear particles (Campbell 1995). The study aimed to determine whether a stable osseointegrated joint implant, when exposed to wear particles, will stay stable and not develop osteolysis.

Material and methods

Implants

The fixation element of the prosthesis was produced from commercially pure (c.p.) titanium (grade 1) in the form of a screw-shaped implant (outer diameter 3.75 mm and a total length 7 mm, NobelBiocare, Göteborg, Sweden). The articulating element of the implant was hand-machined from the same material, the bearing surface being ground and polished (Figure 1). The implants and prosthesis were degreased in trichlorethylene, rinsed in absolute ethanol in an ultrasonic bath, and finally sterilized in an autoclave before insertion.

Animals, anesthesia and surgical technique

12 mature (average 10 months old) lop-eared rabbits of both sexes were included in the study. The experiment was approved by the Animal Ethics Committee of the University of Göteborg. For surgery, the rabbits were anesthetized with intramuscular injections of fentanyl and fluanison in a dose of 0.5 mL per kg body weight and intraperitoneal injections of diazepam in a dose of 2.5 mg per animal. Before surgery, the shaved skin of the hind legs was washed with a mixture of iodine and 70% ethanol. Local anesthesia with 1.0 mL of 5% lidocaine was injected in the medial part of the patello-femoral joint along the planned incision. An incision in each knee joint was performed via a medial approach and the patella was dislocated during the preparation of the femur. All surgical drilling was done at slow speed (not exceeding 2000 rpm) during constant saline cooling. Both knees were prepared in identical fashion and the implant was inserted in the right and left sides by the same surgeon.

The design of the implant was a hemiprosthesis replacing the articulating surface in the femur, but the patellar side was not replaced. The implant consisted of two parts; an articulating surface element and a threaded fixation element (Röstlund et al. 1989). First, a hole was drilled and threaded to receive the threaded fixation element. Secondly, the cartilage was trimmed and the subchondral bone exposed using a 12 mm diameter reamer to create a hole in the cartilage, to place the surface of the articulating element flush with the cartilage surface. The articulating element was press-fit anchored into a hole in the threaded fixation element (Figure 1). The rabbits were kept in separate cages and immediately after surgery were allowed unrestricted weight-bearing. The initial healing time of the implants was 9 weeks. They were then anesthetized every other week and a UHMWPE particle solution was injected in the left knee, but saline alone was injected in the right knee.

Particle isolation

We used bovine serum lubricant from a hip simulator test as a source of submicron particles, as described by McKellop et al. (1995). Briefly, cups made of GUR 415 UHMWPE that had been irradiated at 2.5 Mrad in air were worn against 28 mm CoCr alloy balls in a Shore Western hip simulator, using 90% bovine serum as the lubricant. The serum for one 250,000 interval, corresponding to about 0.78 mg UHMWPE, was collected and lyophilized overnight, then digested in sodium hydroxide. The particles were isolated, using density gradient separation, and examined with a scan-

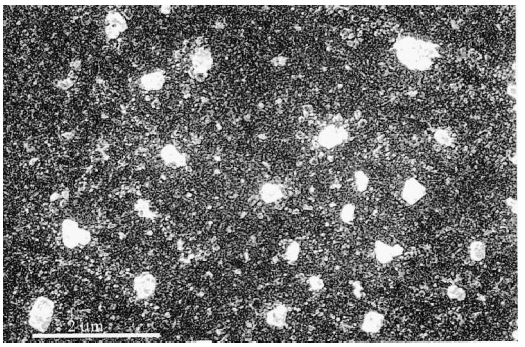

Figure 2. Scanning electron micrograph of UHMWPE particles.

ning electron microscope with image analysis to determine the size and morphology. The size of the particles used was as follows: round particles were about 80% of the total, average diameter 0.192 µm, median diameter 0.17 µm, range 0.14–0.98 µm; fibrillar particles made up most of the remainder; average length 1.59 µm, median 0.98 µm, range 0.42–10.8 µm (Figure 2).

Laboratory preparation of the UHMWPE solution involved agitating 60 µL of the particle and isopropranolol solution in a presterilized glass test tube and evaporating at 40 °C in a clean air cabinet. The dried particles were stored in sterile tubes, pending injection.

The particles were screened for bacteria and fungi. The test for endotoxin was done by Scandinavian QC Laboratories, Göteborg, Sweden. We used the Chromogenic peptide kinetic LAL assay to determine the amount of bacterial endotoxin.

Particle injections

A volume of 0.4 ml of particle suspension, corresponding to 240 µg UHMWPE particles, was injected every other week into each left knee joint during the test period. Previous studies (Goodman 1994) estimated the particle dosage from a radiographic calculation of wear in hips in vivo (Livermore et al. 1990). However, it is probably more realistic to define dosage by the mass of polyethylene rather than by the number of particles, since the particle sample from a hip simulator consists of a realistic particle size distribution which can be scaled to in vivo wear rates expressed in mass. At the time of injection, saline was added to the pellet and mixed well in a standardized manner. The injection was delivered by a 0.6 × 25 mm needle through the patellar tendon using sterile technique (one for each knee). In a previous pilot test, methylene blue solution was injected into rabbit knees to verify that the transpatellar approach was a reproducible method for intraarticular injections. The reproducibility of moving particles from the tube to the syringe through the needle to another tube examination was assessed in a certified Swedish laboratory (SP Swedish National Testing and Research Institute, Borås, Sweden); this method was found to be reproducible. However, about 20% by weight of the UHMWPE particles was lost in the syringe and needle. Consequently, we injected about 200 µg of UHMWPE particles every other week into each left knee joint during the test period.

Radiographs were taken postoperatively and every 8th week and were examined for osteolysis by an independent assessor who was blinded as to the group and treatment. Osteolysis is defined as radiolucency around the implant. The radiolucency could be linear (i.e., along the implant-bone interface) or cystic (a rounded radiolucency within the metaphysis).

The follow-up times were 26 (n = 6) and 42 (n = 6) weeks, which meant that the 26-week group had a total of 8 injections (1600 µg) and the 42-week group 16 injections (3200 µg) in each test knee. The animals were killed by intravenous injections of pentobarbital and ethanol.

Histological preparation and analysis

After killing the animals, the implants were removed en bloc and immersed in 4% neutral buffered formaldehyde (pH 7.0). The samples were divided with a water-cooled band-saw and the screws with surrounding tissue were cut through the long axis, in an anterior-posterior direction, resulting in two halves. One part was decalcified in EDTA solution followed by detachment of the metal part. The tissue was then made into paraffin sections for routine histological staining in haematoxylin and eosin, and Oil Red O for the detection of UHMWPE particles (Schmalzried et al. 1993). Internal organs (liver, kidney, lung, spleen and inguinal lymph nodes) were also immersed in 4% NBF and processed for paraffin sections for routine and Oil Red O staining.

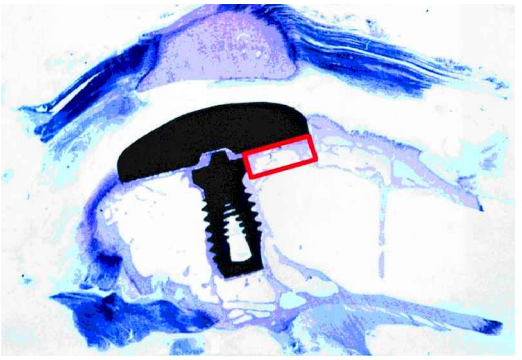

Figure 3. Ground sections of a test knee prosthesis in rabbit femur, inserted for 42 weeks. The diameter of the threaded implant is 3.7 mm. Toluidine blue staining. Drawing of the grid adjacent to the neck of the prosthesis. Three measurements on each side were made.

The second undecalcified half of the knee joint with the implant in situ was further processed and embedded in light-curing resin (Technovit 7200 VLC, Kulzer, Germany). Undecalcified ground sections were prepared with the Exakt cutting and grinding system (Donath 1988). One central section was taken from each sample. First, ground sections of a thickness of 100 µm were prepared and microradiographed. The same section was then ground to a final thickness of about 10 µm before staining. The sections were stained in 1% toluidine blue in 1% borax solution, mixed in a 4: 1 proportion with 1% pyronin-G solution before qualitative and quantitative observations with the light microscope.

Computer-based analysis was carried out in 2 ways: the microradiographed plates (100 µm sections) were quantified by an Image Access system. The mean area of bone in a standard-sized grid of 4.35 mm^2 was calculated from 6 measurements per implant adjacent to the neck of the prosthesis (Figure 3). The stained sections (about 10 µm) were analyzed histomorphometrically with a Leitz Aristoplan light microscope equipped with a Leitz Microvid unit connected to a PC. This permits the observer to quantify the data directly via the eyepiece of the microscope, using a 10X objective and a zoom of 2.5X (Johansson 1991). The histomorphometric studies involved quantification of the entire bone to metal contact and the bone area in all threads around each implant. Bony contacts and bone areas at various levels of the implant threads were measured and between test and control for each thread were compared in the 26- and 42-week groups. Mean values were also calculated for the three uppermost consecutive threads (the first thread is the uppermost, closest to the articulating surface, and the third is located further down in the marrow cavity).

Statistics

We used the Mann Whitney U-test to compare the test versus control sides.

Results

UHMWPE-particles

Screenings for bacteria and fungi were negative. The test for endotoxin showed very low values (< 0.25 IU/200 µg UHMWPE particles).

Qualitative studies of the paraffin sections

Oil Red O positive cells were seen at the outer edges of the synovium in the injected knee joints, but no granuloma formation or osteolysis around the implants. The synovium was slightly thickened in one joint, but its appearance in the other joints was similar in the test and control tissues. Oil Red O staining and polarized light microscopy revealed no polyethylene particles in the remote organs, apart from one case with a few Oil Red O positive cells in the kidney and spleen.

Gross radiographs

Qualitative assessment of the macroradiographed area of interest (knee joint region) showed no differences between the test and control samples and no signs of granulomas or osteolysis. All specimens had radiographically close contact between the bone and implants. No differences were seen between the 26- and 42-week groups.

Qualitative studies of cut and ground sections

In general, we saw no qualitative differences with the light microscope between the test and control samples at 26 and 42 weeks. There were more bone resorption lacunae than remodeling areas in the test sections than in the controls. Some of the test and control sections had a layer of connective tissue under the articulating component. However, in other sections, bone tissue was present in the

Table 1. Median (range) bone volume in percentages, measured in grids (placed below the neck of the knee implant), on microradiographed plates, using an Image analysis program. Bone to metal contacts and areas were quantified around the entire threaded implant on cut and ground sections with the light microscope

	Test side	Control side	P–value
Bone volume			
26 weeks	39 (37–46)	22 (16–47)	0.3
42 weeks	41 (36–47)	34 (27–61)	0.6
Bone-to-metal contact			
26 weeks	24 (14–44)	29 (22–49)	0.2
42 weeks	31 (22–39)	28 (14–49)	0.7
Bone area in threads			
26 weeks	29 (18–46)	37 (30–54)	0.2
42 weeks	42 (29–51)	38 (32–78)	0.7

area close to the implant surface. Macrophages were common in this soft tissue interface area in the uppermost unthreaded part of the implant. We found macrophages in the soft tissue areas, osteoclasts on bone resorption surfaces and multinucleated giant cells in the interface close to the implant surfaces in both types of samples. The upper part of the implant, including the 3 or 4 upper threads and the deep threads and point, were surrounded by bone tissue including bone trabeculae with marrow cavities. The central part of the implant contained solitary islands of newly formed bone inside the threads, but had sparse bony contacts to the implant. In this area, the bone marrow was close to the implant surface in most sections. In some sections, mainly in the midpart of the implant, we found cell clusters of macrophages, polymorphonuclear granulocytes and lymphocytes close to the interface.

Quantitative studies (Tables 1 and 2)

1 section in the test group was excluded due to artifacts from the preparation process. This resulted in a section without an implant, which made it difficult to judge the interfacial contact areas. 2 microradiographed sections, both in the 26-week test group, were unsuitable for analysis because of an error in preparation; they were therefore excluded from the quantification.

Quantitative image analysis of the bone area on the microradiographs showed a higher percentage of bone on the test side than the control sides, in both the 26-week and 42-week groups.

Light microscopic quantification showed a tendency for more bony contacts and bone areas in the threads on the control sections than the test side in both groups. However, no statistically significant differences were found between the test and control in any of the groups.

Discussion

We designed this study to mimic the clinical prosthetic joint and evaluate the influence of osseointegration on granuloma formation and osteolysis secondary to UHMWPE particles. For this purpose, we utilized UHMWPE particles from a hip simulator to ensure that the particles were of clinically appropriate size, shape and concentration. Wear particles from a joint prosthesis are heterogeneous in size and shape. Very probably the number of particles is as important as their size and shape (Campbell 1995). In our study, the number injected each time (200 μg) corresponds

Table 2. Median (range) bony contact and bone area in percentages, measured in the three uppermost consecutive threads of the implants

	Thread 1	P-value	Thread 2	P-value	Thread 3	P-value
Bone-to-metal contact						
26-week test	42 (24–49)	0.5	31 (0–40)	0.1	14 (0–38)	0.6
26-week control	32 (21–66)		42 (19–68)		23 (6–53)	
42-week test	28 (22–37)	0.3	24 (9–62)	0.4	18 (0–57)	0.9
42-week control	44 (13–60)		47 (8–55)		30 (4–37)	
Bone area						
26-week test	44 (37–67)	0.7	40 (6–60)	0.9	34 (4–58)	0.7
26-week control	48 (26–77)		42 (20–75)		36 (20–44)	
42-week test	60 (8–74)	0.8	40 (5–79)	0.7	28 (0–60)	0.7
42-week control	68 (14–82)		52 (5–80)		33 (2–54)	

to about one third of normal wear during 1 year in humans, according to Pietrabissa et al. (1998), which is a large amount of PE particles during an experiment. Green et al. (1998) showed the importance of the size of UHMWPE particles for bone resorption activity and found that submicron particles were significantly more active. The particles in our study were mainly of submicron size and are known to be the most biologically active (Matthews et al. 2000a). Such particles are not visible with light microscopy; ORO staining showed some positive findings, but even with this specific staining, it is difficult to see them with the light microscope. UHMWPE particles are involved in some of the proposed mechanisms of loosening and granuloma formation, but there are alternative explanatory models. The osteolysis problem is the result of a combination of mechanical and chemical factors. Various cytokines are involved in the bone resorption process: prostaglandin E2 (PGE2), interleukin-1 alpha and beta (IL-1α, IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) are all thought to participate in the complex inflammatory cascade leading to osteolysis (Green et al. 1998, Nivbrant et al. 1999, Matthews et al. 2000a)

Polyethylene particles stimulate macrophages to release mediators involved in bone resorption, such as IL-1, PGE2, IL-6 and TNFα. These cytokines modulate osteoblast and osteoclast activity, which in turn increase osteolysis (Murray and Rushton 1990, Howie et al. 1993, Kim et al. 1998).

However, there is no clear experimental evidence that UHMWPE particles alone induce prosthetic loosening. Recent studies have concerned endotoxin on wear particles as a reason for cytokine production and initiation of aseptic loosening (Prabhu et al. 1998, Hitchins and Merritt 1999, Ragab et al. 1999, Daniels et al. 2000). It is essential that particles are tested for endotoxin before using them for in vitro or in vivo experiments. Several other authors have suggested that, apart from PE particles, there are other reasons for osteolysis, such as micromotion (Goodman 1994, Mjöberg 1994, Dowd et al. 1995, Aspenberg and Herbertsson 1996), or high pressure inside the pseudocapsule (Aspenberg and Van der Vis 1998a,b, Van der Vis et al. 1998). Van Der Vis et al. (1997) observed that UHMWPE-particles or HDPE particles induced thickening of the synovial membrane, but not osteolysis in a rat model. Our hypothesis was that a well osseointegrated implant will seal the interface from the effective joint space (Goodman et al. 1998, Lalor et al. 1999) and prevent adverse effects caused by PE wear debris and high pressure in the joint. Our findings support this statement as osteolysis was not induced despite repeated injections of PE particles into a prosthetic joint. An explanation may be that the interface was sealed due to the osseointegration obtained after 9 weeks and the implant was stable when the injection of PE particles started, which is different from the clinical situation in which PE particles are generated from the prosthesis as soon as the patient starts to walk. Goodman et al. (1998) and Lalor et al. (1999) found that a sealed cement mantle inhibited the migration of wear particles and immune cells and reduced the production of cytokines at the interface. Frökjaer et al. (1999) suggested that a press-fit implant and overgrowth of fibrocartilaginous tissue closes the interface against PE particles. Since 9 weeks were allowed for incorporation in our study, stable implant integration was achieved and the fixation screws were most probably osseointegrated before the particle injections (Carlsson et al. 1988, Derezende and Johansson 1993). This differs from the situation when particles are injected into an unstable or fibrous encapsulated interface, as in the model used by Howie et al. (1988), where joint fluid has access to the interface. Brooks et al. (2000) using a rat model, previously described (Allen et al. 1996), found osteolysis around aluminum oxide pins inserted in the tibial plateau in rats exposed to HDPE particles. However, these implants were not osseointegrated, which allowed the HDPE particles access to the interface, and in some animals, the implants were also exposed to motion—leading to more interface exposure. Several authors have shown that some implants never reach a stable situation and more frequently become loose than initially stable implants (Ryd and Linder 1989, Ryd 1992, Snorrason et al. 1993, Kärrholm et al. 1994, Nilsson et al. 1995). A stable implant probably has a sealed interface, like the osseointegrated implants in the present study. This and other studies (Howie et al. 1988, Brooks et al. 2000) show clearly that clinical problems are difficult to

model in the laboratory. Dowd et al. (1995) used a dog model to demonstrate that particles are one of the major problems associated with osteolysis; this was confirmed by Shanbhag et al. (1997) in a similar model. Aspenberg and Van der Vis (1998a,b) proposed that the micromotion and high pressure in artificial joints cause osteolysis and that the increased osteoclast activity is secondary. Robertsson et al. (1997) found an elevated intracapsular pressure in loose hip prostheses. Osteoarthrotic cysts may be caused by high-pressure joint fluid impinging on bone and the osteolysis in the artificial joint may be similar to this (Schmalzried et al. 1997). Synovial hypertrophy may be due to variations in joint volume that can create very high pressures without any large amount of fluid in the joint (Eckerwall et al. 1994). This may be why loose prostheses have high pressures when moving. The synovial hypertrophy may be due to an increase in inflammatory effects caused by UHMWPE or a combination of cement, UHMWPE and metal particles. Osteolysis may be an effect of wear debris being pumped into the effective joint space. Another explanation may be that the sensitivity to UHMWPE differs between species as well as between individuals. This was demonstrated in a recent study which evaluated the response of primary human peripheral blood mononuclear phagocytes (Matthews et al. 2000b). The authors found that the cytokine response to UHMWPE particles from various donors varied 2–15-fold.

Our study has shown that the interface of an osseointegrated stable implant in the rabbit is not affected by exposure to polyethylene particles. This was also shown in dogs with intraarticular osseointegrated hydroxyapatite-coated implants by Rahbek et al. (2000). Polyethylene particles alone did not induce osteolysis in this study. The explanation could be that the interface was sealed, but this was not demonstrated in the present study. Very probably other factors are needed, such as micromotion combined with high pressure, endotoxin at the surface of particles or individual differences, to initiate the loosening process. However, the achievement of interface sealing and implant stability as soon as possible are probably essential for successful joint implant outcome.

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