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Osseointegration in porous coated knee arthroplasty

The influence of component coating type in sheep

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Introduction

Although the idea of cementless total knee arthroplasty is not new, it is not yet clear what its appropriate place is in the management of the arthritic knee. Many surgeons rely exclusively on cement fixation of their total knee components, although realizing that the use of cement has a number of serious disadvantages.[34,46,47,55] Its brittleness, limited fatigue life, poor characteristics for tensile and shear stress transmission, osteolytic and cytotoxic potential, are well known and generally accepted. Due to improvements in prosthetic materials, component designs, surgical technique and postoperative rehabilitation, long term results of total knee arthroplasty are improving, leaving cement as one of the remaining factors prohibiting durable success. For these reasons cementless knee arthroplasty is becoming increasingly attractive and popular.

Fixation in cementless knee arthroplasty relies on bone ingrowth fixation or osseointegration. The term osseointegration, used for the first time in 1977, was for the first time defined in a paper by Brånemark a few years later.[10,11,12] Osseointegration was regarded as "direct, on a light microscopical level, contact between living bone and an implant".[10] Although little or nothing is known about the actual osseointegration in cementless knee arthroplasty, the basic general principles governing bone ingrowth have been well known for some time.

It is generally accepted that porous coated implants will become attached to the skeleton by bone ingrowth if three major prerequisites are fulfilled:[15,98] 1) there needs to be an intimate contact between the implant and the living host bone, 2) the relative bone-implant displacement has to be sufficiently small, and 3) the implant should have an appropriate porous surface (3).

The host bone should in addition to these prerequisites be in good condition, and not damaged by heat generation during preparation of the saw cuts. Whether this is routinely achieved is questionable: modern saw blades are known to be able to raise the temperature with approximately 8 °C, while it has been shown that bone necrosis starts to occur at a temperature of 44– 47 °C.[30]

Intimate contact

Gaps at the interface between the implant and the underlying bone are known to decrease ingrowth. An exact surgical fit has been found to be most important for proper bone incorporation. Several authors have reported the critical gap size to be 0.5 mm.[18,26,107]

While osseointegration can occur in gaps smaller than 0.5 mm, larger gaps show a lack of bone ingrowth and become filled in with fibrous connective tissue. The lack of bone ingrowth in large interface gaps is not surprising. Basically the process of bone ingrowth is comparable to the normal healing response to bone trauma or bone surgery.[35] When a hole is drilled in bone, the first part of the healing response involves formation of a hematoma and development of mesenchymal tissue, which differentiates in the healing process leading to the formation of woven bone. Lamellar bone is then formed on cores of woven bone, and the marrow is reestablished. This sequence of events is similar to the development of a medullar callus under conditions of rigid internal fixation.

Exactly the same process occurs in the presence of orthopedic implants, when the interface gap between the implant and the underlying bone is smaller than 0.5 mm, and when the other two prerequisites for osseointegration are fulfilled.[26,107] When the interface gap is larger, however, the effective concentration of bone-forming cells is decreased. In this case, therefore, a fibrous connective tissue is formed (which may be highly organized and provide some degree of fixation). There has been recent speculation that hydroxyapatite coated implants may enhance bone ingrowth and fixation in the presence of initial interface gaps larger than 0.5 mm, although it remains unclear to which extents this can be extrapolated to knee arthroplasty components.[26,110,113]

Relative displacement

Another factor that has been demonstrated to inhibit bone ingrowth is excessive interface motion. Bone ingrowth has been noted in mechanically stable implants, and fibrous ingrowth in less stable implants.[14,90] Achieving initial mechanical stability and thus minimizing micromotion is therefore a prime consideration in cementless total knee arthroplasty. Relative displacement less than 150 µm of motion have been found to be consistent with bone ingrowth.[14,90,98] In animal cylinder plug models with controlled initial bone-implant interface motions greater than 150 µm, the interface was formed by a fibrous tissue. Although most authors agree on 150 µm being the critical amount of motion for osseointegration, it is clear that the parameters of time and motion interact in a complex manner. Toksvig-Larsen et al. reported fibrous ingrowth with interface motion of 500 µm 20 times per 30 seconds, while reproducible bone ingrowth was seen with 250 µm micromotion 20 times per 30 seconds. Even 500 µm of motion once a day was compatible with bone ingrowth.[116]

Appropriate implant surface

Much of the initial research on porous ingrowth physiology utilized ceramics and polymers, but these have been deemed unsuitable (by most) for prosthetic fixation purposes due to their inadequate material properties. Commercially available devices nowadays consist almost exclusively of porous metallic coatings. These surfaces meet the ingrowth requirements for porosity, while providing requisite mechanical properties, such as strength and fatigue resistance. Both titanium and cobalt-chrome alloys have been used. While claims have been made that there is a small carcinogenic risk in cobalt-chrome alloy implantation, titanium has been shown to be a poor bearing surface unless properly treated.

Bobyn has shown that the optimum effective pore size for bone ingrowth should be minimum 50 µm.[8] Taking into account a (realistic) micromotion of 100–150 µm for knee arthroplasty components, this means that the pore size in reality should be minimally 150–200 µm for knee arthroplasty components to end up with a minimum effective pore size of 50 µm (Figure 1).[8,17]

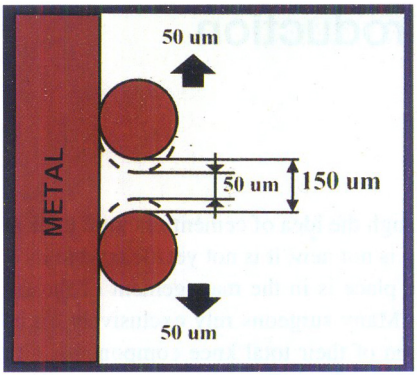

Figure 1. An effective pore size of minimum 50 µm requires a real pore size of minimum 150 µm, when 100 µm micromotion occurs.

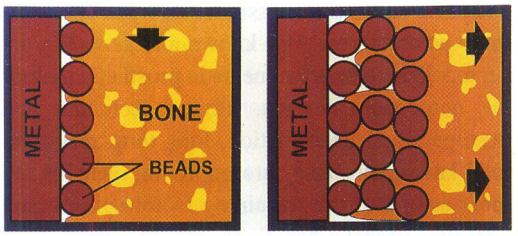

Figure 2. A multilayer of beads gives resistance to both shear and tensile loads.

Whether this pore size is achieved by a titanium or cobalt-chrome substrate, does not seem to make a major difference, although some authors suggest a slightly higher ingrowth rate in titanium coatings.[25,98]

In theory an adequate pore size can be obtained by several surface textures. Today most commonly a beaded surface texture is used. It has been shown that when such a beaded surface is used, a multilayer of beads performs better than a monolayer of beads, certainly when the implant is loaded in tension.[9,17] The reason for this is that a monolayer of beads gives only adequate resistance to shear loads, while a multilayer of beads gives both resistance to shear and tensile loads, since the bone spiculae that enter the first bead layer take the shear load, while the tensile load is taken by the bone spiculae in the deeper bead layers (Figure 2). No data are available, whether a fiber texture performs better or worse than a multilayer bead texture.

Although these general principles of osseointegration are well accepted, a lot of questions on osseointegration remain unanswered, certainly when applied to the field of knee arthroplasty.

While some data are available on the magnitude of the interface gap that is routinely achieved in total knee arthroplasty surgery, and while a number of data are available on the type of micromotion that occurs between knee arthroplasty components and the underlying bone, the porous multilayer bead textured coating has never been really challenged in clinical or laboratory studies.

Another remarkable finding is that—notwithstanding our knowledge on general osseointegration biology—retrieval studies of uncemented knee arthroplasty tibial components show invariably very poor or nonexisting bone ingrowth. Cook et al. reviewed 26 femoral, 34 tibial, and 25 patellar ingrowth components retrieved for malposition, instability, unexplained pain, late infection, post mortem, post amputation, or after trauma.[22] All components appeared macroscopically to be more or less well fixed to host bone, but on light microscopy half of the femoral components showed no ingrowth, and one third showed only 2% or less ingrowth. Tibial components failed even worse, with two thirds showing no ingrowth, and only 1 showed more than 5% ingrowth. Kienapfel et al. and Major et al. reported similar data in 18 and 40 retrieved tibial components, with an average ingrowth of 10% and 0%, respectively.[64,79]

Although these poor results might be partly caused by relatively high micromotion between the implant and the bone (due to the possibly insufficient rigid initial fixation of the component), the question remains whether better results could be achieved with another type of coating. Assessment of the clinical performance of such a newly developed coating is, however, a dilemma. It supposes in vivo implantation into a human knee without really knowing its (beneficial or catastrophic) effects, unless a reasonable animal model is available.

Moreover, when such a model is not available, one will have to rely on secondary observations to assess the amount of bone ingrowth, such as clinical performance, radiographic analysis and eventually radiostereometric analysis. Clinical performance is influenced by many other factors than the amount of bone ingrowth. Radiographic analysis and radiostereometry can not visualize bone ingrowth, but could demonstrate component migration or loosening secondary to a lack of bone ingrowth, but even this remains to be proven.

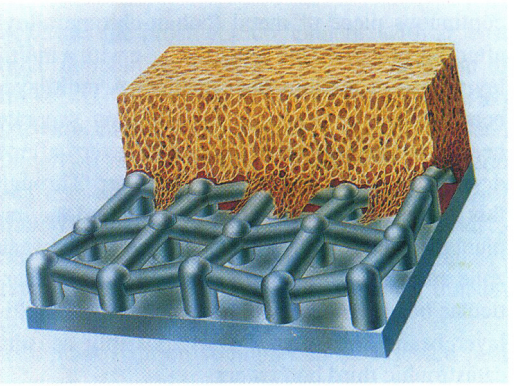

Figure 3. The newly developed "mesh coating".

It is the aim of this study to provide a clearer insight into the above raised issues. Therefore, in this work, a newly developed coating was tested using the animal model that was developed in the first part of this dissertation.[4] The newly designed coating is a mesh type structure with identical square shaped pores, measuring 1.5x1.5 mm (Figure 3). A "woven" texture was created by alternatively using higher and lower corner struts for the fibers.

The theoretical advantages of this type of coating compared to a standard porous coating, such as a multilayer of beads or random fiber coating, are numerous. With this new "mesh" coating a well-controlled pore size is available, which is not the case in a (random) multilayer bead or fiber coating. The pore size is also much greater (1.5 mm) than usually achieved in beaded coatings (250–450 μm). The ingrowth area (2.25 mm^2) is therefore much larger than in a multilayer bead or random fiber texture, as is the overall porosity (79% versus 30–40%). The newly developed coating also has a much lower surface area (2.9) compared to the existing coatings that have surface areas between 9 and 12.

Besides these biological advantages of providing a large window for ingrowth of mature vascularized bone, providing optimal interlock between bone and implant, the newly developed texture also has certain metallurgical benefits.

The mesh coating is produced by a casting process (cast mesh) and consequently can not become detached since the implant consists of a single

continuous piece of metal (cobalt-chrome alloy) after this process. This is not the case with a multilayer bead or random fiber coating. A multilayer bead coating is produced by sintering separate beads onto the implant in successive layers, after a drying procedure between every layer. Through this process the beads join each other and the implant by a "neck". Such a neck is a relatively weak zone and it is not uncommon to see loose intraarticular beads in patients with uncemented multilayer beads knee components, possibly causing catastrophic third body wear.

Random fiber coatings are usually achieved by a combination of heat and pressure, a process called diffusion bonding. Since this process also implicates a relatively weak link between the fibers and the implant, this type of coating is usually recessed into the implant, to protect the coating from delamination. When the fiber coating is recessed, however, a smooth ring is always present, surrounding the random fiber coating. This smooth ring prevents ideal seating of the component into the host bone, so that a certain amount of bone upgrowth needs to occur to achieve ingrowth into the porous coating. A cast mesh does not have these disadvantages, and moreover, since there are no separate thermal treatment processes required, the fatigue strength of the rest of the implant is not affected.

Another major advantage of the mesh coating is that it is particularly well suited to be used with an additional hydroxyapatite coating. Animal studies have shown that implanted cylindrical plugs can become osseointegrated even with an interface gap as large as 1 mm, as long as the implanted plug is treated with a hydroxyapatite plasma sprayed coating.[110,111] Non-hydroxyapatite coated plugs became only osseointegrated when the interface gap was smaller than 0.5 mm. Whether this can be extrapolated from nonloaded stable cylindrical plugs to loaded knee arthroplasty components that inevitable show some degree of micromotion, is not clear.

Indeed, very little information is available in the literature whether a hydroxyapatite coating can enhance bone ingrowth in the presence of interface motion. Plasma sprayed hydroxyapatite coatings with present technology have a minimal thickness of 50–60 μm and are applied through vacuum plasma spraying at 5000 °C, starting from a 100% crystalline starting powder with an exact calcium-phosphate ratio of 1/1.54, resulting in a minimal final crystallinity of 75%, a final hydroxyapatite content of more than 90%, a final calcium-phosphate ratio of 10/6, and a final porosity of less than 10%. This means that an original coating with a pore width of 200 μm will be converted into a 100 μm (200 – 50 μm x 2) pore sized coating by covering it with an additional 50 μm of hydroxyapatite. When the original pore width is much higher (for example 1.5 mm as in our mesh coating), the reduction in pore width by plasma sprayed hydroxyapatite is much less dramatic (1.5 mm – 2 x 50 μm = 1.4 mm).

It remains to be proven that an additional hydroxyapatite coating is beneficial in the osseointegration of uncemented knee arthroplasty components. It also needs to be shown that an additional hydroxyapatite coating has no potentially negative longer-term effects. Indeed, the hydroxyapatite coating might become dissolved (after all it is a biologic material). The coating might break or even become delaminated due to the high interface forces that are generated at the level of knee arthroplasty components. It might become abraded or resolved by osteoclasts and it could even induce a local phagocytic reaction.

Using an animal model not only allows the study of the performance of this newly developed coating, but also allows the in vivo study of the process of osseointegration in knee arthroplasty components over time, its influence on clinical performance, implant stability, and implant fixation strength. Furthermore any correlation between all these parameters can be examined. No literature data are available on this matter, and it was the purpose of this study to get a clearer insight and provide answers to the above raised issues.

The set-up of this study, therefore, was to investigate the newly developed mesh both with and without an additional hydroxyapatite coating, using a standard type coating as a control.

Clinical performance with the new coating can relatively easily be assessed by a detailed and previously determined clinical rating scale.[4] Implant stability over time is by necessity evaluated by radiographic means. Routine radiography, however,

does not have an accuracy better than 2–3 mm for translations, and 3° to 4° for rotations.[44,51,73,102]

The reasons for such a low accuracy are the lack of bony landmarks and the difficulty of obtaining reproducible projections. Comprehensive methods to encompass these difficulties are available from literature. Of these, the radiostereometric analysis (RSA) as described by Selvik nowadays is considered to be the most adequate.[19,44,51,73,87,101,108]

Radiostereometric analysis combines the principles of bone markers for exact identification of landmarks, stereophotogrammetry for three-dimensional data, and high precision digitizing combined with rigid body kinematics to describe the motion between two objects of interest, such as an orthopedic implant and its underlying bone. Radiographs are obtained by discharging two X-ray tubes simultaneously. The RSA examination involves exposure of both the patient and a calibration cage, which defines the coordinates system.

By providing each object of interest (i.e. the bone and the prosthetic component) with at least three noncolinear markers, the exact position of these two objects relative to each other can be assessed accurately. Consequently, motion between these two objects can be evaluated when several analyses are performed over a certain period of time. The accuracy of RSA has been determined to be much higher than the accuracy of plain radiography; 0.3° for rotations and 0.2 mm for translations at the 95% confidence limit.[102,103]

Implant fixation strength can be assessed post mortem by subjecting the implant to relevant loading types, and measuring the displacement relative to the underlying bone in the six degrees of freedom.

Finally, and most importantly, actual osseointegration can be measured with histomorphometric and contact radiographic techniques, using highly specific and well controlled dehydration, embedding, cutting and grinding procedures. Additionally, these histologic sections can be evaluated concerning the fate of the hydroxyapatite coating, when used.

Materials and methods

40 adult Suffolk sheep underwent implantation of a knee prosthesis, which was specifically developed for animal research in the field of knee arthroplasty.[4]

The prosthesis consisted of a cobalt-chrome alloy anatomic bicondylar femoral component with a V-shaped stem, and a nonconstrained ultrahigh molecular weight polyethylene tibial bearing component, which fitted onto a cobalt-chrome alloy anatomic tibial base plate with a V-shaped stem (Figure 4).

Three types of prosthesis were inserted, creating 3 groups in which each group received a standard uncemented tibial component with each time a different porous coating, together with a standard cemented femoral component. *Group 1* received a newly developed cast mesh coated cementless tibial component. *Group 2* received an identical cast mesh coated tibial component as sheep from group 1, but with an additionally hydroxyapatite plasma sprayed coating. *Group 3* (control group) received a multilayer beads coating.

The animals that were included in the study were all healthy, fully skeletally mature, but non pregnant adult ewes of a registered Suffolk breading stock. Preoperatively all animals were assessed by an attending veterinarian on their general condition. Animals with an abnormal walking pattern, or with a weight smaller than 75 or larger than 95 kg were excluded from the study. All sheep had been wormed and vaccinated against clostridium preoperatively.

A standard preoperative protocol was followed in all cases.[4] Each animal was classified into one of the three groups by drawing a card that showed both the group and subgroup number. Each of these groups was divided into four subgroups, depending of the period after which the animal was planned to be killed: 3 months, 6 months, 1 year or 2 years after implantation.

There were 16 sheep in group 1, 16 in group 2 and 8 in group 3 (controls).

All operations were performed by the same surgeon and two scrubbed-in operating assistants. All operations were performed under general anesthesia, with the sheep in lateral decubitus on the left side. Intubation and anesthesia itself was performed by the same veterinarian in all cases. A standard anesthetic protocol, was followed in all cases.[4]

The operation was performed through a standard lateral parapatellar approach, and the surgical technique was followed as described in part 1 in all cases. The bone cuts were made with standard knee arthroplasty saw blades and a pneumatic Hall-Zimmer® saw, which is known to cause an 8 °C increase of the temperature when sawing time goes beyond 1 minute.[30] For this reason water cooling was used whenever the sawing procedure was estimated to be longer than 45 seconds.

A standard uncemented, stemmed tibial component was inserted press-fit into the prepared proximal tibia. According to the drawn group number, the distal surface of this tibial base plate was: *group 1*—a cast mesh, 1.5 mm^2 constant pore sized (ingrowth area of 2.25 mm^2), open and woven coating, with a surface area of 2.89 and a porosity of 79%; *group 2*—the same cast mesh with an additional 50 µm plasma sprayed hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ coating; and *group 3*—a three layer 210-µm-diameter beads coating with a pore size varying from a few up to 110 µm, and a porosity of 35%.

The hydroxyapatite coating in group 2 was applied by vacuum plasma spraying at 5000 °C, from a 100% crystalline starting powder with an exact calcium/phosphate ratio of 1/1.54, resulting in an X-ray diffraction tested minimal final crystallinity of 75%, a final hydroxyapatite content of more than 90%, a final calcium/phosphate ratio of 10/6, a final porosity of less than 10%, and a final thickness between 50 and 60 µm.

In all three groups a standard femoral component was inserted after preparation of the distal femur, and a standard polyethylene insert was used with a thickness of 4 mm, 7 mm or 9 mm, accord-

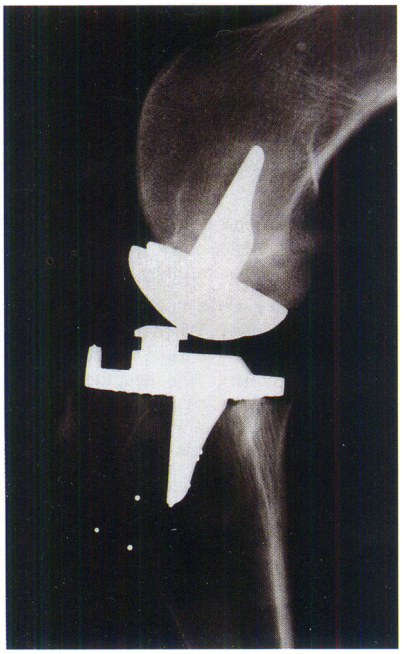

Figure 4. Sheep stifle joint with the prosthesis implanted

ing to the operative principles that were described above.

After every operation, but with the sheep still under anesthesia, an operative score was calculated according to the criteria outlined in Table 1 with a maximum score of 10 points. When manual dislocation of the joint was possible or in case only an overall range of motion of maximum 45° could be achieved after closure of all muscle and skin layers, the procedure was considered as failed, and the animal was withdrawn from the study. In this case it was replaced by a new animal, which underwent the same protocol as the original animal, as determined by the drawn card.

All animals underwent a postoperative program according to a standardized protocol.[4] All animals were kept alone in a pen during the first postoperative six weeks, after which they were released to free growing when comfortable standing and walking through walkways was achieved.

Clinical and functional performance

A clinical and functional score was and calculated in all cases at 3 months postoperatively, and repeated eventually at 6 months, 1 year and 2 years postoperatively. Both functional and clinical parameters were included in this score (Table 2).

Table 1. Operative score

	Points
Range of motion	
Normal	2
Deficit less than 10 degrees	1
Deficit more than 10 degrees	0
Anteroposterior joint laxity	
Normal	2
Increased laxity less than 5 mm	1
Increased laxity more than 5 mm	0
Mediolateral laxity: normal	2
Increased laxity less than 10°	1
Increased laxity more than 10°	0
Patellar tracking	
Normal without medial patellar release	2
Normal after medial patellar release	1
Patellar dislocation	0
Alignment of the prosthetic components:	
Neutral ± 5°	2
Neutral ± 10°	1
Neutral ± more than 10°	0
Negative points:	
Operating time more than 75 min	–1
Bleeding more than 200 mL	–1
Maximum score	10

Animals that developed a suppurative infection of the joint, or whose joint became dislocated, or that died during follow-up, were withdrawn from the study and replaced by a new animal.

Poor clinical and functional performance, and evidence of implant loosening due to lack of osseointegration, were no reasons for exclusion from the study.

Radiostereometric analysis

All animals underwent RSA at 2 weeks, 3 months, 6 months, 1 year and 2 years postoperatively, unless they were planned to be killed at an earlier stage according to the protocol. Radiostereophotograms were obtained using the uniplanar convergent-ray mode, by simultaneous discharging of two X-ray tubes. Simultaneous exposure of both the operated limb and the calibration object was obtained by radiographing the operated limb placed within a specially designed rectangular calibration frame. Stable positioning of the sheep's limb without radiographic superpositioning by the abdomen, was achieved by suspension of the animal in a sling (Figure 5). The sling causes an up-

Table 2. Clinical and functional score

	Points
Active range of motion	
Full extension – full flexion	5
Full ROM minus 10° or less	3
Full ROM minus 20° or less	2
Full ROM minus more than 20°	1
Passive range of motion	
Full extension – full flexion	5
Full ROM minus 10° or less	3
Full ROM minus 20° or less	2
Full ROM minus more than 20°	1
Pain sensation on passive mobilisation of the joint	
No pain	4
Moderate pain	2
Severe pain	0
Joint swelling	
None	3
Moderate	1
Severe	0
Patella tracking	
Normal	2
Dislocated	0
Anteroposterior laxity	
Normal	3
Increased laxity less than 10 mm	1
Increased laxity more than 10 mm	0
Mediolateral laxity	
Normal	3
Increased laxity less than 5°	1
Increased laxity more than 5°	0
Maximal spontaneous activity level	
Running + jumping	10
Walking without limp	7
Walking with limp but apparently full weight bearing on operated leg	5
Walking with limp with partial weight bearing on the operated limb	2
Walking with limp and non weight bearing on the operated leg	0
Maximal stimulated activity level	
Running + jumping	5
Walking without limp	3
Walking with limp but apparently full weight bearing on operated leg	2
Walking with limp with partial weight bearing on the operated leg	1
Walking with limp but non weight bearing on the operated leg	0
MAXIMUM SCORE	40

Footnotes to Table 2:

All scores are counted together (maximum 40 points) and multiplied with factor 2.5 to obtain the total score (percentage).

Active range of motion is evaluated compared to the contralateral hind limb without manual interference by the examinator.

Passive range of motion is evaluated compared to the contralateral hind limb by bringing the joint into maximal flexion and extension by the investigator.

Pain is assessed on passive mobilisation of the joint into full flexion and extension. When this is allowed by the sheep without any external signs of discomfort, pain is determined to be absent. Whenever there is a degree of resistance towards mobilisation the pain score is determined to be moderate. When this resistance is severe, the pain score is determined to be severe.

Anteroposterior laxity is evaluated compared to the contralateral side by manual assessment of the maximal anteroposterior translation.

Mediolateral laxity is also evaluated compared to the contralateral side by manual assessment of the maximal medial and lateral laxity under varus and valgus stress.

Maximal *spontaneous* activity level is determined as the maximal activity level that is obtained by the sheep without external stimulation.

Maximal *induced* activity level is determined as the maximal activity level that is obtained while the sheep is aroused as much as possible by the investigator, usually through a combination of shouting and pushing.

The animal is considered to be fully weight bearing on its operated limb, when normal powered hoof touching occurs during walking, compared to the contralateral side. The sheep is considered to be partially weight bearing on the operated limb, when less powerful hoof touching occurs during walking compared to the contralateral limb, or when a tiptoeing gait pattern is present. The sheep is considered to be non-weight bearing, when there is no contact between the operated limp and the ground during walking.

ward migration of the abdomen, leaving the hind leg free to be radiographed. Using a single large sized film, the two exposures from each X-ray focus could be captured together.

A number of other installation techniques were tried out, but with non of them equally comparable high quality radiostereophotograms could be obtained, not even when the sheep was mounted in a special chair (shepherd shaving chair) or with the sheep in lateral decubitus.

The used X-ray sources were two Practix XB1021 tank units (Philips) with portable control desk XB7008 supplying 20 mA at voltages up to 100 kV and switching times from 0.04 sec up to 5 sec, and with a 1.8 mm large focal spot. Both sources were mounted on mobile standings, in such a way that they could be positioned independently from each other.

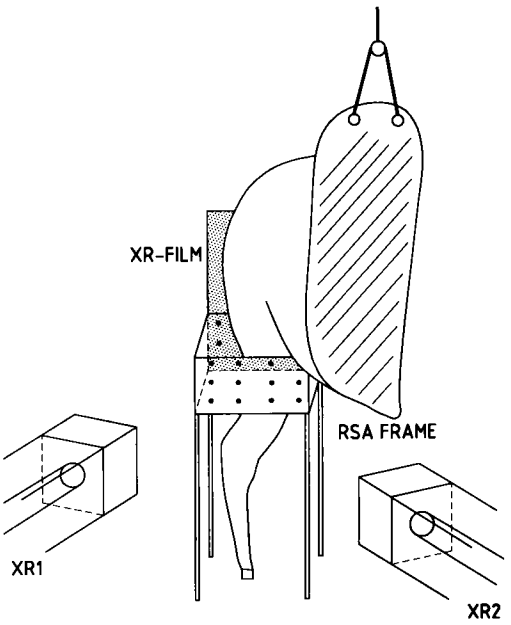

Figure 5. RSA set-up. The sheep is suspended in a sling with the right hind limb located within the calibration frame.

Curix RP1 films (Agfa Gevaert) were used, sized 30 x 40 cm. The advantage of this type of film is that it is more coarsely granulated than for example Structurix D7 films (Agfa Gevaert), needing far shorter exposures. Using Curix RP1 and a Siemens super high speed cassette, with a film focus distance of 1 m, the following settings were used, resulting in acceptable contrast and sharpness: 80 kV, 20 mA, 0.5 sec.

As calibration object a three dimensional rectangular frame was constructed of plexiglass, with 1 mm spheric tantalum markers with an exactly known distance relative to each other on two sides of this frame. The relative positions of the different tantalum markers on the frame were measured with a high precision 3D-coordinate measuring machine with an accuracy of 1 μm. The calibration frame was positioned between the two X-rays sources and the film, in such a way that one of the two marker containing sides was facing the film, and the other side facing the X-ray sources (Figure 5). After obtaining a radiostereogram by exposure of both the calibration frame and the operated joint by simultaneous discharging of both X-ray sources, the film was digitized. This was always started by digitizing the calibration markers of both the fiducial side (film side) and the control side (object side) of the calibration frame. The fiducial marks thereby served to define the laboratory coordinate system, whereas the markers on the control side were used to determine the position of each X-ray focus. Doing so, the coordinate system coupled to the film (two dimensional) is transferred to a three dimensional coordinate system defined by the calibration cage.

Next, the markers from the two objects of interest, i.e. the proximal tibia and the tibial prosthetic component, were digitized. 8 to 9 markers on the tibial components were always applied after its machining and prior to its sterilization by a spot welding procedure, onto the inferior aspect of the base plate and circumferentially along the margins of the stem. Tibial bone markers were inserted during the operation, immediately after the proximal tibial cut was made. Using a special template for maximal reproducibility, 4, but preferably 6 spherical tantalum beads, with a diameter of 1 mm, were inserted through a cannulated needle.

For accurate analysis at least 3 noncolinear marker beads needed to be visible in both the bone and on the tibial component with both projections. Since one or more of the beads could migrate during follow-up, it was therefore advantageous to insert more than 3 beads (preferably 6). Moreover, the use of more beads allows cancelling out random errors during digitization of the film through least square approximation, leading to a more accurate determination of positions and relative displacements. Two beads were always inserted in the posterior trabecular bone, approximately 1 cm distal to the resected surface. Four beads were inserted in the anterior trabecular bone, two 1 cm distal to the resected surface, and two 2 cm distal to the resected surface (Figures 6 and 7).

Analysis of the radiostereophotograms was performed as described by Selvik, following the principles of stereophotogrammetry, and rigid body kinematics.[108] The projected image of each marker on the film and the calculated focus define two points on a straight line, onto which the marker must be situated (Figure 8). Given two foci (by simultaneously discharging the two X-rays) two such lines can be drawn. These two lines will intersect at the three dimensional position of the specific marker (Figure 9).

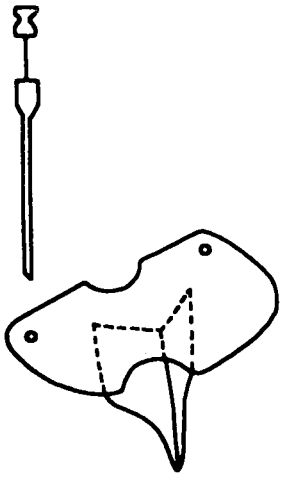

Figure 6. Template and canulated needle for insertion of the tantalum tibial markers.

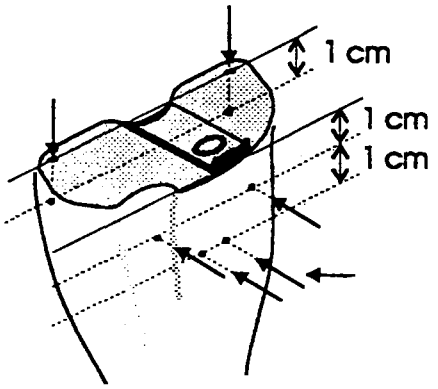

Figure 7. Positions of the tantalum tibial markers.

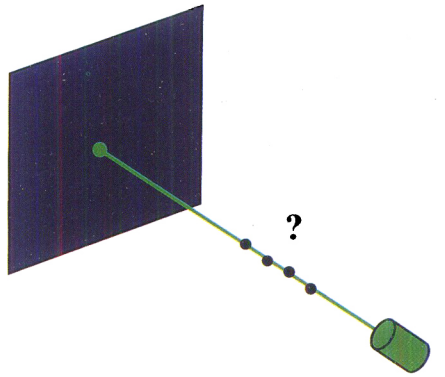

Figure 8. (See text).

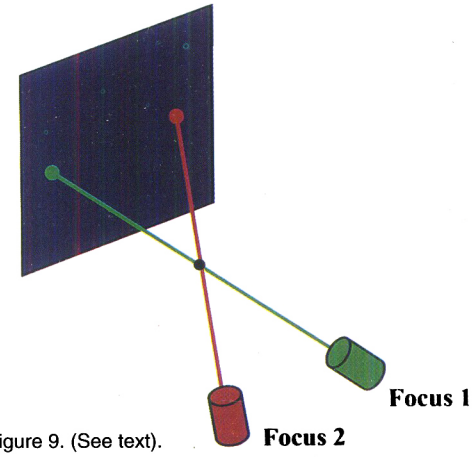

Figure 9. (See text).

The software that was used to calculate this was developed as originally described by Selvik, and is based on the law of central projection.[108] This law of central projection states that the projection of a point (for example a tantalum marker) on a plane (for example the X-ray film) can be described mathematically by two equations:

$$x = \frac{L_1X + L_2Y + L_3Z + L_4}{L_9X + L_{10}Y + L_{11}Z + 1} \quad (1)$$

$$y = \frac{L_5X + L_6Y + L_7Z + L_8}{L_9X + L_{10}Y + L_{11}Z + 1} \quad (2)$$

With:

x and y: coordinates of the projection of the point (marker) onto the film.

X, Y, Z: the coordinates of the marker in space.

L_1, ... L_{11}: eleven unknown variables depending on the geometric set up.

L_1, L_2, L_3: the coordinates of the X-ray focus.

L_4, L_5, L_6, L_7, L_8, L_9: the position and orientation of the film (three coordinates of one point, and three angles for the orientation around this point).

L_{10}, L_{11}: two unknown variables depending on the crimp and stretch of the film during its development.

In these two equations x and y are known (they can be measured on the film). X, Y, Z are the three dimensional coordinates that we want to know. L_1, ... L_{11} are unknown parameters which are calculated by use of the calibration frame, since we exact-

ly know X, Y and Z for each of the markers in our calibration frame. Therefore every calibrating marker gives us two equations ((1) and (2)). Thus since there are 11 unknown parameters (L_1–L_{11}), at least 6 calibration points are needed to calculate L_1 to L_{11}. When L_1 to L_{11} are calculated, we still don't know the position of our unknown marker by its radiographic projection, since two equations remain (1 and 2), with 3 unknown variables (X, Y, Z). From (1) and (2) we can only calculate X / Z en Y / Z. This is logical since it means that the marker is situated on a straight line, defined by the projected image of the marker onto the film and the X-ray focus. This is the reason why a second projection is needed for RSA, which gives us for the same point two additional equations, through which X, Y, Z are calculated (as the intersection point of 2 lines).

Once the coordinates of the prosthesis and bone markers have been calculated, eventual migration of the prosthesis over time relative to the bone can be calculated by comparing sequential radiostereophotograms. Determination of the relative movement of the prosthesis with respect to the bone must be done in different steps. First of all, the position of the bone in the calibration cage is not exactly the same during sequential RSA exposures. This displacement needs to be taken into account to determine the true relative displacement of the prosthesis.

The displacement of the bone over time is defined by the translation of the center of gravity of the bone markers $\tau(b)$ and rotation around the centre of gravity $\Gamma(b)$.

Defining the following vectors:

b_{1i} = position vector of bone marker i, during first postoperative exposure.

b_{2i} = position vector of bone marker i, during secondary exposure at 3 months, 6 months, 1 year or 2 years postoperatively.

p_{1i} = position vector of prosthesis marker i, during first postoperative exposure.

p_{2i} = position vector of prosthesis marker i, during secondary exposure at 3 months, 6 months, 1 year or 2 years postoperatively.

b_{1c},b_{2c},p_{1c},p_{2c}: the centres of gravity of the respective markers.

The following equations can be written:

$$\tau(b) = b_{2c} - b_{1c}$$

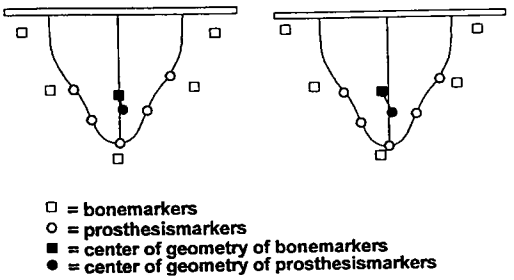

Figure 10. Segment motion.

$$\Gamma(b).(b_{1i} - b_{1c}) = b_{2i} - b_{2c}$$

The relative displacement of the prosthesis can be represented by a translation of the centre of gravity of the prosthesis markers $\tau^r(p)$ and a rotation of the prosthesis markers around the centre of gravity $\Gamma^r(p)$.

$\tau^r(p)$ and $\Gamma^r(p)$ can than be found by solving the following set of equations:

$$\tau^r(p) = p_{2c} - \Gamma(b).(p_{1c} - b_{1c}) - b_{2c}$$
$$\Gamma^r(p).[\Gamma(b).(p_{1i} - p_{1c})] = p_{2i} - p_{2c}$$

For convenience and comparison with literature, it is the translation of the center of gravity of the prosthesis markers relative to the center of gravity of the bone markers (so called "segment motion") that is considered as the actual migration ($\tau^r(p)$) (Figure 10).

Before the first RSA examination was performed, the accuracy of the RSA set up was examined with both a sliding caliper, with beads attached to both the moving and stable arm, and by consecutive radiostereophotograms of operated sheep, assuming that between the consecutive radiographs (time interval less than 1 minute), no motion had taken place between the implant and the bone. The mean difference between the RSA calculation of the markers on the calipers was 0.143 mm for the X-axis, 0.093 mm for the Y-axis, and 0.197 mm for the Z-axis. The mean difference for all three coordinates of the prosthetic markers was 0.2 mm.

Post mortem protocol

Animals were killed at the predetermined follow-up period with an injection of T61, after assessment of the final follow-up clinical and functional score. Subsequently the final follow-up RSA was taken, together with AP and lateral plain radio-

graphs. Overall alignment of the limb, anteroposterior and mediolateral joint stability, and range of motion were examined and noted in the postmortem report. Both hind limbs, the operated as well as the reference limb, were disarticulated and examined. Inguinal and popliteal lymph nodes were dissected and fixed in formaldehyde for histologic examination. Next the stifle joint was dissected free and synovial fluid was aspirated for microscopic examination.

During dissection, samples of the medial collateral ligament, the lateral capsule and the posterior capsule were taken and fixed in formaldehyde for histologic examination, after routine paraffin embedding and hematoxylin–eosin staining. The presence of any extraarticular heterotopic ossification during the dissection was noted. Next all remaining soft tissue was removed and the tibial polyethylene insert was unscrewed and removed from the baseplate. After decontamination during 1 hour at room temperature in a 10% solution of sodium hypochlorite 5.25%, it was inspected for creep and wear. Any pitting, delamination or cold flow was noted.

Subsequently the proximal tibia and distal femur was resected with a pneumatic saw at a level of 10 cm distant to the joint line, with only the distal femur with its femoral component, the proximal tibia with its tibial component, and the patellar mechanism being retained. Subsequently the tibial component was mechanically tested, after which it was prepared for histomorphometric and contact radiographic analysis.

Mechanical testing

Fixation strength of the tibial component was evaluated by a nondestructive mechanical test, to avoid damaging the bone-implant interface prior to histologic analysis.

Implant stability was measured by three-dimensional displacement measurements of the tibial implants, when subjected to 5 different loading situations, considering both the tibial component and underlying bone as two separate undeformable objects, being able to move relative to each other in the 6 degrees of freedom (3 translations and 3 rotations).

The movement of the tibial component relative to the bone therefore can unambiguously be determined by carrying out 6 independent displacement measurements. This was done by attaching a rigid aluminum frame with 3 orthogonal planes to the tibial component. An aluminum ring was then attached to the proximal tibia, as close as possible to the tibial component. This aluminum ring carries 6 high precision linearly variable differential transformers (LVDT's) with an accuracy better than 5 μm. 3 of these LVDT's measured the displacement of the aluminium frame in the proximal-distal direction, 2 LVDT's measure the displacement of the frame in the anteroposterior direction, and 1 LVDT measures the displacement of the frame in the mediolateral direction (Figure 11).

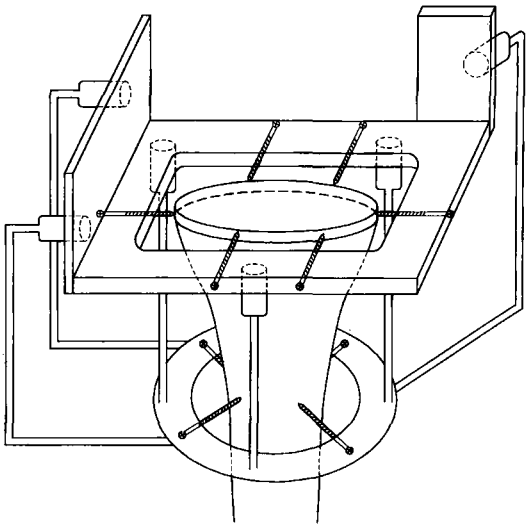

Figure 11. Mechanical displacement measurements set-up. 6 linear variance displacement transducers, connected to an aluminium ring fixed on the proximal tibia, measure the displacement of a triple orthogonal plane frame, connected rigidly to the tibial component.

The five loading situations that were applied on the tibial component are respectively (Figure 12):

straight axial compression (F_c = 550N),

axial compression combined with mediolateral bending (F_c = 500N, M_{ml} = 5Nm),

axial compression combined with anteroposterior bending (F_c = 500N, M_{ap} = 5Nm),

axial compression combined with mediolateral shear (F_c = 490N, F_m = 90N),

axial compression combined with anteroposterior shear (F_c = 490N, F_a = 90N).

For every load situation the displacement for each of the 6 LVDT's was noted. This means that

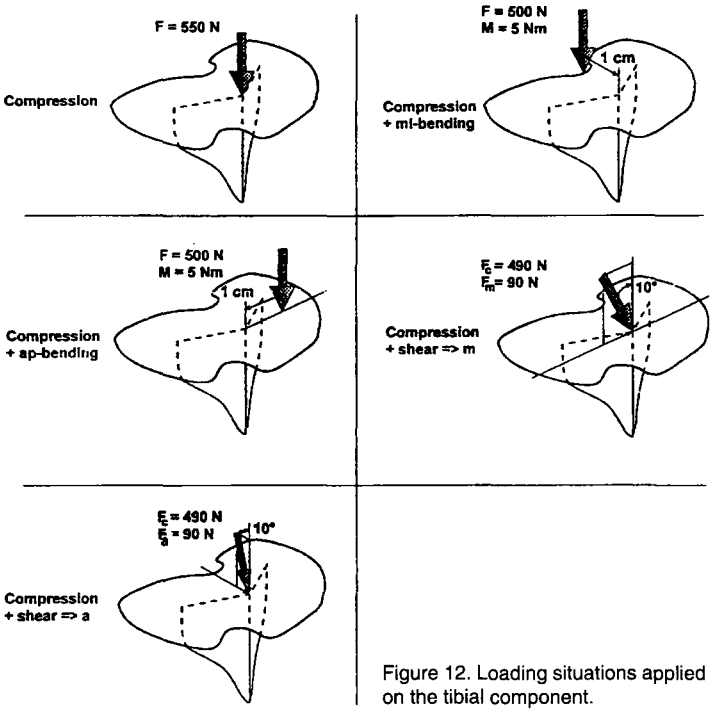

Figure 12. Loading situations applied on the tibial component.

for every implant thirty different LVDT measurements were taken. From these 30 measurements a displacement figure (Δ) was calculated according to the following formula:

$$\delta_i = (|t_i| + 1/2\ (\theta_x L + \theta_y L + \theta_z W))$$

$$\Delta = 1/5\ \Sigma\delta_i$$

with:

δ_i: the displacement figure for loading situation i.

t_i: the translation of the tibial component for loading situation i.

θ_x: rotation of the tibial baseplate around the x-axis (proximodistal axis).

θ_y: rotation of the tibial component around the y-axis (anteroposterior axis).

θ_z: rotation of the tibial component around the z-axis (mediolateral axis).

L,W: length and width of the tibial baseplate.

The fixation stiffness was defined as the inverse of the displacement figure (1/Δ).

Histological examination

Routine histological examination was performed on samples from the medial collateral ligament, lateral capsule, posterior capsule and the popliteal and inguinal lymph nodes, after fixation in buffered formaldehyde and embedding for routine paraffin sectioning. Sections were specifically inspected for inflammatory changes and cell necroses, and for particulate debris (polyethylene particles) by polarized microscopy.

Histomorphometrical analysis

Immediately after mechanical testing of the tibial component, the proximal tibia with its tibial component was fixed in a buffered formaldehyde solution (one part formaldehyde 33%, two parts alcohol 80%, 50 g $CaCO_3$/L).

The proximal tibia with the tibial component was then sectioned mediolaterally just anterior to the tip of the stem, and transversely through the midportion of the stem, 17 mm distal to the distal surface of the tibial base plate (Figure 13). This was performed using a high precision diamond Exakt® saw, through which 4-mm-thick sections were obtained. These sections were subsequently dehydrated and embedded according to the Exakt procedure.

After embedding, these sections were cut, ground and polished until a thickness of 40 μm was achieved, and subsequently they were stained with toluidine blue. The sections underwent histomorphometric analysis with the use of a computer image analysis system (Emagyn®).

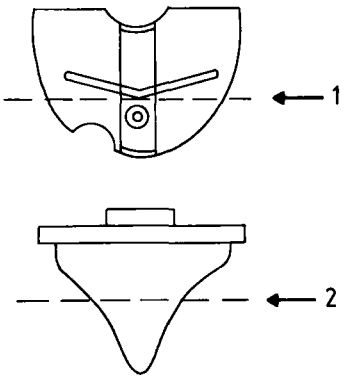

Figure 13. Section levels for the tibial component.

A quantitative assessment of the following parameters was performed:

bone ingrowth: the fraction of the void space within the porous coating occupied by mineralized bone,

bone ongrowth: the fraction of the outer surface of the porous coating being in direct contact with bone,

fibrous ingrowth: the fraction of the void space within the porous coating occupied by fibrous tissue,

fibrous ongrowth: the fraction of the outer surface of the porous coating being in direct contact with fibrous tissue,

foreign body giant cells,

thickness of the fibrous tissue layer,

surface area occupied by mineralization defects (osteoid seams or demineralization seams),

hydroxyapatite coating defects: maximum hydroxyapatite coating disintegration over 10 mm surface area.

The following parameters were non-quantitatively evaluated in the same sections:

presence of lymphocytes,

presence of increased vascularization,

presence of delamination or fracture of the hydroxyapatite coating,

orientation of the fibrous tissue layer,

presence of necrotic bone areas,

presence of marginal osteophytes.

Contact radiographic analysis

The same mediolateral sections were additionally evaluated using high resolution contact radiographs obtained with a Faxitron® source for the following parameters:

bone ingrowth: the fraction of the void space within the porous coating occupied by mineralized bone,

bone ongrowth: the fraction of the outer surface of the porous coating being in direct contact with bone.

The same computer image analysis system (Emagyn®) as for the histomorphometric analysis was used to assess these parameters quantitatively, after scanning of the obtained radiographs.

Statistics

Standard unpaired two-tailed t-testing was applied for group data analysis. Data for the subgroups at 3 months, 6 months, 1 year and 2 years were analyzed using nonparametric two-sample and two-sided unpaired Wilcoxon rank sum tests. Correlation analysis for group data was performed using Pearson's product moment, and for the subgroup data using Spearman's rank correlation. The significance limit for p was determined at 0.1 for all tests.

Results

Of the original group of 40 sheep, 6 were withdrawn from the study and, in all but 1 case, replaced by another animal receiving the same implant according to the study protocol. Thus, 45 sheep were operated on. The average preoperative weight of the sheep was 78 kg, and was not significantly different in any of the 3 groups ($p > 0.1$, student t). The reason for withdrawal was perioperative death in 2 cases, dislocation of the implants in 2 cases, and presence of a deep suppurative infection in another 2 cases.

The perioperative death of 2 sheep was caused by anesthesia-related problems. Both animals were replaced by another, receiving the same type of implant as scheduled for the original animal—1 cast mesh (group 1) and 1 hydroxyapatite coated cast mesh (group 2).

One of the 2 dislocations was immediately apparent after closure of all muscle and skin layers, and could be provoked manually with the animal still under anesthesia. Therefore this animal was immediately replaced by another that received the same type of arthroplasty as the original, as determined by the drawn card—multilayer beads (group 3). The second dislocation was noted during the 3-month follow-up examination. Although this animal too was scheduled to be replaced by another one, receiving the same component—hydroxyapatite coated cast mesh (group 2)—this was not possible since a new hydroxyapatite coated cast mesh tibial component could not be supplied by the manufacturing company within a reasonable time period to finish the study.

The 2 animals that sustained a suppurative infection were also replaced by 2 new animals, again receiving the same type of implant as planned for the original animals—1 multilayer beads (group 3) and 1 hydroxyapatite coated cast mesh (group 2).

Operative score

The average operative score was 8 (maximum 10). No significant differences were seen between any of the groups (Table 3).

Postoperative range of motion was normal in 36 cases, and a deficit less than 10° was noted in 3 cases. In no case a deficit more than 10° was seen. Anteroposterior joint laxity was normal in 9 cases. Increased anteroposterior joint laxity less than 5 mm was noted in 25 cases. In no case increased anteroposterior laxity more than 5 mm was seen. Mediolateral joint laxity was normal in 31 cases. Increased mediolateral laxity less than 10° was seen in 8 cases. In none of the cases increased laxity more than 10° was seen.

Patellar tracking was normal without medial parapatellar release in 21 cases. A medial parapatellar release was necessary to restore normal patellar tracking in 18 cases. Immediate postoperative patellar dislocation did not occur, although in 1 case an additional lateral plication procedure, with "pants over vest" suturing of the vastus lateralis and lateral retinaculum onto the lateral patellar border was necessary to prevent the patella from medial dislocation, after a medial parapatellar release had been performed.

A neutral component alignment ± 5° could be obtained in 35 cases. In 4 cases the components were positioned between 5° and 10° compared to the neutral alignment. In none of the cases was the alignment in excess of 10° compared to the neutral.

The average total operating time was 75 minutes. In all cases the operating time was less than 90 minutes. In all cases blood loss was small with

Table 3. Average operative score

Months	Group 1	Group 2	Group 3
3	7.75	7.25	7.5
6	7.75	8	7.5
12	8.5	8	8
24	8	7.75	8
Overall	8	7.75	7.75

Table 4. Evolution of the average clinical and functional score, percentages

Months	Group 1	Group 2	Group 3
3	81	59	70
6	77	87	75
12	74	86	77
24	65	81	72
Overall	74	78	74

Table 5. Radiostereometric migration (mm)

Months	Group 1	Group 2	Group 3
3	0.62	0.57	0.26
6	1.38	0.84	0.82
12	1.40	0.27	1.63
24	4.60	3.20	5.60
6 to 24	3.63	2.02	3.13
12 to 24	2.60	0.83	1.01
18 to 24	1.01	0.01	0.05

only 4 cases showing an estimated blood loss higher than 200 mL.

Clinical and functional score

Overall the average clinical and functional score was 75%. The average clinical and functional score was 74% in group 1, 78% in group 2, and 74% in group 3 ($p > 0.1$, two-tail unpaired t). The evolution of the average clinical and functional score is shown in Table 4. In none of the subgroups was this average clinical and functional score different at the 0.05 level (Wilcoxon rank sum).

The average range of motion was 45°, without any significant difference between the 3 groups (43° in group 1, 49° in group 2, 40° in group 3) ($p > 0.1$, two-tail unpaired t).

Pain on passive mobilization of the joint was absent in 74% of the observations. Moderate pain on passive mobilization was seen in 26%. No cases of important pain on passive mobilization were noted.

As spontaneous maximal acitivity level, 9 sheep were observed to be running and jumping. Another 9 were walking without limp. 12 were walking with a limp but apparently with full weight bearing on the operated leg. 7 were walking with a limp with only partial weight bearing on the operated leg. 2 were non-weight bearing on the operated leg. When the animals were additionally stimulated, the maximal activity level was running and jumping in 14 cases. Walking without a limp was seen in 12, and walking with a limp but apparently with full weight bearing on the operated leg in 3. Walking with a limp with partial weight bearing on the operated leg was seen in 7 of the cases. Non-weight bearing on the operated leg was noted in 3.

During follow-up no patellar dislocations were noted. Anteroposterior and mediolateral laxity did never exceed 10 mm or 10° respectively, compared to the contralateral side. No significant differences in any of these clinical and functional parameters could be detected between the three groups at a level of 0.05 (chi-square). Correlation analysis of operative score and clinical-functional score did not demonstrate any correlation between these two scores ($r < 0.1$, $p < 0.1$, Pearson's product moment).

Radiostereometric migration

The average RSA migration data are shown in Table 5. In one sheep from group 3 an exact measurement of the migration at 6 months was not possible due to migration of several bone markers. 2 sheep from group 1 showed a migration of more than 15 mm after 1 and 2 years, respectively, and were considered as manifestly loosened. Since a precise RSA measurement of their migration was not possible, these analyses were not included in the calculation of the average migration for the group. In another sheep from group 1 an exact measurement of the migration at 2 years was not possible due to migration of several bone markers.

The radiostereometric migration was lower for group 2 at 12 months and between 18 months and 24 months ($p < 0.1$, Wilcoxon rank sum).

Correlation analysis did not show any correlation between RSA migration and operative score or clinical-functional score ($r < 0.1$, $p < 0.1$, Pearson's product moment). Positive correlations were noted between RSA migration and mechanical displacement, weak at 3 months ($r = 0.41$, $r^2 = 0.17$, $p > 0.1$, Spearman's rank correlation) and 6 months ($r = 0.47$, $r^2 = 0.22$, $p > 0.1$), but strong and significant at 12 months ($r = 0.74$, $r^2 = 0.55$, p

Table 6. Average displacement at post mortem mechanical testing, μm

Months	Group 1	Group 2	Group 3
3	44	44	57
6	83	14	63
12	59	13	48
24	70	28	95
Overall	64	25	74

< 0.02), 24 months ($r = 0.81$, $r^2 = 0.66$, $p < 0.02$) and between 12 and 24 months ($r = 0.97$, $r^2 = 0.94$, $p < 0.01$).

Negative correlations were seen between RSA migration and bone ongrowth, being significant at 12 months ($r = -0.82$, $r^2 = 0.67$, $p < 0.01$), and between RSA migration and bone ingrowth at 6 months, 12 months and 24 months ($-0.55 < r < -0.33$, $p > 0.1$), although not reaching significance (Spearman's rank correlation).

Strong positive and significant correlations were noted between RSA migration and fibrous ongrowth at 12 months ($r = 0.74$, $r^2 = 0.54$, $p < 0.02$), 24 months ($r = 0.69$, $r^2 = 0.48$, $p < 0.05$), and between 12 and 24 months ($r = 0.60$, $r^2 = 0.37$, $p < 0.1$) and between RSA migration and fibrous ingrowth at 12 months ($r = 0.66$, $r^2 = 0.44$, $p < 0.05$), Spearman's rank correlation).

Post mortem mechanical analysis

The post mortem mechanical tests of the fixation strength showed an average displacement figure (Δ) of 64 μm for group 1 (stiffness 18 mm^{-1}), 25 μm for group 2 (stiffness 63 mm^{-1}) and 74 μm for group 3 (stiffness 16 mm^{-1}) (Table 6). The average displacement figure in group 2 was significantly lower than in group 1 and 3 ($p < 0.01$, two-tail unpaired t), and the average mechanical stiffness was significantly higher in group 2 ($p < 0.01$).

The 2 sheep from group 1 that had been identified as manifestly loosened by RSA analysis showed displacement figures higher than 300 μm, and were not included for calculation of the average displacement figure of the group, since an exact measurement of their mechanical displacement was not possible.

The separate displacement measurements for each of the 5 applied loads showed a significantly smaller average displacement in group 2 than in group 1 and 3 for pure compression ($p < 0.02$, two-tail unpaired t), compression + mediolateral bending ($p < 0.02$), compression + mediolateral shear ($p < 0.01$), compression + anteroposterior bending ($p < 0.002$) and compression + anteroposterior shear ($p < 0.003$).

The separate displacement measurements were lower in group 2 for pure compression, compression + mediolateral bending, compression + anteroposterior bending, compression + mediolateral shear and compression + anteroposterior shear at 6 months and 12 months, and for pure compression, compression + mediolateral bending and compression + mediolateral shear at 24 months ($p < 0.1$, Wilcoxon rank sum). No significant difference was noted for any of the five loads at the 3 months ($p > 0.1$).

Correlation analysis demonstrated a strong positive correlation between mechanical fixation stiffness and bone ongrowth ($r = 0.90$, $r^2 = 0.81$ and $p < 0.01$, Pearson's product moment; Figure 14), and between mechanical fixation stiffness and bone ingrowth ($r = 0.82$, $r^2 = 0.68$ and $p < 0.01$), together with a strong inverse correlation between mechanical fixation stiffness and fibrous ongrowth ($r = -0.88$, $r^2 = 0.77$ and $p < 0.01$) and between mechanical fixation stiffness and fibrous ingrowth ($r = -0.87$, $r^2 = 0.76$ and $p < 0.01$).

No correlation between mechanical fixation stiffness and operative score or functional and clinical score was demonstrated ($r < 0.1$, $p > 0.1$, Pearson's product moment).

Histological examination and histomorphometric analysis

Histological examination showed increased inflammation in sections from the medial collateral ligament, lateral capsule, or posterior capsule in 3 cases. These 3 cases were equally divided over the 3 groups, and all were seen in the 3-month subgroups. Inflammatory changes in the popliteal or inguinal lymph nodes were noted in 11 cases. 5 of these were seen in group 1, 3 in the 3-month subgroup, and 2 in the 6-month subgroup. 3 cases were seen in group 2, all in the 3-month subgroup. Another 3 cases were seen in group 3, 1 in the 6-month subgroup, and 2 in the 12-month subgroup.

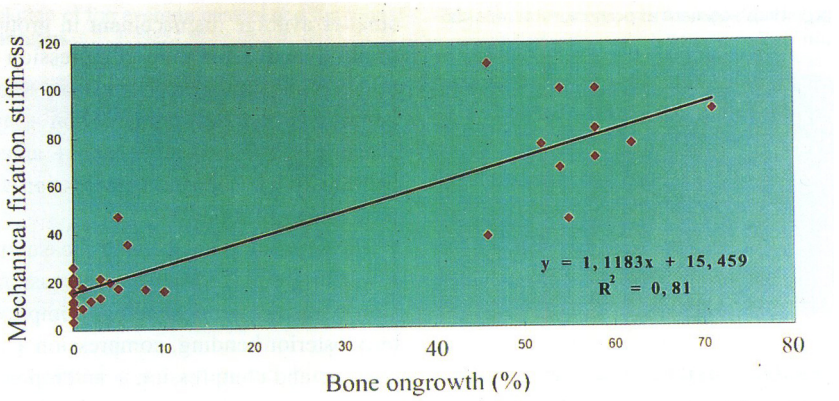

Figure 14. Mechanical fixation stiffness versus bone ongrowth, showing a strong positive correlation ($r = 0.9$, $r^2 = 0.81$, $p < 0.01$).

Polarized microscopy showed the presence of polyethylene particles in 3 cases. All these cases were noted in group 2, 1 in the 3-month subgroup, and 2 in the 12-month subgroup.

Histomorphometric analysis showed an average bone ongrowth of 1% in group 1, 43% in group 2, and 1%.in group 3 (Table 7). The average amount of bone ongrowth in group 2 was significantly higher than in group 1 and 3 ($p < 0.0001$, two-tail unpaired t).

The average bone ingrowth was 1% in group 1, 25% in group 2, and 0% in group 3 (Table 8). The average amount of bone ingrowth was significantly higher in group 2 than in group 1 and 3 ($p < 0.0001$).

The average fibrous ongrowth was 94% in group 1, 34% in group 2, and 89% in group 3 (Table 9). The average fibrous ongrowth was significantly smaller in group 2 than in group 1 and 3 ($p < 0.0001$).

The average fibrous ingrowth was 89% in group 1, 35% in group 2, and 95% in group 3 (Table 10). The average fibrous ingrowth was significantly smaller in group 2 than in group 1 and 3 ($p < 0.0001$).

The average thickness of the fibrous tissue layer

Table 7. Average bone ongrowth, percentages

Months	Group 1	Group 2	Group 3
3	1	28	3
6	0	43	0
12	1	58	1
24	1	41	0
Overall	1	43	1

Table 8. Average bone ingrowth, percentages

Months	Group 1	Group 2	Group 3
3	1	18	0
6	1	35	0
12	3	20	0
24	1	28	0
Overall	1	25	0

Table 9. Average fibrous ongrowth, percentages

Months	Group 1	Group 2	Group 3
3	92	50	80
6	95	49	85
12	94	12	93
24	95	34	95
Overall	94	34	89

Table 10. Average fibrous ingrowth, percentages

Months	Group 1	Group 2	Group 3
3	84	55	95
6	86	33	95
12	91	20	93
24	92	30	95
Overall	89	35	95

Table 11. Average thickness of the fibrous tissue layer, mm

Months	Group 1	Group 2	Group 3
3	1.5	1.0	0.8
6	1.5	1.1	0.7
12	0.9	0.9	1.0
24	0.8	0.4	0.8
Overall	1.1	0.8	0.8

was 1.1 mm in group 1, 0.8 mm in group 2, and 0.8 mm in group 3 (not significant)(Table 11).

The average histomorphometric values were significantly higher for group 2 concerning bone ongrowth at 6 months, 12 months, and 24 months, and for bone ingrowth at 3 months, 6 months, and 24 months (Wilcoxon rank sum, $p < 0.05$). They were significantly lower for group 2 concerning fibrous ongrowth at 6 months, 12 months and 24 months, and for fibrous ingrowth at 3 months, 6 months, 12 months and 24 months (Wilcoxon rank sum, $p < 0.05$). None of the histomorphometric parameters showed a significant correlation with the operative score or clinical-functional score ($r < 0.1$, $p < 0.1$, Pearson's product moment).

The occasional presence of multinuclear giant cells was noted in 10 cases, but in none of the cases was their total number per section higher than 10. Three of these cases were seen in group 1 (all in the 12-month subgroup), 5 in group 2 (2 in the 3- and 6-month subgroups, 1 in the 12-month subgroup), and 2 in group 3 (1 in the 3-month and in the 6-month subgroup) ($p > 0.1$, Fisher Exakt).

Mineralization defects, increased vascularization, delamination or fracture of the hydroxyapatite coating, or the presence of necrotic bone areas were not seen in any of the sections. The average percentage of hydroxyapatite coating defects in group 2 was 7% at 3 months, 35% at 6 months, 56% at 12 months and 100 % at 24 months ($p < 0.05$, Wilcoxon rank sum).

Bead loosening was noted in one case from group 3, where 5 loose beads were seen in a sheep from the 12-month subgroup.

The fibrous tissue layer was always orientated parallel to the tibial baseplate in all sheep from group 1 and 3, where minimal to absent bone ongrowth was seen. In sheep from group 2 with substantial bone ongrowth, the orientation was much more at random. In sheep from group 2 with limited bone ongrowth the orientation was again parallel to the tibial baseplate.

Marginal osteophytes were seen in 3 sections, with one case in every group (1 in the 6-month subgroup in group 1, 1 in the 3-month subgroup in group 2, and 1 in the 12-month subgroup in group 3).

The ***contact radiographic analysis*** for bone ongrowth and ingrowth showed identical values as the histomorphometric analysis for these parameters as shown in Tables 7 and 8.

Typical sections for each group are shown in Figures 15–23.

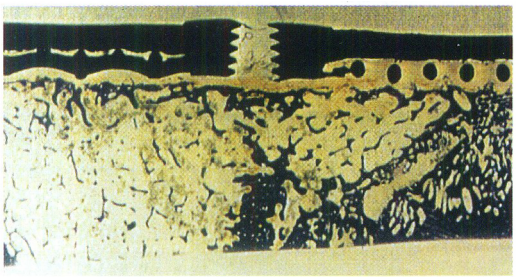

Figure 15. Typical section for group I (cast mesh coated component at 6 months), showing fibrous integration.

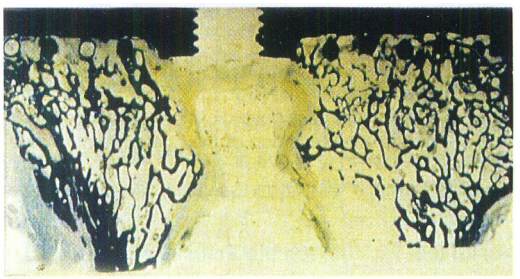

Figure 16. Typical section for group II (hydroxyapatite coated cast mesh component at 3 months), showing both bone ongrowth and bone ingrowth.

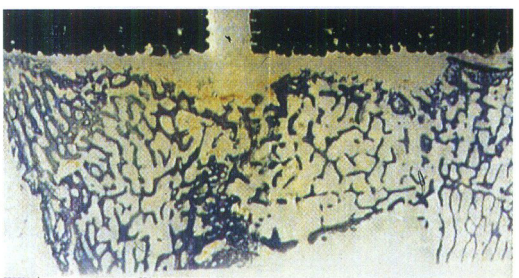

Figure 17. Typical section for group III (multilayer beads coated component at 3 months), showing predominantly fibrous integration.

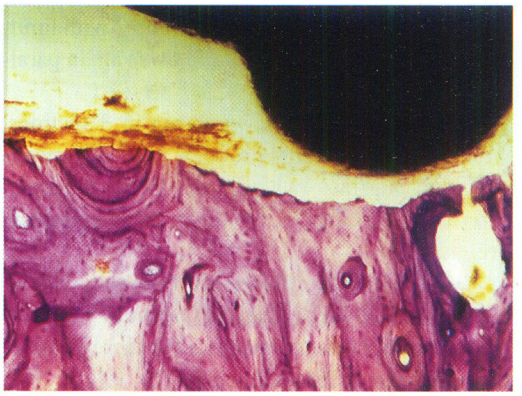

Figure 18. Cast mesh coated component at 1 year—fibrous integration. The fibrous tissue layer is oriented parallel to the baseplate.

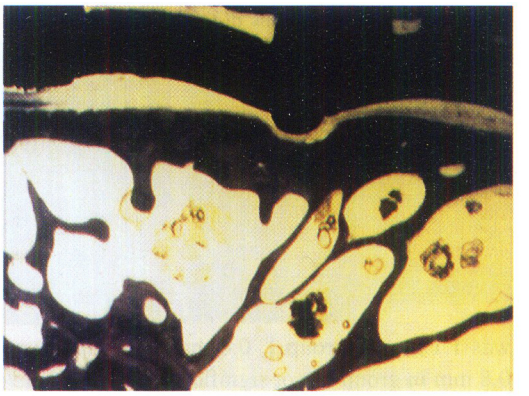

Figure 19. Cast mesh coated component at 2 years—fibrous integration.

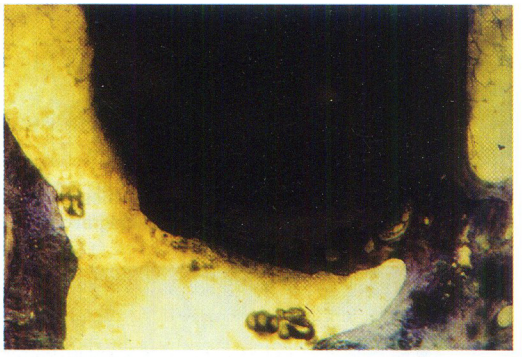

Figure 20. Hydroxyapatite coated cast mesh component at 1 year—partial desintegration of the hydroxyapatite coating.

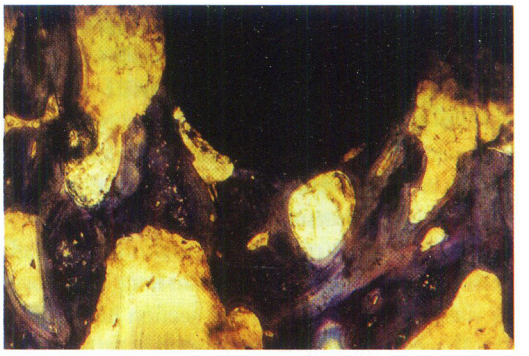

Figure 21. Hydroxyapatite coated cast mesh component a 2 years—bone ongrowth with absent hydroxyapatite layer.

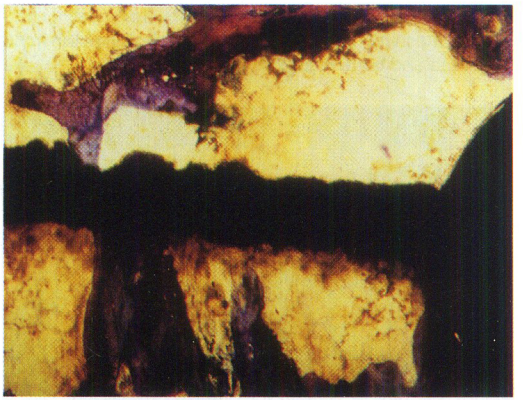

Figure 22. Hydroxyapatite coated cast mesh component at 2 years—bone ingrowth within the coating.

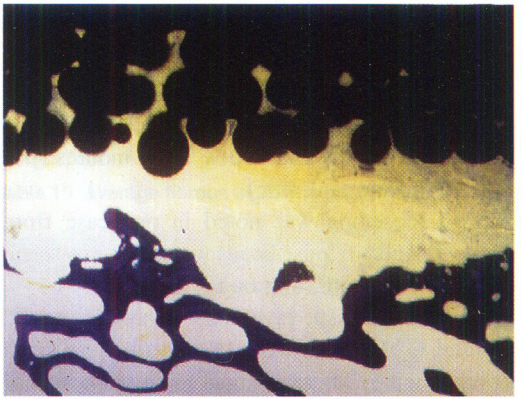

Figure 23. Multilayer bead coated component at 1 year—fibrous integration.

Discussion

Total joint replacement surgery using man made prostheses to replace diseased joints has provided dramatic relief of pain and improvement in function for many patients with end stage arthritis.[75,91,92,93,94,95] In the past the vast majority of these prostheses were attached to the skeleton using surgical bone cement made of polymethyl methacrylate.

Although this form of prosthetic fixation has been remarkably successful over a relative short period of time, several problems have been noted, with approximately 10% of the components becoming loose by 10 years, necessitating further surgery. Although the etiology of prosthetic loosening in total knee arthroplasty is complex, polymethyl methacrylate bone cement and its specific characteristics have been considered to play a major role in this process of loosening.[34,46,49,55,98]

Porous surfaced, uncemented prosthetic components have recently been introduced to avoid these problems of cement failures and long-term mechanical loosening.[32] Bone ingrowth into the porous surfaces of these prosthetic components is believed to provide remarkable long-term fixation of the prosthetic components to the skeleton. Bone ingrowth, however, does not occur automatically. The body's way of reacting to a foreign material is to shield off the alien substance from the tissue through the formation of an enveloping fibrous layer, which is generally poorly vascularised.

In fact, it has been suggested that the thickness of this fibrous layer is inversely related to the degree of tissue acceptance of the implanted material. The ideal biomaterial therefore is truly integrated into the body without any type of shielding-off reaction. It is not surprising that cement anchored bone implants will become largely or totally anchored in fibrous tissue, some of the reasons for this tissue reaction being the exothermic, monomer releasing, and cytotoxic reactions during curing of the cement, as well as long-term adverse reactions to the hardened fixative.[34,55]

However, also around uncemented joint components there is generally evidence of an interfacial soft tissue reaction, even if a biomaterial of presumed excellent biocompatibility has been used, such as titanium or a chrome-cobalt alloy. In such cases the soft tissue encapsulation may be related to the surgical technique and the operative fit between the implant and the bone that was achieved, the surface of the implant, the initial stability of the implant, and the surface of the host bed. These parameters may, if inadequately controlled, prevent the desired bone healing after implantation, and instead stimulate the formation of low differentiated scar tissue around the foreign device.[8,14,18,26,90,107] Once such a soft tissue reaction has become manifest, bone ingrowth is unlikely to occur at a later stage, just as in a pseudarthrosis.

It was Brånemark who was the first to report in 1969 of bone tissue growing onto a metallic implant with direct contact between the bone and the implant. Later he coined the term osseointegration to describe this phenomenon.[11,12] Initially this idea of any type of direct bone-metal contact without intervening soft tissue layers was not at all accepted. On the contrary, some type of fibrous encapsulation of metallic implants was considered inevitable.

However, Brånemark did not only present histologic evidence of a direct bone anchorage of titanium implants, he also developed an uncemented dental implant that gave excellent clinical results, a sharp contrast to previously used fibrous tissue anchored dental devices.

The Brånemark definition of osseointegration, being "a direct structural and functional connection between ordered, living bone, and the surface of a load carrying implant" illustrates that osseointegration is more a concept than a precisely quantified biological term.

To date, no consensus has been achieved to define what minimal portion of an implant must be in direct contact with bone for the term osseointegration to be justified. Although reports have been

published on the positive correlation between bone-implant interfacial strength and the amount of direct bone-implant contact, no data are available on the actual amount of bone contact that is needed for adequate implant integration.

Less controversy exists on the resolution level required to judge direct bone-implant contact. This resolution level should be on the micron scale, and thus the analysis should be based on light microscopic investigations. Radiographs with a maximum resolution capacity of 0.1 mm are not sufficient for the diagnosis of osseointegration.[15,25]

Osseointegration of knee arthroplasty components

As a hypothesis it was stated earlier in this work that osseointegration of knee arthroplasty components, defined as both bone ongrowth and bone ingrowth, leads to better clinical and functional performance, compared to implants that show fibrous integration.

Obtaining osseointegration in knee arthroplasty components seems to be problematic. Cook et al. and Major et al. have examined porous surfaced knee prostheses retrieved from human patients and found minimal or no bone ingrowth in the majority of the components.[22,79] Retrieval studies of non-cemented porous coated hip prosthesis too have failed to show extensive bony ingrowth, although some authors as Collier et al., Sumner et al., and Engh et al. have reported greater amounts of bone ingrowth.[21,31,114] Nevertheless cementless knee prostheses have been inserted for several years now, with satisfying success rates.[45,85,124,125]

It seems that cementless knee prosthesis function through fibrous integration rather than osseointegration, which leads to the assumption that fibrous integration, although mechanically inferior to osseointegration, is probably adequate for knee arthroplasty components.

No literature data are, however, available on the relation between clinical performance and the rate of osseous ingrowth versus fibrous ingrowth of the prosthetic components. The reason for such a lack of data is obvious: the amount of osseointegration can only be assessed through microscopic examination, and is therefore not possible in a functioning knee. Post mortem analysis could theoretically provide some answers, but have not been reported in the literature.

In this study the relation between the amount of osseointegration, fibrous integration and clinical performance of knee arthroplasties was investigated using an in vivo functioning animal model. No significant correlation, however, could be detected between clinical performance and the amount of bone ingrowth or fibrous ingrowth. Although our study group showed a large spectrum of bone ingrowth quantity, ranging from 0% to 42%, this did not have a significant influence on the clinical and functional status of the animal, within a follow-up period of 2 years.

The starting hypothesis therefore can not be confirmed from the data in this work, although the reason for this might be an insufficiently sensitive clinical and functional scoring scale.

Mechanical characteristics

Although clinical and functional performance are probably influenced by many other factors then just osseointegration, this study shows that implants with fibrous integration can function as well as osseointegrated implants, when evaluated on a scoring scale. However, whether this is still true in the long-term is not proven. Johansson et al. have shown, using titanium screws implanted in the rabbit tibial metaphysis, much lower interfacial bone-implant strength for fibrous integrated screws compared to osseointegrated screws.[54] Extrapolating this to knee arthroplasty components, the hypothesis in this work was that osseointegrated knee components are mechanically much better fixed to the bone than fibrous integrated components, and that—although this does not immediately influence the clinical and functional performance—fibrous integration could lead to a less stable implant which might eventually become loose.

Again, in the literature no data are available on the mechanical characteristics of fibrous integrated knee components versus osseointegrated components, and certainly not on the correlation between mechanical fixation strength and the amount of osseointegration. Also, no data are available on the relation between the actual mechanical fixation strength of knee components and

their stability or migration over time. Mechanical fixation studies of tibial components have been performed in vitro by several authors, using explanted cadaver tibiae, and mainly for purpose of comparative load-displacement testing of various fixation options, such as keels, stems, screws, pegs, and combinations of these.[80,109,121,127]

Volz et al. have used eccentric medial compressive loads with one-plane displacement measurements for lift-off and subsidence.[121] Shimagaki et al. used four different loading configurations, with again one-plane displacement measurements for subsidence and lift-off.[109] Miura et al. and Yoshii et al. both used compressive and shear loads with two-plane displacement measurements for subsidence, lift-off, and translations in the plane of the base plate.[80,127] None of these studies, however, addressed the three-dimensional displacement of a prosthetic component when subjected to certain loads, in the six degrees of freedom.

In this study—using a newly developed mechanical displacement frame, consisting out of 3 orthogonal planes connected with 6 LVDT's—we were able to measure the three-dimensional displacements of the tested component under 5 different loading situations, making this set-up much more extensive and valuable, compared to the above reported set-ups. In this work, for the first time a strong positive correlation between mechanical fixation strength, represented by a newly defined mechanical displacement figure, and the amount of osseointegration could be demonstrated in knee arthroplasty components, while a strong negative correlation between mechanical fixation strength and the amount of fibrous integration was seen. The sheep from group 2 (hydroxyapatite coated cast mesh) showed a significantly higher osseointegration compared to group 1 and 3, as well as significantly lower mechanical displacement figures.

This study therefore proves the presumed hypothesis that fibrous integration of tibial knee arthroplasty components leads to mechanically less rigidly fixed implants, although this does not seem to affect the clinical and functional performance.

Migration over time

When mechanical fixation is less rigid, however, one could assume that these implants might show migration over time, and eventually become completely loose. In this work the hypothesis was raised that osseointegration leads to both more rigid mechanical fixation of the implant and less migration over time, compared to fibrous integrated components.

Migration studies are by necessity done by radiographic means. Since the actual accuracy of plain radiographs is less than 2–3 mm for translations and 3–4° for rotations, more sophisticated radiographic methods have recently been developed, of which radiostereometric analysis (RSA) is the most promising.[42,57,60,67,86,104,105,106,108]

The accuracy of RSA for the knee has been determined to be 0.3° for rotations and 0.2 mm for translations at the 95% confidence limit.[102,103] Several RSA follow-up studies have been performed, both in patients with cemented and uncemented knee prostheses.[20,86,103,104] Ryd et al. have repeatedly reported a consistent migration of both cemented and uncemented tibial components during the first year, after which they tend to stabilize. It has also been shown by these authors that when components continue to migrate after the first year, they are at risk of becoming loose.[101-106] Recently it was established by Ryd et al. that additional migration of 200 µm during the second postoperative year was indicative for subsequent loosening with a predictive power of 82%.[101]

No data, however, are available on the relationship between RSA migration and mechanical fixation strength of a prosthetic component, neither on the relationship between the quantitative amount of osseointegration of uncemented components and RSA migration.

It has been possible to address these issues in this work, through the use of an animal model in which the combination of RSA migration studies, mechanical fixation tests and microscopic assessment of osseointegration is possible. This study demonstrated that RSA migration indeed correlated with mechanical fixation strength of the component, as determined by its mechanical displacement figure. Indeed, mechanically less rigidly fixed components showed higher RSA migration than more rigidly fixed components.

This study also showed that an inverse correlation exists between RSA migration and osseointe-

gration. Osseointegrated components showed less migration than fibrous integrated implants. Both of these correlations became significant at 1 year postoperative. Sheep from group 2 showed significantly less migration on RSA at 1 year postoperative. In the same time these sheep from group 2 showed a significantly higher osseointegration, and were significantly more rigidly fixed under mechanical testing.

The hypothesis can therefore be confirmed: it can be concluded that osseointegration leads to less migration on RSA analysis, and that a rigid mechanical fixation too leads to less migration on RSA analysis.

These results also indicate that fibrous integration of knee components eventually might lead to complete loosening through this process of continuous migration.

Moreover, these results indicate that RSA analysis is an adequate tool to assess indirectly the amount of osseointegration and the amount of mechanical fixation of knee arthroplasty components.

Osseointegration capacity of the newly developed coating

This study was also undertaken to investigate the osseointegration capacity of a newly developed coating type. The rationale for this new coating was the starting hypothesis that a surface texture with theoretically superior osseointegration capacity could be provided, by offering a larger and better controlled pore size, with higher ingrowth area compared to conventional bead type coatings. Additionally this coating would have better metallurgical characteristics, and would be very well suited for additional hydroxyapatite coating.

The study, however, has shown that in reality the theoretical advantages concerning bone ingrowth do not occur. Bone ingrowth in sheep from group 1 with the newly developed cast mesh coating was just as in the sheep from group 3—receiving a conventional multilayer beads type coating—absent or minimal.

The reasons for this lack of bone ingrowth are probably the same as in the human situation, where retrieval studies have shown the same low bone ingrowth percentages in knee arthroplasty components.

Rigid implant fixation and a precise surgical technique with bone-implant interface gaps less than 500 μm are known to be absolute prerequisites for reliable bone ingrowth.[14,18,26,90,98,107] Pilliar et al. and Burke et al. have reported that micromotion less than 150 μm is required for osseointegration to occur.[14,90] Carlsson et al., Sandborn et al. and Dalton et al. have established separately a critical bone-implant interface gap of 500 μm.[18,26,107] These authors have demonstrated reliable osseointegration with interface gaps smaller than 500 μm, and fibrous connective tissue formation with larger interface gaps.

Interface gaps smaller than 500 μm, however, are hard to achieve in routine total knee arthroplasty procedures.

Otani et al. have shown that, even using precisely matching saw blades and cutting blocks, an average maximum cutting error of 488–802 μm occurs, resulting in component-bone interface gaps in the region of 500 μm or higher.[88] Dueringer et al. even reported an average maximum cutting error of 2 mm with another type of sawing instrumentation. These authors also measured the flatness of the cuts (as the distance between the uppermost point and the lowermost point) using a highly accurate coordinate measurement machine, and found it to be 0.3 mm for the femoral cuts, but as high as 1.1 mm for the tibial cuts.[30]

Toksvig-Larsen et al. too measured the surface flatness of knee arthroplasty cuts with a third sawing instrumentation set, and found it to be 1.0 mm to 2.4 mm (uppermost point to lowermost point), which again is much higher than the acceptable interface gap of 500 μm.[117] Not only seems the magnitude of the interface gaps to be a problem in total knee arthroplasty, rigid initial fixation with micromotion less than 150 μm seems equally hard to achieve, certainly for the tibial component.

The femoral component, by its box-like configuration, appears to provide adequate intrinsic resistance to rigid body motion by virtue of its shape alone. The more precise the press fit of the anterior and posterior condylar surfaces, the greater the increase in frictional forces tending to immobilize this component. The anterior and posterior surfaces tend to resist anteroposterior translation, flexion-extension tilt and rotation. The routine use of metaphyseal lugs or pegs distally further prevent

mediolateral tilt, mediolateral translation and rotation.[98]

For the tibial component, however, obtaining rigid fixation is problematic. Tibial trays fixed with simple interference fit peg fixation have been shown to move 400–800 µm, with or without additional fixation of a central screw.[109,121] Tibial trays fixed with a central stem show initial micromotion of 200–400 µm, which is still to high for reliable osseointegration.[16,121,122] The addition of cruciate-shaped blades to a central stem inhibit motion more than a simple stem alone, but even then micromotion was seen to be in the region of 150–200 µm.[122] Volz et al. and Miura et al. have shown that when tibial trays are fixed with 4 screws, micromotion is between 100–200 µm, which might be compatible with osseointegration.[80,121]

Adding a central stem to the four screws does not seem to improve micromotion in good quality tibial bone, but can lead to substantially less micromotion in osteopenic bone.[68,127] The routine combination of 4 screws and a central stem for fixation of uncemented tibial components therefore seems to be the best choice. The addition of interference pegs, however, might be additionally beneficial, as has been shown recently by Natarajan et al., who reported the presence of relative tangential displacements as high as 200 µm when subjecting tibial components to compressive loads.[84] This so called tangential displacement is a consequence of the variation in elastic modulus between the metal tibial tray and the underlying bone, leading to tangential displacements of the opposing surfaces under compressive loads.[33,50,126] Using both finite element analysis and in vitro measurements, the same authors have reported a substantial decline in relative tangential interface motion to less than 150 µm.[84]

As stated above, these pegs, however, do not influence the so-called rigid body motion, which is to be controlled by use of screws and an additional stem. In view of these studies, the lack of bone ingrowth in knee arthroplasty components, and certainly in tibial components, is therefore not surprising. Interface gaps less than 500 µm and micromotion less than 150 µm are absolutely required for reliable osseointegration, but are not routinely achieved.

The same is probably true for this study, in which an in vivo animal model was used, with a comparable surgical technique and with use of similar prosthetic components, exactly with the purpose to reproduce maximally the human situation. Although this has not been quantified in the study, the achieved magnitude of the interface gaps and the micromotion of the components is thought to be in the same order as for the human situation, and this is probably the reason for the same lack of osseointegration in both the sheep stifle and the human knee joint.

The implantation of components covered with a newly developed, theoretically advantageous, large and constantly pore sized coating, did thereby not make a big difference and did not lead to a higher degree of osseointegration. The starting hypothesis could therefore not be confirmed.

Application of an additional hydroxyapatite coating

A major advantage of the newly developed coating, however, is its high suitability for application of an additional hydroxyapatite coating. The reason for this is its large and constant pore size. Conventional bead type coatings have much smaller and irregular pores, which become completely filled after applying an additional hydroxyapatite spray, leaving no more pores available for bone ingrowth. This obviously is not the case when much larger pores are available on the implant.

Starting with pores of 1.5-mm size, additional application of a 50–60 µm thick plasma spray of hydroxyapatite only reduces the pore size to 1.4 mm. Even taken into account a micromotion of 100 µm, this leaves an effective pore size greater than 1 mm available for bone ingrowth.

The idea of additional hydroxyapatite coating of prosthetic knee components has been a consequence of the above-mentioned lack of osseointegration that has been noted with uncemented knee implants. As a hypothesis it was stated in this work that additional hydroxyapatite coating of the implant would enhance its osseointegration, defined as both bone ingrowth and bone ongrowth.

Apart from hydroxyapatite, the use of other potentially osseointegration enhancing agents, such as autogenous and allogenic bone grafts, calcium

phosphate preparations, and electrical stimulation have been suggested, but none of them seemed to be as promising as hydroxyapatite. With bone grafting, either autogenous or allogenic, results have been variable, with both osseointegration enhancement and inhibition being noted.[58,65,72,96,123] The same results have been seen with non-hydroxyapatite calcium phosphate coatings, with some studies showing a positive effect on osseointegration, and others showing a negative or variable influence.[3,5,52,53] The same inconsistency in results has been noted with electrical stimulation.[5,89,97]

Concerning hydroxyapatite coatings, however, several promising studies have been reported in recent years.[56,61,62] Cook et al., Jasty et al., and others have shown that hydroxyapatite displays a lack of local or systemic toxicity, a lack of inflammatory response, and a lack of pyrogenic response.[23,28,40,41,47,48,74] Its osteoconductive characteristics have been noted by several authors.[36,113,115,118] Geesink et al. implanted hydroxyapatite coated titanium cortical plugs in dogs, and found radiological and histological evidence of new bone formation and bone-implant bonding from 6 weeks on.[36] Block et al., Hayshi et al., Kent et al., and others have noted the same rapid ongrowth of bone onto dental, hydroxyapatite-coated implants in animal models.[6,43,61,63]

Using transcortical plugs in canine femora, De Groot et al. and Cook et al. found that hydroxyapatite coated plugs had a significantly higher pull-out strength compared to non-coated plugs, and they assumed that this increased strength was due to a lack of fibrous tissue interposition at the hydroxyapatite-bone interface.[24,27] The same has been noted by Manley et al. and Dalton et al., comparing hydroxyapatite coated and uncoated titanium intramedullary implants in canine and rabbit femora. In these experiments too, a higher degree of bone ingrowth and higher pullout strength was noted for the hydroxyapatite coated implants.[26,77]

Søballe et al. demonstrated that the positive effects seen with hydroxyapatite are probably due to an osteoconduction effect, making the bone-implant interface gap less critical. Using unloaded titanium plugs in a canine model, these author showed that hydroxyapatite coated plugs became osseointegrated, even in the presence of 1 mm interface gaps, while uncoated implants did not become osseointegrated under these circumstances. The authors therefore concluded that, although tight interference fit appeared to aid implant fixation, hydroxyapatite coatings could compensate for initial lack of such a press fit.[110]

Although all these studies have shown beneficial effects for hydroxyapatite coatings for unloaded or minimally loaded implants, little or no data are available on the effect of hydroxyapatite for loaded implants with or without the presence of micromotion, as is the case in a situation of an uncemented knee arthroplasty.

Geesink et al. have reported on a radiographic analysis of canine hip implants, coated with a mixture of hydroxyapatite and calcium oxide ceramic.[37-39] Although this coating was not a pure hydroxyapatite coating, they did notice intimate contact between the cortical bone and the implant. Munting has recently confirmed the findings of Geesink et al., using a stemless canine hip prosthesis inserted as a hemi-arthroplasty.[81-83]

Direct deposition of newly formed bone onto most of the implant surface was found in the hydroxyapatite coated implants, whereas minimal to no bone contact was seen in the non-coated implants.

In both studies, however, only a limited number of animals were included, with only 8 dogs receiving an hydroxyapatite coated implant in each study, and in both studies evaluation was limited to radiographic and histological analysis. Mechanical data, stability measurements, or migration patterns have not been reported. Nevertheless, although these data (using animal hip models) are limited, and although the situation in the knee is completely different to the situation in the hip, they certainly have their value.

Since to date no animal model has been available for in vivo research in the field of knee arthroplasty, it has been impossible so far to examine adequately in vivo the effects of hydroxyapatite coatings on the osseointegration of knee arthroplasty components.

With this study, however, it is now demonstrated that a 50 μm hydroxyapatite plasma sprayed coating does improve significantly the osseointegration of tibial components, inserted in an in vivo

functioning animal model.

Sheep from group 2 with a hydroxyapatite coated cast mesh tibial component showed significantly higher bone ingrowth and bone ongrowth on histomorphometric analysis, compared to the sheep from group 1 and 3 with uncoated cast mesh components and multilayer beads coated components, respectively.

While osseointegration was minimal or absent in groups 1 and 3 (with respectively average bone ingrowth and bone ongrowth of 1% or less in both groups) substantial osseointegration was seen in group 2 with an average bone ongrowth of 43% and an average bone ingrowth of 25%.

This study therefore proves that hydroxyapatite coatings do enhance both bone ongrowth and ingrowth, under conditions where osseointegration of non-hydroxyapatite coatings is absent, and the above stated hypothesis can therefore be accepted. Extensive three-dimensional testing has also shown that these hydroxyapatite coated components are significantly stronger fixed to the host bone, and that this fixation strength seems to be durable, at least for the investigated follow-up time of 2 years. Moreover, using RSA analysis, this study also demonstrated a significantly smaller amount of migration for hydroxyapatite coated implants after 1 year compared to non-coated implants.

Degradation of the hydroxyapatite coating

An important concern is the degradation of the hydroxyapatite coating over time that was noted. Although this was not exactly formulated as a hypothesis at the start of this work, it was assumed that the hydroxyapatite coatings would be fairly durable and would show only minimal disintegration over the study period. The data from this study, however, are not the first to question the durability of hydroxyapatite coatings.

Buma and Gardeniers have recently reported a retrieval case of a hydroxyapatite coated bipolar hip prosthesis, which was revised for mid-thigh pain 4 years after implantation, showing a complete disappearance of the hydroxyapatite coating layer.[13] Bauer et al. reported on a another 4 retrieval cases, all on the Osteonics (Omnifit) titanium hydroxyapatite coated hip prosthesis, which showed osteoclast mediated hydroxyapatite degradation after an average in situ period of 12 months.[3] Whether this hydroxyapatite degradation is an alarming observation is not very clear.

Some resorption or dissolution is of course essential to trigger the basic osteoconductive effect of a hydroxyapatite coating.[2,69-71,112] Calcium and phosphate ions are released from the coating, resulting in reprecipitation of crystals and ion exchange with the surrounding tissue. This leads to the formation of a carbonated calcium phosphate layer of micro-crystals and macro-crystals, with the incorporation of a collagenous matrix.

It has been suggested that the rate of resorption might have a major influence on the actual implant fixation.[7] Fast resorption could lead to disintegration of the coating, with rapid loss of the bonding strength between the coating and the prosthesis, resulting in delamination, the production of particles, and loss of mechanical fixation. Slow resorption might give the opportunity to the surrounding bone to replace the resorbed coating, resulting in a durable implant fixation.

This study seems to indicate that this "race" (has bone apposition taken place before the hydroxyapatite coating is resorbed ?) is won by the bone, since in all cases where degradation of the hydroxyapatite coating was seen, substantial osseointegration was noted, suggesting that indeed the hydroxyapatite coating had been replaced by ingrowing bone.

It thereby should be noted that in this study ultra-high quality plasma sprayed coating was used. A vacuum plasma spray technique at 5,000 °C was employed, which is known to be superior to air plasma sprays at a temperature of 20,000 °C.

The other specifications of the used hydroxyapatite coating included a 100 % crystalline starting powder with an exact calcium-phosphate ratio of 1–1.54, an X-ray diffraction tested minimal final crystallinity of 75%, a final hydroxyapatite content of more than 90%, a final calcium/phosphate ratio of 10–6, a final porosity of less than 10%, and a final thickness between 50 and 60 µms.

Although many of the currently available hydroxyapatite coated human knee arthroplasty components do not meet these strong criteria; they are generally accepted as being the norm.[29,66,119] Hydroxyapatite coatings that do not meet these criteria, might become desintegrated more rapidly

before being replaced by ingrowing bone tissue, which might lead to loosening of the components.

Again, this study indicates that this is not the case when a high quality hydroxyapatite coating is used. Contrary to the assumption, however, this study also shows that even high quality hydroxyapatite coatings can show substantial disintegration over time, with even total disappearance after only 2 years.

Summary

Although cementless knee arthroplasty is a commonly performed procedure, to date very little was known about the process of osseointegration of knee arthroplasty components.

Using a knee prosthesis that was specially designed for the sheep stifle joint, this process of osseointegration could be studied in vivo, together with its effects on clinical and functional performance, its influence on mechanical fixation, and its influence on component stability or migration over time. Additionally, the osseointegration capacity of a newly developed cast mesh porous coating could be examined. The rationale for this newly developed coating was to provide a surface texture with theoretically superior osseointegration capacity, by offering a larger and better controlled pore size, with higher ingrowth area compared to conventional bead type coatings.

In summary, the conclusions that are drawn from this work are the following:

1. The degree of osseointegration of knee arthroplasty components is not correlated with clinical and functional performance. Knee arthroplasty components with fibrous integration can function as well as osseointegrated components at least during the first years after implantation. This explains the occasional reports in the literature of post mortem retrieved, well functioning knee arthroplasty components, with purely fibrous integration on histomorphometric analysis.
2. Fibrous integration of tibial knee arthroplasty components, however, leads to less mechanical fixation strength of these components. Osseointegrated components are much more strongly fixed to the underlying bone. This difference in mechanical fixation strength is detectable under physiologic loads.
3. Fibrous integration of tibial knee arthroplasty components leads to increased migration, becoming apparent after 1 year with radiostereometric analysis (RSA). Osseointegrated components are significantly more stable over time.
4. Fibrous integration is less desirable, since it leads to mechanically less rigidly fixed implants, and subsequently to migration over time. On the long-term, fibrous integration might therefore lead to loosening.
5. RSA is an effective tool to assess migration of knee arthroplasty components. The RSA migration of an uncemented component is also an indicator of its degree of osseointegration and its mechanical fixation strength, since RSA migration is correlated with these two parameters. RSA is therefore especially useful during the first postoperative years, since increased migration indicates fibrous integration and low mechanical fixation strength, suggesting an increased risk for subsequent loosening at a later stage. Patients with increased early component migration on RSA might therefore be advised to impose specific restrictions on their knee arthroplasty.
6. Osseointegration is not routinely achieved in conventional porous coated tibial knee arthroplasty components. The development of a theoretically superior cast mesh coating did not lead to a significantly higher degree of osseointegration. It is suggested that the lack of sufficiently small interface gaps and the lack of sufficiently small interface micromotion—two known prerequisites for reliable osseointegration to occur—are the main reasons inhibiting osseointegration, both in this animal model and in the human situation.
7. Significant osseointegration, however, does occur in the newly developed cast mesh coated components, when they are additionally coated with a vacuum plasma sprayed 50 μm hydroxyapatite layer. The newly developed cast mesh coating is ideally suited for such an additional hydroxyapatite coating. Remarkably

high percentages of both bone ingrowth and ongrowth can be seen with these hydroxyapatite coated cast mesh coatings, higher than so far reported for current tibial knee arthroplasty components. These osseointegrated hydroxyapatite coated cast mesh components show significantly higher mechanical fixation strength and lower RSA migration than non-hydroxyapatite coated components.

8. Disintegration of the hydroxyapatite layer over time occurs, becoming substantial at 6 months on histology sections, with total disappearance of the hydroxyapatite layer at 2 years. This disintegration process does not affect the degree of osseointegration and the mechanical fixation strength, neither does it cause a phagocytic reaction.

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