PERIPROSTHETIC BONE RESORPTION

PARTICLES VERSUS MOVEMENT

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Using a rat model, we created a bone-to-titanium interface and applied phagocytosable high-density polyethylene particles between the bone and implant, either initially or when the interface had matured. No fibrous membrane developed and no bone resorption was found.

If sliding movements were initiated at the interface after two weeks, there was formation of a fibrous membrane. The additional application of particles did not change the thickness of the membrane, and there were only minor qualitative changes. Creation of a membrane by movement followed by cessation of movement and the application of particles caused the membrane to persist, whereas in a particle-free control group bone-to-metal contact was re-established.

Our findings suggest that mechanical stimuli are of primary importance for prosthetic loosening, and that particles may modulate the later stages of the loosening process.

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Two factors appear to be important in the aetiology of prosthetic loosening. The first is a lack of initial stability (Freeman and Plante-Bordeneuve 1994; Walker et al 1995). Early migration, as detected by roentgen stereophotogrammetric analysis (RSA), is a strong predictor of later symptomatic loosening which leads to revision surgery (Kärholm et al 1994; Ryd et al 1995). For migration to take place the prosthesis-bone interface must have a soft-tissue membrane which is the result of remodelling of the devitalised bone bed. Later, the membrane may be maintained by movement (Aspenberg et al 1992).

The second factor is the presence of particulate debris. Particles of polyethylene, bone cement and metal collect at membranous interfaces. They have been shown both in vivo and in vitro to activate macrophages which produce resorption-stimulating factors which may lead to increased bone resorption (Maloney and Smith 1995). Support for this hypothesis is strong, based on a large number of studies, mainly on fetal mouse calvarial cultures. The presence of particles, however, may be an effect of prosthetic loosening rather than a cause. Few experimental studies show bone resorption after the application of particles in vivo. Howie et al (1988) reported bone resorption in rats around a cement-bone rod which protruded from the femur into the knee. Resorption around the cement was induced by massive injections of particles into the knee which caused arthritis. Later, they reported difficulty in quantitating these results (Howie et al 1993), and no further data have been published.

We have developed a model which can differentiate between particles and movement as a cause of bone resorption at an established bone-titanium interface. We have used this model to study whether particles induce bone resorption in the absence of arthritis, whether a fibrous membrane will develop at a bone-metal interface due to the presence of particles or movement or both, and whether these particles have a detrimental effect once a fibrous membrane has been formed.

MATERIALS AND METHODS

We used 68 male Sprague-Dawley rats with a mean body-weight of 350 g. Our institutional guidelines for the use and care of laboratory animals were strictly followed.

We screwed a 4×13 mm commercially-pure titanium plate on to the medial surface of the proximal tibia of each rat using one 1.5 mm cortical screw at each end of the plate. Between the two screw holes, a depression in the tibial cortex was milled out to correspond to the detachable middle part of the plate. This had a circular area of diameter 2.5 mm protruding 0.5 mm into the underlying depression in the bone. This area provided the test surface which, after insertion, faces traumatised bone and haematoma. The bone will grow towards this test surface until there is a fit (Fig. 1).

Without removing the plate itself, the circular test surface can be unscrewed to expose the underlying tissue so
that particles can be applied before the test surface is replaced. This surface can be stable or unstable. When required to be unstable, the circular surface can be rotated by a wing nut which protrudes into the subcutaneous tissue and can be gripped through the skin (Fig. 2). After a few days, the rats become used to this procedure; the surface can be rotated against the underlying tissue without signs of fear or pain and with no need for anaesthesia.

Particles. The particles which we tested (Fig. 3) were produced by Shamrock Technologies, Newark, New Jersey, using a proprietary method and were reported to be 100% pure, highly crystalline high-density polyethylene (HDPE) with a specific gravity of 0.95. They averaged $4.7 \pm 2.1 \mu m$ in size, and were from the same batch as has been used in a number of experimental studies reviewed by Goodman (1994).

**Effect of particles in a stable bone-metal interface.** Sixteen rats received bilateral stable plates. The test surface was removed six weeks after implantation to expose the bone which had developed in contact with the titanium surface. On one side, HDPE particles were deposited on the bone surface before the test surface was replaced and on the other, the plate was opened but no particles were deposited. We used a sterile, fine artist’s brush which was dipped into the test-tube containing the particles and then lightly brushed over the tissue surface. This created a layer on the surface which was just visible to the naked eye. In eight rats, the titanium test surface was brushed in the same way. This caused deposition of a smaller amount of particles on the surface, visible only under the operating microscope at a magnification of $\times 5$. The rats were killed six weeks after application of the particles.

In another eight rats with bilateral plates particles were added on one side only when the plates were inserted. These rats were killed after six weeks (Fig. 4).

**Effect of movement.** In 25 rats unstable plates were placed on both sides. At 14 days after implantation, the flat test surface was rotated 20 half-turns (180°) twice daily, five days a week, to create a sliding movement between the titanium surface and the adjacent tissue. These rats were killed at 0 ($n = 5$), 2 ($n = 10$) or 6 ($n = 9$) weeks after movement had been started. One animal was lost due to tibial fracture (Fig. 4).

**Effect of movement and particles.** Nine rats received bilateral unstable plates, and particles were applied on to the bone on one side. Both plates were moved as described above. The rats were killed after six weeks (Fig. 4).

**Effect of particles in a stable fibrous interface.** Ten rats received bilateral unstable plates, and both were moved as described above. After six weeks they were opened and particles were deposited directly on to fibrous tissue on the left side and the test surface was replaced, and not moved.
thereafter. These rats were killed six weeks after the addition of particles (Fig. 4).

**Evaluation.** The entire tibial segment beneath the test surface was decalcified and prepared by standard histological techniques. Sections were produced at a right angle to the test surface, through the middle of the circular surface, and stained with haematoxylin and eosin. Particles in a stable bone-metal interface were evaluated by point counting with a Mertz grid down to 0.18 mm and to 0.45 mm below the plate. The proportion of bone per total area was analysed. All groups were also examined by a computerised video system attached to the microscope (Videoplan TM Kontron Bildanalyse GmbH, Esching, Germany) and by drawing on a digital table with a screen magnification of ×40. Measurements included the length of the interface surface, the length of each part of the contact surface which did not consist of bone (soft tissue and cartilage), and the area of soft tissue which had contact with the surface. By dividing these areas by their length along the interface, the mean thickness of the fibrous membrane or the fibrous areas was calculated.

**Statistics.** Paired comparisons (particles vs no particles) were analysed by Student’s t-test. Comparisons at 0, 2 and 6 weeks of movement were made using one-way ANOVA, entering only the mean values of the two sides. P values of <0.05 were considered significant.

**RESULTS**

The titanium surface was always easily separated from the underlying tissue, and under loupe magnification no residual material was seen on the titanium. Histological examination showed that the layer nearest the titanium did not appear to be disrupted.

**Effect of particles in a stable bone-metal interface.** Histological examination showed no signs of bone resorption when plates remained in place. Almost the entire contact area showed bone adjacent to the metal and usually with no covering fibrous layer. Plates which had had particles applied immediately or after six weeks did not differ qualitatively, and there was no difference in the bone architecture between specimens with particles and control specimens. A large number of HDPE particles was seen in the marrow cavities between the bone trabeculae and sometimes on the surface towards the titanium. In one case there was subcutaneous inflammation around the implant with a large resorption cavity under the plate, filled by granulomatous tissue with particles, together with numerous osteoclasts on the surrounding bone walls. In all specimens taken together the proportion of bone per total area was unchanged by the particles (Table I). The power of the method to show significantly a decreasing proportion from 0.7 to 0.6 with this number of observations was 75%.

**Effect of movement.** Two weeks after insertion of the plate

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**Table I.** The effect of particles in a stable bone-titanium interface on the proportion of bone per total area below the plate (mean ± SD)

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>Proportion of bone per total area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Particles</td>
</tr>
<tr>
<td>0.18</td>
<td>0.75 ± 0.14</td>
</tr>
<tr>
<td>0.45</td>
<td>0.71 ± 0.14</td>
</tr>
</tbody>
</table>

**Table II.** The effect of movement with particles on bone contact, soft-tissue thickness (mm) and cartilage (mean ± SD)

<table>
<thead>
<tr>
<th>Movement over time (wks) (mean from bilateral moved plates)</th>
<th>Movement with particles (wks) (paired experiment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone contact (fraction)</td>
<td>Control, Particles</td>
</tr>
<tr>
<td>0</td>
<td>0.53 ± 0.29, 0.61 ± 0.16, 0.14 ± 0.17, 0.12 ± 0.14, 0.10 ± 0.14, 0.06 ± 0.11</td>
</tr>
<tr>
<td>2</td>
<td>0.61 ± 0.16, 0.24 ± 0.07, 0.12 ± 0.05, 0.11 ± 0.07, 0.10 ± 0.14, 0.03 ± 0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.14 ± 0.17, 0.12 ± 0.05, 0.11 ± 0.04, 0.10 ± 0.14, 0.06 ± 0.11, 0.03 ± 0.10</td>
</tr>
<tr>
<td>Soft-tissue thickness (mm)</td>
<td></td>
</tr>
<tr>
<td>0.06 ± 0.008</td>
<td>0.24 ± 0.07, 0.12 ± 0.05, 0.11 ± 0.04, 0.10 ± 0.14, 0.06 ± 0.11</td>
</tr>
<tr>
<td>Cartilage (fraction)</td>
<td></td>
</tr>
<tr>
<td>0.27 ± 0.24</td>
<td>0.23 ± 0.19, 0.12 ± 0.14, 0.10 ± 0.14, 0.06 ± 0.11</td>
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(when movement was about to start) all but one of the specimens showed that new bone had already reached most parts of the metal surface. In one rat there was a very thin layer of fibrous tissue or organised haematoma bilaterally.

After two weeks of movement, the surface against the metal still consisted of bone but there were also local areas of soft tissue. These foci had an appearance similar to that seen later, when an entire membrane had formed (Fig. 5). At six weeks of movement, only small areas of bone contact were seen. The different soft-tissue foci had united to form a fibrous tissue membrane with a mean thickness of 0.1 mm (Table II). This membrane was thinner than the original localised soft-tissue foci (ANOVA and Fisher PLSD: p < 0.01).

The membrane consisted of cells with spindle-shaped nuclei and an abundant extracellular matrix rich in fibrous material orientated parallel to the surface. There was an abrupt but irregular border between the fibrous tissue and the underlying bone, similar to that between articular cartilage and its underlying bone. The deepest layer of the fibrous tissue was rich in capillaries and larger vessels. In some regions, small areas of fibrocartilage could be seen. These were either in the middle layer or close to the surface.

Effect of movement and particles. Membranes had formed similar to those described for movement alone (Fig. 6). There was no difference in thickness between specimens that had received particles and the opposite control specimens, but there was a trend towards less bone contact (p < 0.07). In specimens that had received particles, cartilage occurred less often (Wilcoxon signed-rank test, p < 0.04). There was no obvious qualitative difference between the membranes. There were few particles within the entire soft-tissue volume and large concentrations in the deepest layer. In some cases, the particles appeared to have been transported into the marrow cavities of the underlying bone, where they lay in concentrations together with cells, the nuclei of which were deformed. There was no obvious inflammatory reaction around these areas.

Effect of particles in a stable fibrous interface. In the particle-free control specimens, seven of the nine implants had regained bone-to-metal contact over almost the entire surface, whereas two implants still had intact membranes. The specimens with particles showed bone contact on most parts of the surface in only one of eight cases (blinded observations, Fisher’s exact test p = 0.01). The membranes appeared thicker than those studied after six weeks of movement and consisted predominantly of cells with spindle-shaped nuclei surrounded by fibrous material parallel to the surface. Most of the particles were found in the deepest layer and in many cases had been transported into intertrabecular areas in the bone (Fig. 7). No obvious inflam-
information was seen, but the fibrous orientation was somewhat less regular than in the specimens which had been harvested directly after six weeks of movement.

DISCUSSION

This is the first study in which the effect of particles has been investigated at a stable, mature interface outside a joint and in which the effects of particles and movement have been compared. We did not find evidence of osteolysis due to particles at the stable interface, although particles were seen in marrow cavities just beneath the interface. We do not think that this was caused by a short exposure time, because in one case, in which there was inflammation around the implant for unknown reasons, possibly infection, we saw dramatic bone resorption. This demonstrates that a large volume of bone underneath the plate can be resorbed if the right stimulus is applied. The test implants were placed in a fresh bone wound, similar to a joint replacement and the tissue that formed along its surface was newly regenerated. Whether or not this membrane grew from traumatised endosteal or cortical bone is unlikely to influence its characteristics. Since it has been shown that macrophages are activated by particles of the size that we used (Gelb et al 1994), it is striking that they did not cause resorption. It is possible that submicron particles could have a different effect, as their larger total surface area could cause a stronger macrophage response (Gelb et al 1994), but almost all experimental support for particle-induced loosening is based on particles of the size which we used.

One main difference between our model and the interface with a prosthesis is the absence of synovial fluid. Under all the conditions which we tested, the response to particles appeared to be more benign than the response to movement. Two weeks after insertion, when movement was started, a bone-metal interface had developed. After two weeks of movement, localised areas of bone resorption and soft-tissue metaplasia had increased in thickness to more than the thickness of the final membrane. Later, after two to six weeks of movement, these soft-tissue foci had combined to form a continuous fibrous membrane. This spreading pattern of the fibrous tissue suggests that membrane formation is an effect of local factors close to the surface; its depth indicates that this is an adaptation to mechanical demands rather than a direct effect of abrasion. When movement and particles were tested at the same time, the particles appeared to have only minor effects. This again seems to indicate the relatively benign character of the presence of particles.

The only situation in which we were able to demonstrate a clear effect of the particles was when a fibrous interface had been created and then left without further movement. In the presence of particles the membrane was preserved whereas without particles it changed back to bone.

In our model the particles were larger than most of those in the human loosening membrane, and there was no joint cavity. No conclusions can therefore be drawn with regard to the clinical loosening of implants. Our findings, however, would fit in with a concept of loosening of prostheses in which initial instability together with necrosis of the superficial layer of the bone bed leads to the formation of a fibrous tissue membrane. Later, when particles have accumulated in this fibrous tissue, their presence prevents direct contact between the bone and implant, which may cause the more aggressive granulomas often found in the final stage.

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REFERENCES


