Fluid pressure may cause periprosthetic osteolysis

Particles are not the only thing

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Early prosthesis migration predicts late clinical failure, as also does the shape or position of, e.g., a femoral stem. These factors appear unrelated to wear particles. Thus, the initiation of the loosening process has other causes. After this process has started (i.e., the prosthesis migrates), particles may play a role, at least by inhibiting new bone formation at the membrane, but the hypothesis of pressure-induced bone resorption appears easier to support by animal experiments and accords with mechanical risk factors.

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Particles do not initiate loosening

The hypothesis of particles as the primary cause of prosthetic loosening has become an orthopedic paradigm. However, this hypothesis is hard to reconcile with some recent observations, mainly the fact that femoral stem migration exceeding 0.8 mm during the first postoperative 6 months can predict loosening several years later (Kärrholm et al. 1994). Similar relations exist for knee prostheses. The only explanation of a role for particles in the connection between early migration and late loosening would be that early instability causes increased particle production. This is possible, but the role of particles (if any) then becomes secondary to instability. A concise but comprehensive review by Mjöberg (1994) reveals that the "theory of wear-induced loosening" requires more ad hoc assumptions than the "theory of early loosening". The idea that particles are the single cause that sets off loosening is therefore obsolete.

Once the prosthesis is loose, as defined by roentgen stereometric assay (RSA; Selvik 1989), it must be surrounded by a membrane of non-osseous tissue. Not all prostheses that are loose according to this criterion (initial loosening) will gradually cause osteolysis and symptoms that indicate revision (i.e., "clinical loosening"). We cannot explain what drives the process from initial loosening to clinical loosening. However, we know that mechanical factors are important, since the risk is higher for physically more active patients (Sutherland et al. 1982). Mechanical factors may increase particle production, but they may also cause bone loss by other, more direct mechanisms.

It is theoretically impossible to prove that particles are harmless: we can only introduce particles into various in vivo models and demonstrate the absence of bone resorption. Experiments are models, and it can always be claimed that the model differs from reality. However, we have failed to induce bone loss by introducing HDPE particles into a bone implant interface in rats, whereas osteolysis was easily induced by mechanical instability in the same model (Aspenberg and Herbertsson 1996). In other experiments, large amounts of particles of UMWPE, HDPE, Ti alloy, CoCr alloy, zirkonium oxide or latex failed to induce bone resorption after intra-articular injection and after placement in the marrow cavity together with a PMMA implant (Van Der Vis et al. 1997a). Other models, which have been interpreted to show particle-induced osteolysis (e.g., the dog hip prosthesis model by Dowd et al. 1995), may in fact, have shown instability-induced osteolysis due to particles inhibiting porous ingrowth, so that initial stability was never achieved. Particles are found in granulomas associated with osteolysis (Maloney et al. 1990a, Santavirta et al. 1990). Since such granulomas are difficult to induce by intraosseous particle implantation (Aspenberg and Herbertsson 1996, Van Der Vis et al. 1997a) and, since particles are not always present in the granulomas (Linder et al. 1983, Maloney et al. 1990b), it appears that other factors, related to a synovial environment, are necessary for granuloma formation, and the role of the particles is not clear.

There is one deleterious effect of particles which is not often mentioned, but which may be important: particles can *inhibit bone formation* in several models, such as bone chambers (Goodman et al. 1995, Goodman et al. 1996), the instability model in which HDPE particles, by themselves, appeared harmless (Aspenberg and Herbertsson 1996) or the marrow cavity with a PMMA implant (Van Der Vis et al. 1997a). Since bone resorption around an implant is the result of a negative balance between formation and resorption (Linder et al. 1983, Kadoya et al. 1996), this finding allows for a role of particles, once a membrane is formed around the prosthesis. However, particles are only one of several possible causes of net bone loss at this stage.

The aim of this paper is not to refute the paradigm that particles initiate loosening (which was already done by Mjöberg 1994), but to describe fluid pressure as a possible cause of the progress from initial lack of stability to large periprosthetic osteolysis and clinical loosening.

Pressure can cause osteolysis

Several years ago, we tried to create models for particle-induced osteolysis in vivo. First, we tried to repeat the study by Howie et al. (1988) in which particles were injected into rat knee joints with a PMMA plug in the femur. We never managed to produce any bone resorption. Howie later reported difficulties with the same model (Howie et al. 1993). In order to obtain meaningful interpretations also of a negative result, we instead analyzed synovial reactions to particle injections into joints and the effect of particles directly placed in bone marrow adjacent to intraosseous PMMA implants (Van Der Vis et al. 1997a). At the same time, we tried to modify the chamber model in which we had shown decreased bone ingrowth in the presence of micromotion or particles (Aspenberg et al. 1992, Goodman et al. 1995) to study the resorption of preexisting cortical bone after infusion of particles. Since we had concluded from the rat studies that particles were rather benign (Van Der Vis et al. 1997a), and it appeared that pressure could be a cause of osteolysis (Landells 1953), we decided to use the new chamber model for pressure studies instead. The idea was to test the hypothesis that fluid pressure waves around a prosthesis not only provide a mechanism for particle transport, but in themselves may cause osteolysis (Anthony et al. 1990, Mjöberg 1994).

In brief, we applied a cp titanium surface towards cortical bone in rabbits, after excising the periosteum. At 6 weeks, there was a tight fit between bone and titanium, as is generally seen with osseointegrated titanium. Then a small area under the implant was subjected to a constant fluid pressure of 150 mm Hg for 2 weeks (Van Der Vies 1997, Van Der Vies et al. 1997b). This led to massive bone resorption, exactly under the pressurized area. Further, the granulation tissue replacing parts of the resorbed bone appeared histologically similar to a "loosening granuloma". We found large amounts of macrophages containing particles! These particles appeared, using von Kossa staining, to be bone debris. The experiment was then repeated with 2 hours of daily pressurizing using a fluctuating pressure between 50 and 150 mmHg (Van Der Vis 1997, Van Der Vis et al. 1998). Bone resorption in this case was also reproducible, but much smaller volumes were resorbed. In a third experiment, micromotion was instead applied to the implant (Van Der Vis 1997). Again, this led to local bone resorption, but also to the formation of fibrocartilage in the loaded areas. These simple experiments clearly show that a moderate pressure rise at a bone implant interface can lead to considerable bone resorption, replacement of the resorbed bone with granulation tissue and even the production of debris particles in the absence of micromotion.

Is a similar pressure present in clinical situations? Yes, indeed. Fluid pressures in pseudojoints after hip replacements have reached 700 mmHg (Hendrix et al. 1983). High intracapsular pressures are common in loose hip prostheses, and cause capsular distension by ultrasound (Robertsson et al. 1997). The capsular distension is less in cases without clinical loosening, indicating indirectly that the pressure also may be lower (Robertsson et al. 1997). It is of course hard to measure the pressure in the interface, but there is one report of 200 mmHg in an osteolytic resorption cavity adjacent to a hip prosthesis (Anthony et al. 1990). Further, by finite element analysis the pressure under, e.g., a tibial knee component can reach 0.7 Mpa (5,000 mmHg; Giori et al. 1995). The cystlike osteolytic areas involved in prosthetic loosening are quite similar to osteoarthrosis cysts (Schmalzried et al. 1997), which may also be caused by pressure increase in the joint, forcing fluid through cartilage defects into the surrounding bone (Landells 1953).

Local fluid pressure gradients will lead to interstitial fluid flow. This may have a strong effect on differentiating mesenchymal tissue (e.g., an attempt to repair the interface). In the model of an unstable implant by Søballe 1993, it was shown with a type of finite element analysis that differentiation towards bone formation is inversely related to the local tissue flow in the periprosthetic tissue (Prendergast et al.

1997). The pressure changes in our model as well as in the clinical measurements are probably orders of magnitude higher than those pressures which induce intraosseous fluid flow on the loading of healthy bone. At these normal levels, the intraosseous fluid flow is thought to mediate bone formation (Duncan and Turner 1995). On the other hand, the much higher flows that may be induced by prosthesis instability, and which were used in our experiments, caused osteocytes to disappear from the bone close to the pressurized area. It appears that a high pressure or flow can damage superficial osteocytes or cause osteocyte apoptosis, which can spread further down into the bone (Qui et al. 1997). Thus, we believe that the effect of high pressure is to kill osteocytes rather than somehow stimulate osteoclasts. The dead bone will then be resorbed by osteoclasts just as in other cases of osteonecrosis (Resnick and Niwayama 1995). Indeed, this is a parallel to the initial situation, when the joint replacement is implanted: Osteocytes immediately adjacent to the implant can hardly survive the surgical trauma (not to mention high-pressure lavage, cement-curing heat, monomer leakage, etc). The dead superficial bone layer towards the cement is likely to be resorbed as an osteonecrotic zone. As with osteonecrosis of the femoral head, this causes a risk of a transient phase of mechanical failure, leading to instability (Glimcher and Kenzora 1979, Resnick and Niwayama 1995). Once the prosthesis is unstable, motion will cause dramatic fluid pressure changes at the interface. In the extreme case, with an easily deformed interface tissue and nowhere for its fluid content to escape, the entire load will be transformed to fluid pressure. This means that we can connect instability with fluid pressure changes as in our experiment with the unstable chamber. In this experiment, we used repeated mechanical loading of an interface with a 50 μm fluid and soft tissue gap between metal and bone. Appearantly a deleterious fluid pressure was created: a compressive force that was lower than what the bone can resist mechanically, caused death and resorption close to the fluid space (Van Der Vis 1997). In clinical cases of loosening, disappearance of osteocytes has been noted in the bone adjacent to lytic lesions (Maloney et al. 1990b). The opposite finding—living osteocytes near a lesion—would conflict with our hypothesis only if one assumes that lytic lesions expand continuously.

In summary, both pseudojoints and periprosthetic membranes have shown highly elevated local pressures during motion. A fluid pressure of the same magnitude induces osteocyte death and subsequent bone resorption in an animal model. This explanation of prosthetic loosening appears to accord with clinical observations, such as the predictive value of mechanical risk factors and early migration.

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