INTRODUCTION
Particles, instability or fluid pressure have been proposed as mechanisms leading to periprosthetic bone resorption. High intracapsular pressures have been reported in hip joints with loose prosthetic components (1). Animal experiments indicate that oscillating fluid pressure can lead to osteolysis (2,3). Osteolysis is caused mainly by osteoclastic activity. Osteoclasts can be inactivated by alendronate, a drug in clinical use against osteoporosis (4). We investigated whether treatment with alendronate can inhibit pressure-induced bone resorption. We used a previously described rat model, in which hydrostatic pressure fluctuations were applied to bone via body fluids by compressing a soft tissue membrane adjacent to bone (3).

METHODS
The pressure plate consists of a titanium plate with a threaded hole in the middle containing a pressure piston. The piston is connected to a surrounding spring, which is also connected to the plate, in order to keep the piston away from the bone, when being unloaded. When external loading (described below) counteracts this spring, the piston moves 0.5 mm towards the bone from a starting position 1 mm away. The size of the plate is 6 x 13 mm. The piston is 9 mm high and has a polyethylene lining around it with a total diameter of 3 mm (Figure 1).

The plate is implanted without the piston, to allow a flat bone surface to form under the central hole while the implant osseointegrates. During this period, the hole in the plate holds a Ti-plug. In a second operation 5 days prior to loading, the plug is replaced by the piston. When the piston is in place, there is a 1 mm wide space between the piston and the cortical bone, which has formed under the plug. This gap allows soft tissue formation. By applying force on the piston, load is transmitted to this soft tissue. This is done through the skin using a dynamometer. When loading is interrupted, the piston returns to its original position by means of the spring. The movement of the piston is limited to prevent it from reaching the bone.

21 Sprague-Dawley rats were operated on at the proximal tibia. The tibial cortex was abraded corresponding to the central plug and the plate was implanted. After 28 days of osseointegration the central plug was replaced by the piston. 5 days were given for fibrous tissue to form between the plug and the bone after the second operation. Thereafter, a cyclic pressure of 0.17 Hz. The rats were killed after 5 days of loading. 14 animals were treated with alendronate and 7 animals served as unloaded controls. Among the loaded animals, 7 were given alendronate in a dose of 205 µg/kg and day, and 7 animals were given corresponding volumes of NaCl, in all cases as subcutaneous injections three times a week starting one week after the initial operation. Histological sections were produced at a right angle to the loaded surface. Evaluation was made by blinded observation of whether the cortical bone under the plate had an intact continuity or not. Statistics was done with Fishers exact test. Approval of the Institutional Review Board was obtained before the study was started.

RESULTS
Results are given in table 1. One animal was lost during operation. All loaded controls except one had lytic lesions in the cortical bone under the plate, so that communication between the pressurized membrane and the marrow cavity had been established. New woven bone had formed deeper in the marrow and walled off a cystic lesion. The lesions contained a granulomatous tissue with fibroblasts, macrophages and capillaries, but few polymorphonuclear or round cells. When studied under polarized light, no sign of polyethylene debris was seen. In alendronate treated rats the cortical bone under the plate was intact, although with increased numbers of trabeculae in the underlying marrow space. In some specimens, signs of bone resorption and multi-nucleated cells were seen in Howship’s lacunae. Some of these suppressed osteoclasts had an altered morphology. Most unloaded controls showed intact cortical bone. The difference between loaded and unloaded controls was significant (p=0.05), and so was the effect of alendronate (p=0.004).

<table>
<thead>
<tr>
<th>Bone Condition</th>
<th>Pressure+ saline</th>
<th>Pressure+ alendronate</th>
<th>No pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact bone</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Resorbed bone</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1.

DISCUSSION
This study confirms that a hydrostatic pressure rise at a bone implant interface leads to considerable bone resorption. Furthermore, it would seem that alendronate can reduce this resorption. Alendronate inactivates osteoclasts, so we conclude that the pressure-induced bone resorption in this model is mediated by osteoclasts.

However, the used alendronate dose was high. In humans, the recommended dose for treatment of osteoporosis is 1 µg/kg/day. This dose has effect on osteoclastic activity associated with bone remodelling. In previous rat studies we used a similar dose (3,8 µg/kg/day) and instability without pressure rise for inducing bone resorption (5). This dose had a strong effect on the remodelling of normal bone but not on the instability-induced bone resorption. In the present study we used 205 µg/kg/day. Even with this high dose we could see multi-nucleated cells in Howship’s lacunae in some alendronate treated animals. The bone resorption in these specimens was however not enough to penetrate the entire thickness of the cortical bone. This would imply that osteoclasts are being recruited and activated in large numbers but are inactivated by the alendronate after a comparatively short period of resorptive activity. This is in accordance with proposed mechanisms of action for alendronate, which is supposed to adhere onto bone mineral and inactivate the osteoclasts when sufficient amounts of alendronate-containing material has been ingested. In order to achieve a total inhibition of osteoclastic activity, high doses of alendronate might be necessary when the bone resorbing stimuli is strong, as seems to be the case with oscillating fluid pressure.

References:
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