# Increased metal release from cemented femoral components made of titanium alloy

## 19 hip prostheses followed with radiostereometry (RSA)

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**In 19 patients the concentrations of metal were measured in serum, urine and joint fluid 2 years after implantation of uncemented commercially pure titanium acetabular cups and cemented or uncemented femoral components made of titanium alloy. A ceramic against the polyethylene articulation was used. The fixation of the components was followed with radiostereometry (RSA). Samples from 12 patients scheduled for hip or knee prostheses and without any metallic implant were used as controls.**

**High levels of titanium were found in cemented hips and when large acetabular cups had been inserted. Increased aluminum levels were also noted in the cemented hips. Vanadium was not detected in any of the samples. Micromotions were detected in most of the implants, but the magnitude of these movements could not be used to predict the release of metal into the synovial fluid.**

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The release of metals from joint implants made of titanium alloy has not been systematically investigated and its clinical consequences have not been established. Increased levels of titanium in serum (Dorr et al. 1990, Jacobs et al. 1991) and synovial fluid (Brien et al. 1990a, Dorr et al. 1990) have been documented in clinically loose implants. However, some of these studies were difficult to interpret because of potential methodological errors and a multitude of hip prosthetic designs with varying times of implantation (Jacobs et al. 1991, Sampath 1992).

We evaluated the influence of fixation on titanium, aluminum and vanadium levels in serum, urine and synovial fluid 2 years after surgery in patients with hip joint replacements of the same design. Radiostereometry (RSA, Selvik 1974, 1989) was used to measure accurately the migration of the prosthetic components.

## Patients and methods

In 19 (11 men, 8 women) out of 36 consecutive patients operated in a series randomized to cemented or cementless fixation of the femoral component, samples of blood, urine and joint fluid were obtained 2 years after surgery. The aspiration of joint fluid was approved by the local ethics committee.

The mean age at surgery was 54 (38–66) years. 2 surgeons performed the operations through a posterior approach. In the cemented group, femoral canal preparation included high pressure lavage, brushing, distal cement restrictor, tamponade and retrograde filling of vacuum-mixed cement. In the cementless group, the surgeons aimed at an optimum fill, using intramedullary reamers and broaches supplied with the instrumentation. A modular 32 mm ceramic (aluminum oxide) femoral head was used in all patients. Press-fit cementless acetabular cups with titanium fiber mesh and fixed with screws (Harris-Galante I or II, Zimmer, Inc.) were inserted in all the hips.

All patients received a Tifit femoral component (Smith and Nephew) of the same basic design and made of Ti-6%Al-4%V alloy. 9 were cemented. The surface of the prostheses used for cemented fixation was grit-blasted, using aluminum oxide (surface roughness 0.75–1.0 μm, Ra). 7 of the 10 cementless prostheses were coated with hydroxyapatite (HA, Cerasiv). The coating surrounded the proximal third of the prostheses. According to the specification of the manufacturer, this coating had a thickness of 200 ± 50 μm, purity of 98%, porosity of 20% and a shear strength of 17 MPa. The distal two thirds had a grit-blasted surface. 3 implants had proximal porous coating (P) made of commercially pure titanium beads (average pore size 230 μm).

Samples from 12 patients scheduled for hip or knee prostheses, and without any metallic implant, were used as controls.

Clinical and conventional radiographic follow-ups were done 2 years after surgery.

### Collection of specimen and analytical procedures

Materials which did not release detectable amounts of aluminum, titanium and vanadium were used for sampling and sample storage. The following materials were found to be suitable for the study: syringes for sampling of blood and synovial fluid, i.e., Viggo Venflow and Terumo (0.8 × 80 mm), respectively; containers for storing blood, urine and joint fluid-acid-washed polypropylene.

Metal concentrations were determined by atomic absorption spectrometry, using a transverse heated electrothermal atomizer with longitudinal Zeeman-effect background correction (Perkin-Elmer Model 4100 ZL). Serum and joint fluid samples were dissolved before the determinations. For this, an aliquot of the samples was transferred to a quartz Erlenmeyer flask with concentrated nitric acid, which had been purified by sub-boiling distillation in a quartz chamber (Slanina et al. 1984). All sample manipulations, except for the determination, were performed in a class 100 environment. For aluminum, which is most prone to contamination, accurate results were obtained when analyzing lyophilized human reference serum with a certified value of 1.8 ng Al/mL in the reconstituted serum. Urine samples were determined without pretreatment. Vanadium in urine was determined according to Shuttler (1992).

Addition of standards was used for calibration. The detection limits for the instrument, defined as the concentrations corresponding to 3 standard deviations for a series of 40 μL blank measurements, were 1.3, 0.8, and 0.4 ng/g for titanium, aluminum and vanadium, respectively. To include uncertainties introduced by sample manipulations, the detection limit was regarded as twice as poor.

### Radiostereometry

At the operation, the hips were prepared for the subsequent radiostereometry (Selvik 1974, 1989) by the insertion of 4–9 tantalum markers in 3 locations: the pelvis, the proximal femur and the polyethylene liner of the cup. Before surgery, 6 tantalum markers had been inserted into the femoral component after predrilling. 2 markers with a distance between each other of 3–4 cm had been inserted into the prosthetic shoulder. 2 markers represented the tip, 1 central and 1 medial. Another 2 were placed along the medial border of the prosthesis.

Radiostereometric examinations were done within 1 week after surgery and at 2, 6, 12, and 24 months after the operation. Uniplanar technique was used at the radiostereometric examination, initially with separate calibration equipment and reference plates (Baldursson et al. 1979). At the 2-year follow-up, a more modern cage was used which was placed under the examination table and immediately above the film cassettes. This set-up has a better precision than the older one (Önsten et al. 1994). In the present study, the precision of the older technique was used. Motion exceeding 2.7 SD of the error of the radiostereometric method was regarded as significant (Kärrholm and Snorrason 1992, Kärrholm et al. 1992).

Proximal-distal migration of the femoral component was measured at the prosthetic center corresponding to the gravitational center of the prosthetic markers. If all markers not could be visualized on the radiographs, the mean migration of the tip and shoulder markers were recorded. In addition, the total translation (vectorial sum of the medial-lateral, proximal-distal and anterior-posterior translation) of the markers inserted in the prosthetic shoulder and tip was recorded. Migration of the acetabular component was measured as translation of the gravitational center of the markers inserted into the edge of the polyethylene insert. Rotations could be evaluated in 13 femoral and 17 acetabular components. In 2 acetabular prostheses, both with cemented femoral components and 6 femoral prostheses (2 C, 4 HA), poor visualization or configuration of the prosthetic markers made evaluation of rotation uncertain or impossible.

## Results

### Titanium

Increased concentrations of titanium were found in the prosthetic joints (cemented vs. controls: $P < 0.0005$; cementless vs. controls: $P < 0.03$, Wilcoxon rank sum test, Figure 1). The cemented components displayed higher values than the uncemented ones ($P < 0.0005$, Wilcoxon rank sum test). The 2 groups of uncemented fixation were similar. Titanium could not be detected in serum or urine.

### Aluminum

Increased concentration of aluminum was found

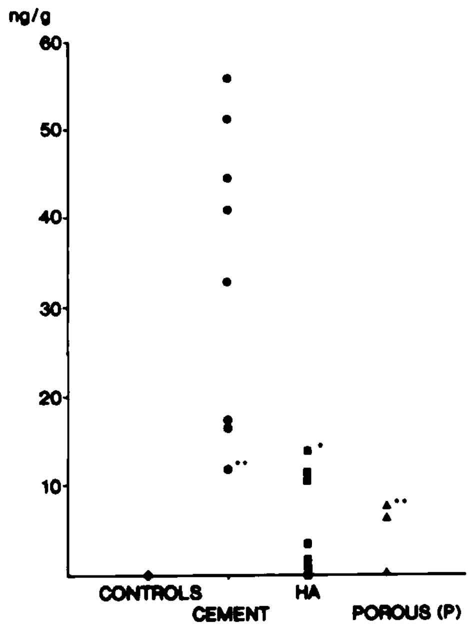


Figure 1. Concentration of titanium in synovial fluid. Controls indicated by the median value. One of the samples (cemented femoral component) could not be analyzed for titanium. No migration (* stem and ** stem and cup) indicates that all the parameters measured to represent migration were smaller than the error in the RSA (99 percent confidence limit, 2.7 SD).

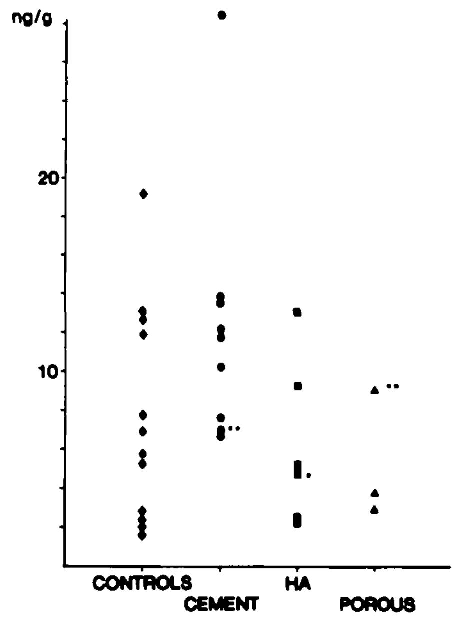


Figure 2. Concentration of aluminum in synovial fluid. No migration (* stem and ** stem and cup), see Figure 1.

**Table 1. Metal concentrations (ng/g) in synovial fluid, serum and urine. Median (range)**

| | Cemented | HA-coated | Porous | Controls |
|---|---|---|---|---|
| Ti/synovial fluid | 37 (12–56) | 3.5 (0–14) | 6.4 (0–7.8) | 0 (0–7.5) |
| Al/synovial fluid | 12 (6.7–28) | 5.2 (2.6–13) | 3.8 (2.9 –9.1) | 7.3 (1.9–19) |
| Al/serum | 2.1 (0–11) | 1.4 (0–5.9) | 5.7 (2.1–16) | 3.7 (0–17) |
| Al/urine | 6.2 (1.7–17) | 4.9 (1.7–7.0) | 4.2 (3.7–4.6) | 4.6 (2.1–14) |

when cemented fixation of the femoral component had been used (cement vs. no cement: $P < 0.01$, Wilcoxon rank sum test, Figure 2, Table 1), but did not differ from the controls (cement vs. controls $P > 0.05$).

The serum and urine levels varied between 0 and 17 ng/g in the patients with hip prosthesis and the controls (not significant, Kruskall-Wallis one way ANOVA). In the controls and in the cemented group, the concentration of aluminum in joint fluid was higher than in serum ($P < 0.05$, sign test). Increased aluminum in joint fluid also tended to imply increased amounts of titanium ($r$ 0.52, $P < 0.05$, Spearman rank correlation).

### *Vanadium*

No significant levels of vanadium were detected in any of the samples.

### *Radiostereometry*

The median proximal-distal migration of the femoral components varied between –0.13 and +0.13 mm throughout the observation period (Table 2). Smaller total translations were recorded at the shoulder than at the tip of the prostheses ($P < 0.01$–$0.001$, sign test, Table 3). 2 years after the operation, the most pronounced rotations had occurred when measured around the longitudinal axis. One porous-coated hip which, 2 years after surgery, displayed the most pro-

Table 2. Proximal (+) or distal (–) migration (mm) of the center of the femoral component. Median (range)

| | Cemented | HA-coated | Porous-coated |
|---|---|---|---|
| 2 months | 0.02 (–0.27–0.21) | 0.04 (–0.42–0.16) | 0.02 (–0.07–0.10) |
| 6 months | 0.06 (–0.20–0.37) | 0.10 (–0.9–0.22) | 0.04 (–0.18–0.06) |
| 1 year | 0.00 (–0.18–0.15) | 0.13 (–1.2–0.40) | –0.09 (–0.44–0.06) |
| 2 years | –0.13 (–0.59–0.28) | 0.04 (–1.2–0.25) | 0.07 (–1.25–0.11) |

Table 3. Total translations (mm) of the shoulder and tip in the femoral components. Median (range)

| | Cemented | | HA-coated | | Porous-coated | |
|---|---|---|---|---|---|---|
| | Shoulder | Tip | Shoulder | Tip | Shoulder | Tip |
| 2 months | 0.22 (0.10–0.42) | 0.53 (0.38–0.92) | 0.3 (0.08–0.60) | 0.89 (0.39–1.97) | 0.22 (0.05–0.50) | 0.74 (0.69–1.20) |
| 6 months | 0.20 (0.12–0.36) | 0.72 (0.29–0.96) | 0.25 (0.14–1.91) | 1.35 (0.35–7.85) | 0.37 (0.13–1.28) | 0.68 (0.20–1.70) |
| 1 year | 0.23 (0.19–0.56) | 0.92 (0.16–2.40) | 0.32 (0.19–1.73) | 1.23 (0.31–7.44) | 0.32 (0.23–1.35) | 1.32 (0.81–1.49) |
| 2 years | 0.35 (0.13–0.75) | 1.04 (0.50–2.20) | 0.45 (0.17–1.01) | 1.48 (0.30–7.05) | 0.25 (0.12–2.83) | 1.72 (0.81–2.06) |

Table 4. Translations (mm) of the acetabular cup center. Total translations refer to the vectorial sum of the medial-lateral, proximal–distal and anterior–posterior translations. Median (range)

| | Medial–Lateral | Proximal–Distal | Anterior–Posterior | Total |
|---|---|---|---|---|
| 2 months | 0.25 (0.00–0.62) | 0.10 (0.00–0.28) | 0.22 (0.01–0.69) | 0.36 (0.12–0.67) |
| 6 months | 0.28 (0.02–1.02) | 0.13 (0.02–0.48) | 0.30 (0.03–1.60) | 0.56 (0.10–1.67) |
| 1 year | 0.21 (0.01–1.20) | 0.09 (0.01–0.54) | 0.50 (0.09–1.59) | 0.58 (0.24–2.0) |
| 2 years | 0.24 (0.03–1.22) | 0.12 (0.00–1.06) | 0.47 (0.01–1.80) | 0.56 (0.16–1.8) |

nounced retroversion (7.7 degrees) also subsided more than any of the other implants. There were no differences among the 3 groups of fixation for any of the motions evaluated (Kruskall-Wallis one-way ANOVA).

The median migration of the cup center along the 3 coordinate axes reached 0.5 mm or less during the 2 postoperative years (Table 4). The vectorial sum of these translations increased up to 6 months after the operation (2 versus 6 months, $P$ 0.02, sign test). Thereafter, most of the cups tended to stabilize (6 vs. 12 and 24 months, $P > 0.05$, sign test). The median cup rotations were smaller than 1 degree. One cup, however, displayed pronounced rotations about the transverse (11.2 degrees) and longitudinal axes (11.8 degrees). The magnitude of cup migration did not differ between the 3 groups of femoral fixations (Kruskall-Wallis one-way ANOVA).

The migration or rotation of both of the prosthetic components exceeded the chosen detection limit (2.7 SD of the error of the RSA method) in 16 of the 19 hips. In another case, only cup motions were detected (Figures 1 and 2).

Conventional radiographic examination 2 years after surgery revealed no signs of osteolysis.

### Regression analysis

The use of cement ($P < 0.00005$), high weight ($P < 0.01$) and increasing size of the press-fit cup ($P < 0.01$) were associated with high levels of titanium in the synovial fluid (stepwise linear regression analysis; adjusted $R^2$ 0.83), whereas the size of the migration of either component was not. Aluminum in joint fluid was more difficult to predict. Of the variables recorded, only the use of cement had an influence ($P < 0.05$, adjusted $R^2 = 0.28$).

## Discussion

Metal ions and metallic debris released or abraded from joint implants may have local effects in terms of toxicity and may also play a part in aggressive granulomatous lesions. Particulate titanium and titanium alloy have been shown to increase the calcium release from mouse calvaria (Molnar et al. 1991) and increase interleukin-1 and $PGE_2$ levels in the culture media of human macrophages (Bennet et al. 1991). Metallic debris can be found in lymphoreticular tissue far away from the prosthesis (Langkamer et al. 1992) and increased serum levels of metal ions have been found in patients with loose implants exposing distant organs (Brien et al. 1990a, Dorr et al. 1990, Jacobs et al. 1991). Formation of tumors has been reported around prostheses made of stainless steel or chromium-cobalt alloy (Penman and Ring 1984, Weber 1986, Brien et al. 1990b, Troop 1990) but, according to our knowledge, not in association with titanium alloy.

Jacobs et al. (1991) investigated serum and urine levels of titanium, aluminum and vanadium in 12 hips with chromium cobalt against the polyethylene articulation 2 years or more after implantation. All had clinically successful and radiographically stable cementless Harris-Galante prostheses. Moreover, one group of patients had hip prostheses with a femoral head made of titanium alloy. Neither of the groups had increased levels of metal compared to controls. In an update of this study, high serum titanium levels were recorded in loose prostheses with titanium alloy bearings (Jacobs et al. 1992) and it was suggested that articular wear was the dominant source of metal. On the contrary, Witt and Swann (1991) believed that stem abrasion was more important, based on the finding of surface marks in 13 TiAlV alloy femoral components reoperated because of early loosening. In a retrieval study of well-functioning hip prostheses, Jasty et al. (1991) found signs of stem motions inside the cement mantle in all 16 specimen analyzed. In our study of prostheses with non-metallic articulations, micromotion of the femoral stem could be detected in almost all patients suggesting that abrasive wear of the stem against the cement and, in the cementless cases, against the bone was of importance.

Jacobs et al. (1991) noted that serum levels of aluminum were slightly lower than ours, whereas the urine levels were equal or slightly higher, depending on the type of prosthesis studied. Neither this study nor ours showed increased serum levels in patients with hip replacements, but this does not rule out accumulation in the tissue (Woodman et al. 1984)

For unexposed persons, the levels of urinary vanadium have been reported to be 0.29–0.33 ng/mL (Apostoli et al. 1984, Fleischer et al. 1991), which is below our detection limit. In serum of unexposed persons, vanadium is present in less than 1 part per billion. Thus, an absence of vanadium in the serum and urine could be expected if no excessive release was present. No vanadium was detected in the synovial fluid but, based on the relative amount of vanadium in the alloy, this substance could be expected in samples with high titanium levels. Faster clearance of vanadium from the synovial fluid might be one explanation. The source of the titanium may also partly be wear of the acetabular component.

Increased abrasive wear on the femoral component implies that there are elevated amounts of cement and metallic particles in the joint exposing the softer titanium in the acetabular shell. In the laboratory, titanium particles have been found to seriously increase the wear of metallic femoral heads (McKellop and Röstlund 1990). In our study, cement and titanium alloy particles from the femoral component might have increased the release of titanium from the junctions between the acetabular shell and the screws or the polyethylene insert (Guffman et al. 1994). The recorded rotations could have indicated movements of the polyethylene insert inside the metallic shell, particularly in the implant that displayed rotations of about 11 degrees about the transverse and longitudinal axes. The correlation between titanium and aluminum in joint fluid might reflect concomitant release of aluminum from the alloy or increased wear of the ceramic-polyethylene articulation.

Absence of measurable levels of titanium and vanadium in serum and urine in our patients is encouraging, even if this finding does not rule out long-term effects. No adverse effects could be attributed to the high levels of titanium and aluminum in the synovial fluid, but possible effects such as accelerated wear, osteolysis and loosening cause concern.

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