Metal ion levels after metal-on-metal proximal femoral replacements

A 30-YEAR FOLLOW-UP

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Metal-on-metal hip bearings are being implanted into younger patients. The consequence of elevated levels of potentially carcinogenic metal ions is therefore a cause for concern. We have determined the levels of cobalt (Co), chromium (Cr), titanium (Ti) and vanadium (Va) in the urine and whole blood of patients who had had metal-on-metal and metal-on-polyethylene articulations in situ for more than 30 years. We compared these with each other and with the levels for a control group of subjects.

We found significantly elevated levels of whole blood Ti, Va and urinary Cr in all arthroplasty groups. The whole blood and urine levels of Co were grossly elevated, by a factor of 50 and 300 times respectively in patients with loose metal-on-metal articulations when compared with the control group. Stable metal-on-metal articulations showed much lower levels. Elevated levels of whole blood or urinary Co may be useful in identifying metal-on-metal articulations which are loose.

The first recorded metal-on-metal articulation was performed by Wiles in 1938, but it was not until the late 1950s that McKee and Watson-Farrar popularised this bearing surface using cobalt chrome-molybdenum. Various prostheses, including the McKee-Farrar, Ring, Stanmore and Müller total hip replacements employed this bearing surface. In the late 1970s, metal-on-metal articulation lost favour mainly because of the success of the Charnley metal-on-high-density-polyethylene bearing.

There were concerns about increasing friction which was shown in vitro to cause ‘cone-clutching’, and about carcinogenesis and metal sensitivity.

The association between polyethylene wear debris and osteolysis in cases of aseptic loosening when a polyethylene cup is used has led to a resurgence of interest in metal-on-metal articulations. New designs of such articulations are being used in younger patients whose life expectancy may be more than 40 years. Concerns are now being raised about metal wear debris and its systemic distribution through the body, with particular reference to potentially carcinogenic metal ions.

Our aim, therefore, was to study a group of patients who had metal-on-metal articulations in situ for more than 30 years and to measure the concentrations of metal ions in their blood and urine.

 Patients and Methods

Between 1965 and 1979, 25 metal-on-metal proximal femoral replacements were carried out for the treatment of primary bone tumours. Of the 25 patients, 13 (52%) have died, nine (36%) from metastatic disease and four (16%) from other causes. Eleven (44%) are still alive and one (4%) has been lost to follow-up. The diagnoses included a mixture of benign and malignant tumours including chondrosarcoma (13), osteoclastoma (six), fibrous histiocytoma (two), Ewing’s sarcoma (one), fibrous dysplasia (one), osteosarcoma (one) and synovial chondromatosis (one).

There were 14 men and ten women with a mean age at the time of surgery of 45 years (15 to 70). The mean follow-up period was 30 years (24 to 38).

The mean age at the time of surgery of the 11 survivors (five men and six women) was 33 years (15 to 49) and the mean follow-up period was 33 years (26 to 38). All the surviving patients have led full, independent and active lives. Five retain their original metal-on-metal prostheses (mean follow-up 32 years) while the rest have been revised to a metal-on-polyethylene articulation because of aseptic loosening, mainly of the acetabulum, at a mean of 22 years after surgery (18 to 26).

Prostheses. Throughout the period of our study, there has been an evolution in design as described by Dobbs et al. All implants were...
manufactured from vacuum-cast cobalt-chrome-molybdenum alloy. The acetabular fixation was changed from a two-component uncemented three-prong design ("milking stool") to a less invasive cemented circumferential ring construct. All the femoral components in our series had heads and necks made from cast cobalt-chrome-molybdenum alloy fitted to cemented intramedullary shafts of commercially pure titanium or titanium alloy.

There were five study groups as follows: group 1, control (four subjects with no implants); group 2, metal-on-polyethylene (two); group 3, metal-on-metal revised to metal-on-polyethylene (five); group 4, metal-on-metal radiologically stable (three) and group 5, metal-on-metal radiologically loose (two). The five surviving metal-on-metal articulations had been implanted for a mean of 32 years (26 to 38); two of the acetabular components were deemed to be radiologically loose (Fig. 1).

Blood sampling. Whole blood and urine specimens were obtained from ten survivors and from the control subjects who were matched for age and gender, and from the two patients with two metal-on-polyethylene components (group 2) of the same era which had been in situ for a mean of 27 years. The femoral components of these two arthroplasties were of the same design and composition as the prostheses described above. The all-polyethylene, cemented cups had been manufactured from ultra-high molecular-weight polyethylene (RCH 1000; Hoescht AG, Frankfurt, Germany). Blood was obtained from the subjects using a stainless-steel hypodermic needle attached to a plastic collecting tube. The needle and collecting tubes were from the same batch and were analysed for possible contamination.

The same person (APS) obtained all the blood samples and the venepuncture was undertaken in the same room for all subjects. The blood and urine specimens were immediately frozen. The levels of cobalt (Co), chromium (Cr), titanium (Ti) and vanadium (Va) were determined using high-resolution inductively-coupled mass spectroscopy, the analysis being performed by Harwell Scientifics, Didcot, UK.

Analysis of samples. The samples were stored at -80°C until analysed. The concentrations of Co, Cr, Ti and Va in whole blood and urine were determined using a GV Instruments Plasmatrace 2 (Manchester, UK). Samples of whole blood were diluted with ultra pure water (Elga Maxima, High Wycombe, UK) with 0.1% Triton X-100; urine samples were diluted with ultra pure water alone. An internal standard of indium (20 ug/l) was added to all samples to monitor and to correct for any instrumental alterations. Calibration was performed using a method of standard additions. For accurate determination of Cr, Ti and Va the instrument was operated at a resolution of approximately 4000 in order to resolve polyatomic interferences present at those mass-to-charge ratios. Quality control samples were prepared by spiking samples of each matrix with known amounts of Co, Cr, Ti and Va obtained from sources different from those used in the calibration. All reagents used were of Sp quality (Romil, Cambridge, UK) and the same ultra pure water was used throughout.

Statistical analysis. The results of the five groups were initially analysed individually in order to calculate the mean level of each ion in whole blood and urine, with a 95% confidence interval (CI). Analyses of variance were then performed for intergroup comparison with respect to the level of each ion in the blood and urine. Given the small number of patients in each group, a p value of < 0.01 was required to define significance. The Scheffe test was used to determine those particular groups which were different.

Results

The mean (95% CI, ng/g) blood and urinary levels of the individual ions presented in Table I.

Cobalt. Blood cobalt levels in group 5 were more than 50 times greater than those of the control group, and urinary levels were more than 300 times greater (p < 0.001). Group 5 also had significantly higher levels in both urine and blood compared with all other groups. Group 4 had considerably higher mean blood and urinary levels of cobalt compared with groups 1, 2 and 3, but this was not statistically significant.

Chromium. Although statistically insignificant, the mean blood level of Cr of group 5 (loose metal-on-metal) was considerably higher (2.7 ± 0.006 ng/g/l) than that of the
other three groups, which were all close to 2.16 ng/g. Comparing the urinary levels of Cr, there was a significant difference among the five groups (p = 0.01).

Each of the control patients had a level less than 1.0 ng/g, but this was equated to 1.0 in order to facilitate statistical analysis. Group 2 (metal-on-polyethylene) had a mean of 1.65 ± 0.03 ng/g (95% CI). There was a significant difference between any groups which had been exposed to a metal-on-metal articulation (groups 3 to 5) when compared with either group 1 or group 2. The urinary level for group 3 (2.16 ± 0.02 ng/g) was lower than that of group 4 (2.93 ± 0.03 ng/g), but this did not reach significance. Group 5 had the highest levels which were two to three times lower than those of the other four groups (p < 0.01). There was no significant difference between any groups which had been exposed to a metal-on-metal articulation.

**Titanium.** The blood level of titanium was significantly raised in all groups compared with the control group (p < 0.01). There was no difference between the blood levels of the four arthroplasty groups. All had a level 50% higher than the control group (mean 1.52 ng/g vs 0.995 ng/g). There was no significant difference in the urinary levels of titanium in the five groups.

**Vanadium.** The control group had levels of Va in the blood which were two to three times lower than those of the other four groups (p < 0.01). Group 5 had the highest levels (mean 0.86 ng/g) and was significantly different from all other groups. There was no significant difference between groups 2 and 4. The urinary levels of all the arthroplasty groups were significantly higher than those of the control group (p = 0.006).

**Discussion**

The concentration of metal released from metal implants, either from dissolution, fretting or wear, has long caused concern about carcinogenicity, either locally or systemically. The carcinogenic properties of wear particles of cobalt-chrome alloy were reported in 1971, but fewer than 30 cases of malignancy occurring around joint replacements have been reported. Even in these rare cases, the pathology was so varied that there could be no certainty that the two were associated. Two early reports suggested an increased incidence of lymphatic and haemopoietic malignancies but more recent reports show no such correlation.

The Finnish registry showed a increase of 3.77 in the rate of leukaemia with metal-on-metal compared with metal-on-polyethylene articulations, although this was found not to be significant.

Some wear of a prosthetic joint is inevitable. Retrieval and hip simulator studies have shown that there is a bedding-in period with metal-on-metal articulations. It has been demonstrated that the metal debris from such implants is disseminated to lymph nodes, liver, spleen and bone marrow.

A number of studies have been undertaken to establish the concentrations of various metal elements in patients with arthroplasties. The metals of interest have mainly been Co, Cr, Ti and molybdenum and all have been found as trace levels in subjects who did not have metal implants. However, there has been considerable variation in concentration levels in these studies. One of the principal reasons for this may have been the analytical equipment used. Techniques have included graphite-furnace atomic absorption spectroscopy, neutron activation analysis and inductively-coupled mass spectroscopy. Atomic absorption spectroscopy (resolution of 1 part per billion) has been one of the most widely used for the analysis of tissues and other organic materials and has been available for 25 years. Inductively-coupled mass spectroscopy (resolution of 0.5 to 1 part per billion) is a less well-known technique for sampling biological material and has been available for 15 years. We have used high-resonance inductively-coupled mass spectroscopy (resolution of 1 part per trillion) which has superior sensitivity. Most other blood studies have been performed on serum (no corpuscles or fibrinogen) for analysis but, we believe that certain metal elements such as Cr have an affinity for red blood cells and therefore discarding this constituent of blood will adversely affect the

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**Table I. Mean (ng/g, 95% confidence interval) blood and urinary levels of Co, Cr, Ti, Va in the five groups (see text)**

<table>
<thead>
<tr>
<th>Group (number of subjects)</th>
<th>Co</th>
<th>Cr</th>
<th>Ti</th>
<th>Va</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Mean (%95 CI)</td>
<td>Mean (%95 CI)</td>
<td>Mean (%95 CI)</td>
<td>Mean (%95 CI)</td>
</tr>
<tr>
<td>1 (4)</td>
<td>0.69 (0.43 to 0.99)</td>
<td>2.18 (1.9 to 2.3)</td>
<td>1.0 (0.89 to 1.10)</td>
<td>0.27 (0.10 to 0.42)</td>
</tr>
<tr>
<td>2 (2)</td>
<td>0.48 (0.46 to 0.48)</td>
<td>2.0 (1.8 to 2.2)</td>
<td>1.45 (1.4 to 1.5)</td>
<td>0.64 (0.62 to 0.66)</td>
</tr>
<tr>
<td>3 (5)</td>
<td>0.65 (0.3 to 1.1)</td>
<td>2.16 (1.9 to 2.4)</td>
<td>1.52 (1.3 to 1.7)</td>
<td>0.71 (0.62 to 0.8)</td>
</tr>
<tr>
<td>4 (3)</td>
<td>1.97 (1.1 to 2.4)</td>
<td>2.17 (1.7 to 2.5)</td>
<td>1.47 (1.4 to 1.5)</td>
<td>0.71 (0.62 to 0.8)</td>
</tr>
<tr>
<td>5 (2)</td>
<td>35.5 (19 to 52)</td>
<td>2.7 (2.6 to 2.8)</td>
<td>1.65 (1.5 to 1.8)</td>
<td>0.86 (0.76 to 0.96)</td>
</tr>
<tr>
<td>LOD*</td>
<td>0.07</td>
<td>1.0</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine</th>
<th>Co</th>
<th>Cr</th>
<th>Ti</th>
<th>Va</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (4)</td>
<td>0.6</td>
<td>&lt; 1.00</td>
<td>0.88</td>
<td>0.24</td>
</tr>
<tr>
<td>2 (2)</td>
<td>1.0</td>
<td>1.65</td>
<td>0.52</td>
<td>1.0</td>
</tr>
<tr>
<td>3 (5)</td>
<td>2.88</td>
<td>2.16</td>
<td>0.67</td>
<td>1.11</td>
</tr>
<tr>
<td>4 (3)</td>
<td>12.20</td>
<td>2.93</td>
<td>0.79</td>
<td>1.67</td>
</tr>
<tr>
<td>5 (2)</td>
<td>520</td>
<td>3.4</td>
<td>0.5</td>
<td>1.56</td>
</tr>
<tr>
<td>LOD*</td>
<td>0.07</td>
<td>1.0</td>
<td>0.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Co, cobalt; Cr, chromium; Ti, titanium; Va, vanadium
† LOD, level of detection
true reading. We are only aware of one other study\textsuperscript{17} in the literature which has measured metal ion concentrations (serum only) in patients who have had implants in situ for more than 20 years.

With regard to the whole blood levels of Ti, all the arthroplasty groups had a significantly (p < 0.01) elevated level, compared with the control group. There was no significant difference among the arthroplasty groups, suggesting that the elevated levels were mainly due to corrosion of the implant and abrasive wear of soft tissues.

Whole blood showed higher mean levels of Cr in the loose metal-on-metal group but this did not reach statistical significance. There were no statistical differences in any of the groups. This is in contrast with other studies\textsuperscript{19,20} which detected elevated levels, although mainly in serum rather than whole blood. The urinary levels of Cr in all our arthroplasty groups showed a significant elevation, compared with those of the control group. All of the groups with a metal-on-metal articulation showed a significantly elevated level of urinary Cr compared with both control and metal-on-polyethylene groups. Those patients in whom there was a radiologically loose metal-on-metal articulation had a significantly raised level, compared with all other groups. This suggests that metal-on-metal articulations do give significant levels of Cr wear debris, particularly when loose, but that this is then excreted in the urine rather than accumulating over time (30 years) in the blood.

With regard to Va, both the whole blood and urinary levels were significantly elevated (p < 0.01 and p = 0.006, respectively) in all the arthroplasty groups, compared with the control subjects. Again, the radiologically loose metal-on-metal articulations showed whole blood levels which were significantly elevated compared with all other groups. The whole blood Co levels in the loose metal-on-metal articulating group were more than 50 times that of the control group, and the urinary levels were more than 300 times greater (p < 0.001). This group also had significantly elevated levels in both whole blood and urine, compared with all other groups, suggesting that the greatly increased Co load was only partly excreted in the urine.

The lack of a significant difference between those with a stable metal-on-metal articulation and those whose metal-on-polyethylene (primary or revised metal-on-metal) articulation had been revised suggests that the former had bedded in and that the resultant ion load had been reduced. The metal ion load may well, therefore, reduce over time in a stable articulation.

The greatly elevated levels of Co in the whole blood and urine may well be helpful in identifying those patients in whom implants are loose and generating a higher volume of debris, and may therefore assist in the timing of revision surgery.

We appreciate that the implants used in our study were historical (30-year follow-up) and that their surface roughness and finish may have differed from those of metal-on-metal articulations available today. Improvement in manufacure and surgical technique may make extrapolation of our results to modern metal-on-metal articulations open to criticism. However, the basic metallurgical microstructure and chemistry of our prostheses\textsuperscript{22} were similar to modern designs. All our patients were young at the time of their joint replacement and all have led full and active lives which, in our view, makes extrapolation reasonable. Modern metal-on-metal prostheses are being used in ever-younger patients whose life expectancy may be more than 40 years.

**Supplementary material**

A further opinion by Mr Richard Villar and Mr Vejay Shetty is available with the electronic version of this article on our website at www.jbjs.org.uk

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**References**