Metal ion levels following resurfacing arthroplasty of the hip

SERIAL RESULTS OVER A TEN-YEAR PERIOD

We report serum metal ion level data in patients with unilateral and bilateral hip resurfacing over a ten-year period. In these patients there is an increase in both cobalt and chromium levels above the accepted reference ranges during the first 18 months after operation. Metal ion levels remain elevated, but decline slowly for up to five years. However, the levels then appear to start rising again in some patients up to the ten-year mark. There was no significant difference in cobalt or chromium levels between men and women. These findings appear to differ from much of the current literature.

The clinical significance of a raised metal ion level remains under investigation.

The use of a metal-on-metal articulation eliminates polyethylene wear debris and is also associated with a favourable wear pattern and a lower incidence of osteolysis.\(^1\)\(^-\)\(^4\) Hip resurfacing preserves bone and has a low risk of dislocation.\(^\text{5,6}\) Therefore, metal-on-metal hip resurfacing seems particularly suitable for the young, active patient who requires a hip replacement.\(^\text{7-10}\) It has become increasingly common in the United Kingdom and elsewhere. Resurfacing now accounts for up to 10% of all hip replacements.\(^\text{11}\) The increasing use of these bearings has led to concerns about raised serum levels of metal ions,\(^\text{2,3,12-15}\) which have been reported in both conventional hip replacements\(^\text{16-23}\) and hip resurfacings.\(^\text{17,24,25}\) Possible associations include malignancy, hypersensitivity, reduced Cd8 levels, soft-tissue reactions,\(^\text{26,27}\) metallosis, teratological effects and cell death.\(^\text{3,13,16,21,28-30}\) Although we have not identified any published evidence of adverse effects, these anxieties remain. In order to establish acceptable levels of safety and determine the significance of elevated ion levels, data will need to be analysed over extended periods of time. In addition, it may be important to identify not only the absolute level, but also any trends of the metal ion levels with time.\(^\text{31,32}\)

We present the results of serial serum cobalt and chromium ion measurements in a prospective series of patients who have had a resurfacing arthroplasty of the hip over approximately ten years.

Patients and Methods

A series of 56 patients who underwent metal-on-metal hip resurfacing (Corin, Cirencester, United Kingdom) were followed prospectively over a ten-year period. All had their surgery under the care of a single surgeon (SK), using a posterior approach, an uncemented acetabular component, a cemented femoral component and a standard rehabilitation protocol. Patients with renal impairment were excluded. During the study period several patients required resurfacing of the contralateral hip, and these are included in the series as bilateral procedures. A total of 20 men and 22 women had unilateral resurfacing, and 11 men and three women had bilateral surgery. Their mean age was 51.8 years (26 to 65) at the time of surgery. All implants remained in situ throughout the course of the study.

Patients attended for annual radiological and clinical review as well as serum cobalt and chromium level analyses. No patients were lost to follow-up, but no patient attended for every annual assessment. All patients had normal creatinine levels throughout the study.

Metal ion sampling. Blood samples were taken using a standard technique to minimise the risk of contamination: a plastic intravenous cannula was inserted, the metal needle removed and 5 ml of blood withdrawn and discarded. The samples were then taken with a plastic syringe and placed in 2 ml lithium heparin tubes (Teklab, Durham, United Kingdom) which had been tested to exclude cobalt and chromium contamination. The samples were centrifuged and the plasma transferred into trace-metal-free polycarbonate tubes (Teklab). Two samples were taken from each patient, and the levels were determined from both
samples in order to identify any contamination during sample collection and handling.

All samples were analysed at the Trace Metals Unit, Southampton University. During the first three years of the study, cobalt and chromium levels were determined by atomic absorption spectrometry with electrothermal atomisation (ETA-AAS), using Zeeman 5000 and 4100ZL atomic absorption spectrometers (Perkin-Elmer, Beaconsfield, United Kingdom). Samples were diluted 1+2 in 0.1% nitric acid; calibration was by standard additions, and the limit of detection was 0.2 μg/l (5 nmol/l). Measurements of certified reference material: Seronorm 704121 (Nycomed, Pharma AS, Asker, Norway), gave a between-batch imprecision of 0.5 (SD 0.2) μg/l (target value = 0.2 μg/l) for cobalt and 1.4 (SD 0.1) μg/l (target value = 1.3 μg/l) for chromium. Analysis by inductively coupled mass spectrometry was used for the remainder of the study after demonstrating close correlation with measurements by ETA-AAS. The instrument used was an Elan 6100DRC plus (Perkin-Elmer, Beaconsfield, United Kingdom). Samples were diluted 1+2 in 0.1% nitric acid, using matrix-matched calibrants. For level 1 (lot no: M10181), between-run imprecision was 1.2 (SD 0.1) μg/l and 1.3 (SD 0.1) μg/l for cobalt and chromium, respectively, target values for both metals being 1.0 μg/l. For level 2 (NO0371), 3.1 (SD 0.1) μg/l was obtained for cobalt (target value = 3.2 μg/l) and 4.6 (SD 0.3) μg/l for chromium (target value = 5.1 μg/l).

**Statistical analysis.** Linear regression analysis was used to model the metal ion levels over time, after appropriate logarithmic transformation. The variation in ion levels was complex, and so rather than attempt to formulate a specific functional relationship between time after surgery and ion levels, cubic splines were used to model the relationship. Cubic splines are commonly used for applications requiring data interpolation or smoothing, and are constructed from piecewise third-order polynomials which pass through a set of selected control points.33 Splines were incorporated into standard multiple linear regression models using the functions available in the R software package.34 A series of nested models were tested and model selection was based on changes in residual sums of squares; significance tests were at the 5% level and based on the chi-square test.

### Results

One patient died from unrelated causes early in the study and was excluded. Three patients had a sudden rise in metal ion levels and were also excluded from the statistical analysis, but are addressed in the Discussion. This left 52 patients in the series. Mean cobalt and chromium levels are shown pre-operatively, at six, 12 and 18 months, and then every year or two years up to ten years in Table I. The cobalt and chromium levels rose steeply over the initial two years to a peak of approximately 95 nmol/l for cobalt and 117 nmol/l for chromium. After this, there was a steady overall decline for both metals to five years. However, there then appeared to be another increase between five and ten years (Figs 1 and 2). The data in Figures 1 and 2 are presented on a logarithmic scale (base 10), as is conventional for measurements of this type. The smoothed line on each plot is the fitted cubic spline curve indicating the best fit to the time trends in ion levels. Chi-squared tests showed that the best-fit models, for both metals, were based on five degrees of freedom (d.f.) for the spline function; the fitted models for cobalt and chromium were significantly better than those based on four d.f. (p = 0.003 and 0.001, respectively). The addition of an additive term to model differences of gender in ion levels was not significant for either

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**Table I. Mean cobalt and chromium metal ion levels after surgery**

<table>
<thead>
<tr>
<th>Time</th>
<th>Cobalt (nmol/l)</th>
<th>Chromium (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI)</td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>Mean (95% CI)</td>
<td>Number</td>
</tr>
<tr>
<td>Pre-operative</td>
<td>10.0 (6.3 to 16.0)</td>
<td>18</td>
</tr>
<tr>
<td>6 months</td>
<td>52.3 (31.9 to 85.7)</td>
<td>23</td>
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<tr>
<td>12 months</td>
<td>80.4 (58.6 to 110.3)</td>
<td>25</td>
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<tr>
<td>18 months</td>
<td>78.3 (55.1 to 111.3)</td>
<td>14</td>
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<tr>
<td>2 years</td>
<td>95.5 (77.6 to 116.5)</td>
<td>28</td>
</tr>
<tr>
<td>3 years</td>
<td>86.9 (68.5 to 110.3)</td>
<td>30</td>
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<tr>
<td>4 years</td>
<td>74.5 (58.0 to 95.7)</td>
<td>27</td>
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<tr>
<td>5 years</td>
<td>64.9 (51.6 to 81.6)</td>
<td>27</td>
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<tr>
<td>6 years</td>
<td>68.9 (49.7 to 95.7)</td>
<td>26</td>
</tr>
<tr>
<td>7 years</td>
<td>87.4 (60.2 to 126.8)</td>
<td>16</td>
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<tr>
<td>8 years</td>
<td>102.9 (49.8 to 213.0)</td>
<td>11</td>
</tr>
<tr>
<td>9 years</td>
<td>81.8 (47.6 to 140.5)</td>
<td>13</td>
</tr>
<tr>
<td>10 years</td>
<td>86.5 (39.0 to 191.8)</td>
<td>9</td>
</tr>
</tbody>
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* CI, confidence interval
cobalt (p = 0.155) or chromium (p = 0.183), indicating that ion levels did not differ significantly between genders. The levels of cobalt ions were significantly higher in patients undergoing bilateral procedures than in those undergoing unilateral procedures (p = 0.001), but this was much less clear for chromium levels (p = 0.086); estimated cobalt and chromium ion levels were approximately 45% and 23% higher for bilaterals than for unilaterals, respectively. Cobalt and chromium ion levels were strongly correlated for individual patients at all time points; the Pearson’s correlation coefficients were 0.78, 0.80, and 0.92 at one, four and ten years after surgery.

Post-operative levels were within the reference range for occupational exposure (chromium 0.8 nmol/l to 76 nmol/l, depending on occupation; cobalt 170 nmol/l to 1600 nmol/l), but considerably outside the range for non-occupational exposure (cobalt 1.7 nmol/l to 6.8 nmol/l; chromium < 20 nmol/l). Occupations related to chromium exposure include pigment production, stainless steel manufacture, welding and electroplating. Occupations related to cobalt exposure include the manufacturer of magnets and chemicals.  

Discussion

Although the levels of metal ions remain fairly constant within any given patient, there is a relatively large variation between patients (Figs 1 and 2). It is conventional to discuss the mean level in a cohort; however, around this mean there is considerable scatter, and so mean data in this scenario must be interpreted with caution. Our method uses a regression analysis that models the temporal variation in ion levels using the full time course of available data for each individual patient.

There were two key findings. First, following the initial peak in ion levels at 18 months to two years, levels declined...
or levelled off up to five years before gradually rising again. Second, there was no evidence for a significant difference in ion levels between men and women. Both these findings are novel and contradict other data in the literature, where women typically have higher circulating ion levels and where ion levels do not show a second rise after they have fallen or reached a plateau.36-38

Although it is clear that metal ions are raised and remain so following metal-on-metal hip resurfacing, the clinical significance of these raised levels is unclear. Metal-on-metal hip prostheses (conventional stemmed replacements and resurfacing) have been implanted for over 50 years, and we have not identified any published evidence of adverse effects related to elevated serum metal ions. In 2004, MacDonald described the safety and reference ranges for metal ions following the use of metal-on-metal hip prostheses. There are two current reference ranges for cobalt and chromium: one for non-occupational exposure and another to take occupational exposure into account. The occupational level is much higher, although it is widely acknowledged that the reference ranges are arbitrary. All the patients in this study had cobalt and chromium levels which were within the occupational range. The absence of systemic effects of metal toxicity at these levels suggests that the reference ranges should be reviewed in light of the extensive use of metal prostheses in orthopaedic practice.

Regarding the local effects of raised metal ion levels, De Smet et al investigated the levels of cobalt and chromium in synovial fluid following hip resurfacing. They consistently found that the levels in synovial fluid could reach up to twice the serum concentration, especially in joint surfaces with insufficient lubrication. Patients with high local levels had a higher incidence of metallosis at revision. Although this study had few patients and only three years’ follow-up, their findings are significant if the high serum levels that we observed reflect even higher levels in the synovial fluid. De Smet et al suggested that serum ions could be monitored as an early indicator of metallosis and failure. However, there is no clear view as to what serum level of metal ions represents a ‘risk’.

In this series there were three patients in whom there was a large change in ion concentrations (these patients are not included in our statistical analysis). One of these had a high inclination angle of the acetabular component and had an early post-operative dislocation. Although this was reduced closed and she subsequently had no further problems with instability, the metal ion levels remained high 14 years later, suggestive of edge loading. She has been clinically reviewed annually and in light of recent concerns she has had imaging studies recently but has no signs of any abnormal swellings or tissue reactions. The second patient also had an acetabular component with a high inclination angle. She underwent acetabular revision after six years because of increasing pain, suggestive of subluxation. At surgery both components were well fixed, although there was macroscopic wear of the rim of the acetabular component. All the soft tissues were healthy with no visible metallosis. A new acetabular component was introduced in a more closed and anteverted position. Within ten months the cobalt and chromium levels had fallen by a factor of 10. The third patient had increasing pain and rising ion levels at eight years. Loosening of the acetabular component was diagnosed radiologically. At revision the soft tissues were healthy, but with some metallic staining; acetabular bone loss meant it was not possible to fit an appropriately sized socket for the resurfaced head, so the head was removed, a slightly larger socket was inserted and a total hip replacement (THR) was performed. Thus a steep increase in serum ion levels may indicate impending failure. One further patient (patient 29) had a rise in ion concentrations, six years post-operatively. The levels, however, returned to normal at year eight. Her renal function remained stable and she had no illnesses. She did, however, experience trauma to that hip and felt it ‘crack’; it is possible that this induced a release of ions, which then returned to normal as they were excreted.

The consistent rise during the first 18 months to two years has been widely attributed to the ‘running-in’ period, when small irregularities on the bearing surfaces are worn down. This ‘polishing’ phenomenon has been demonstrated in simulator studies over the first million cycles of testing, equating to about one year of use in conventional THR, but this is likely to underestimate the number of cycles in the young, active hip resurfacing population.40 The particles of wear debris generated in this study were much smaller (approximately 10 nm to 250 nm) than those produced by ultra-high-molecular-weight polyethylene surfaces and may not elicit the same osteolytic reaction.41,42 However, this running-in process seems to explain the early rise in metal ion levels. After the running-in period a steady state of ion production versus renal excretion is reached, when the levels remained static or even slightly decreased. The new finding from these data is that the ion levels may appear to start rising again after the first five years. This may reflect increased production or reduced excretion, but as the patients had normal renal function, it seems more likely that it is production that starts to rise again at this time. The concern is that this gradual increase may reflect wear and/or early loosening. As previously discussed, there is considerable scatter, so a small rise in a mean value may represent a real rise in a few patients, with no change in the majority. However, at present there is no evidence to implicate serum ion levels in functional decline.

Recent evidence suggests that optimal implant positioning (inclination and anteversion) and component sizing prevents early failures in hip resurfacing.43-46 The effect of bilateral hip resurfacing was to raise absolute ion levels significantly over those in patients having unilateral surgery. There were no adverse events in the bilateral patients included in this study. However, it may be appropriate to ensure stricter monitoring of systemic ion levels in patients with bilateral metal-on-metal resurfacing,
and to monitor their renal function. It is, however, possible that the ion levels in the synovial fluid in the bilateral group will be similar to those in the unilateral group, and therefore bilateral resurfacing may not increase the risk of metallosis.

A potential limitation of our study was the change in technique for measuring the ion levels part-way through the investigation. This reflects the improved technology; the analytical method of inductively coupled mass spectrometry is thought to be more accurate. However, owing to the different analytical methods used and demographic differences between the study groups, direct comparisons with other studies may be difficult. We chose to measure serum levels. At the time our study started, this was the standard technique. Whole blood and urine levels may give different information, but this has not been addressed in this study. A further limitation of our study may be the absence of data on patient activity levels.

There have been recent concerns about adverse reactions to metallic debris with destruction of soft tissues around the hip.47-49 This is not a common complication in any reported series of metal-on-metal hip replacements; nevertheless, increasing concerns have led the Medicines and Healthcare Products Regulatory Agency, a United Kingdom government body, to issue a medical device alert.50 These guidelines suggest that serum metal ion levels should be measured in patients with metal-on-metal hip replacements if there are concerns. There is no clear correlation between serum ion concentrations and adverse tissue reactions. Our study included three patients with very high metal ion levels; further surgery was indicated in two, and we found no adverse tissue reactions. The third has now reached 14 years without any adverse clinical effects, and a recent MR scan, obtained in the light of the Regulatory Agency release, has shown no evidence of adverse tissue reaction. On the basis of our study, there is no evidence that measuring metal ion levels is a useful screening tool for adverse tissue reactions.

In conclusion, our study suggests that cobalt and chromium levels following metal-on-metal hip resurfacing have a different long-term profile from that currently reported in the literature. Our results indicate that, following the initial running-in period, levels decline or plateau for five years, but may gradually rise again up to ten years. There was no evidence of a significant difference in ion levels between men and women.

In the future, metal ion level measurements in serum, whole blood or urine may be shown to correlate with functional outcome. However, at present the clinical significance of raised metal ion levels in patients after resurfacing arthroplasty of the hip remains unknown.

Supplementary material

Two tables with serial cobalt and chromium levels for all subjects are available with the electronic version of this article on our website at www.jbjs.org.uk

References

50. No authors listed. MHRA Medical Device Alert: all metal-on-metal (MoM) hip replacements. http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON079157 (date last accessed 21 June 2010).