Blood and urine metal ion levels in young and active patients after Birmingham hip resurfacing arthroplasty

FOUR-YEAR RESULTS OF A PROSPECTIVE LONGITUDINAL STUDY

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This is a longitudinal study of the daily urinary output and the concentrations in whole blood of cobalt and chromium in patients with metal-on-metal resurfacings over a period of four years.

Twelve-hour urine collections and whole blood specimens were collected before and periodically after a Birmingham hip resurfacing in 26 patients. All ion analyses were carried out using a high-resolution inductively-coupled plasma mass spectrometer. Clinical and radiological assessment, hip function scoring and activity level assessment revealed excellent hip function.

There was a significant early increase in urinary metal output, reaching a peak at six months for cobalt and one year for chromium post-operatively. There was thereafter a steady decrease in the median urinary output of cobalt over the following three years, although the differences are not statistically significant. The mean whole blood levels of cobalt and chromium also showed a significant increase between the pre-operative and one-year post-operative periods. The blood levels then decreased to a lower level at four years, compared with the one-year levels. This late reduction was statistically significant for chromium but not for cobalt.

The effects of systemic metal ion exposure in patients with metal-on-metal resurfacing arthroplasties continue to be a matter of concern. The levels in this study provide a baseline against which the *in vivo* wear performance of newer bearings can be compared.

The increasing number of metal-on-metal hip resurfacing arthroplasties which are being undertaken in young patients has led to renewed concerns about the effects of systemic metal ion exposure. Metal wear, however, cannot be measured by conventional radiological methods. The urinary levels of metal ions can be used as an *in vivo* index of wear.[1] The biological risks of exposure to metal ions, if any, can be assessed by haematological monitoring. Earlier studies have shown that, as a surrogate measure of systemic metal exposure, serum or plasma levels are not as reliable as whole blood levels.[2,3] Daily output of metal ions in urine and whole blood metal ion levels offer an indirect indication of metal wear and systemic exposure.

Cross-sectional studies require a large number of patients to reduce the influence of individual variability in metal transport and excretion when compared with longitudinal studies. We undertook a longitudinal study of the daily output of metal ions in urine, and cobalt and chromium concentrations in whole blood over a period of four years in patients with modern metal-on-metal hip resurfacings.

Patients and Methods

A total of 26 consecutive patients who underwent a unilateral Birmingham hip resurfacing (Midland Medical Technologies, Smith and Nephew, Bromsgrove, United Kingdom) carried out by a single surgeon (DJWM) were recruited into a prospective longitudinal study after giving informed consent. The Birmingham Hip Resurfacing arthroplasty has a hydroxyapatite-coated porous uncemented acetabular component and a cemented femoral component, both made of high-carbon cobalt-chrome (CoCr) alloy, and are in the 'as-cast' state.

The inclusion criteria were unilateral end-stage arthritis of the hip in patients in whom femoral head component sizes of 50 mm and 54 mm were used. Only two femoral sizes were chosen to reduce confounding variables. Patients with other metallic devices in the body, diagnoses other than osteoarthritis, and those living abroad were excluded. No patient had a history of renal impairment. The mean age at operation was 52.9 years (29 to 67) and the mean height, weight and body mass index

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(BMI) of these patients pre-operatively was 177 cm (165 to 187), 87 kg (59 to 119) and 27.9 kg/m^2 (21.5 to 36.3), respectively. Their mean pre-operative Oxford hip score[4] was 35 (48%) (25 to 48; 27% to 75%).

Twelve-hour urine collections were obtained pre-operatively and at 5 days, 2 months, 6 months, 1 year, 2 years and 4 years post-operatively. Whole blood samples were taken pre-operatively, at 1 year and 4 years post-operatively. The one-year follow-up visit was chosen as the first point for combined blood and urine measurement because we expected an early peak to occur at this time, based on an earlier cross-sectional study.[5]

Specimen collection. Our patients were routinely admitted to hospital the day before a resurfacing procedure when the technique of obtaining a 12-hour collection of urine without contamination was explained. The five-day post-operative collection was also obtained while the patients were in hospital. The patients were also reviewed clinically and radiologically at 2 months, 1 year and 4 years. There was no review at six months and two years. The patients were sent the necessary containers and clear instructions a few days before the scheduled review, and they brought their 12-hour urine collections to these reviews. At the six-month and two year stages, urine collections were obtained through a courier. At the six-month stage only 19 patients (73%) returned their specimens within the specified period.

Further details of specimen collection, instrumentation and quality control are given in an earlier publication.[1] All metal ion analyses were carried out using a high-resolution inductively-coupled plasma mass spectrometer (HR-ICP-MS, Thermo Fisher Scientific GmbH, Bremen, Germany). The limits of detection for cobalt and chromium were 0.02 µg/l in the urine, and the reporting limit was three times this (i.e. 0.06 µg/l). The reporting limit in the whole blood was 0.2 µg/l (limit of detection 0.067 µg/l).

Assessment of the hip. Clinical and radiological examinations were performed by one of three clinicians (JD, CP, DJWM) and patients completed an Oxford Hip Score questionnaire.[4] The scores are also expressed as a percentage, increasing with increasing pain and loss of function.[4] Their occupational and leisure activities were assessed using the ULCA Activity Level Assessment scale.[6] On this scale, patients who score 5 and 6 are moderately active and are not limited in housework or shopping, swimming etc, those who score 7 are active, 8 and above are very active, and 9 and 10 participate in impact sports.

The StepWatch 2 system (Prosthetics Research Study, now Cyma Corporation, Mountlake Terrace, Western Australia) was used to monitor step rates in the patients at the four-year follow-up. This system allowed us to roughly measure patient activity, which can relate to wear. This parameter provides us with a measure of the *in vivo* backdrop in which these measurements have been made. The device was fitted in the clinic on the appropriate leg above the ankle and patients were instructed to wear it during all waking hours for the next five to seven days. The monitors were then returned by courier and the data stored.

Radiological assessment included an anteroposterior view of the pelvis centred on the symphysis pubis, with a tube-film distance of 100 cm, and a horizontal shoot-through lateral film of the operated hip. Radiographs were assessed by a clinician (JD) for lucent lines, osteolysis and loosening using the same criteria as those used in earlier reports on resurfacings.[7] Brooker grading[8] was used to assess heterotopic ossification (HO). The inclination angle of the acetabular component and the position of the femoral component were assessed as previously described.[9]

The data relating to the metal ion output in urine were asymmetrically distributed, and therefore non-parametric methods were used for analysis. However, parametric methods were considered appropriate for whole blood metal ion levels; 95% confidence intervals (CI) were used to indicate statistical significance in both the urine output and the whole blood data.

Results

All patients had well-functioning resurfacing arthroplasties at the four-year follow-up. None had persistent pain or disability. One patient with severe osteoarthritis of the contralateral hip had an Oxford hip score of 42 (63%) and is awaiting contralateral resurfacing arthroplasty. He was excluded from activity assessment. The remainder had a mean Oxford score of 12.7 (1%) (12 to 17; 0% to 10%) at four years, the best possible Oxford score being 12 (0%).

The mean step activity rate was 2.1 million cycles per year (1 to 4.3) at four years. No patient was asked to change their activities following the resurfacing and at four years none scored below 6 on the UCLA activity level scale. Three patients (12%) scored 6, one (4%) scored 7, and the remaining 21 (84%) scored 8 to 10. Their activities included heavy occupational work and pursuing impact-loading leisure activities such as running, mountain hiking, hockey, tennis and squash.

The mean acetabular component inclination angle for the 26 patients was 43.3° (35° to 49°). All femoral components were in the desired range (neutral to 10° valgus). There were no radiolucent lines and no evidence of loosening or osteolysis at the latest follow-up. None of the components showed migration appreciable to the naked eye, and no component tilted into varus or valgus. All patients showed radiological evidence of good osseointegration of the acetabular component. Two patients (7.7%) had Brooker grade I HO, four (15.3%) had grade II, and the remaining 20 (77%) showed no evidence of HO.

The daily urinary output of cobalt increased for six months and declined thereafter (Fig. 1). The median cobalt output at six months (12.1 µg/day) was almost 50% greater than that at four years (8.1 µg/day), although the difference was not statistically significant. The five-day levels were significantly higher than the pre-operative levels, and the two-month levels significantly higher than the pre-operative and

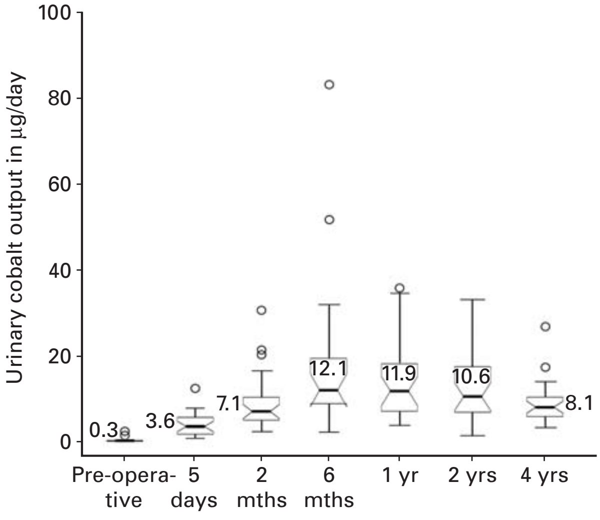

Fig. 1

The daily urinary output of cobalt. Values shown are medians (horizontal lines), 95% confidence intervals of medians (notches) and interquartile ranges (boxes). The whiskers extend from the edges of the box to the largest and smallest values that are outside the box, but within 1.5 times the corresponding box length. All outliers beyond the whiskers are shown as individual data points.

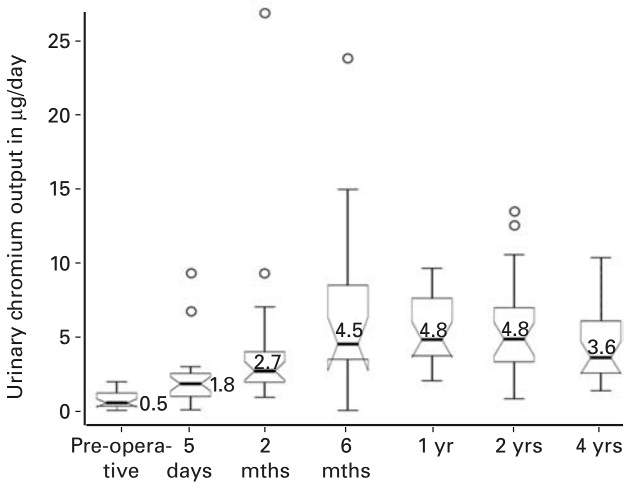

Fig. 2

The daily urinary output of chromium. Values shown are medians (horizontal lines), 95% confidence intervals of medians (notches) and interquartile ranges (boxes). The whiskers extend from the edges of the box to the largest and smallest values that are outside the box, but within 1.5 times the corresponding box length. All outliers beyond the whiskers are shown as individual data points.

five-day levels. The median levels between six months and four years are significantly higher than the pre-operative and five-day levels. The differences between the output at two months and four years are not statistically significant.

The daily urinary output of chromium shows a similar but less pronounced increasing trend up to the one- and two-year stages, followed by a decrease at four years (Fig. 2). The median chromium output at one and two years (4.8 µg/day) was 33% greater than that at four years (3.6 µg/day), but this difference is not statistically significant. The five-day levels were significantly higher than the pre-operative levels. The levels between six months and four years were all significantly higher than the pre-operative and five-day levels. Between two months and four years the differences between individual time periods were not statistically significant.

The mean whole blood cobalt and chromium concentrations at the one-year follow-up were 1.3 µg/l (0.43 to 3.77) and 2.4 µg/l (0.7 to 3.82), respectively. At four years they were 1.2 µg/l (0.65 to 2.55) and 1.1 µg/l (0.59 to 2.04), respectively. The difference between the pre-operative and one-year levels for cobalt was statistically significant (Fig. 3). This reduces by a small margin at four years. The difference between the pre-operative and one-year level for chromium was also significant with a significant reduction (21.3 mg/l) at four years.

Discussion

Cobalt and chromium are the principal elements in the CoCr alloy used in metal-on-metal implants. Cobalt is a constituent of the cobalamin (vitamin B_{12}) molecule, and chromium assists in enabling the cellular response to insulin and the uptake of glucose. They are essential elements.

Prolonged exposure to elevated levels of metals raises the possibility of metabolic, mutagenic, teratogenic and immunological sequelae. Both lymphocyte suppression[10] and lymphocyte-dominated cell-mediated hypersensitivity reactions[11] have been reported in patients with metal-on-metal devices. Chromosomal aberrations, including aneuploidy and sister chromatid exchanges, have been reported in the peripheral blood of patients with both conventional bearing devices[12] and metal-on-metal devices.[13,14] However, no correlation between metal ion levels and the degree of chromosomal aberrations could be demonstrated in these studies. Laboratory tests have indicated the presence of DNA damage in patients with both CoCr-on-CoCr devices as well as CoCr-on-polyethylene devices.[15] However, there are mechanisms in the body that monitor and repair metal-induced DNA changes, and there are systems that protect against their effects.[16] The possibility of nephrotoxicity[17] from cobalt and the transplacental transfer of metal ions[18] is also being investigated. An epidemiological study on patients with first-generation metal-on-metal hip replacements, with a maximum follow-up of 30 years, has shown no increase in

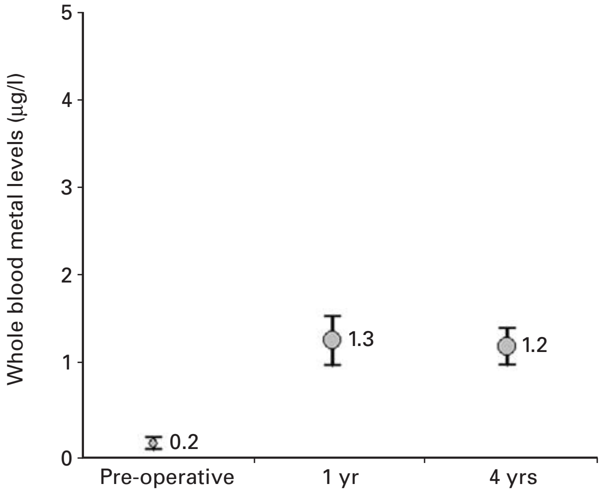

Fig. 3a

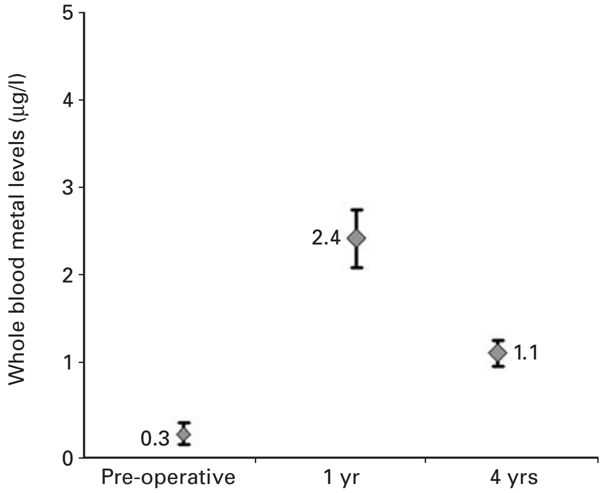

Fig. 3b

Whole blood concentrations of a) cobalt and b) chromium pre-operatively, and at one and four years.

the incidence of cancer in these patients compared with the general population.[19]

All types of metallic implants including conventional hip implants[20] and metal-on-metal implants lead to elevated metal levels in blood and urine.[21-23] The levels in patients with metal-on-metal bearings are significantly higher than in those with conventional implants.[10,23] There have been several studies of metal ions in patients with artificial hip joints, measuring concentrations of metal ions in whole blood or its derivatives (serum,[20,21] plasma[22] or erythrocytes[23]). Chromium has a tendency to be sequestered in cells, and therefore serum and plasma levels are incomplete assessment measures.

Although whole blood is a good measure of systemic metal exposure it only represents a dynamic balance between release and excretion. Individual variations in thresholds and rates of renal clearance can influence blood levels. Urinary metal ion output based on timed excretion is a useful measure of the body burden of metal ions.[24] Taking account of only the concentration of metal in urine is unsatisfactory and subject to error from differential urinary dilution.

Therefore, it is important to assess both whole blood levels and urinary metal ion output as an *in vivo* measure of metal wear and exposure in patients with hip arthroplasty. There has been only one report[25] of daily urinary metal ion output employing HR-ICP-MS analysis in patients with metal-on-metal arthroplasties. In that study, in addition to the daily urinary output of metal, erythrocyte metal levels were assessed rather than whole blood levels. The metal output with the metal-on-metal device used in that study was found to be so great that further use of the device was reportedly discontinued[23] in that centre after two years. Our study was a four-year longitudinal study of daily urinary output and whole blood levels of metal in patients with well-functioning modern metal-on-metal resurfacings where the current state and function of the hip were assessed by clinical and radiological review, Oxford hip score, UCLA scale activity level assessment and step activity monitoring.

Hip simulator results[26,27] and studies on retrieved components[28] suggest that metal-on-metal bearings exhibit an early running-in phase in the first one million cycles (Mcyc), followed by a very low steady-state wear rate. This is explained on the basis of a self-polishing effect, whereby metal surfaces reach extremely low surface roughness during the first one million cycles. It is postulated that this has the effect of dramatically reducing further wear thereafter. Step activity studies on the patients in our study confirm that hips in young patients are subject to around two Mcyc of use per year.

In our study the urinary output of cobalt reached a peak six months after the operation and that of chromium at around one to two years. There is a reduction of blood metal ion levels between the one- and four-year periods. The steady increase of metal ion output in the first six months (Figs 1 and 2) appears to fit in with the one million cycles of run-in wear predicted by simulator and retrieval studies.[26-28] If the wear regimen *in vivo* were to continue to follow the predicted laboratory results, one would expect a phase of dramatically reduced output. In our observations, metal ion levels do not show such a dramatic reduction. However, metal release with the Birmingham implant does show a reducing trend over the subsequent years (Figs 1 to 3). This allays the fear that all metal-on-metal bearings lead to a cumulative build-up of metal in the system, with progressively increasing blood levels.

Metal-on-metal resurfacings continue to demonstrate promising clinical results and survival rates. The present report provides a measure of the *in vivo* wear performance of the Birmingham hip resurfacing (large-diameter, large-clearance, metal-on-metal) device in young and active patients, and the sequential change in metal levels over a four-year period.

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