The association between metal ions from hip resurfacing and reduced T-cell counts


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We have studied the relationship between metal ion levels and lymphocyte counts in patients with metal-on-metal hip resurfacings. Peripheral blood samples were analysed for lymphocyte subtypes and whole blood cobalt and chromium ion levels in 68 patients (34 with metal-on-metal hip resurfacings and 34 with standard metal-on-polyethylene total hip replacements). All hip components were radiologically well-fixed and the patients were asymptomatic. Cobalt and chromium levels were significantly elevated in the patients with metal-on-metal hip resurfacings, compared with the patients with standard metal-on-polyethylene designs (p < 0.0001). There was a statistically significant decrease in the level of CD8+ cells (T-cytotoxic/suppressor) (p = 0.005) in the metal-on-metal hip resurfacing group. A threshold level of blood cobalt and chromium ions was associated with reduced CD8+ T-cell counts. We have no evidence that our patients suffered as a result of this reduced level of CD8+ T-cells.

Metal-on-metal bearing technology is being used in anticipation of extending the durability of hip replacements and reducing the requirement for revision. Metal-on-metal bearings have been reported to release at least three times more cobalt and chromium ions than metal-on-polyethylene hip replacements. It is estimated that this new metal technology has been used in approximately 150 000 small diameter and 70 000 large diameter hip replacements, mainly in Europe. Concern has been expressed that the cobalt and chromium ions released from metal-on-polyethylene hip replacements can cause DNA damage and immune dysfunction. Large diameter bearings have been favoured by some in an effort to increase fluid film lubrication and subsequently, to decrease wear. However, one short-term report suggests that the advantages of this are merely theoretical and may not extend to clinical use.

Other studies have identified abnormalities in white blood cells in the presence of loose hip replacements. We measured the number of different subtypes of lymphocyte, in order to examine the possibility that raised metal ions may cause an abnormality in the number of blood cells (blood dyscrasia). Abnormal numbers of blood cells may arise for many different reasons, for example the precancerous states of leukaemia, or as an indication of immune dysfunction. Therefore, blood dyscrasias are a sensitive but not specific measurement of both the risk of cancer and of immune dysfunction. If metal ions cause significant effects on white blood cells, we might reasonably expect to detect this by measuring the relative number of white blood cell populations.

Patients and Methods

We obtained consent for this study from the Trust Research Ethics Committee. From our database we gathered the medical records of all patients who had undergone either a unilateral hip resurfacing or metal-on-polyethylene hip replacement at least six months earlier.

We excluded patients who had experienced occupational exposure to cobalt or chromium, patients who were taking medication containing cobalt or chromium, or medication shown to cause blood dyscrasias. In addition, patients were excluded if they had other metallic implants, including joint replacements, unless manufactured from titanium, titanium alloy, or ceramic. Other exclusion criteria included previously diagnosed blood dyscrasias or malignancy, an abnormal pre-operative creatinine clearance, radiological or clinical evidence of a loosened prosthesis and bilateral hip arthroplasty. Patients with dental implants were not excluded as these have been shown not to release measurable amounts of metal ions.

The patients were invited to dedicated clinics where a questionnaire was completed and
Table I. Summary data of patients in our study

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of hips</th>
<th>Prosthesis type</th>
<th>Mean age in yrs (range)</th>
<th>Mean follow-up in mths (range)</th>
<th>Diagnosis*</th>
<th>HHS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal-on-metal</td>
<td>34 (20M 14F)</td>
<td>32 BHR‡ (Smith &amp; Nephew) 2 Duron</td>
<td>54 (30 to 73)</td>
<td>21 (6 to 40)</td>
<td>32 OA</td>
<td>93</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>1 Dysplasia</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1 AVN</td>
<td></td>
</tr>
<tr>
<td>Metal-on-polyethylene</td>
<td>34 (19M 15F)</td>
<td>Femoral components: Stanmore 25 (Biomet)</td>
<td>63.5 (42 to 76)</td>
<td>36 (11 to 58)</td>
<td>29 OA</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetabular components: Stanmore 9</td>
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<td>2 AVN</td>
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<tr>
<td></td>
<td></td>
<td>Charnley 5</td>
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<td></td>
<td>2 Dysplasia</td>
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<tr>
<td></td>
<td></td>
<td>Charnley 4 (DePuy)</td>
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<td>Ultima 1 (DePuy)</td>
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<td>1 Pagets</td>
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</tbody>
</table>

* OA, osteoarthritis; AVN, avascular necrosis
† HHS, Harris hip score
‡ BHR, Birmingham hip resurfacing

Fig. 1
Whole blood cobalt ion concentration vs time since operation.

Fig. 2
Whole blood chromium ion concentration vs time since operation.
concerns were answered, informed consent was obtained and a blood sample was taken.

The two groups were matched to obtain ages within a ten-year range, a weight range of 10 kg and an activity level, assumed from Harris hip scores, within five points.

Blood samples were obtained from 68 patients, 34 of whom had received a primary metal-on-polyethylene total hip replacement (THR). These made up the standard group. A further 34 patients had received a metal-on-metal resurfacing arthroplasty (the metal-on-metal group) (Table I).

Blood specimens were obtained using a disposable 20-gauge intravenous cannula. The cannula was sited in an antecubital vein, removing the central stainless steel needle, and 10 ml of blood was withdrawn through the in situ plastic tube. The syringe containing this initial sample was discarded to eliminate metal ion contamination from the trocar. A new syringe was then used to withdraw a further 10 ml of blood, which was transferred to two ethylenediaminetetraacetic acid (EDTA) tubes. One sample was used for metal analysis and the other for T-lymphocyte analysis. All blood samples were taken in the morning, kept at room temperature and processed within 12 hours.

Whole blood levels of cobalt and chromium were determined using an inductively-coupled plasma DRC Elan* mass spectrometer with a dynamic reaction cell (DRC ICP-MS; Perkin Elmer Life, Monza, Italy) at the Medical Research Council collaborative centre for Human Nutrition Research (Cambridge, United Kingdom). The lymphocyte populations were analysed by fluorescence-assisted cell sorting at the Royal Free Hospital (London, United Kingdom). This technique uses two laser beams, allowing the use of four-colour staining. Monoclonal antibodies were used to measure relative and absolute counts of total T-cells (CD3*), helper-T cells (CD4*), cytotoxic-T cells (CD8*), B cells (CD19*) and natural killer cells (CD16*, CD56*).

Statistical analysis was undertaken using probability plots to look for normal distribution of metal concentration and absolute lymphocyte populations. All statistical analysis was carried out on MINITAB 14 (MInItab Inc., Philadelphia) for PC and Microsoft Excel 2003 for PC. Logarithmic transformation of the data was performed to give a normal distribution. An unpaired two-tailed Student’s t-test was used to determine p values. Statistical significance was accepted when p ≤ 0.05.

Results

Cobalt and chromium analysis. We calculated the values for r² in order to assess any correlation between time since operation and metal ion concentration (Figs 1 and 2). No correlation was observed. Metal ion concentrations were significantly elevated in the metal-on-metal group compared with the standard group (p < 0.0001) (Fig. 3).

Lymphocyte analysis. Table II summarises our findings. In the metal-on-metal group there was a significant decrease in the total lymphocyte count (p = 0.023), absolute CD3* count (T-lymphocytes) (p = 0.033) and absolute CD8* count (cytotoxic T-cells) (p = 0.005) (Fig. 4). It may be important to note that the mean age of the standard group was 63.5 years (42 to 76) compared with 54 years (30 to 73) for the metal-on-metal group, which may conceal an even greater difference as absolute T-cell counts decrease with age.

We identified a threshold level of 5 ng/ml of combined cobalt and chromium which was related to a reduction of CD8* cells below 0.5 x 10⁹/l (Fig. 5).

Discussion

We studied levels of peripheral blood lymphocytes in two groups of patients who differed only in the articulating sur-
face of their hip arthroplasty, with a large-diameter metal-on-metal bearing in one group and a standard metal-on-polyethylene bearing in the other. We considered several options for our reference group; age-matched healthy controls without arthroplasties, small diameter (28 mm) metal-on-metal arthroplasties, loose metal-on-polyethylene arthroplasties and patients immediately preceding total hip replacement. We chose well-fixed standard metal-on-polyethylene THRs to reduce confounding variables. These included pain, which affects the lymphocyte count and would have been present in an untreated arthritic hip or a loose total hip replacement. We wished to have comparable activity levels, which affect both lymphocyte counts and metal ion levels and wanted to avoid any other metal-on-metal articulation for which lymphocyte counts and whole blood metal ion levels have not been agreed.

Metal ion levels were not linked to the time since operation (Figs 1 and 2). We did not find higher ion levels in the patients with shorter periods of implantation of the metal-on-metal bearings, but we accept that we have not obtained serial measurements from individual patients and that the blood samples may have been taken after the bedding-in period.9,16

The mean absolute levels of cobalt (4.18 ng/ml (ppb) for metal-on-metal and 2.48 ng/ml (ppb) for metal-on-polyethylene) and chromium (1.78 ng/ml (ppb) for metal-on-
metal and 0.28 ng/ml (ppb) for metal-on-polyethylene) in our study differed slightly from other research which has looked at loose hip replacements, but these studies generally examined serum rather than whole blood levels. The chromium levels were the most disparate. Because chromium is stored in red blood cells, the use of serum measurements may be misleading.

Previous studies have shown that loose, standard hip replacements with raised metal ions cause elevated levels of total lymphocytes, unlike the depressed levels which we found. It has been proposed that a metal ion hypersensitivity may occur, which is responsible for the increased lymphocyte reactivity seen in these patients. The clinical significance of such hypersensitivity is small and can be overcome by revision to a stable prosthesis. We found no clinical evidence of hypersensitivity in our patients, which is possibly because the metal ion exposure was limited in duration, with a mean of 22 months (6 to 40). Also, the association of raised metal ions and CD8+ reduction may be stronger and mask any hypersensitivity effects.

A previous study has shown an association between loose metal-on-polyethylene hip replacements and DNA damage, measured by fluorescent in situ hybridisation of peripheral blood lymphocytes or peri-prosthetic tissue. However, another study from the same group showed only a weak association between cobalt and chromium levels and DNA damage.

Our study is the first demonstration of a significant decrease in T-lymphocytes in patients with metal-on-metal hip resurfacings compared with standard metal-on-polyethylene hip replacements. The decrease was limited to cytotoxic T-lymphocytes (CD8+) with normal levels of helper T-cells (CD4+), B cells (CD19+) and natural killer cells (CD16+). This study not only correlates metal ion levels and lymphocytes, but for the first time proposes a threshold level for this effect. It is not clear whether these results are applicable to all types of metal-on-metal articulation. We would encourage further study into the possibility of immune suppression in other types of hip resurfacing and smaller diameter (28 mm) metal-on-metal articulations.

The CD8+ levels seen in our study form part of the normal spectrum of CD8+ levels. There were nine metal-on-metal patients who had CD8+ counts below 0.5 x 10^9/l and combined cobalt and chromium ion levels less than 5 ppb. These values are consistent with a threshold effect of metal ions and form part of the normal variation of lymphocyte counts seen in many immunological studies. We emphasise that there were only two metal-on-metal patients with CD8+ counts greater than 5 x 10^9/l and that these patients had a cobalt and chromium ion combined level of less than 5 ng/ml.

It is thought that there may be design features, other than the metal-on-metal bearing, of hip replacements that cause an increased level of metal ions. One example is modular metal stems, although this was refuted in a study by Hardinge et al. Regardless of the design variable, our study suggests that immune suppression is seen when a threshold whole blood level of combined cobalt and chromium is greater than 5 ng/ml.

A recent study has suggested a synergistic effect of cobalt and chromium as a cause for chromosomal aberrations in patients with a worn total hip replacement. In our study, synergism could be deduced if the CD8+ threshold was crossed in patients with combined cobalt and chromium ion levels greater than 5 ng/ml because of isolated high levels of either cobalt or chromium, but absent when cobalt and chromium levels were high when added together. However, we found that cobalt levels were directly proportional to chromium levels, which provides no evidence to support or reject the possibility of metal ion synergy.

Known confounding variables for both metal ions and blood lymphocyte levels were excluded, strengthening the association of reduced CD8+ lymphocytes with raised cobalt and chromium ion levels. The reduction was limited to CD8+ cytotoxic T-cells, the defence against intracellular pathogens (e.g. viruses) and cancerous cells. A generalised bone marrow effect is unlikely as all patients had normal B and natural killer cell levels. To determine the clinical importance of our findings we have begun lymphocyte function analysis of the remaining CD8+ cytotoxic T-cells and will continue to monitor this cohort of patients for any increased risk of infection and cancer.

In conclusion, we have shown a reduction in cytotoxic T-cells (CD8+) when patients were exposed to cobalt ion levels greater than 4 ng/l (ppb) and chromium ions greater than 1.5 ng/ml (ppb) in whole blood for at least six months.

Supplementary Material

A further opinion by Professor Ian Learmonth is available with the electronic version of this article on our website at www.bjs.org.uk

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References


