Metal ion levels after metal-on-metal Ring total hip replacement
A 30-YEAR FOLLOW-UP STUDY

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Metal-on-metal bearings for total hip replacement (THR) are becoming increasingly popular. Improved wear characteristics mean that these articulations are being inserted into younger patients in the form of THR and resurfacing procedures. This has led to concerns regarding potential carcinogenicity because of the increased exposure to metal ions that the procedure brings.

We have studied the serum cobalt and chromium concentrations in patients who had primary, well-fixed Ring metal-on-metal THRs for more than 30 years. The levels of cobalt and chromium were elevated by five and three times, respectively compared with those in our reference groups. Metal-on-metal articulations appear to be the source of metal ions throughout the life of the prosthesis. In three patients who had undergone revision of a previous metal-on-metal THR to a metal-on-polyethylene replacement the levels of metal ions were within the normal range. The elevations of cobalt and chromium ions seen in our study were comparable with those in patients with modern metal-on-metal THRs.

Some first-generation metal-on-metal hip replacements have now reached their third decade. Osteolysis is recognised as a significant complication of metal-on-polyethylene articulations and this has precipitated renewed interest in metal-on-metal implants. Ring used this bearing surface and first described it in 1968. The Ring total hip replacement (THR) (Downs Bros, Mitcham, United Kingdom) was designed for implantation without acrylic cement. The acetabular component consisted of an articular surface with a threaded stem 75 mm long and 9.5 mm in diameter which was inserted along the ilipubic bar so that it followed the weight-bearing line of the proximal femur. Prostheses were manufactured from a cast alloy of cobalt, chromium and molybdenum with a relatively high carbon content of 0.25%. This cobalt-chromium alloy was not heat-treated.

The Ring prosthesis showed rates of aseptic loosening of up to 15.7% at a follow-up of 2.5 years. The femoral component was particularly prone to loosening. A long-term follow-up study by Ring showed survivorship, with revision as the end-point, ranging between 68% and 95% at 15 years. Various factors led to these prostheses being abandoned in favour of metal-on-polyethylene THR. Early failure of many Ring THRs was attributed to poor matching between the femoral and acetabular components resulting in clutching of the head in the socket.

Concerns have been expressed regarding the carcinogenic potential of metal ions produced from wear of these metal-on-metal articulations. Both in vivo and in vitro studies have demonstrated chromosomal abnormalities in the presence of increased levels of cobalt and chromium. Our study therefore aimed to investigate whether metal ions continue to be produced throughout the life of the prosthesis.

Patients and Methods
Between 1968 and 1974, we inserted 310 THRs using the Ring metal-on-metal articulation. In 241 hips the indication for THR was osteoarthritis, in 56 failure of a previous hip operation and in seven rheumatoid arthritis. The mean age of the patients at the time of surgery was 64.5 years (30 to 86).

The patients were traced using the on-line National Health Service Strategic Tracing Service. This is a database of people, places and NHS organisations in England and Wales. Access to this resource is through approved organisations only, such as NHS trusts, primary-care trusts, strategic health authorities, etc. Our local ethics committee gave approval for the study.
Of the 310 Ring THRs, only six (five patients) were identified as being still in situ. All the surviving patients were women with a mean age of 47 years (38 to 64) at the time of surgery. The mean follow-up was 33 years (30 to 36). Data obtained from this metal-on-metal group were compared with those of other THR groups.

The first reference group, identified from surgical records, comprised three patients who had a first-generation metal-on-metal bearing revised to a metal-on-polyethylene bearing. Two had a Ring metal-on-metal articulation revised to a cobalt-chromium-on-polyethylene Stanmore hip (Biomet Europe, Bridgend, United Kingdom) because of aseptic loosening approximately 18 years after implantation. The third patient in this reference group had a McKee-Farrar metal-on-metal THR (Howmedica International Inc., Limerick, United Kingdom) also revised to a Stanmore THR approximately 30 years after the original surgery.

Further reference groups were assembled from patients currently attending orthopaedic clinics for review. In total there were five groups. Group A had a Ring metal-on-metal (cobalt-chromium) prosthesis (five patients, six hips), group B had a metal-on-metal (cobalt-chromium) prosthesis revised to a Stanmore metal (cobalt-chromium)-on-polyethylene prosthesis (three patients, three hips), group C had a Stanmore metal (cobalt-chromium)-on-polyethylene prosthesis (three patients, three hips), group D had an Exeter (stainless-steel 316L)-on-polyethylene prosthesis (Stryker, Newbury, United Kingdom) (six patients, six hips); and finally group E, an osteoarthritic control group with no implants (eight patients). These patients had no other implants in situ.

All the surviving patients with a Ring THR were called for review and asked to complete a questionnaire and undergo a clinical and radiological examination. We assessed each patient's general health and ability to perform usual activities using the SF-12 health survey. The Western Ontario and McMaster University (WOMAC) score was calculated to determine the severity of hip disease at review.

A consultant musculoskeletal radiologist independently reviewed plain radiographs of the hips with Ring prostheses in situ (Fig. 1) which were stored on the Trust Patient Archiving and Communication System (GE Centricity, GE Healthcare, Chalfont St Giles, United Kingdom). Venesection was performed on all the surviving and reference patients according to a standardised protocol. Stainless-steel hypodermic needles were used to gain access to a peripheral vein. A plastic cannula was inserted into the vein and the needle discarded. Two 10 ml plastic syringes were used to withdraw blood from each patient without the use of a tourniquet. The first 2 ml of venesected blood were discarded and the second 2 ml collected in a new syringe for analysis. Blood was collected in 2 ml Lithium Heparin tubes (Teklab, Durham, United Kingdom) as supplied by the unit performing the analysis. These containers had been certified to be free from cobalt and chromium.

The analyses were performed by inductively-coupled plasma mass spectrometry at the Trace Elements Unit, University of Southampton. Each blood sample was centrifuged at 2500 rpm for ten minutes, and the plasma separated into plain 2 ml polycarbonate tubes (Teklab) using an Elan 6100 DRC plus centrifuge (SCIEX Perkin-Elmer, Beaconsfield, United Kingdom). Samples were run against a bovine serum (Sigma, Poole, United Kingdom) calibration curve, which was spiked with 0, 1, 5, 10, 20 and 50 µg l⁻¹ of cobalt or chromium (Spectrosol cobalt standard solution 1000 mg l⁻¹; BDH). Sample volumes of 100 µl for the calibration, test and quality control were diluted 1 + 14 in 0.01% nitric acid, with rhodium or gallium added as an internal standard for the cobalt and chromium samples, respectively.

We used ammonia gas at 0.7 ml/min as the reaction gas in the Dynamic reaction cell to remove argon-based interferences at mass 52.

**Statistical analysis.** Data were stored anonymously on a spreadsheet. The Kruskal-Wallis test, the rank analogue of one-way analysis of variance, was used to analyse our results since our data were not normally distributed with constant variance. The statistical package StatsDirect (StatsDirect Ltd, Altrincham, United Kingdom) was used. Statistical significance was set at \( p \leq 0.005 \).
The mean serum cobalt and chromium ion concentrations with ranges are shown in Table I.

The mean serum cobalt level in group A was 34.09 nmol/l (17 to 57) which was approximately five times greater than that of all the reference groups. The detection limit for cobalt was 2 nmol/l. Multiple comparisons (Conover-Inman) indicated that group A patients had significantly higher serum cobalt levels compared with those of groups B, C, D and E (p = 0.0024, < 0.0001, 0.0003 and 0.0029, respectively). None of the observed differences in the reference groups was statistically significant.

The mean serum chromium level in group A was 58.37 nmol/l (35 to 85) which was approximately three times greater than that of all the reference groups. The detection limit for chromium was 2 nmol/l. Multiple comparisons (Conover-Inman) indicated that group A patients had significantly higher serum chromium levels compared with those of groups B, C, D and E (p = 0.0009, 0.0016, 0.0012 and 0.0002, respectively). None of the observed differences in the reference groups was statistically significant.

The SF-12 health-survey scores revealed that the Ring metal-on-metal hip group A had a mean 46% (29% to 64%) optimum physical performance and 53% (31% to 74%) optimum total performance. The mean WOMAC pain subscore was 1 of 20 (0 to 24). In one patient the severity of hip disease at review was minimal, in three patients moderate, in one patient mild and in five patients the severity of hip disease at review was minimal.

Table I. Mean (range) serum cobalt and chromium levels (nmol/l) in all the groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Cobalt (range)</th>
<th>Chromium (range)</th>
</tr>
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<tbody>
<tr>
<td>A (5)</td>
<td>34.09 (17 to 57)</td>
<td>58.37 (35 to 85)</td>
</tr>
<tr>
<td>B (3)</td>
<td>6.28 (6 to 7.0)</td>
<td>20.00 (19 to 21)</td>
</tr>
<tr>
<td>C (3)</td>
<td>4.95 (4 to 6.0)</td>
<td>20.29 (18 to 21)</td>
</tr>
<tr>
<td>D (6)</td>
<td>6.64 (5 to 9)</td>
<td>21.52 (20 to 23)</td>
</tr>
<tr>
<td>E (8)</td>
<td>7.82 (5 to 11)</td>
<td>19.70 (11 to 25)</td>
</tr>
</tbody>
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*Number in parentheses is the number in each group.

Discussion

Despite early failure of the Ring and other metal-on-metal THRs, some have survived into their fourth decade. The reasons for this may include a polar bearing with sufficient clearance and good orientation of the component avoiding impingement. The absence of polyethylene and subsequent osteolysis together with wear rates between 40 and 100 times lower than those of metal-on-polyethylene bearing surfaces have renewed interest in the all-metal THR.2

Metal-on-metal bearing surfaces have two wear phases. The first occurs within the first year of life or one million cycles while the bearing surfaces bed in.21 During this period surface carbides are shed with resultant third-body abrasive damage which is later partially or totally polished out of the main bearing zone. After this, levels of wear decrease to a steady state.11 The initial volumetric wear rate is up to five times greater than the subsequent long-term wear rate of the self-polished bearing surfaces.15 Levels of metal ions may rise again when the components become loose.16 Our data have shown that the levels of cobalt and chromium are approximately five and three times, respectively, those of normal. They are comparable with those from patients with modern metal-on-metal resurfacing THRs at least one year after insertion and therefore in the steady-state phase of wear.17-21 We refer here to ratios rather than to exact figures since there appears to be a variation in the concentrations of metal ions in the various studies. The levels may be elevated, to a less degree, in metal-on-plastic bearings22 and this elevation may be attributed to the couple between the head and neck of a modular femoral component. It has not been seen in the Stanmore THRs in our study which were of a monoblock design.

The Ring implants in our series remained well-fixed with no radiological evidence of loosening. The activity levels of patients with these metal-on-metal THRs are low, but this may be explained by their age. This is supported by the low WOMAC pain subscore scores.

Serum analysis was used to assess the systemic metal exposure. Whole-blood analysis may be a better measure of this exposure since it includes both intra- and extracellular compartments in which metal ions are transported. At low concentrations there may be a poor correlation between concurrent whole blood and serum specimens from patients.23 However, we feel that our results were not compromised since the significantly elevated metal ion concentrations recorded from the Ring metal-on-metal hip replacement group were compared with the other groups analysed in the same manner.

Metal ions arising from wear and corrosion are released into the circulation and excreted through the kidney.20 Metal particles are in the nanometre range24 which may explain the wide distribution of these particles throughout the body.25,26
Cobalt-chromium prostheses may cause increases in aneuploidy and chromosomal translocations in peripheral blood lymphocytes. Chromosomal abnormalities were found to be evident in cells adjacent to THR at the time of revision surgery compared with cells from iliac-crest marrow from the same patient or from femoral bone marrow at the primary THR. In vivo studies have shown peri-vascular infiltration of lymphocytes into the peri-prosthetic tissue surrounding a cobalt-chromium alloy metal-on-metal articulation. An accumulation of plasma cells in association with macrophages which contained metal debris has also been described. Cobalt and chromium metal debris identified in in vitro studies has been shown to reduce osteoblastic activity. Cobalt was shown to inhibit the production of type-I collagen and osteocalcin and alkaline phosphatase activity and increase levels of chromium also inhibit alkaline phosphatase activity. In an experimental study cobalt was seen to be toxic to cultured human synovial fibroblasts. Peripheral blood CD+ T-cell counts are significantly reduced in patients exposed to elevated cobalt and chromium levels. Clinical sequelae from this reduction were not demonstrated. However, caution must be taken in women of child-bearing age since these cobalt ions have been shown to cross the placenta.

These findings give rise to concern about the potential for malignant change after the insertion of metal-on-metal articulations. This has been discussed previously in the literature, but no histological pattern has shown a true association between THR and local malignancy and there have been conflicting results regarding the incidence of malignancy after THR. One study showed a significant increase in tumours of the lymphatic and haemopoietic systems in the ten years after all types of THR. However, data from the Finnish Cancer registry showed an incidence of cancer in line with that of the general population when considering mainly metal-on-polyethylene prostheses. Similar findings were reported for the McKee-Farrar metal-on-metal THR after follow-up for 28 years. Temporary increases in haemopoietic cancers at different follow-up periods have been seen in some series.

A Swedish study did not identify an increased incidence of leukaemia and lymphoma after THR. In another study data from the Swedish Cancer Registry showed that patients who had a THR had rates of most types of cancer similar to those of the general population. Although these Ring metal-on-metal articulations were implanted at a relatively young age, few of the patients retain these prostheses because of revision of the implant or morbidity and mortality. This is not surprising since most of the patients would now be in their tenth decade of life. Unfortunately, this means that few patients are available for investigation. Only five patients in our study had the original Ring THR in situ and only three were available who had a metal-on-metal THR revised to a different prosthesis.

Our study is unique in demonstrating the levels of metal ions in well-fixed primary Ring metal-on-metal THRs with follow-up beyond 30 years albeit at a single point in time. These implants continue to release metal ions at levels which are comparable with those of modern metal-on-metal THRs in the steady-state phase of wear.

The three patients who had revision from metal-on-metal articulations to metal-on-polyethylene bearings had serum levels of metal ions which were not statistically different from those of the other reference groups. The time at which these levels return to normal limits is unknown and it is also not known whether ions persist at distant sites after revision. Since metal-on-metal bearings are being implanted into younger patients the need for research to determine the true association between metal ions and cancer remains a priority.

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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


