Metal ion levels in patients with a lumbar metal-on-metal total disc replacement

SHOULD WE BE CONCERNED?

P. Bisseling, D. J. Zeilstra, A. M. Hol, J. L. C. van Susante

From the Department of Orthopaedics, Rijnstate Hospital, Arnhem, The Netherlands

The purpose of this study was to evaluate whether concerns about the release of metal ions in metal-on-metal total hip replacements (THR) should be extended to patients with metal-bearing total disc replacements (TDR).

Cobalt and chromium levels in whole blood and serum were measured in ten patients with a single-level TDR after a mean follow-up of 34.5 months (13 to 61) using inductively-coupled plasma mass spectrometry. These metal ion levels were compared with pre-operative control levels in 81 patients and with metal ion levels 12 months after metal-on-metal THR (n = 21) and resurfacing hip replacement (n = 36). Flexion-extension radiographs were used to verify movement of the TDR.

Cobalt levels in whole blood and serum were significantly lower in the TDR group than in either the THR (p = 0.007) or the resurfacing group (p < 0.001). Both chromium levels were also significantly lower after TDR versus hip resurfacing (p < 0.001), whereas compared with THR this difference was only significant for serum levels (p = 0.008). All metal ion levels in the THR and resurfacing groups were significantly higher than in the control group (p < 0.001). In the TDR group only cobalt in whole blood appeared to be significantly higher (p < 0.001). The median range of movement of the TDR was 15.5º (10º to 22º).

These results suggest that there is minimal cause for concern about high metal ion concentrations after TDR, as the levels appear to be only moderately elevated. However, spinal surgeons using a metal-on-metal TDR should still be aware of concerns expressed in the hip replacement literature about toxicity from elevated metal ion levels, and inform their patients appropriately.

Total disc replacement (TDR) is one surgical procedure used to treat degenerative disc disease. The theoretical advantage of TDR over spinal fusion is that movement is preserved at the involved level and accelerated degeneration of the adjacent segment is prevented.1-3 As found in any joint replacement, the bearing surfaces of the implant might wear and release particles. Ideally, any volumetric wear should be as low as possible: metal-on-metal (MoM) articulations were introduced in an attempt to achieve this goal. At the hip, despite the relatively low volumetric wear of well-positioned MoM articulations compared with polyethylene bearings, the total number of particles released is much higher.4,5 These particles measure between 6 nm and 834 nm in diameter4 and are transported throughout the body, resulting in elevated levels of cobalt and chromium ions in blood and urine.6-11

There is increasing concern in the literature on MoM hip replacement about the potentially hazardous side-effects of these elevated metal ion levels. Numerous studies, especially on MoM resurfacings, have reported serious adverse events, including implant-induced hypersensitivity reactions,12-14 osteolysis,13,15 pseudotumour formation16,17 and focal peri-prosthetic soft tissue necrosis.13,17,18 Such adverse events frequently demand relatively early revision. In the United Kingdom these studies have led to an official alert from the Medicines and Healthcare products Regulatory Agency (MHRA), which suggests that metal ion levels should be measured in patients with a MoM hip replacement if they have features which place them at risk of an adverse reaction or pain.19

By comparison, very little attention has been paid to this phenomenon in spinal surgery. A search of the literature revealed only two single-centre studies on increased metal ion levels after an MoM TDR20,21 They concluded that metal ion levels in patients with an MoM TDR are similar to those found after MoM hip replacement, which is a cause for concern.
given the official alert regarding MoM hip replacement. Accordingly, further evaluation of metal ion levels in patients with a TDR are required.

In this study we evaluated cobalt (Co) and chromium (Cr) ion levels in whole blood and serum of patients with an MoM TDR and compared these with levels from an ongoing trial comparing metal ion levels after resurfacing versus conventional MoM total hip replacement (THR).

**Patients and Methods**

Between January 2004 and June 2010, cobalt and chromium ion levels in whole blood and serum were prospectively assessed in an ongoing randomised controlled trial (RCT) comparing resurfacing with conventional MoM THR, and in a prospective cohort of patients with a resurfacing arthroplasty of the hip. Patients received either a Conserve Plus resurfacing (Wright Medical Technology, Arlington, Tennessee) with a median femoral head diameter of 49 mm (42 to 54) or an uncemented metal-bearing Zweymuller THR (Zimmer Orthopaedics, Warsaw, Indiana) with a 28 mm Metasul head. Metal ion levels in patients from these two cohorts were available at several intervals. For this study the 12-month data from patients with a unilateral hip replacement were used, as the metal ion levels are known to be elevated during a running-in phase of approximately 6 to 12 months, after which they stabilise. The baseline metal ion levels of all these patients were assessed pre-operatively and regarded as controls.

The cobalt and chromium ion levels were also determined in ten consecutive patients with a single-level MoM Maverick TDR (Medtronic Sofamor Danek GmbH, Köln, Germany), undertaken between December 2009 and August 2010, at their routine yearly follow-up. Given the phenomenon of the running-in phase in MoM hip replacements, a minimum follow-up of one year was also chosen for TDR patients. The median follow-up for the TDR patients was 34.5 months (13 to 61). The median follow-up for patients with a hip replacement was exactly 12 months, as they had all been recalled for blood samples one year after implantation as part of the study protocol.

Regional ethics committee approval had been granted for the study of all the hip patients but no approval was required for the TDR patients, as the evaluation was considered part of their routine care. Informed consent was still obtained in all cases.

**Study population.** A total of ten patients with a single-level TDR, 36 with a unilateral hip resurfacing and 21 with a unilateral THR were included in the study and were tested for cobalt and chromium ion levels in whole blood and serum. The pre-operative baseline metal ion levels of 81 patients in the hip replacement trials were used as controls. The number of control patients exceeds the sum of the patients with a resurfacing or THR, as only hip replacement patients with a follow-up of at least one year were included. None of these had been exposed to cobalt or chromium, either environmentally or medically, according to a standardised screening questionnaire.

All patients who underwent a TDR had suffered from discogenic back pain that failed to respond to conservative treatment over a period of at least 12 months; they had single-level disc degeneration on MRI; no spondylolisthesis or congenital abnormality; a body mass index (BMI) < 30; no previous back operations; and were aged between 25 and 55 years. Failed conservative treatment included anti-inflammatory drugs, physiotherapy, pain treatment and modification of activity.

Maverick TDR plates come in small, medium and large sizes and vary in height between 9 mm and 14 mm. None of the patients included in this study had a small implant, three had a medium implant and seven a large implant; their median height was 10 mm (9 to 11). The TDR was at L4-5 in eight cases and at L5-S1 in two. Additional demographic data are summarised in Table I.

**Clinical scoring, TDR positioning and TDR range of movement.** A visual analogue scale (VAS) for low back pain and an Oswestry Disability Index (ODI) were obtained...
Anteroposterior (left) and lateral (right) radiographs showing a Maverick metal-on-metal total disc replacement, with a ball-and-socket articulation. The percentage deviation of the prosthesis from the midline of the vertebral body on the anteroposterior view was defined as the difference between the midline of the body (yellow line C) and the midline of the prosthesis (dotted red line D) divided by the distance between points A and B. On the lateral view an adequate position was defined as implant position within 5 mm of the posterior boundary of the endplate (distance between lines A and C).

pre-operatively and at regular intervals post-operatively in the TDR group. The range of movement of the TDR was also routinely measured by an author (DJZ): this was defined as the angle between the caudal endplate of the upper vertebral body and the cranial endplate of the lower vertebral body in the sagittal plane on conventional flexion-extension radiographs.

Because malpositioning of the implant is known to elevate metal ion levels after THR, consistent satisfactory placement of each TDR was confirmed on anteroposterior (AP) and lateral radiographs. On the AP view the centre of the implant was compared with the midline of the vertebrae and any deviation was expressed as a percentage of the width of the superior endplate of the inferior vertebra (Fig. 1). Central positioning with < 5% deviation was considered satisfactory. On the lateral view, a satisfactory position was registered if the implant was sited within 5 mm of the posterior border of the endplate.

Blood collection. Blood samples were collected in three metal-free vacutainers, a 6 ml BD ‘EDTA’ and a 5 ml BD ‘SST II Advance’ system (both Becton Dickinson, Franklin Lakes, New Jersey). The first 5 ml were discarded to eliminate any form of metal contamination from the needle. After blood collection the tube with clot activator was set to rest for at least 30 minutes and was then centrifuged at 3600 rpm for ten minutes. Both tubes were stored at 2°C to 8°C and forwarded to the Laboratory of Toxicology at the University Hospital, Ghent, Belgium, for analysis. The metal ion levels were determined using an inductively coupled plasma mass spectrometer (ICP-MS) on a Perkin Elmer Elan DRC-e equipped with a standard cross-flow nebuliser and a dynamic reaction cell (Perkin Elmer SCIEX Instruments, Ontario, Canada). Results were quantitatively reported if concentrations exceeded the detection threshold of 0.5 μg/l; all values below the detection limit were registered as 0.1 μg/l for statistical analysis.

Statistical analysis. The data were processed using SPSS 15.0 (SPSS Inc., Chicago, Illinois) and analysed for statistical differences. Variables were controlled for their normal distribution with the Kolmogorov-Smirnov test. A value of < 0.05 was defined as an absence of normal distribution. Median, range and non-parametric tests (Mann-Whitney U, Wilcoxon signed-rank and Kruskal-Wallis tests) were used for all parameters owing to the absence of normal distribution and the small number of patients in the TDR group. Pearson’s chi-squared test was used for categorical variables (gender). Statistical significance was defined as a p-value < 0.05.

Results
The characteristics of all implant subgroups are presented in Table I. The clinical scores, range of movement and metal ion levels of each of the TDR patients are shown in Table II. The VAS for low back pain and the ODI both improved significantly after surgery (both p = 0.005, Wilcoxon signed-rank test). At the latest follow-up the VAS pain score had decreased by a median of seven points out of ten (4 to 8) against pre-operative levels. The ODI revealed an median post-operative decrease of 39% (24% to 80%).

All TDRs remained mobile at the median follow-up of 34.5 months (Table II) when the median range of movement was 15.5° (10° to 22°).

Regarding the position of the implants, the median deviation of the centre of the TDR from the midline of the vertebra was 2.4% (0% to 4.8%) on the AP view. On the lateral view all TDRs were placed within 5 mm of the posterior border of the adjacent endplate. Accordingly, all ten TDRs could be classified as being appropriately sited on both AP and lateral views.

Coil and chromium levels in whole blood and serum. The median cobalt and chromium levels in whole blood and serum for each subgroup of implants are given in Table III and the relationship between them is shown in Figure 2.

TDR versus THR and hip resurfacing. Cobalt and chromium levels in whole blood and serum were significantly lower in the TDR group than in both the resurfacing and the THR groups, particularly in the resurfacing group (p < 0.001, Mann-Whitney U test; Table III). The difference between the THR subgroup and the TDR patients was less pronounced, but with significantly higher cobalt levels in both whole blood and serum and chromium levels in serum for the THR group (p = 0.004, p = 0.007 and p = 0.008, respectively, Mann-Whitney U test). Chromium levels in whole blood were also relatively high in the THR group, but this difference was not statistically significant (p = 0.053, Mann-Whitney U test).
Compared with the metal ion levels in the control group, the cobalt and chromium ion levels in whole blood and serum were all significantly higher ($p < 0.001$, Mann-Whitney U test) after both resurfacing and THR. For the TDR patients, however, the cobalt levels in serum and the chromium levels in both whole blood and serum did not differ statistically from those in the control group (Fig. 2). The only metal trace that appeared to be significantly higher after TDR was cobalt in whole blood ($p < 0.001$, Mann-Whitney U test).

**Discussion**

In this study, patients with a well-functioning single-level TDR appeared to have cobalt and chromium levels that were in most cases similar to those measured preoperatively in control patients without any form of MoM implant. Only cobalt levels in whole blood showed a significant median increase (to 0.6 μg/l) after a TDR; this is just above the detection limit of 0.5 μg/l. Metal ion levels in the TDR group were also significantly lower than those after resurfacing or THR, particularly after resurfacing.

These results are at odds with those of the two other single-centre studies in the literature. In these studies of mono- and bisegmental TDR the authors reported a median cobalt serum level of 4.97 μg/l and a chromium serum level of 1.78 μg/l at a median follow-up of 14.8 months. At 36.7 months these median values of cobalt decreased to 1.64 μg/l and chromium increased to 2.50 μg/l, respectively. These figures are much higher than we found in our study, where serum levels of both cobalt and chromium remained below the detection limit at a median follow-up of 34.5 months. Cobalt levels of 4.97 μg/l should cause concern, as they approach levels of toxicity equivalent to the ‘exposure equivalent of carcinogenic substances’ (EKA values) for industrial workers and the references of the Mayo Medical Laboratories interpretive handbook. In these references, the upper limit of cobalt is defined at 5 μg/l in whole blood. In addition to these reference values, Desmet et al analysed metal ion levels in patients with well- and poorly functioning resurfacings and proposed that serum cobalt and chromium levels of 4.4 μg/l (odds ratio (OR) for revision 6.0) and 5.1 μg/l (OR for revision 4.3), respectively, should be the upper limits of acceptability.

We do not have a clear explanation for the differences in metal ion levels found between our study and the earlier studies of Zeh et al. Both were performed on patients with the same type of TDR (Maverick TDR). In the studies of Zeh et al, patients with both single- and two-level

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**Table II.** Clinical scores, range of movement and metal ion levels (Co, cobalt; Cr, chromium) in the total disc replacement (TDR) group

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Level</th>
<th>Follow-up (mths)</th>
<th>VAS* (0 to 10)</th>
<th>ODI † (0 to 100)</th>
<th>ROM‡ (°)</th>
<th>Blood (μg/l)</th>
<th>Serum (μg/l)</th>
<th>Blood (μg/l)</th>
<th>Serum (μg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L4/L5</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>17</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>L4/L5</td>
<td>15</td>
<td>8</td>
<td>2</td>
<td>24</td>
<td>0</td>
<td>15</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>L4/L5</td>
<td>24</td>
<td>8</td>
<td>0</td>
<td>40</td>
<td>2</td>
<td>12</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>L4/L5</td>
<td>29</td>
<td>8</td>
<td>1</td>
<td>46</td>
<td>10</td>
<td>16</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>L4/L5</td>
<td>31</td>
<td>7</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>12</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>L4/L5</td>
<td>38</td>
<td>8</td>
<td>4</td>
<td>68</td>
<td>30</td>
<td>17</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>L4/L5</td>
<td>60</td>
<td>7</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>22</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>L4/L5</td>
<td>61</td>
<td>7</td>
<td>0</td>
<td>54</td>
<td>0</td>
<td>21</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>9</td>
<td>L5/S1</td>
<td>59</td>
<td>8</td>
<td>0</td>
<td>80</td>
<td>0</td>
<td>10</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>L5/S1</td>
<td>60</td>
<td>8</td>
<td>2</td>
<td>56</td>
<td>2</td>
<td>10</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Median (range)

<table>
<thead>
<tr>
<th>Control (n = 81)</th>
<th>TDR (n = 10)</th>
<th>Hip resurfacing (n = 36)</th>
<th>THR (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt whole blood</td>
<td>0.1 (0.1 to 0.8)</td>
<td>0.6 (0.1 to 1.2)</td>
<td>1.3 (0.6 to 11.5)</td>
</tr>
<tr>
<td>Cobalt serum</td>
<td>0.1 (0.1 to 2.6)</td>
<td>0.1 (0.1 to 1.1)</td>
<td>1.1 (0.1 to 7.7)</td>
</tr>
<tr>
<td>Chromium whole blood</td>
<td>0.1 (0.1 to 1.2)</td>
<td>0.1 (0.1 to 1.1)</td>
<td>1.0 (0.1 to 6.0)</td>
</tr>
<tr>
<td>Chromium serum</td>
<td>0.1 (0.1 to 2.9)</td>
<td>0.2 (0.1 to 0.9)</td>
<td>1.8 (0.1 to 10.2)</td>
</tr>
</tbody>
</table>

* VAS, visual analogue scale for pain
† ODI, Oswestry Disability Index
‡ ROM, range of movement in the sagittal plane

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**Table III.** Median metal ion levels in μg/l (range) in the different prosthesis groups (TDR, total disc replacement; THR, total hip replacement)

<table>
<thead>
<tr>
<th>Control (n = 81)</th>
<th>TDR (n = 10)</th>
<th>Hip resurfacing (n = 36)</th>
<th>THR (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt whole blood</td>
<td>0.1 (0.1 to 0.8)</td>
<td>0.6 (0.1 to 1.2)</td>
<td>1.3 (0.6 to 11.5)</td>
</tr>
<tr>
<td>Cobalt serum</td>
<td>0.1 (0.1 to 2.6)</td>
<td>0.1 (0.1 to 1.1)</td>
<td>1.1 (0.1 to 7.7)</td>
</tr>
<tr>
<td>Chromium whole blood</td>
<td>0.1 (0.1 to 1.2)</td>
<td>0.1 (0.1 to 1.1)</td>
<td>1.0 (0.1 to 6.0)</td>
</tr>
<tr>
<td>Chromium serum</td>
<td>0.1 (0.1 to 2.9)</td>
<td>0.2 (0.1 to 0.9)</td>
<td>1.8 (0.1 to 10.2)</td>
</tr>
</tbody>
</table>
TDRs were included, whereas we only included patients with a single-level replacement. However, the previous studies state that there was no statistically significant difference in metal ion levels after TDR at one or two levels.\textsuperscript{20,21}

From the literature on hip replacement we know that an optimal implant position is mandatory to ensure low friction and subsequently low metal ion levels.\textsuperscript{27} Adequate positioning of the TDR is also a prerequisite for normal spine kinematics,\textsuperscript{1,2,31} and it seems reasonable to assume that appropriate positioning of the TDR has an influence on low metal ion release as it does for hip replacement.

The range of movement of the device may also influence the amount of metal ion release, as loss of movement would inevitably lead to a decrease in wear. All TDRs appeared to have maintained a substantial range of movement on flexion-extension radiographs, with a median of 15.5° (10° to 22°) at final follow-up. Therefore, we can conclude that the low metal ion levels cannot simply be explained by an absence of movement of the implants. No information on implant position and range of movement is given in the studies of Zeh et al.\textsuperscript{20,21}

The differences we found are probably related to differences in the protocols we used for blood collection and processing. Adequate and reliable measurement of ultra-low levels of metal ions is a delicate process and vulnerable to potential contamination, such as traces of metal from the needle. In our protocol the first 5 ml of blood were discarded to avoid potential contamination. In addition, we used ICP-MS on a Perkin Elmer Elan DRC-e equipped with a standard cross-flow nebuliser and a dynamic reaction cell (Perkin Elmer SCIEX), which is currently considered the optimal processing technique.\textsuperscript{32}

Another advantage of our study is that we were able to correlate the metal ion levels found after TDR with control levels and levels after resurfacing and THR. Samples from all these subgroups were evaluated at the same laboratory using the same rigid protocol.

In our study both cobalt and chromium levels in the TDR group were significantly lower than after THR (p = 0.053) and resurfacing (p < 0.001). Given the current concern about the serious adverse events that have occurred after MoM hip replacements, and in particular after resurfacing, this is an important finding. We conclude that the chances of a significant increase in metal ion levels in both whole blood and serum after TDR are substantially lower than after THR or resurfacing. Apparently the amount of wear debris from a well-positioned TDR is relatively low. This corresponds with an earlier study where wear debris from a Maverick TDR was estimated to be between 0.38 mm\textsuperscript{3} and 0.44 mm\textsuperscript{3} per year, compared with 1 mm\textsuperscript{3} to 5 mm\textsuperscript{3} for a MoM hip replacement.\textsuperscript{3,33} This difference in wear is almost certainly due to the fact that the kinematics of a TDR, such as loading, shear forces, contact area and range of movement, are profoundly different from those of any hip replacement. The range of movement in a TDR is relatively limited and the shear forces are rather low, owing to the contained position of the device. This will result in lower friction of the articulating surfaces and reduced wear.

There are limitations to our study. No pre-operative metal ion levels were assessed in the TDR group, which made it impossible to determine the actual increase in metal ion levels after surgery. As cobalt levels in serum and chromium levels in both whole blood and serum remained generally below the detection limit of 0.5 µg/l at a median of 34.5 months after a TDR, one can argue whether this limitation is truly relevant. We believe that the available dataset of 81 control patients from an ongoing hip trial provides an appropriate surrogate value.

In addition, it should be noticed that there is a difference in follow-up between the different implant groups. Patients in the TDR group had a longer median follow-up (34.5 months) than the resurfacing and THR groups (12 months), but we do not believe that this difference is a major confounding factor, as the metal ion levels of the TDR are certainly beyond their running-in phase and must have stabilised. These levels are also lower than the long-term figures for MoM THR and resurfacings given in the literature.\textsuperscript{7,8,24}

The TDR group was small. A larger population would, however, probably not have shown any greater difference between the TDR and the control group, as all values...
were in a limited range and almost always below the limit of detection.

In conclusion, we believe that there is only limited cause for concern, as in this study the post-operative metal ion levels were significantly lower after TDR than after THR and resurfacing, and were generally comparable to those in the general population. These findings are more reassuring than those previously published. Local soft-tissue necrosis or pseudotumour formation as a result of metal ion debris reaching toxic release levels, as has been described after MoM hip replacement, would seem unlikely to occur after an MoM lumbar TDR. However, the exact pathology of pseudotumour formation is far from fully understood, and as well as a toxic reaction to an abundant volume of metal particles, a delayed hypersensitivity reaction to these particles has also been described as a causative factor. With a hypersensitivity reaction metal ions do not have to be elevated beyond toxic levels in order to cause a soft-tissue reaction. So far, only two case reports are available in the literature after a TDR, where the authors describe a soft-tissue mass posterior to the implant encroaching on the spinal cord. Revision surgery was performed and histology showed a lymphocyte-dominated response in the tissue similar to those reported in patients with an MOM hip prosthesis. These case reports and other similar unpublished reports still justify caution when using TDRs. We encourage spinal surgeons using MoM TDR to follow their patients at regular intervals, particularly if they complain of increasing pain, when investigation should include measurement of metal ion levels.

References

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Financial support for the metal ion measurements was obtained from Wright Medical Technology (Arlington, Tennessee). 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.

The Journal of Bone and Joint Surgery