The effectiveness of blood metal ions in identifying bilateral metal-on-metal total hip arthroplasty patients at risk of adverse reactions to metal debris

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We investigated whether blood metal ions could effectively identify bilateral metal-on-metal total hip arthroplasty (THA) patients at risk of adverse reactions to metal debris (ARMD). Whole blood metal ions were sampled in 50 patients with bilateral 36mm Corail-Pinnacle THAs. Patients were divided into ARMD (n=10) and non-ARMD groups (n=40), with optimal ion thresholds for identifying ARMD determined using receiver operating characteristic analysis. Maximum cobalt or chromium produced the highest area under the curve (71.8%). The optimal ion threshold for distinguishing between patients with and without ARMD was 4.0µg/l (90.0%=sensitivity, 65.0%=specificity, 39.1%=positive predictive value, 96.3%=negative predictive value). Fixed regulatory authority thresholds missed more patients with ARMD (10%-12% missed) compared to our threshold (2% missed). Bilateral THA patients with blood metal ions below our threshold were at low-risk of ARMD. Compared to currently recommended fixed authority thresholds, our threshold appears preferable for managing patients with these particular implants.

Keywords: adverse reactions to metal debris; blood metal ions; metal-on-metal; revision; total hip arthroplasty.

INTRODUCTION

High failure rates of most metal-on-metal hip implants have been observed, mainly due to adverse reactions to metal debris (ARMD) (15,28). Given outcomes following ARMD revision are poor (21), worldwide regulatory authorities currently recommend regular follow-up of metal-on-metal hip patients to identify ARMD early (5,24,29). This follow-up includes blood metal ion levels, which reflect in-vivo bearing wear (3). In 2010 the United Kingdom (UK) Medical and Healthcare Products Regulatory Agency (MHRA) published blood metal ion thresholds for concern, recommending cross-sectional imaging if cobalt and/or chromium were above 7µg/l (23). Optimal...
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PATIENTS AND METHODS

We performed a prospective single-centre cohort study of consecutive patients receiving bilateral metal-on-metal Corail-Pinnacle THAs. This study was registered with the hospital board, however ethical approval was not required because patients were assessed according to published guidance (24). Between 2004 and 2010, 578 primary Corail-Pinnacle THAs were implanted in 511 patients (22). The Corail femoral stem is a fully hydroxyapatite coated titanium alloy stem with a 12/14 taper onto which a cobalt-chromium alloy metal femoral head is impacted which articulates with a metal liner. Information regarding patient selection, surgical technique, and follow-up for Corail-Pinnacle THA patients at our centre has been described previously (22).

Follow-up

Our institution’s routine follow-up for patients with Corail-Pinnacle THAs was adapted according to MHRA recommendations (23,24). All patients underwent clinical assessment (history, examination, anteroposterior pelvic radiographs, and Oxford Hip Score questionnaire (2)) and blood metal ion sampling.

All symptomatic patients had cross-sectional imaging, regardless of symptom severity. As per MHRA guidance, all asymptomatic patients with blood metal ions above 7µg/l (MHRA upper-limit) underwent cross-sectional imaging (24). At the lead surgeon’s discretion, cross-sectional imaging was also performed in selected asymptomatic patients with blood metal ions of 7µg/l or below. Reasons for performing cross-sectional imaging in such patients included continued concerns about radiological abnormalities despite normal ion results, and cases where the contralateral THA was eligible for cross-sectional imaging.

The institution’s protocol for imaging recommends ultrasound for symptomatic patients and metal artifact reduction sequence magnetic resonance imaging (MRI) for asymptomatic patients, with recent evidence confirming both imaging modalities have important roles in assessing metal-on-metal implants (6,19). As asymptomatic patients...
patients were likely to need repeat imaging, serial MRIs were considered simpler to compare than ultrasound. Ultrasound was performed when MRI was contraindicated.

By September 2014, 67 bilateral Corail-Pinnacle THA patients (134 hips) had undergone blood metal ion sampling and were initially eligible for study inclusion.

Inclusion and exclusion criteria

Patients with bilateral, primary large-diameter (36mm) Corail-Pinnacle THAs with blood sampling performed at least one-year following the most recent arthroplasty were included. Patients undergoing blood sampling and subsequently revised for non-ARMD indications (infection, periprosthetic fracture, loosening, unexplained pain, dislocation) were excluded to reduce the presence of confounding factors when devising ARMD specific thresholds. In these instances, the absence of ARMD was confirmed from the intra-operative revision findings, histopathology, and microbiology. The final study cohort for analysis comprised 50 bilateral patients with 100 Corail-Pinnacle THA implants (Table I).

Definitions

As only one blood result was available for each patient, the unit of analysis was patients rather than hips as recommended previously (30). Patients were considered to have failed if one or both hips failed within the same patient, otherwise the patient was considered not to have failed.

Patients eligible for final inclusion (n = 50) were divided into two groups based on their status in September 2014. The ARMD group (n = 10) included all patients revised or awaiting revision for ARMD, and patients with ARMD confirmed on cross-sectional imaging (periprosthetic effusions and pseudotumours) (10,13,25) and under surveillance but not listed for revision due to clinician and/or patient preference. Revision surgery was recommended based on findings from the clinical assessment, radiographs, and cross-sectional imaging. Blood metal ions alone were never used to decide on revision (9). The non-ARMD group (n = 40) consisted of all patients with bilateral primary Corail-Pinnacle THAs in-situ and no evidence of ARMD on cross-sectional imaging, regardless of symptoms.

Table I. — Patient demographics for the study cohort (100 Corail-Pinnacle total hip arthroplasties in 50 patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>ARMD group</th>
<th>Non-ARMD group</th>
<th>p value: ARMD v. non-ARMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>50 (100)</td>
<td>10 (20)</td>
<td>40 (80)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>27 f / 23 m</td>
<td>7 f / 3 m</td>
<td>20 f / 20 m</td>
<td>0.435</td>
</tr>
<tr>
<td>Age at blood test (yr)*</td>
<td>65.3 (41.8-85.6)</td>
<td>64.6 (45.8-72.4)</td>
<td>65.5 (41.8-85.6)</td>
<td>0.771</td>
</tr>
<tr>
<td>Time from latest primary to blood test (yr)*</td>
<td>6.1 (2.5-9.7)</td>
<td>5.4 (4.0-7.7)</td>
<td>6.3 (2.5-9.7)</td>
<td>0.059</td>
</tr>
<tr>
<td>Total time in-situ for both hips before blood test (yr)*</td>
<td>13.3 (6.0-19.5)</td>
<td>12.7 (9.9-18.2)</td>
<td>13.5 (6.0-19.5)</td>
<td>0.359</td>
</tr>
</tbody>
</table>

ARMD = adverse reactions to metal debris; f = female; m = male
* Mean (range) values provided.
All statistical analysis was performed using 2-sided unpaired t-tests apart from for gender, which was compared using a Chi-squared test with Yates’ correction.
Blood metal ion analysis

Whole blood was collected from the antecubital vein of patients for metal ion analysis as described (18). Samples were analysed in an MHRA approved laboratory, with excellent measurement accuracy and reproducibility previously reported (7). Cobalt and chromium concentrations were measured with an inductively-coupled plasma mass spectrometer (Agilent 7500cx, Agilent Technologies Inc., Santa Clara, US; limit of detection = 0.06µg/l and reporting limit = 0.6µg/l).

Statistical analysis

The four blood metal ion parameters of interest were cobalt, chromium, the maximum cobalt or chromium (the higher value of the pair), and the cobalt-chromium ratio (cobalt divided by chromium, and non-dimensional). Two-sided t-tests were used to compare the logarithms of the four ion parameters between ARMD and non-ARMD groups (p-value < 0.05 considered significant). The logarithm was necessary to transform the asymmetric blood metal ion distributions to approximately normal distributions as recommended (1).

Receiver operating characteristic (ROC) analysis is an established method of assessing diagnostic test performance (4). A ROC curve is drawn by plotting sensitivity (true positive rate) against 1-specificity (or 100-specificity if presented as a percentage) for all possible test thresholds. A useful test produces a curve lying to the left of a 45° line. The further the curve is towards the top left corner, the higher the area under the curve (AUC) and the better the discriminatory performance of the test (100% AUC=perfect discriminatory test; 50% AUC = non-discriminatory test). ROC analysis can also be used to identify the optimal threshold to maximise discriminatory ability for a test.

ROC analysis was used to determine optimal blood metal ion thresholds for identifying patients with ARMD. The optimum is defined as the threshold corresponding to the point on the curve nearest the top left corner. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated (all with 95% confidence intervals (CIs)) for the optimal thresholds for each of the four blood metal ion parameters. The DeLong test was used to compare the AUCs between the different metal ion parameters (26).

RESULTS

Blood metal ions

The four blood metal ion parameters are summarised (Table II). All four parameters were

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>ARMD group</th>
<th>Non-ARMD group</th>
<th>p value: ARMD v. non-ARMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>50 (100)</td>
<td>10 (20)</td>
<td>40 (80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cobalt (µg/l)</td>
<td>3.51 (1.97-8.78)</td>
<td>6.72 (4.28-12.71)</td>
<td>3.07 (1.73-7.34)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chromium (µg/l)</td>
<td>1.87 (1.10-3.55)</td>
<td>2.75 (1.14-8.63)</td>
<td>1.84 (1.12-3.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum cobalt or chromium (µg/l)</td>
<td>3.75 (2.06-8.78)</td>
<td>7.64 (4.41-12.71)</td>
<td>3.12 (1.99-7.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cobalt-chromium ratio</td>
<td>1.65 (0.94-2.95)</td>
<td>1.89 (1.02-3.98)</td>
<td>1.65 (0.83-2.61)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ARMD = adverse reactions to metal debris

p-values for all statistically significant results are highlighted in bold text

Table II. — Median (interquartile range) blood metal ion parameters for bilateral Corail-Pinnacle total hip arthroplasty patients
and the proportion of ARMD patients missed with each threshold. Maximum cobalt or chromium was used for this comparison as this parameter provided the optimal diagnostic test characteristics and AUC results.

Threshold analysis for bilateral Corail-Pinnacle THAs (Table III and Figure I).

The optimal blood metal ion thresholds for discriminating between bilateral Corail-Pinnacle THA patients with and without ARMD depended on the specific metal ion parameter used.

Compared to the other three ion parameters, maximum cobalt or chromium produced the highest AUC for Corail-Pinnacle THAs of 71.8% (95% CI 52.2%-91.3%). There were no significant differences between the AUCs of the four metal ion parameters (all p>0.160). The maximum cobalt or chromium threshold for identifying Corail-Pinnacle THA patients with ARMD providing optimal diagnostic test characteristics was 4.0µg/l (90.0% sensitivity, 65.0% specificity, 39.1% positive predictive value, 96.3% negative predictive value).

**Implant Specific Threshold vs. fixed regulatory authority thresholds (Table IV)**

Fixed blood metal ion thresholds for concern currently proposed by the US (10µg/l=high-risk group) (12), and UK MHRA (7µg/l) (24) were applied to the cohort and compared to our Implant Specific Threshold in terms of the diagnostic test characteristics for identifying patients with ARMD, and the proportion of ARMD patients missed with each threshold. Maximum cobalt or chromium was used for this comparison as this parameter provided the optimal diagnostic test characteristics and AUC results.

Compared to fixed regulatory thresholds, the maximum cobalt or chromium Implant Specific Threshold provided better diagnostic test characteristics. The Implant Specific Threshold

![Fig. 1 — Receiver operator characteristic curve showing the ability of four blood metal ion parameters for distinguishing between bilateral Corail-Pinnacle total hip replacement patients with and without adverse reactions to metal debris](image)

Table III. — Summary of the receiver operator characteristic analysis for bilateral Corail-Pinnacle total hip arthroplasty patients

<table>
<thead>
<tr>
<th>Ion parameter</th>
<th>AUC (95% CI)</th>
<th>Optimal thresholds</th>
<th>Sensitivity (95% CI) %</th>
<th>Specificity (95% CI) %</th>
<th>PPV (95% CI) %</th>
<th>NPV (95% CI) %</th>
<th>Misclassification %</th>
<th>+ve LR (95% CI)</th>
<th>-ve LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt</td>
<td>67.9 (47.4-88.4)</td>
<td>4.0 µg/l</td>
<td>80.0 (50.0-100.0)</td>
<td>65.0 (50.0-80.0)</td>
<td>36.4 (16.3-56.5)</td>
<td>92.9 (83.3-100)</td>
<td>32.0</td>
<td>2.29 (1.35-3.86)</td>
<td>0.31 (0.09-1.08)</td>
</tr>
<tr>
<td>Chromium</td>
<td>60.0 (35.9-84.1)</td>
<td>3.5 µg/l</td>
<td>50.0 (20.0-80.0)</td>
<td>80.0 (67.5-92.5)</td>
<td>38.5 (12.0-64.9)</td>
<td>86.5 (75.5-97.5)</td>
<td>26.0</td>
<td>2.50 (1.04-6.01)</td>
<td>0.63 (0.33-1.18)</td>
</tr>
<tr>
<td>Maximum cobalt or chromium</td>
<td>71.8 (52.2-91.3)</td>
<td>4.0 µg/l</td>
<td>90.0 (70.0-100.0)</td>
<td>65.0 (50.0-80.0)</td>
<td>39.1 (19.2-59.1)</td>
<td>96.3 (89.2-100)</td>
<td>30.0</td>
<td>2.57 (1.61-4.11)</td>
<td>0.15 (0.02-1.00)</td>
</tr>
<tr>
<td>Cobalt chromium ratio</td>
<td>57.2 (34.1-80.4)</td>
<td>2.2</td>
<td>50.0 (20.0-80.0)</td>
<td>70.0 (55.0-85.0)</td>
<td>29.4 (7.8-51.1)</td>
<td>84.8 (72.6-97.1)</td>
<td>34.0</td>
<td>1.67 (0.76-3.64)</td>
<td>0.71 (0.37-1.37)</td>
</tr>
</tbody>
</table>

AUC = area under the curve; CI = confidence intervals; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio.
Table IV. — Summary of the receiver operator characteristic analysis for various thresholds (implant specific and fixed) for maximum blood cobalt or chromium ions in bilateral Corail-Pinnacle total hip arthroplasty patients

<table>
<thead>
<tr>
<th>Threshold</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Misclassification</th>
<th>Number of patients with ARMD not identified</th>
<th>+ve LR (95% CI)</th>
<th>-ve LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 µg/l</td>
<td>71.8 (52.2-91.3)</td>
<td>40.0 (9.6-70.4)</td>
<td>85.0 (73.9-96.1)</td>
<td>40.0 (9.6-70.4)</td>
<td>85.0 (73.9-96.1)</td>
<td>24.0</td>
<td>6</td>
<td>2.67 (0.93-7.69)</td>
<td>0.71 (0.42-1.19)</td>
</tr>
<tr>
<td>7 µg/l</td>
<td>50.0 (19.0-81.0)</td>
<td>72.5 (58.7-86.3)</td>
<td>31.2 (8.5-54.0)</td>
<td>85.3 (73.4-97.2)</td>
<td>32.0</td>
<td>5</td>
<td>1.82 (0.82-4.04)</td>
<td>0.69 (0.36-1.32)</td>
<td></td>
</tr>
<tr>
<td>4.0 µg/l</td>
<td>90.0 (70.0-100.0)</td>
<td>65.0 (50.0-80.0)</td>
<td>39.1 (19.2-59.1)</td>
<td>96.3 (89.2-100)</td>
<td>30.0</td>
<td>1</td>
<td>2.57 (1.61-4.11)</td>
<td>0.15 (0.02-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

AUC = area under the curve; CI = confidence intervals; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio

provided the best balance between sensitivity and specificity, with higher negative predictive values, but lower positive predictive values. Applying the Implant Specific Threshold to the cohort resulted in 1 patient with ARMD being missed (2% of cohort). More patients with ARMD were missed when using fixed regulatory thresholds: 7µg/l = 5 patients missed (10%); 10µg/l = 6 patients missed (12%). Using the UK threshold of 7µg/l resulted in five-times more missed patients with ARMD compared to Implant Specific Thresholds (p = 0.134; McNemar test). The US high-risk 10µg/l threshold resulted in six-times more missed patients with ARMD compared to Implant Specific Thresholds (p = 0.074).

DISCUSSION

This represents the only study assessing whether blood metal ions could effectively identify patients with bilateral THAs who were at risk of ARMD. Bilateral Corail-Pinnacle THA patients with blood metal ions below our Implant Specific Threshold (maximum cobalt or chromium = 4.0µg/l) were at low-risk of ARMD. Our Implant Specific Threshold missed fewer patients with ARMD compared to fixed thresholds currently proposed (12,24). This Implant Specific Threshold therefore appears to be preferable for managing patients with bilateral Corail-Pinnacle THAs.

A study recently reported for the first time that Implant Specific Thresholds exist for identifying unilateral Corail-Pinnacle THA patients with ARMD (18). The present findings support our hypothesis that an Implant Specific Threshold also exists in bilateral THA patients with these implants. We observed that blood metal ions were most effective for identifying bilateral THA patients at low-risk of ARMD, rather than identifying those with ARMD. This supports the findings in unilateral patients (18). We consider this the most important finding because clinically we wish to rule out patients with ARMD, thereby allowing us to focus resources on patients who may have ARMD. Asymptomatic patients above Implant Specific Thresholds require cross-sectional imaging. Asymptomatic patients below these thresholds are at low-risk of ARMD. However, given the high failure rates associated with metal-on-metal THAs (15,28), it is recommended such patients remain under regular clinical surveillance with a low threshold exercised for performing cross-sectional imaging.

Our study is the first establishing optimal metal ion thresholds in bilateral THA patients. Although some authorities recommend sampling blood cobalt alone in metal-on-metal patients (5), our findings suggest that both cobalt and chromium are required for bilateral Corail-Pinnacle patients. A threshold of 4.0µg/l provided good sensitivity and reasonable specificity for identifying bilateral Corail-Pinnacle THA patients with ARMD. This Implant Specific Threshold is lower than that proposed in a previous bilateral hip resurfacing cohort (cobalt = 5.0µg/l);
chromium = 7.4\mu g/l) (30). Although it is difficult to make comparisons between our bilateral THA cohort and previous studies on hip resurfacing patients (8,9,17,27,30) given the clear implant design differences, it is important to acknowledge some of the methodological differences between these studies. Previous studies included symptomatic patients and non-ARMD revisions as failures (8,9,30). However our definition was more robust and specific for ARMD. We also included non-revised patients with ARMD on imaging and under surveillance as failures, which is in contrast to some previous studies that may not have classified such patients as failures if they were asymptomatic (8,9).

Doubling optimal unilateral metal ion thresholds may be considered a crude estimate for bilateral thresholds. Doubling the unilateral Corail-Pinnacle Implant Specific Thresholds from a recent study (7.1\mu g/l) (18) gives a very different value compared to the present bilateral cohort with identical implant designs (4.0\mu g/l). This emphasises the importance of applying Implant Specific Thresholds in both unilateral and bilateral THA patients. In addition, our bilateral Implant Specific Threshold was considerably lower than fixed thresholds currently recommended by US (10\mu g/l) and UK (7\mu g/l) authorities (12,24). These fixed thresholds missed more patients with ARMD compared to our bilateral Implant Specific Threshold. Although the differences between the numbers of patients with ARMD missed when applying these various thresholds were not statistical significant, presumably due to small numbers, these differences are considered clinically important given the destructive potential of ARMD and poor outcomes reported following ARMD revision (21). Hence the false-negative rate must be minimised to ensure patients with this potentially destructive complication are not missed. We therefore consider our Implant Specific Threshold preferable to currently recommended fixed thresholds (12,24) for managing patients with bilateral Corail-Pinnacle THAs. It is expected that similar Implant Specific Thresholds will be identified for other THA designs in the future, which may also be preferable to fixed regulatory thresholds (12,24).

This study has recognised limitations. The main limitation is the selection bias introduced by using targeted cross-sectional imaging in asymptomatic patients with blood metal ions above 7\mu g/l. Despite this approach being in-line with current recommendations (5,24) and other centres (14), a small number of asymptomatic individuals in our study did not undergo cross-sectional imaging and may have silent ARMD, but would have been incorrectly classified in the non-ARMD group. A further limitation included this being a cross-sectional study with blood metal ions sampled only once, so recommendations cannot be made regarding the intervals for repeat blood testing. Renal function was not assessed at the time of blood sampling, and patients were not specifically questioned about the use of medications and supplements containing trace metals. It is recognised that these factors can influence the interpretation of blood metal ion results, and so this represents another study limitation. The study may be considered small which could have affected the proposed Implant Specific Threshold and diagnostic test characteristics. However, no study has assessed blood metal ion thresholds for concern in patients with any bilateral metal-on-metal THA design, so our work provides some interim guidance for managing these patients. Furthermore, the Corail-Pinnacle implant system was the most commonly implanted large-diameter metal-on-metal THA worldwide (16). Finally, our Implant Specific Threshold only applies to patients with bilateral Corail-Pinnacle THA implants, and therefore does not apply to bilateral patients with any other combination of THA design.

CONCLUSIONS

Bilateral Corail-Pinnacle THA patients with blood metal ions below our Implant Specific Threshold were at low-risk of ARMD. Our Implant Specific Threshold missed fewer patients with ARMD compared to currently recommended fixed authority thresholds. It is therefore suspected that our newly devised threshold is preferable for managing patients with bilateral Corail-Pinnacle THAs. Our findings support recent observations that Implant Specific Thresholds exist in patients
with unilateral Corail-Pinnacle THAs (18). However, we recommend these Implant Specific Thresholds undergo external validation prior to clinical implementation.

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