Systemic Health Effects of Chronic Metal Exposure after Metal-on-Metal Hip Resurfacing
+1,2Prentice, J; 1,2Clark, M; 1,2Hoggard N; 1,2Stockley, I; 1,2Morton, AC; 1,2Tooth, C; 1,2Hadjivassiliou, M; 1,2Wilkinson, JM
+1NIHR Musculoskeletal Biomedical Research Unit, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, United Kingdom, 2University of Sheffield, 3Sheffield Teaching Hospitals NHS Foundation Trust, 4NIHR Cardiovascular Biomedical Research Unit, Sheffield
j.m.wilkinson@sheffield.ac.uk

INTRODUCTION:
In recent years metal-on-metal hip resurfacing (MoMHR) has been a common alternative to total hip arthroplasty (THA) using conventional bearings in younger patients with hip disease. However, adverse events including failure of implant osseointegration, femoral neck fracture, and unexplained pain occur more frequently following MoMHR versus THA, resulting in a higher early revision rate. Cobalt (Co) and chromium (Cr) are released from MoMHR prostheses at higher levels than following THA. These metals have an adverse effect on bone cells in-vitro that might contribute to the higher rate of bone-related complications in these patients. Evidence from industrial and accidental over-exposure also shows that these metals can also affect solid organs including the brain, heart, liver and kidneys. Recent Food and Drug Administration (FDA) guidance suggests clinical monitoring of MoMHR patients for these effects together with assay of metal levels. However, to date there is no data to quantitate the potential late systemic effects of metal exposure in the MoMHR population.

In this cross-sectional study we examined whether clinically ‘healthy’ men who have previously received a MoMHR have evidence of late altered bone and solid organ function versus individually-matched men who have received a conventional non-MoM THA.

METHODS:
Thirty-one male MoMHR subjects and 31 male conventional THA subjects were recruited at a mean of 8 years after surgery. All had well-functioning prostheses and were in good self-reported health. General health was assessed using the EQ-5D questionnaire, and hip function was assessed using the Oxford Hip Score. Serum and 24 hour urinary excretion of Co and Cr were measured by inductively-coupled plasma-mass spectroscopy. Haematology, urea, creatinine, and electrolytes were measured using standard methods.

The primary outcome measure in this study was whole body bone mineral density (WB-BMD) measured by dual energy x-ray absorptiometry, and adjusted for pre-morbid osteoporosis risk factors using the FRAX tool. Biochemical markers of bone turnover were also measured in fasting morning serum or 24-hour urine collection and assayed by electro-chemiluminescent assay.

The secondary outcome measures included the following assessments: Neurological assessments were made using standardised neuropsychological screening tools and adjusted for pre-morbid IQ; Clinical examination for extra-pyramidal features was made using the modified Unified Parkinson’s Disease Rating Scale (UPDRS), visual acuity using the Snellen chart, and optic chiasm volume by magnetic resonance imaging (MRI); Cardiac function was assessed using trans-thoracic echocardiography (TTE), the New York Heart Association (NYHA) functional classification, and by electrocardiography (ECG); Hepatic function was assessed by liver function tests and clotting score and metal deposition within the liver and spleen were assessed using MRI; Renal function was measured by serum creatinine and electrolytes, and urinary metal and creatinine clearance. Renal injury was measured by ELISA using markers of renal tubular damage KIM-1, NAG, and NGAL; Endocrine function was assessed by assay of the hypothalomo-pituitary axis hormones and by measurement of pituitary volume by MRI.

RESULTS:
General characteristics and metal levels: The subjects both groups had similar demographic characteristics, time since surgery, self-reported general health, and hip function (Table 1, p>0.05, all tests). Serum and urinary excretion of Co and Cr were elevated in MoMHR versus THA subjects (p<0.001).

Bone health: In the MoMHR group versus THA, WB-BMD was 7% higher (1.05 versus 0.987/cm², P=0.002), bone formation measured by serum osteocalcin was 17% lower (18.2 versus 21.1ng/mL, P=0.02) and osteoclast number measured by TRAP 5b was 23% lower (3.4 versus 3.9/L, P=0.008). WB-BMD and bone turnover were correlated with serum or urinary Co or Cr level (P<0.05).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MoMHR (n=31)</th>
<th>THA (n=31)</th>
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<tbody>
<tr>
<td>Age at surgery (years)</td>
<td>52 ± 7</td>
<td>52 ± 8</td>
</tr>
<tr>
<td>Time since surgery (years)</td>
<td>8 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Oxford hip score</td>
<td>46 (43-47)</td>
<td>45 (39-49)</td>
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<tr>
<td>EQ-5D</td>
<td>1.0 (0.7-1.0)</td>
<td>0.9 (0.7-1.0)</td>
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<tr>
<td>*Serum Co: Cr (μg/L)</td>
<td>1.48 : 2.51</td>
<td>0.15 : 0.24</td>
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<tr>
<td>*24-hour urinary excretion Co/Cr (μg/hr)</td>
<td>14.04 : 6.23</td>
<td>0.40 : 0.45</td>
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</tbody>
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DISCUSSION:
Male ‘asymptomatic’ subjects in the late period after MoMHR have higher BMD and lower bone turnover versus their THA counterparts. They also have decreased optic chiasm area that may indicate optic atrophy, increased left ventricular end diastolic diameter and haematoctit, and evidence to suggest metal deposition within the liver and spleen. All of these effects were subtle and are not previously described in the setting of MoMHR. Most were correlated with serum metal level, and are recognized in accidental or occupational over-exposure to Co or Cr. Our findings also suggest that the kidney is better able to excrete circulating Co versus Cr.

MoMHR remains a treatment choice in the young male population. Our study was conducted within this population demographic and suggests subtle effects on multiple solid organs. Larger scale studies examining in more detail the effects on bone, neurological and cardiovascular systems are needed to accurately quantify and confirm these effects so that regulatory authority guidance might more specifically target these areas. Further work to elucidate the mechanism of differential handling of Co versus Cr may help to provide treatment strategies for metal accumulation in solid organs after MoMHR.

SIGNIFICANCE:
Concerns regarding the release of metals following MoMHR have become publicized in the literature and guidelines now recommend monitoring of systemic metal levels and, in the case of the FDA, potential targeted organs. This study helps to inform such guidance.

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