Early Markers of Nephrotoxicity In Patients With Metal on Metal Bearings For Over Ten Years

Joseph Daniel1, Hena Ziaee1, Rosella Alinovi2, Massimo Corradi2, Antonio Mutti2, Derek McMinn1

1Joint Reconstruction Research, The McMinn Centre, Birmingham, United Kingdom; 2Dept of Clinical Medicine, Nephology And Health Sciences, University of Parma, Parma, Italy

henaziaee@mcminncentre.co.uk

Introduction: Release of metal ions is an unavoidable consequence of using metal-metal (MM) bearings. Renal excretion is the predominant route of clearance of excess metal. Studies performed in cobalt workers who were exposed to levels approaching safety limits did not show any adverse renal effects [1]. Chromate-induced ATN has been reported following accidental intake [2] of massive doses of chromic acid or potassium chromate which was sometimes fatal [3] and at other times reversible [4]. The urinary excretion of a brush border antigen was reported to be raised in workers occupationally exposed to water-soluble chromium(VI) compounds [5]. However, others report no metal-induced renal disease in chromium workers [6,7] even amongst those exposed at high levels. The present study is an investigation to examine if renal markers are elevated in a group of patients with unilateral and bilateral hip resurfacings with and without radiological features of impending failure.

Materials and Methods: Thirty one patients (24 male and 7 female, current mean age 62, range 34 to 76 years and mean BMI 27.6, range 21 to 41) who underwent unilateral (26) or bilateral (5) hip resurfacings in 1996 and were attending a routine 10-year clinicologically and metal ion level follow-up were included in this study after informed consent. Three out of the 26 unilateral had a MM device implanted in their contralateral hip before or after 1996 rendering them currently bilateral in effect. Renal marker levels in thirty age-matched subjects with no metal exposure or renal problems were used as controls.

Patients brought along a 12-hour specimen of urine, collected the previous day, for estimation of metal ion output. The reviewing clinician filled in a proforma containing details of patient diagnosis, demographics, general medical conditions, regular medications, smoking and alcohol intake, and the clinical and radiographic status of the hip. None of these patients had a history of renal failure. Patients with diabetes mellitus were excluded.

Whole blood specimens were collected without contamination for metal ion analysis and serum was obtained for creatinine estimation. A spot-specimen of urine was collected directly in a 30 ml bottle (Sarstedt Ltd Leicester UK) for renal markers. High resolution inductively coupled plasma mass spectrometry (HRICPMS) was used for metal ion analysis. The test battery of urinary markers and the techniques used were the same as described in an earlier publication[8].

Results: The median serum creatinine level in the whole group was 1.1 mg/dl (interquartile range 1.0 to 1.2 mg/dl). The median creatinine clearance was within the reference range. The levels of renal markers in this cohort of patients were within the expected range as shown in Table 1. None of the renal markers showed an association with either cobalt or chromium output.

Discussion: Early renal markers have been standardised and used extensively to monitor large population groups who are environmentally or occupationally exposed to potential nephrotoxins. In studying renal markers it must be borne in mind that transient changes can be produced by several physiological and pathological processes including the hour of the day, posture, physical activity, protein intake, hydration, diabetes etc. Therefore one or more positive tests in an individual at one time point does not indicate impending renal disease. Such variations are found in unexposed cohorts of subjects as well.

There are four domains in which kidney function may be monitored: a) Global kidney function is assessed from glomerular filtration rate (creatinine clearance). b) Glomerular proteinuria: High molecular weight proteins such as albumin and globulin do not pass through the glomerular filter under normal conditions. Their leakage occurs due to increased glomerular permeability and signifies glomerular disease. c) Tubular proteinuria: Low molecular weight proteins such as β2m and RBP are normally filtered by the glomerulus and extensively reabsorbed in the renal tubule. Increased LMW proteinuria indicates tubular dysfunction. d) Finally, enzymuria of NAG or the excretion of BBA, are useful to assess the presence of renal microtissue damage.

We chose a group of patients who underwent a device which has been shown to be associated with high wear [9], and included those with adverse radiology in order to look at the worst case scenario. Systemic metal output is believed to be greater from loose or migrating implants than from stable well-fixed implants. Furthermore, it is believed that, if elevated metal leads to renal damage in arthroplasty patients through interstitial nephritis, this may not occur for a few years after implantation. By choosing the ten-year follow-up for this investigation we allowed ample time for marker elevation to occur. The absence of significant elevation of renal markers in this cohort of patients ten years after MM bearing implantation is reassuring. However, continued surveillance through further large-scale controlled studies may be necessary to rule out or prove the possibility of nephrotoxicity from arthroplasty-induced low intensity exposure to these trace elements.

References:
4) Toxicological profile for Chromium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service

Table 1. Levels of serum creatinine and early markers of nephrotoxicity in patients with metal-metal devices and in matched controls

<table>
<thead>
<tr>
<th>Marker</th>
<th>Reference Unit</th>
<th>Normal Range ± SD (mmol/L)</th>
<th>Number of Subjects with values above LIM (n)</th>
<th>Concordance with no mental exposure (Chi-squared test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>mmol/L</td>
<td>0.01-0.03</td>
<td>3/30 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ferritin</td>
<td>g/L (µmol/L)</td>
<td>30-120</td>
<td>2/0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mmol/L</td>
<td>0.8-1.2</td>
<td>3/30 (10%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Chi-squared Test (NS = not significant)