Optimal acetabular component orientation estimated using edge-loading and
impingement risk in patients with metal-on-metal hip resurfacing arthroplasty

Stephen J. Mellon¹, George Grammatopoulos¹, Michael S. Andersen², Hemant G. Pandit¹,
Harinderjit S. Gill¹,³ and David W. Murray¹

1. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences,
   University of Oxford, United Kingdom
2. Department of Mechanical and Manufacturing Engineering, Aalborg University,
   Denmark
3. Department of Mechanical Engineering, University of Bath, United Kingdom

Original Article

Word Count: 2970

stephen.mellon@ndorms.ox.ac.uk

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
University of Oxford,
Nuffield Orthopaedic Centre,
Windmill Road,
OXFORD,
OX3 7LD
+44 (0)1865 227454

Keywords: Hip, Metal-on-Metal, Impingement, Edge-loading, Kinematics,
Abstract

Edge-loading in patients with metal-on-metal resurfaced hips can cause high serum metal ion levels, the development of soft-tissue reactions local to the joint called pseudotumours and ultimately, failure of the implant. Primary edge-loading is where contact between the femoral and acetabular components occurs at the edge/rim of the acetabular component whereas impingement of the femoral neck on the acetabular component’s edge causes secondary or contrecoup edge-loading. While the relationship between the orientation of the acetabular component and primary edge-loading has been identified, the contribution of acetabular component orientation to impingement and secondary edge-loading is less clear. Our aim was to estimate the optimal acetabular component orientation for 16 metal-on-metal hip resurfacing arthroplasty (MoMHRA) subjects with known serum metal ion levels. Data from motion analysis, subject-specific musculoskeletal modelling and Computed Tomography (CT) measurements were used to calculate the dynamic contact patch to rim (CPR) distance and impingement risk for 3416 different acetabular component orientations during gait, sit-to-stand, stair descent and static standing. For each subject, safe zones free from impingement and edge-loading (CPR <10%) were defined and, consequently, an optimal acetabular component orientation was determined (mean inclination 39.7° (SD 6.6°) mean anteversion 14.9° (SD 9.0°)). The results of this study suggest that the optimal acetabular component orientation can be determined from a patient’s motion and anatomy. However, ‘safe’ zones of acetabular component orientation associated with reduced risk of dislocation and pseudotumour are also associated with a reduced risk of edge-loading and impingement.
Introduction

Metal-on-metal hip resurfacing arthroplasty (MoMHRA) became an established surgical option in the late 1990s/early 2000s, particularly for the young active patient with end-stage hip disease. In England and Wales in 2006, 10% of all primary total hip replacements performed were MoMHRA. However, subsequent concerns about high revision rates and soft tissue reactions meant that by 2012 usage had fallen to 1%.

Occurrence of soft tissue or fluidic masses local to the hip joint (pseudotumour (Pandit et al., 2008a), adverse reaction to metal debris (Langton et al., 2010)), aseptic lymphocytic vasculitis associated lesions (Willert et al., 2005), adverse local tissue reaction (Schmalzried, 2009)) are associated with high blood, serum and hip aspirate levels of cobalt (Co) and chromium (Cr); the principal elements of the metal alloy used to manufacture MoMHRA implants (De Smet et al., 2008a; Kwon et al., 2009; Langton et al., 2009a). This indicates these reactions are associated with increased levels of wear. Retrieval studies have confirmed that implants revised for pseudotumour have higher wear than implants revised for other reasons (Kwon et al., 2010). Retrieval studies have also shown that implants revised for pseudotumour are more likely to have experienced edge-loading (Kwon et al., 2010; Langton et al., 2011).

Primary edge-loading is the result of contact between the femoral and acetabular components at the edge of the acetabular component while contact between the femoral neck and the cup edge causes secondary or countrecoup edge-loading. The occurrence of primary edge-loading has shown an association with acetabular component orientation (De Haan et al., 2008b). The risk of pseudotumour is reduced for an acetabular component orientation of 45° (±10°) inclination and 20° (±10°) anteversion (Grammatopoulos et al., 2011). This relationship
between acetabular component orientation and risk of edge-loading has been further highlighted by studies that have calculated the distance of the hip contact force vector from the edge of the acetabular component (contact patch to rim distance). This has been carried out using two methods: by using the average hip contact force (HCF) vector of four subjects with instrumented prostheses standing (Bergmann et al., 2001) and calculating the 3D position of the acetabular component from Computed Tomography (CT) scans or radiographs (Langton et al., 2009b; Matthies et al., 2014; Yoon et al., 2013) or by carrying out motion analysis and CT scans of subjects and musculoskeletal modelling to define the HCF vector for activities of daily living (Mellon et al., 2013).

The contribution of secondary edge-loading (impingement) to wear of metal-on-metal hip resurfacing arthroplasty (MoMHRA) is more difficult to determine and consequently fewer studies have investigated this. Radiographic signs of impingement have been shown to have an association with elevated serum ion levels of cobalt and chromium but only in combination with poor acetabular component orientation (Le Duff et al., 2014).

The relationship between component positioning and the occurrence of high metal ion levels and/or pseudotumours is not clear-cut. Subjects with “well-placed” components have developed pseudotumours, albeit it in small numbers (Donell et al., 2010; Grammatopoulos et al., 2011; Kwon et al., 2011; Matthies et al., 2012) and some patients with mal-positioned components avoid high metal ion levels (Grammatopoulos et al., 2011; Matthies et al., 2012). The reasons for this are unclear although it has been suggested that high wear and/or the occurrence of pseudotumours are associated with other factors such as implant design, metal hypersensitivity (Pandit et al., 2008b), or an individual’s motion patterns (Mellon et al., 2013).
The aim of this study was to identify the optimal acetabular component orientation for a group of MoMHRA patients based on primary edge-loading and impingement (secondary edge-loading) risk calculated dynamically for four activities of daily living.

**Method: Patients**

In an on-going study, a cohort of 158 (201 hips) MoMHRA patients have their serum metal ion levels measured regularly. Sixteen subjects (seven females and nine males) from this 158 with unilateral MoMHRA with metal ion levels that represented the range of the whole cohort responded to a written request and agreed to participate in the current IRB approved study. The subjects had either a Birmingham Hip Resurfacing (BHR) (Smith and Nephew, Birmingham, UK) (n=8) or a Conserve Plus (Wright Medical Technology, Memphis, TN, USA) hip resurfacing (n=8). The Laboratory of Clinical Biology, University Hospital Ghent, Belgium used inductively-coupled plasma mass spectrometry (ELAN DRC II, PerkinElmer Life and Analytical Sciences, Shelton, CT, USA) to determine the subjects’ serum levels of cobalt and chromium (De Smet et al., 2008b).

**Method: Motion Analysis**

A laboratory equipped with 12 camera Vicon MX system (Oxford Metrics Ltd., Oxford, UK) and three force platforms (2 × OR6 AMTI R6-6-1000, 1 × OR6 AMTI R6-7-1000, Advanced Medical Technology Inc., MA, USA) was used to conduct motion analysis. An established (Kadaba et al., 1990) marker configuration with extra markers on the medial femoral condyles, the tibial tuberosities, the medial malleoli, the distal 5th and 1st metatarsals was used (25 markers total).
The subjects’ motion was measured during four activities of daily living (ADL): walking, sit-to-stand, static standing and stair descent. Kinematic and force plate data were collected with a sampling rate of 100 Hz and 1000 Hz, respectively.

Method: Computed Tomography (CT) Scans

Immediately following motion analysis, retro-reflective motion analysis markers were removed and replaced with radio-opaque markers and CT scans (Siemens Somatom, Siemens Medical Solutions USA, Inc., NY, USA) of each subject’s pelvis and lower limbs were obtained. The 3D coordinates of the markers, the anatomical pelvic landmarks, the MoMHRA components, the points around the femoral neck and hip joint centre were determined (SliceOmatic, V4.2, TomoVision, Virtual Magic Inc., Montreal, Canada).

Method: Musculoskeletal Modelling

Subjects were modeled performing static standing, gait, sit-to-stand and stair descent in the AnyBody Modeling System (v.5.0, AnyBody Technology A/S, Aalborg, Denmark). Each model incorporated subject-specific hip joint centres (HJC) derived from the individual CT scans, as well as nonlinear scaling methods to adapt the lower limb model to a given geometry. The musculoskeletal model used a three-stage procedure. Firstly, the patient-specific joint kinematics were estimated based on a stick-figure model constructed from the standing reference frame and the estimated HJCs. Secondly, the Twente Lower Extremity Model (TLEM) (Klein Horsman et al., 2007) implemented in the AnyBody Managed Model Repository v.1.2 was non-linearly morphed using Radial Basis Functions (RBF) (Lund, 2011) to match the segment lengths, joint parameters of the stick-figure model and subject-specific pelvis bony landmarks (ASIS and PSI) and estimated hip joint centres estimated from the CT scan. Inverse dynamic analysis was performed for the morphed TLEM model with the
measured ground reaction forces as external loads and polynomial muscle recruitment criterion of power 3 to estimate muscle and joint contact forces (Klein Horsman et al., 2007). The capsular ligaments were not included in the model.

Method: Edge-loading & Impingement Risk

Edge-loading and impingement risk was determined for all possible cup orientations, in 1° intervals, between 20° and 80° inclination and -15° and 40° anteversion (3,416 orientations). The edge-loading risk for every orientation was determined using the Contact Patch to Rim (CPR) distance. The CPR distance is the location of the intersection of the HCF with the inner surface of the acetabular component relative to the edge/rim of the component. The point of intersection is assumed to be the centre of the contact patch between the two components. All CON implants were modeled with an acetabular component with a coverage angle (α) of 170° and a diametrical clearance of 173 µm (Campbell et al., 2006). The coverage angle for the BHR acetabular component was dependent on the size of the implant and varied from 159.1° to 166.2° (Board and Walter, 2010).

The CPR distance was calculated for each subject for gait, stair descent, static standing and sit-to-stand. The analysis was limited to the periods during the dynamic activities when loads were highest i.e. stance phase during gait and stair descent and after seat-off for sit-to-stand. CPR distance was calculated as a percentage of half the inner circumference of the acetabular component to allow comparison between subjects with different sized components. At each acetabular component orientation, the lowest CPR distance out of the three ADLs was recorded.
Impingement risk was calculated for the same cup orientations examined for edge-loading risk. The 3D coordinates of points around the femoral neck on the implanted side were transformed into a coordinate system local to the femoral component (i.e. ‘Z’ axis parallel with the stem, origin at the HJC). The points were projected into the pelvic transverse plane and an ellipse was fitted to them (Figure 1). The 3D position of this ellipse, relative to the HJC, was determined by the size of the subject’s femoral component. The position of the ellipse relative to the cup edge for each of the 4 ADLs at each orientation was calculated. If the height of the ellipse was greater than the height of the cup edge at any point during any of the ADL, then this was considered as impingement.

Contour plots for edge-loading (Figure 2(a)) and impingement risk (Figure 2(b)) were generated for each subject. These were combined and a safe zone of orientations free from impingement or edge-loading was established (CPR < 10%) (Figure 2(c)). An optimum acetabular component orientation was calculated by finding the orientation where edge-loading and impingement risk was lowest. This was not simply the highest value of CPR within the safe zone as in the majority of cases, this would have occurred immediately adjacent to the impingement boundary. The risk of impingement for orientations within the safe zone was lowest for orientations furthest from the boundary. In order to factor this into the definition of optimal orientation, the distance to the boundary was calculated using Delaunay triangulation and added to the CPR distance at each orientation within the safe zone (Figure 2(d)). Within the safe zone, the orientation with the highest value was taken as the optimal orientation. The optimal orientations for all sixteen subjects were then compared to zones associated with reduced risk of dislocation (Lewinnek et al., 1978a) and pseudotumour (Grammatopoulos et al., 2010).
Method: Statistical Analysis

The change in angle required to move the subjects’ actual acetabular component orientation to the optimal was calculated. The relationship of this angle with the concentration of serum chromium and cobalt ions was tested using Pearson Correlation (SPSS v20.0, IBM Inc, Chicago, USA). The $R^2$ correlation coefficient was also calculated.

The smallest distance from the subjects’ actual acetabular component orientation to the boundary of the safe zone (implant position to boundary, IPB) was calculated (Figure 3). This value was positive when the subject’s implant position occurred inside the safe zone and negative when outside. Pearson correlation was used to test the relationship between IPB and serum metal ion levels of cobalt and chromium (SPSS v20.0, IBM Inc, Chicago, USA). The $R^2$ correlation coefficient was also calculated for metal ions and IPB. The identification of a safe zone for each subject using edge-loading and impingement risk would be deemed valid if, for example, the acetabular component orientation of subjects with the lowest serum metal ion levels were within the safe zone with the highest values of IPB or subjects with the highest serum metal ion levels had actual implant orientations outside or close to the boundary.

Results

The optimal orientations calculated for each subject based on the orientation within their safe zone and furthest from its boundary can be seen in Table 1. The mean optimal acetabular component inclination was 39.7° (St.Dev. 6.6°) which was lower than the mean actual inclination at 51.1° (St.Dev. 9.2°). The mean optimal anteversion was 14.9° (St.Dev. 9.0°) whereas the actual anteversion was 13.9° (St.Dev. 11.1°). Four subjects’ optimal orientation were outside zones associated with reduced risk of pseudotumour (Grammatopoulos et al.,
223 2010) or dislocation (Lewinnek et al., 1978a) (Figure 4). For the subjects’ actual acetabular
224 component orientation, both the Lewinnek and Grammatopoulos boxes contained the same
225 number (37.5%) of subjects. For the calculated optimal acetabular component orientation, 12
226 (75%) of the subjects were in the Lewinnek box while 8 (50%) were in the Grammatopoulos
227 box.
228
229 The angle from the subjects’ actual acetabular component orientation to the calculated
230 optimal orientation (Table 1) did not correlate with the concentration of serum chromium (p >
231 0.05, $R^2 = 0.02$) or serum cobalt (p > 0.05, $R^2 = 0.0004$).
232
233 The position of the subjects’ actual acetabular component orientation relative to the safe zone
234 boundary was calculated (IPB). There was a statistically significant correlation between the
235 IPB and the concentration of both serum chromium ions (p = 0.01, $R^2 = 0.33$) and serum
236 cobalt ions (p = 0.016, $R^2 = 0.29$) (Figure 5).
237
238 Discussion
239 In this study, we examined a group of sixteen MoMHRA subjects. The risk of edge-loading
240 and impingement were calculated during gait, sit-to-stand, stair descent and static standing
241 for 3,416 possible orientations of the acetabular component. A safe zone of orientations free
242 from edge-loading and impingement was identified for each subject and consequently the
243 optimal orientation was calculated. The results of this study suggest that zones, associated
244 with reduced risk of dislocation or pseudotumour, are also associated with reduced risk of
245 impingement and edge-loading.
Previous studies of acetabular component positioning have suggested that “well-positioned” acetabular components improve hip movement, minimise contact stresses and reduce the risk of impingement and/or dislocation (D’Lima et al., 2000; Del Schutte et al., 1998; Kennedy et al., 1998; Lewinnek et al., 1978b; Widmer and Zurfluh, 2004). However, a universally applicable set of evidence-based guidelines for achieving the optimal orientation for the acetabular component in total hip replacement (THR) does not exist. On the basis of radiographic analysis, Lewinnek et al., (1978b) suggested that an acetabular component orientation of 40° (±10°) inclination and 15° (±10°) anteversion, reduced the risk of dislocation. Perhaps as a result, the importance of acetabular component orientation in hip resurfacing may have been initially underestimated because of the lower dislocation risk associated with large diameter femoral components (Grammatopoulos et al., 2010; Schmalzried, 2009). However, it is now known that there is an association in patients with acetabular components with inclination angles >55° and elevated levels of serum metal ions (De Haan et al., 2008a; Langton et al., 2008; Langton et al., 2009b). Furthermore, an inverse relationship between component positioning, metal ion levels and static (Langton et al., 2009b; Matthies et al., 2014; Yoon et al., 2013) and dynamic (Mellon et al., 2013) hip contact forces has been identified using the CPR distance.

Impingement in previous incarnations of hip resurfacing have been reported (Chandler et al., 1982; Wiadrowski et al., 1991); In 109 retrieved Wagner metal-on-polyethylene resurfacing components, Wiadrowski et al. (1991) found evidence of eccentric wear at the rim of the acetabular component secondary to impingement of the femoral neck in 84% of cases (Beaulé et al., 2007). Several studies have identified cases of femoral neck to cup impingement at a prevalence ranging from 6% to 22% (Gruen et al., 2011; Le Duff et al., 2014; Lim et al., 2012; Yoo et al., 2011). The contribution of impingement to wear of
MoMHRA is not clear. It has been shown previously that signs of impingement, detected in radiographs, influenced serum levels of cobalt and chromium only when the functional head coverage was insufficient due to poor socket positioning. Radiographic impingement signs alone were not a good predictor of elevated metal ion levels (Le Duff et al., 2014).

The smallest distance from the boundary of the safe zone to the subjects’ implant position (IPB) correlated with concentrations of both serum levels of cobalt and chromium ions. These results suggest that wear of MoMHRA for a range of acetabular component orientations can be predicted using a patient’s motion and anatomy. The current study is the first to relate the effects of component positioning, component design, bony anatomy and the individual’s motion patterns to implant wear. However, the inclusion of an activity that induced significant hip abduction/adduction may have improved the predictive capabilities of the model in the current study. It has been suggested that the risk of edge loading is dramatically reduced by combining deep hip flexion with hip abduction (van Arkel et al., 2013).

Our long term aim is to develop a pre-operative patient-specific method for determining optimal acetabular component orientation. In this study, which will contribute to the aim, we are limited to post-operative data. Also, ideally we would address this aim with studies on conventional (metal-on-plastic) Total Hip Arthroplasty (THA), as the majority of patients with end-stage hip osteoarthritis will receive these. However, patients with MoMHRA are a useful analogue because wear of the prosthesis is proportional to serum metal ion levels. Metal-on-Metal THA does not provide the same opportunity for study as in these patients, metal ions levels may come from the trunnion as well as the articular surface.
When simulating all the possible orientations between 20 to 80° of inclination and -15 to 40° of anteversion, the acetabular component was rotated about a fixed point, the HJC. In reality, this centre of rotation would have been different for different component orientations. Also, this model was developed under the assumption that the patient’s kinematics and estimated hip contact forces would remain the same throughout all the acetabular component orientations that were analysed. The CPR calculations carried out in this study were based on the assumption that the hip contact force vector passed through the centre of a contact patch between the femoral and acetabular components. The size of this patch is determined by the force magnitude, the size/geometry/material properties of the components, the clearance between the components and the presence of lubrication. It was not possible to include this complex contact condition in our calculations of CPR.

True optimal orientation is patient-specific and can be determined with dynamic assessment, however, zones of acetabular component orientation associated with reduced risk of dislocation (Lewinneke et al., 1978a) and pseudotumour (Grammatopoulos et al., 2010) are also associated with reduced risks of impingement and edge-loading in MoMHRA.

Acknowledgements: Financial support was provided by ORUK, Depuy, McMinn Bursary (British Hip Society) and NIHR BRU.

References


Kwon, Y.M., Ostlere, S., McLardy-Smith, P., Gundle, R., Whitwell, D., Gibbons, C.L.M., Athanasou, N., Gill, H.S., Murray, D.W., Year Metal ion levels in pseudotumours associated with metal-on-metal hip resurfacing. In The 55th Orthopaedic Research Society Annual Meeting, Las Vegas, USA.


Tables

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Implant/ head dia. (mm)</th>
<th>Radiographic Inclination/ Anteversion (°)</th>
<th>Serum Chromium level (µg/l)</th>
<th>Serum Cobalt level (µg/l)</th>
<th>Optimum Inclination/ Anteversion (°)</th>
<th>Total Angle (°) Change Actual-to Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>BHR/52</td>
<td>52/20</td>
<td>3.2</td>
<td>2.6</td>
<td>38/24</td>
<td>14.6</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>CON/48</td>
<td>43/14</td>
<td>2.4</td>
<td>1.6</td>
<td>34/26</td>
<td>15.0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>CON/50</td>
<td>46/23</td>
<td>0.5</td>
<td>0.8</td>
<td>48/7</td>
<td>16.1</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>BHR/54</td>
<td>49/14</td>
<td>1.8</td>
<td>1.3</td>
<td>47/7</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>CON/44</td>
<td>44/19</td>
<td>0.6</td>
<td>0.7</td>
<td>26/-1</td>
<td>26.9</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>BHR/58</td>
<td>48/18</td>
<td>0.7</td>
<td>1.2</td>
<td>33/15</td>
<td>15.3</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>CON/48</td>
<td>62/10</td>
<td>2</td>
<td>3.6</td>
<td>34/26</td>
<td>32.3</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>BHR/50</td>
<td>38/33</td>
<td>0.5</td>
<td>1</td>
<td>41/21</td>
<td>12.4</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>CON/46</td>
<td>43/4</td>
<td>1.3</td>
<td>1.6</td>
<td>38/1</td>
<td>5.8</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>BHR/54</td>
<td>65/8</td>
<td>4.4</td>
<td>2.1</td>
<td>45/6</td>
<td>20.1</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>BHR/50</td>
<td>61/1</td>
<td>1.4</td>
<td>1.4</td>
<td>41/21</td>
<td>28.3</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>CON/54</td>
<td>56/13</td>
<td>1.3</td>
<td>2.4</td>
<td>37/20</td>
<td>20.2</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>CON/50</td>
<td>56/34</td>
<td>6.1</td>
<td>3.1</td>
<td>38/14</td>
<td>26.9</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>CON/52</td>
<td>35/-10</td>
<td>5.8</td>
<td>4.7</td>
<td>42/20</td>
<td>30.8</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>BHR/38</td>
<td>60/14</td>
<td>7.8</td>
<td>4.6</td>
<td>40/23</td>
<td>21.9</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>BHR/46</td>
<td>60/8</td>
<td>6.8</td>
<td>9.3</td>
<td>53/8</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Figures

Figure 1. Risk of impingement was calculated using an ellipse fitted to points around the femoral neck in the XY plane of the coordinate system local to the femoral component. The position of this ellipse relative to the cup edge was determined for four activities of daily living. Impingement was defined as the positions of the cup edge and the ellipse overlapping.

Figure 2. (a) Edge-loading, (b) Impingement, (c) Combined and (d) Adjusted plots for Subjects 1. Numbers within Edge-loading and Combined plots represent the %CPR distance. In the impingement plot the white area represents orientations free from impingement for the activities analysed. In the combined plot the ‘safe’ zone are orientations free from impingement and edge-loading (CPR distance < 10%). In the adjusted plot, the distance from the safe zone boundary has been added to the %CPR in order to define the optimal orientation (38/24 Inclination/Anteversion)
Figure 3. Implant Position to Boundary (IPB) was calculated as the smallest distance from the subjects’ actual implant orientation to the boundary of the safe zone.

Figure 4. Actual and optimal orientations for 16 Subjects with MoMHRA. Box with solid sides represents a zone with reduced risk of pseudotumour (Grammatopoulos et al., 2010). Box with dashed sides represents a zone with reduced risk of dislocation in THR (Lewinnek et al., 1978a).
Figure 5. Implant Position to Boundary (IPB) versus serum cobalt and chromium. There was a statistically significant correlation between IPB and serum chromium ($p = 0.01$) and serum cobalt ($p = 0.016$) ions.