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Predictivity and Fate of Metal Ion Release From Metal-On-Metal Total Hip Prostheses

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ABSTRACT

Blood metal ion levels in 72 patients with large head metal-on-metal hip arthroplasty were studied to determine the correlation between the values measured in whole blood and urine. Urinary cobalt and chromium levels of 30 μg and 21 μg, respectively, adjusted to creatinine were found to correspond to the 7 μg/l cut-off value that has been accepted in whole blood. Cobalt and chromium levels in whole blood and urine both significantly correlated with increased acetabular component inclination angle over 50 degrees and pain scores. There was no correlation with socket anteversion angle or femoral head diameter. The data support the use of urinary measurement of metal ions adjusted to creatinine to monitor patients with large head metal-on-metal total hip arthroplasty.

Release of metal ions, prevalently cobalt (Co) and chromium (Cr), from metal-on-metal (MoM) hip prostheses is an undesirable feature due to implant wear characterized by the accumulation of metal debris in the periprosthetic tissue. A consequence of metal accumulation is the so-called metallosis defined as "an infiltration of metallic wear debris into periprosthetic structures, which has been suspected to give rise to soft tissue toxicity and implant failure" [1]. Metallosis macroscopically appears as a gray discoloration of the hip joint [2] and its extent varies from grade I (mild) to grade III (severe) according to the black colour throughout soft tissue and bone [3].

Debris derived from MoM hip prosthesis wear are nanoscale particles [4] causing granulomatous inflammation although this effect is milder than those induced by particles released by prostheses with polyethylene components that are generated in micro-sized scale [5]. In fact, nano-particles are produced in a greater number [6] leading to a severe release of osteolytic enzymes compared to polyethylene particles. After a corrosive action in synovial fluid, metal particles generate metal ions [7].

In the soft tissues, Co appears in a metallic oxidation state, whereas Cr as a Cr(III)-phosphate (trivalent oxidation state), whereas no Cr (VI) is generated [8]. Recently, several studies reviewed by Campbell and Estey [9] report that MoM prosthesis wear causes Co and Cr ion release in biological fluids and the Medicines and Healthcare Products Regulatory Agency (MHRA) in Great Britain states as acceptable a metal ions whole blood concentration below 7 μg/l [10]. Metal ions in biological fluids apparently increase according to time of implant [11] and the peak in blood after replacement depends on the metal (6 months for Co and 9 months for Cr). A gradual decline during the next 15 months has been observed [12].

The goal of the present research was to ascertain 1) whether the measure of metal ions in urine is a suitable way to monitor the follow-up of MoM total hip replaced patients, 2) whether the metal ion release depends on the femoral head diameter, on the inclination and anteversion angle of acetabular components, and other variables such as gender, age at surgery, interval since the surgery, body mass index (BMI) and body surface area (BSA).

Materials and Methods

Study Population

Seventy two patients (age at surgery 55.8 years, range 30–74 years) MoM total hip prostheses with large diameter femoral head ASR DePuy type were identified and enrolled. They were 53 males (age at surgery 55.6 years, range 33–68 years) and 19 females (age at surgery 56.3 years, range 30–74 years). The interval between surgery and first metal ion measurement was 4.5 years (range 2–7 years), 4.4 years for males and 4.9 years for females. The BMI (28.4, range 20.8–45.7) was similar in both genders (28.5, range 22.4–39.8 males, 28.0, 20.8–45.7 females), whereas BSA (all subjects 2.0 m^2) was significantly ($P = 0.0001$) higher in males (2.1, range 1.8–2.5 m^2)

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than in females (1.8, range 1.4–2.4 m^2). The research was based on data gathered according to recall program of Device Alert, therefore evaluation by an ethics committee was not required. Informed consent was obtained for the anonymous treatment of the results.

Analysis of Metals

Whole blood and urine (spot specimen collection) levels of Co and Cr (CoB, CrB, CoU, and CrU, respectively) were measured from 1 to 7 times along a year using graphite furnace atomic absorption spectrophotometer Perkin-Elmer AAnalyst 600 with Zeeman effect background correction. The detection limits of metals were: CoB and CoU 0.56 μg/l, CrB 0.1 μg/l, and CrU 0.08 μg/l. For statistical purposes, the limit of detection value was assigned to all results below this. The reagents and standard solutions used were high purity AAS grade. Standard stock solutions (1 g/l) of the metals were used to prepare the working standards throughout this work. Urinary values were adjusted to creatinine to avoid problems concerned concentration-dilution of spot specimens [13] determined using the basic-picrate Jaffe reaction.

Orthopedics Indices

The inclination angle of the cup was measured of cross-sections determining the median sagittal axis of the pelvis obtained in an orthogonal way with the respect to a horizontal axis that connects two anatomical corresponding points; the anteversion angle is then measured between the antero-posterior orientation axis of the cup and a line parallel to the sagittal axis of the pelvis by the computed tomography images. Measurements were made according to a MedStation (Exprivia, Italy) software for the management of radiological images.

At the time of recall, patients were further subjected to basin X-ray to evaluate if the prosthesis was well positioning and which was the state of the periprosthetic bone tissue.

The pain score was determined according to the grading of the Harris Hip Score (1–6) as follows: none (1), slight/occasional (2), mild (3), moderate (4), marked (5), and strong or totally disabled (6).

Statistics

Linear regression analysis, multiple linear regression, and logistic regression were applied as appropriate to correlate the inclination and anteversion of acetabular components and other variables with metal ions or among metal ions in body fluids. Parametric (variance analysis and unpaired t) and nonparametric (Mann-Whitney) tests were applied to compare means and medians (descriptive). Analysis of trend was performed with Cuzick's trend test (two sided). Receiver operating characteristic (ROC) analysis was applied to evaluate sensitivity and specificity of pain score and inclination angle of the acetabular components to predict increase of metal ions in whole blood and urine (adjusted to creatinine). Cut-off for metal ions in whole blood was stated at 7 μg/l and in urine according to value extrapolated by the regression equation (see below). Other statistical analyses were descriptive. Statistical significance was stated by $P < 0.05$, assumed as two sided unequal variance as appropriate. Statsdirect 2.7.7 version (Statsdirect Ltd, UK) has been used for statistical analyses.

Results

Metal Ions in Body Fluids

Concentration of metal ions in body fluids appeared, on the average, largely increased; in particular, 93.1% of patients had CoB and CrB concentration out of reference values (Table 1). No difference was observed according to gender. In addition, according to MHRA, 34 (47.2%) and 21 (29.2%) patients showed CoB and CrB concentration, respectively, higher than the suggested limit of 7 μg/l. Further, 19 subjects (26.4%) exceeded the threshold value of 20 μg/l of CoB which may be associated with systemic toxicity [14]; moreover, 21 subjects (29.2%) exceeded the threshold of Co and Cr in serum of 19 and 17 μg/l, respectively, suggested as indicative of metallosis [2]. These values correspond to a concentration (calculated from data by Walter et al [15]) of 16 for Co and 7 for Cr μg/l in whole blood.

Table 1
Metal Ions (Co and Cr) in Whole Blood and Urine of Subjects (No. 72, 53 Males and 19 Females) Submitted to MoM Total Hip Prostheses.

	Mean ± SD	Range[a]	Median	Reference Values[b]	BEI[c]
CoB μg/l				0.05–0.1 μg/l	1 μg/l
All	29.1 ± 52.5	0.56–231	6.29		
Males	25.9 ± 45.4	0.56–203	6.46		
Females	38.0 ± 69.3	1.16–231	4.68		
CoU μg/l[d]	96.6 ± 179.0	0.56–767	26.55	0.1–0.5 μg/l	15 μg/l
CoU μg/g of creatinine					
All	139.1 ± 247.3	0.25–1,151	34.65		
Males	110.8 ± 184.8	0.25–790	34.37		
Females	218.0 ± 365.5	1.35–1,151	71.37		
CrB μg/l				0.1–0.5 μg/l	
All	12.8 ± 25.3	0.1–128	2.27		
Males	10.9 ± 20.6	0.1–93	2.04		
Females	18.1 ± 35.3	0.1–128	2.32		
CrU μg/l[d]	26.6 ± 53.5	0.08–257	5.45	0.05–0.35 μg/l	25 μg/l
CrU μg/g of creatinine					
All	39.7 ± 74.9	0.04–323	6.82		
Males	31.1 ± 61.3	0.04–268	5.41		
Females	63.6 ± 104.4	0.65–323	14.80		

Results are showed as mean ± standard deviation (SD), range, and median.
[a] The lower value of the range is the detection limit for each marker (the adjustment to creatinine was done on this value).
[b] Italian Society of Reference Values: http://www.valoridiriferimento.it (accessed Feb 7, 2012).
[c] BEI (biological exposure indices), ACGIG 2013.
[d] Reference values and BEI in urine are commonly unadjusted to creatinine. For this reason the table shows metal ion values in urine unadjusted to creatinine also.

CoB was well correlated with CrB ($r = 0.949$, $P < 0.0001$, Fig. 1A). Further, to investigate the influence of concentration-dilution of urine on spot samples, CoB and CrB were correlated vs. CoU and CrU adjusted and unadjusted to creatinine. Adjustment to creatinine improved the correlation with metals in blood ($r = 0.956$ for Co and $r = 0.913$ for Cr, $P < 0.0001$ for both, Fig. 1B and C, respectively) with respect of unadjusted samples ($r = 0.807$ for Co and $r = 0.815$ for Cr, data not shown). According to these results, all urinary values were adjusted to creatinine. Calculated on the regression equations, value of 30 μg for Co and 21 μg for Cr in urine adjusted to creatinine corresponds to the cut-off of 7 μg/l in whole blood.

No significant correlation was found between metal ions and interval since the surgery, age at surgery, gender, BMI, or BSA.

Metal Ions and Orthopedics Indices

Co and Cr in whole blood and urine appeared significantly correlated (CoB: $r = 0.557$, $P < 0.0001$, CoU adjusted: $r = 0.543$, $P < 0.0001$, CrB: $r = 0.550$, $P < 0.0001$, and CrU adjusted: $r = 0.547$, $P < 0.0001$) with inclination angle of acetabular components but not with anteversion angle (data not shown). No correlation was found with femoral head diameter. Pain score was also slight but significantly correlated ($r = 0.296$, $P = 0.0114$) with inclination angle and inversely correlated with femoral head diameter ($r = -0.273$, $P = 0.0201$) (data not shown). As illustrated in Fig. 2, an inclination angle