
Renal Clearance of Cobalt in Relation to the Use of Metal-on-Metal Bearings in Hip Arthroplasty

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Renal Clearance of Cobalt in Relation to the Use of Metal-on-Metal Bearings in Hip Arthroplasty

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Investigation performed at The McMinn Centre, Birmingham, United Kingdom

Background: A concern regarding the use of metal-on-metal bearings in hip arthroplasty has been that the high levels of metal ions that are released overwhelm the renal threshold for metal excretion, leading to systemic buildup of metals. The purpose of this investigation was to determine if the physiological renal capacity for cobalt clearance and cobalt concentrating efficiency is overwhelmed by the elevation in metal ion levels seen in patients with metal-on-metal-bearing hip devices.

Methods: Concurrent specimens of urine and plasma were obtained from a group of 461 patients (346 men and 115 women) at various intervals after either a unilateral (296) or a bilateral (130) metal-on-metal hip arthroplasty or preoperatively (thirty-five patients; the control specimens). Metal ion analyses were performed with high-resolution inductively coupled mass spectrometry. Renal efficiency was measured as the ratio of urine cobalt concentration to plasma cobalt concentration. Cobalt clearance was calculated by dividing the urine cobalt output in twenty-four hours by the plasma cobalt concentration. Dividing the quotient by 1440 adjusts it to clearance per minute.

Results: The median renal efficiency was found to be 0.9 in the analysis of the preoperative specimens, indicating that there was renal conservation of cobalt. In patients with metal-on-metal bearings, the median renal efficiency was 3.2, indicating that, as a result of cobalt excretion, the cobalt concentration in urine was threefold higher than the concentration in plasma. Linear regression analysis showed that renal efficiency progressively increased at a rate of 9% for every μg/24 hr increase in cobalt release. Cobalt clearance showed a similar trend, increasing from 1.3 mL/min in the preoperative group to 3.7 mL/min in the follow-up group. In the follow-up group, renal cobalt clearance progressively increased from 1.9 to 7.1 mL/min with increasing daily cobalt output, which indicates that with increasing in vivo metal ion release there was a progressive increase in the rate at which the kidneys cleared the plasma of cobalt.

Conclusions: In subjects with no prosthetic device, the kidneys tend to conserve cobalt in the body. We found that, in patients with a metal-on-metal hip prosthesis, there is a progressive increase in cobalt clearance with increasing in vivo wear at the levels of cobalt release expected in patients with an array of metal-on-metal-bearing total joint arthroplasties. We found no threshold beyond which renal capacity to excrete these ions is overwhelmed.

Level of Evidence: Therapeutic Level II. See Instructions to Authors for a complete description of levels of evidence.

Hip and knee arthroplasties of different types[1-3] lead to elevation of serum metal ion levels, with metal-on-metal bearings generally resulting in levels that are higher than those produced by conventional bearings[4,5]. Renal excretion is a major route of clearance of excess metal from the body[6]. Brodner et al.[7] found a very high level of serum cobalt in a patient with a metal-on-metal total hip arthroplasty and end-stage renal failure. Hur et al.[8] studied five patients who had undergone total hip arthroplasty with metal-on-metal bearings in the presence of renal failure. The authors found highly elevated serum cobalt levels but chromium levels within the expected range.

Bitsch et al.[9] studied urine and serum cobalt and chromium concentrations in one patient with normal renal function and found no change in either concentration following high levels of physical activity. Others have observed that

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several factors, including physical activity, hydration, medications, protein intake, alcohol consumption, and diabetes mellitus, affect chromium levels[10]. Malpositioned hip arthroplasty components[11] and failing or loose components[12] generate excessive metal ion levels. It is possible that, in patients with excessive metal ion generation, the renal capacity for metal excretion may be overwhelmed, leading to systemic buildup of metal above the expected levels. To our knowledge, it has not been established whether the renal capacity of renal-competent patients to clear excess metal remains uncompromised through the entire spectrum of metal levels encountered in clinical practice or whether the renal capacity becomes overwhelmed beyond a certain rate of daily metal release.

The purpose of this study was to investigate the rate of renal clearance of cobalt and the renal concentrating efficiency with respect to cobalt and to assess whether the renal metal-ion excretory capacity is overwhelmed at higher rates of in vivo metal release.

Materials and Methods

We studied metal ion levels in concurrently collected specimens of urine and plasma from patients who had been participating in eleven ongoing metal-ion-monitoring studies from September 2005 to September 2008. Specimens were collected at various intervals following surgery. A total of 480 specimens were collected during the period, and the entire data set, consisting of the twelve-hour urine volume, urine cobalt concentration, and plasma cobalt concentration, was available for 461 of them. The only criterion for exclusion was a plasma or urine level below the limit of detection. However, none of the 461 specimens had to be excluded for this reason.

The 461 patients included 346 men and 115 women; 296 underwent unilateral and 130 underwent bilateral metal-on-metal hip arthroplasty. Preoperative specimens from thirty-five patients scheduled for hip arthroplasty were used as controls. One hundred and sixty-seven patients underwent a unilateral Birmingham hip resurfacing arthroplasty (BHR; Smith and Nephew Orthopaedics, Warwick, United Kingdom), 104 patients underwent a bilateral Birmingham hip resurfacing arthroplasty, forty-eight patients underwent a unilateral or bilateral dysplasia Birmingham hip resurfacing, and twenty patients underwent a large-diameter metal-on-metal Birmingham total hip arthroplasty. In addition, sixty-five patients were treated with the McMinn Hybrid Resurfacing metal-on-metal device (Corin Medical, Cirencester, United Kingdom), and twenty-two patients underwent a total hip arthroplasty with the Metasul metal-on-metal prosthesis (Zimmer, Winterthur, Switzerland).

The mean age of the patients was sixty years at the time of specimen collection and fifty-five years at the time of the index operation. We asked all patients about their medical history and specifically whether there was any history of renal or hepatic problems, but we did not perform a renal function assessment routinely. No patient reported a history of renal failure. A diversity of specimens was included in the study in order to ensure a wide range of concentration values and provide a cross-sectional sample of the various metal-on-metal prostheses encountered in clinical practice.

Renal clearance represents the volume of plasma that is cleared of cobalt per unit of time (milliliters per minute). Renal efficiency is the ratio of the urine cobalt concentration to the concurrent plasma cobalt concentration. It represents the ability of the kidneys to concentrate cobalt in the urine. Although the daily output of cobalt in urine does not represent the entire metal burden from the device, it is known to be a good surrogate measure of the relative rate of in vivo metal release in an individual patient at a specific time, as discussed later. Because of the large anticipated scatter of data in the cohort, the patients in the follow-up group were divided into five subgroups on the basis of their daily cobalt output (<5 µg/day, 5 to <10 µg/day, 10 to <15 µg/day, 15 to <25 µg/day, and ≥25 µg/day). The number of patients and the mean age in each subgroup are shown in Table I.

Twelve-hour urine collections were obtained and were decanted into urine specimen bottles (Sarstedt, Leicester, United Kingdom), frozen at –18°C, batched, and sent to the laboratory for analysis. Specimen collection, storage, and contamination prevention were performed as detailed in earlier publications[1,13]. Blood samples were collected at the end of the twelve-hour period during which the urine had been collected. In order to obtain plasma specimens, blood was drawn without contamination into a 6-mL lithium-heparin BD Vacutainer tube (BD Diagnostics, Franklin Lakes, New Jersey) and centrifuged at 4000 rpm for ten minutes. The plasma layer was then trans-

TABLE I Numbers and Age Distributions of Subjects in the Study

	Controls (No Metal-on-Metal Arthroplasty)	Patients with Metal-on-Metal Arthroplasty				
		<5 µg/day*	5 to <10 µg/day*	10 to <15 µg/day*	15 to <25 µg/day*	≥25 µg/day*
No. of specimens	35	78	127	73	75	73
Mean age (range) at time of specimen collection *(yr)*	56 (32-71)	60 (37-85)	61 (38-86)	60 (40-74)	61 (24-84)	61 (47-79)

*Daily output of cobalt in urine.

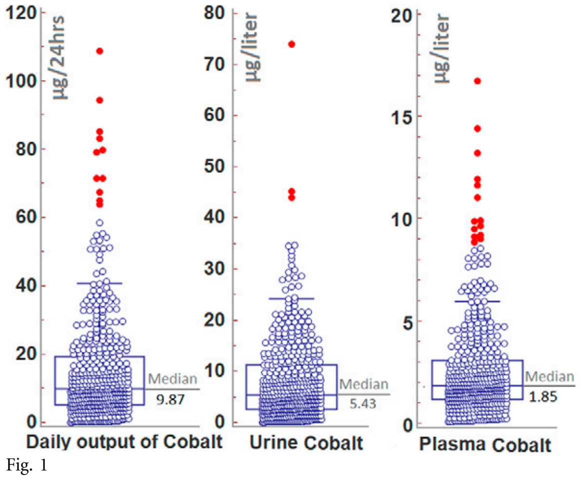

Fig. 1

Distributions of the daily output of metal ions and metal ion concentrations in urine and plasma in the study cohort of 461 patients. The circles represent all data points. The middle line in the box represents the median. The box represents the interquartile range (values from the lower to upper quartile, 25th to 75th percentiles). The red circles represent extreme outliers, defined as values that are greater than the upper quartile plus three times the interquartile range. All other data points are blue circles.

ferred with a disposable pipette into two microtubes and stored frozen at –18°C. Metal ion analysis was performed with high-resolution inductively coupled plasma mass spectrometry, with the reporting limits of 0.06 µg/L for both urine and plasma cobalt concentrations.

Renal clearance of cobalt (in milliliters per minute) was calculated with the formula:

$$\frac{\text{urine cobalt concentration (ng/mL)} \times \text{24-hr volume}}{\text{plasma cobalt concentration (ng/mL)} \times 1440}$$

Renal efficiency with respect to cobalt was calculated with the formula:

$$\frac{\text{urine cobalt concentration (ng/mL)}}{\text{plasma cobalt concentration (ng/mL)}}$$

Linear regression and box-and-whisker plots were used to investigate and illustrate relationships between variables. The grouped variables have skewed distributions and therefore medians with their interquartile ranges are given as measures of location and shown as box-and-whisker plots. A p value of <0.05 with the Mann-Whitney U test and nonoverlapping 95% confidence intervals on the box plots were used to demonstrate the significance of differences.

Source of Funding

No external funding source played a role in investigations performed specifically for this study or in the preparation of this manuscript. However, we receive institutional research funding, including funding for metal ion analyses in the different ongoing studies mentioned above, from Smith and Nephew Orthopaedics.

Results

The distributions of the urine and plasma cobalt concentrations and the daily output of cobalt in urine are shown in Figure 1. The median renal efficiency (the ratio of urine cobalt concentration to plasma cobalt concentration) was 0.9 (interquartile range, 0.7 to 1.6) in the controls and 3.2 (interquartile range, 1.7 to 5.1) in the follow-up group. This difference was significant ($p < 0.0001$). The median renal clearance of cobalt was 1.3 mL/min (interquartile range, 0.8 to 1.9 mL/min) in the controls and 3.7 mL/min (interquartile range, 2.1 to 6.1 mL/min) in the follow-up group. This difference was also significant ($p < 0.0001$). The effects of age and the duration from the time of implantation on renal cobalt clearance and efficiency are shown in Table II.

Figure 2 shows linear regression of renal efficiency on the daily output of cobalt in urine. The intercept is 2.24 ($p < 0.001$) and the slope is 0.09 ($p < 0.001$)—that is, for every unit increase in cobalt output there is a 0.09 increase in renal efficiency. The high probability of these coefficients is illustrated by the confidence intervals (dashed lines) about the line. However, this fit only accounts for 25% of the variance ($R^2 = 0.254$) as can be seen by the wide predictive confidence limits (dotted lines). It should be noted that this analysis and the one illustrated in Figure 3 include the controls.

Figure 3 is a plot of linear regression of renal clearance on the daily output of cobalt in urine. The intercept is 1.44 mL/min ($p < 0.001$), and the slope is 0.23 (i.e., a 0.23-mL/min increase in clearance per unit increase in output) ($p < 0.001$). The high probability of these coefficients is illustrated by the confidence intervals (dashed lines) about the line. This fit accounts for 45% of the variance ($R^2 = 0.453$) as can be seen by the wide predictive confidence limits (dotted lines).

The differences among the box-and-whisker plots for the six subgroups are shown in Figures 4 and 5. The results of this approach clearly show the increase in median efficiency as

TABLE II Regression of Age and Duration from Implantation on Renal Cobalt Clearance and Efficiency

	Coefficient of Determination R^2	Slope
Effect on renal efficiency of:		
Age	0.008973	–0.026
Duration from implantation	0.005867	–0.05994
Effect on renal cobalt clearance of:		
Age	0.000249	–0.0081
Duration from implantation	0.004962	–0.1038

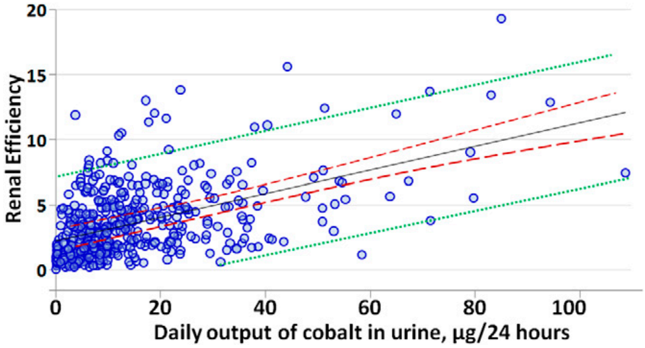

Fig. 2

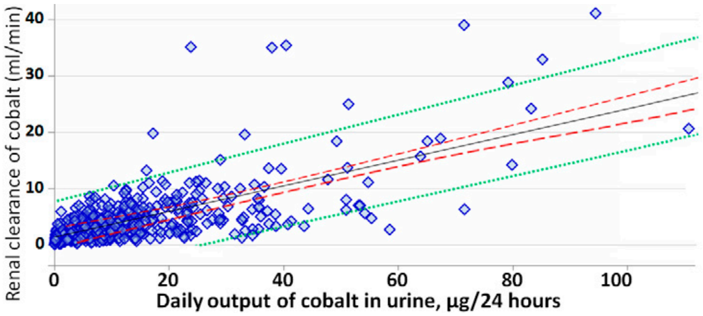

Fig. 3

Fig. 2 Linear regression of renal efficiency on daily cobalt output. The dashed lines represent the 95% confidence intervals about the regression line. The dotted lines represent the predictive confidence limits. **Fig. 3** Linear regression of renal clearance of cobalt on daily output of cobalt. The dashed lines represent the 95% confidence intervals about the regression line. The dotted lines represent the predictive confidence limits.

daily cobalt output increased (Fig. 4). The median efficiency in all of the follow-up subgroups was significantly higher than that in the controls, as indicated by the box-and-whisker confidence intervals. The renal efficiency increased from 1.6 in patients with a cobalt output of <5µg/day to 5.1 in those with an output of ≥25 µg/day (Fig. 4). The renal efficiency in

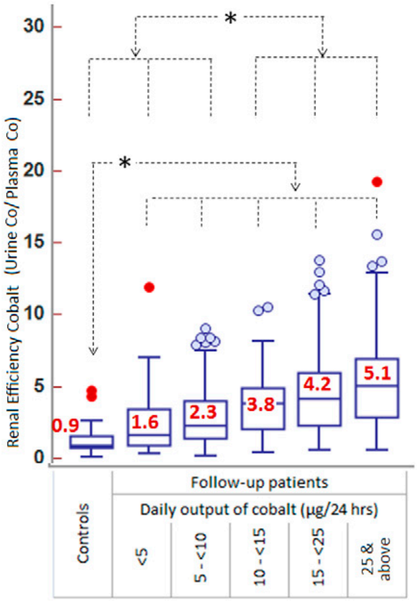

Fig. 4

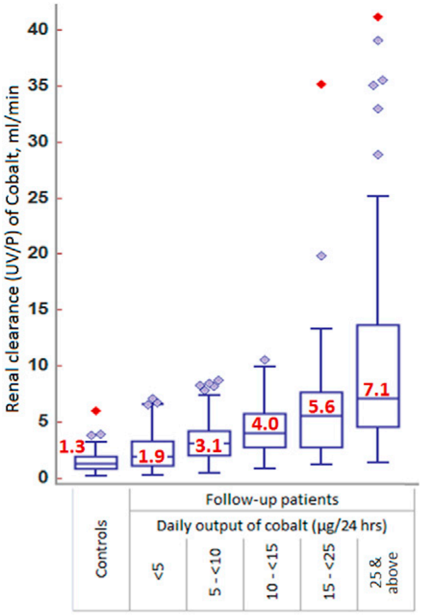

Fig. 5

Fig. 4 Renal efficiency at different levels of daily output of cobalt in the urine. The number of patients in each group and their mean ages are shown in Table I. The median efficiency in all follow-up subgroups was significantly higher (asterisk) than that in the controls. The difference between the medians in the first three groups and those in the latter three groups was also significant (asterisk). The median and the interquartile ranges are shown by the respective boxes. The whiskers (I-bars) represent the highest and lowest values that are within 1.5 times the interquartile range. The blue circles represent outliers, defined as values that are greater than the upper quartile plus 1.5 times the interquartile range (whiskers). The red circles represent extreme outliers, defined as values that are greater than the upper quartile plus three times the interquartile range. **Fig. 5** Renal cobalt clearance at different levels of daily output of cobalt in the urine. The number of patients in each group and their mean ages are shown in Table I. The median clearance in all follow-up subgroups was significantly higher than that in the controls. The difference between the median in each group and that in its preceding group was also significant, except for the difference between the two groups with the highest output (15 to <25 µg/24 hr and ≥25 µg/24 hr). UV/P = urine cobalt output in twenty-four hours divided by plasma cobalt concentration. The median and the interquartile ranges are shown by the respective boxes. The whiskers (I-bars) represent the highest and lowest values that are within 1.5 times the interquartile range. The blue diamonds represent outliers, defined as values that are greater than the upper quartile plus 1.5 times the interquartile range (whiskers). The red diamonds represent extreme outliers, defined as values that are greater than the upper quartile plus three times the interquartile range.

each of the three groups with the highest daily cobalt output (≥10 µg/day) was significantly higher than that in each of the lower-output groups (p = 0.01).

The renal clearance of cobalt (Fig. 5) also had an increasing trend with increasing cobalt output, reaching a median of 7.1 mL/min in patients with a daily cobalt output of ≥25 µg/day compared with a median of 1.3 mL/min in the controls (in whom the average daily cobalt output was 0.4 µg/day). The median cobalt clearance in all of the follow-up subgroups was significantly higher than that in the controls. Furthermore, the median cobalt clearance in each of the follow-up groups (except for the two with the highest output) was significantly higher than that in the preceding group.

The renal efficiency and cobalt clearance in the 10% of the specimens with the highest cobalt outputs are of particular interest. The median cobalt output in this group was 46 µg/day, and the median clearance and efficiency were 8.1 mL/min and 11.6, respectively. The renal cobalt clearance and efficiency in these patients with the highest turnover of metal ions were not lower than those in the rest of the group.

Discussion

The plasma and urine cobalt concentrations in this study compare well with those in other reported studies[2,4,11-16] of patients with metal-on-metal hip resurfacing or replacement. In the process of maintaining internal homeostasis, the kidneys conserve essential substances such as glucose and amino acids and clear unwanted products including urea, creatinine, and excess metal ions from the circulation. Thus, the renal effects on these two types of substances mirror each other. The concept of a renal threshold was originally proposed with reference to glucose because well-functioning kidneys have a fixed limit to glucose conservation[17]. It is not known if there is a similar threshold for metal ion clearance. The questions addressed here are whether there is a fixed limit to renal cobalt clearance and whether higher rates of metal ion release from metal-on-metal hip devices result in progressively lower renal efficiency and a cumulative buildup of metal in the blood, as seen in patients with renal failure.

All modern metal-on-metal-bearing prostheses of which we are aware are manufactured from a cobalt-chromium alloy composed of cobalt (~65%), chromium (25% to 30%), molybdenum (6% to 8%), and trace amounts of other elements. Daily output of cobalt in the urine is a good surrogate marker of device wear for several reasons. First, cobalt is the most abundant metal in the alloy. Second, because it is more soluble than chromium, it readily enters the systemic circulation and is not sequestered in the local tissues to the extent that chromium is[18]. Furthermore, animal experiments have suggested that 85% of injected cobalt is recoverable in the urine within twenty-four hours[6] and 95% is recoverable within three days, resulting in a rapid and predictable excretion of cobalt following in vivo release. In comparison, only 44% of chromium is recoverable in the urine within three days[6], which makes either chromium or a combination of cobalt and chromium less suitable as a measure of real-time in vivo wear. Cobalt is also a good marker of renal efficiency. It has been shown that, after metal-on-metal total hip arthroplasty, the blood cobalt levels in patients with renal failure are increased nearly 100-fold as compared with those in patients with normal renal function[7,8]. Paradoxically, there is not a similar elevation in the chromium level[8]. The content levels of molybdenum and nickel are low in prosthetic alloys, rendering them unsuitable as markers even though they are also rapidly eliminated in the urine.

In the control specimens, the median ratio between the urine and plasma levels of cobalt (renal efficiency) was 0.9, indicating that there is renal conservation of cobalt. The urine from the controls was dilute, in terms of cobalt concentration, compared with the plasma. The median efficiency in the patients with metal-on-metal bearings was 3.2, indicating that the kidneys are able to concentrate cobalt in urine against a gradient. If the renal threshold was being breached at higher levels, then the efficiency should have progressively decreased with higher levels of metal release from the device. The evidence in this study shows a contrary effect, with a trend toward renal efficiency increasing with higher levels of cobalt output.

A similar result was seen with regard to the renal clearance of cobalt. There was a highly significant, 2.8-fold increase in cobalt clearance in patients with metal-on-metal bearings (3.7 mL/min) as compared with that in patients without a metal-on-metal prosthesis (1.3 mL/min). Furthermore, analysis of the different subgroups of patients with metal-on-metal bearings showed renal clearance to have an increasing trend at higher outputs, with the subgroup with the highest cobalt output having a fivefold increase in cobalt clearance compared with that of the controls.

Brodner et al.[7] and Hur et al.[8] reported that patients with a metal-on-metal total hip prosthesis and renal failure had 100-fold elevations of serum cobalt levels compared with the levels in patients with similar prostheses but normal renal function. Thus, in the event of failure of effective renal clearance, there is a progressive cumulative buildup of metal ion levels in the blood. We studied renal cobalt clearance and efficiency only in patients with no history of renal dysfunction, and such a cumulative buildup was not seen in these patients, even in the presence of elevated cobalt release. Since we did not study subjects with a known history of renal failure, our results and findings do not apply to such patients and we do not advocate the use of metal-on-metal bearings in them.

The data in this study revealed that renal cobalt clearance and efficiency progressively increase at higher levels of in vivo cobalt release, demonstrating that, at the levels of cobalt release expected in patients treated with an array of metal-on-metal-bearing arthroplasties, there is no threshold beyond which the renal capacity for excretion of these ions is overwhelmed. ■

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References

1. Rasquinha VJ, Ranawat CS, Weiskopf J, Rodriguez JA, Skipor AK, Jacobs JJ. Serum metal levels and bearing surfaces in total hip arthroplasty. J Arthroplasty. 2006;21(6 Suppl 2):47-52.

2. Daniel J, Ziaee H, Pradhan C, Pynsent PB, McMinn DJ. Blood and urine metal ion levels in young and active patients after Birmingham hip resurfacing arthroplasty: four-year results of a prospective longitudinal study. J Bone Joint Surg Br. 2007; 89:169-73.

3. Luetzner J, Krummenauer F, Lengel AM, Ziegler J, Witzleb WC. Serum metal ion exposure after total knee arthroplasty. Clin Orthop Relat Res. 2007;461:136-42.

4. MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, Leung F. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clin Orthop Relat Res. 2003;406:282-96.

5. Savarino L, Greco M, Cenni E, Cavasinni L, Rotini R, Baldini N, Giunti A. Differences in ion release after ceramic-on-ceramic and metal-on-metal total hip replacement. Medium-term follow-up. J Bone Joint Surg Br. 2006;88:472-6.

6. Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. Clin Orthop Relat Res. 1996;(329 Suppl):S233-43.

7. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. J Bone Joint Surg Am. 2003;85:2168-73.

8. Hur CI, Yoon TR, Cho SG, Song EK, Seon JK. Serum ion level after metal-on-metal THA in patients with renal failure. Clin Orthop Relat Res. 2008;466:696-9.

9. Bitsch RG, Zamorano M, Loidolt T, Heisel C, Jacobs JJ, Schmalzried TP. Ion production and excretion in a patient with a metal-on-metal bearing hip prosthesis. A case report. J Bone Joint Surg Am. 2007;89:2758-63.

10. Bukowski JA, Goldstein MD, Johnson BB. Biological markers in chromium exposure assessment: confounding variables. Arch Environ Health. 1991;46: 230-6.

11. Brodner W, Grübl A, Jankovsky R, Meisinger V, Lehr S, Gottsauner-Wolf F. Cup inclination and serum concentration of cobalt and chromium after metal-on-metal total hip arthroplasty. J Arthroplasty. 2004;19(8 Suppl 3):66-70.

12. Dunstan E, Sanghrajka AP, Tilley S, Unwin P, Blunn G, Cannon SR, Briggs TW. Metal ion levels after metal-on-metal proximal femoral replacements: a 30-year follow-up. J Bone Joint Surg Br. 2005;87:628-31.

13. Daniel J, Ziaee H, Salama A, Pradhan C, McMinn DJ. The effect of the diameter of metal-on-metal bearings on systemic exposure to cobalt and chromium. J Bone Joint Surg Br. 2006;88:443-8.

14. Daniel J, Ziaee H, Pradhan C, McMinn DJ. Six-year results of a prospective study of metal ion levels in young patients with metal-on-metal hip resurfacings. J Bone Joint Surg Br. 2009;91:176-9.

15. Clarke MT, Lee PT, Arora A, Villar RN. Levels of metal ions after small- and large-diameter metal-on-metal hip arthroplasty. J Bone Joint Surg Br. 2003;85:913-7.

16. Heisel C, Streich N, Krachler M, Jakubowitz E, Kretzer JP. Characterization of the running-in period in total hip resurfacing arthroplasty: an in vivo and in vitro metal ion analysis. J Bone Joint Surg Am. 2008;90 Suppl 3:125-33.

17. Butterfield WJ, Keen H, Whichelow MJ. Renal glucose threshold variations with age. Br Med J. 1967;4:505-7.

18. Willert HG, Buchhorn GH, Göbel D, Köster G, Schaffner S, Schenk R, Semlitsch M. Wear behavior and histopathology of classic cemented metal on metal hip endoprostheses. Clin Orthop Relat Res. 1996;(329 Suppl):S160-86.