The exercise-related rise in plasma cobalt levels after metal-on-metal hip resurfacing arthroplasty

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Wear of metal-on-metal bearings causes elevated levels of cobalt and chromium in blood and body fluids. Metal-on-metal bearings have two distinct wear phases. In the early phase, the wear rate is high. Later, it decreases and the bearing enters a steady-state phase. It is expected that as the wear rates decline, the level of cobalt detected in plasma will also decrease. We studied the baseline and exercise-related cobalt rise in 21 patients (13 men and eight women) with a mean age of 54 years (38 to 80) who had undergone successful hip resurfacing at a mean of 44 months (10 to 96) earlier. Our results showed that circulating baseline cobalt levels were not significantly correlated with the time since implantation ($r = 0.08$, $p = 0.650$). By contrast, the exercise-related cobalt rise was directly correlated with the inclination angle of the acetabular component ($r = 0.47$, $p = 0.032$) and inversely correlated with the time since implantation ($r = -0.5$, $p = 0.020$).

Inclination of the acetabular component should be kept less than 40° to decrease the production of wear debris.

Contemporary metal-on-metal hip resurfacing has an excellent early to mid-term clinical outcome¹⁻³ and is being used increasingly in young and active patients.^{4,5} The current results can be attributed largely to improved manufacture and a better understanding of its tribology. *In vitro* studies show low rates of wear ranging from 0.13 mm³/MC to 5 mm³/MC for hard metal-on-metal bearings of various diameters.⁶⁻¹⁰ These rates of wear are too small to be measured from radiographs. One method of determining *in vivo* wear is to measure the rate of release of wear debris from the bearing surfaces. The particles and ions produced, mainly cobalt and chromium are very small and are disseminated throughout the body.¹¹ Their levels can be detected in the circulating blood and body fluids.

The rate of release of metal ions from functioning metal-on-metal bearings is not known. Two distinct phases of wear have been shown in *in vitro* studies. In the early phase, the wear rate is high as the bearing beds in. Later, the wear rate decreases and the bearing enters a steady-stage phase. Several simulator studies have shown this decline in wear rate with time.⁶⁻¹⁰ There is not, however, a corresponding fall in the level of metal ions in the blood. Several clinical studies¹²⁻¹⁶ have found that metal ion levels gradually rise with the passage of time from implantation.

Others¹⁷⁻¹⁹ have noted some decline. The reason for this gradual rise in metal ion levels is not known. If a failed metal-on-metal bearing is revised to a metal-on-polyethylene bearing the level of metal ions may remain elevated for up to two years.²⁰ One possible explanation is that metal particles have a very long half-life in humans. The particles which have been deposited in distant organs may dissolve slowly and increase the levels of metal ions in the circulation. This would make circulating metal ion levels an inaccurate marker for *in vivo* wear.²¹

This effect may be avoided by measuring the exercise-related rise in the level of plasma cobalt.²¹ Exercise has been shown to cause an immediate rise in plasma metal ion levels in patients with a metal-on-metal bearing hip replacement.²² Cobalt is the predominant metal in the alloy used in the manufacture of metal-on-metal hip prostheses. The level of cobalt in the plasma does not fluctuate after exercise in patients who do not have a metallic implant, unlike the chromium level.²² Therefore, cobalt levels might more accurately reflect the *in vivo* behaviour of metal-on-metal bearings. We conducted this study to see whether the exercise-related rise²² in plasma cobalt levels reflected the wear-in and steady-state wear of metal-on-metal hip resurfacing.

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Table I. Demographic data

Distribution of implant types by gender	
Birmingham hip resurfacing	
M:F	9:6
Cormet	
M:F	4:2
Mean age in yrs (range)	54 (38 to 80)
Mean height in cm (range)	172 (137 to 187)
Mean weight in kg (range)	82.7 (62 to 105)
Median femoral head size in mm (range)	50 (42 to 54)
Acetabular component inclination angle (°)(range)	41 (29 to 70)
Mean baseline plasma cobalt levels in nmol/l (range)	55 (14 to 144)

Patients and Methods

Patients who had undergone a metal-on-metal resurfacing hip replacement were identified from the hospital records and invited to take part in the study. We excluded patients with inflammatory arthritis, a painful hip prosthesis, other metal implants, heart disease, renal failure, and a history of occupational exposure to cobalt and chromium. In total, 21 consecutive healthy patients were recruited (Table I). There were 13 men and eight women, with a mean age of 54 years (38 to 80). The Shropshire Research Ethics Committee and the Research Panel in our hospital approved the study. Each patient provided written consent.

Resurfacing arthroplasty implants and surgery. Two types of resurfacing were included in the study: the Birmingham Hip Resurfacing (BHR, Smith and Nephew, York, United Kingdom) and the Cormet 2000 Hip Resurfacing (Corin Medical, Cirencester, United Kingdom). The BHR is made from a high-carbon Co-Cr-Mo alloy and is used 'as cast'. The Cormet 2000 is also used 'as cast', but is heat treated using solution annealing and hot isostatic pressing. All the operations were undertaken by the senior author (JBR) using an anterolateral or posterior approach and a circumferential capsulotomy.

Exercise and blood collection. Each patient was asked to avoid strenuous activity in the week before the experiment. In particular, they were asked to avoid running, jogging, and attending fitness and gymnastic classes. The habitual activity level of each patient was recorded using the Tegner scale,²³ which has 11 levels (0 is disabled and 10 is competitive sports level). Blood samples were taken from a forearm vein through a metal-free polypropylene cannula (Venflon, BD, Helsingborg, Sweden) which was left in the vein for subsequent blood sampling. The first 2 ml to 5 ml of each sample was discarded, a 2 ml or 3 ml blood sample was then collected in a metal-free lithium heparin tube (Teklab, Durham, United Kingdom). The first sample was collected before the patient started to exercise. They then walked or ran on a treadmill at their own pace for one hour in the hospital physiotherapy department. A pedometer

(Fit-Pro, I & M Steiner, Brentford, United Kingdom) worn on the waist counted the number of steps taken. A second blood sample was taken immediately after exercise. A third sample was taken one hour after exercise. The samples were then centrifuged to isolate plasma.

Trace element analysis. All blood analysis was performed at the SAS Trace Metal Unit at Southampton General Hospital. Plasma cobalt was determined using inductively-coupled plasma mass spectrometry (ICP-MS; Elan 6100 DRC plus-SCIEX, Perkin-Elmer, Beaconsfield, United Kingdom). The detection limit for cobalt in plasma was 1 nmol/l.

Acetabular inclination angle. The acetabular component inclination angle was measured on anteroposterior pelvic radiographs. The inclination angle was taken as an angle between the horizontal reference line (the line joining the inferior teardrop points) and the axis of opening of the acetabular component. All the measurements were done by the first author (MK).

Statistical analysis. All data were checked for a normal distribution. Data on plasma cobalt levels, exercise-related cobalt rise and acetabular component inclination angle were square root transformed to allow parametric testing. Independent *t*-tests were used to see whether male and female participants and groups based on either the BHR or Cormet implant differed in terms of age, weight, height, time since surgery, femoral head diameter, number of steps taken, baseline plasma cobalt levels and inclination of the acetabular component. Plasma cobalt levels before exercise were considered baseline, the highest levels after exercise were considered peak, and the difference between peak and baseline was considered the exercise-related cobalt rise. A paired *t*-test was used to compare baseline and peak levels. An independent *t*-test was used to compare the exercise-related rise in cobalt levels between groups, based on gender and on either the BHR or Cormet implant types. Bivariate correlation analysis was used to check the relationship between two outcomes, baseline plasma cobalt levels and exercise-related cobalt rise, and potential predictors including gender, age, body weight, height, femoral head diameter, acetabular component inclination and number of steps. Stepwise multiple regression analysis was then performed to identify independent predictors of the baseline plasma cobalt levels and the exercise-related cobalt rise. Standardised beta (β) values were calculated to determine a one SD change in the outcome variable as a result of one SD change in the predictor variable.

Results

The mean time from hip resurfacing to the exercise experiment was 44 months (10 to 96). The gender and implant (BHR/Cormet) groups were comparable in terms of age, height, weight, femoral head diameter, acetabular component inclination angle, time since surgery, activity level and pre-exercise plasma cobalt levels (Table II). Each patient was able to run or walk for one hour on a treadmill as

Table II. Comparison of groups using independent *t*-tests

	Male	Female	p-value	BHR*	Cornet	p-value
Mean age in years (SD)	55 (11.5)	52 (6.6)	0.53	55.3 (10.8)	50.6 (6.5)	0.78
Gender (M: F)	13	8		9:6	4:2	
Mean height in cm (SD)	177 (6)	165 (13)	0.008	171.3 (11.6)	176.6 (8.4)	0.32
Mean weight in kg (SD)	87 (10.9)	74 (11.6)	0.022	81.4 (12.5)	85.8 (13.3)	0.48
Tegner activity level (0 to 10)	4.8 (3.1)	4.6 (2.9)	0.63	4.3 (2.5)	4.7 (3.2)	0.74
Mean acetabular component inclination angle (°) (SD)	40 (11.8)	42 (10.8)	0.75	40 (11)	43 (12)	0.6
Mean number of steps (SD)	7548 (526)	7186 (418)	0.11	7390 (499)	7462 (580)	0.77
Mean baseline plasma cobalt (nmol/l) (SD)	48.8 (35.8)	64.7 (36.8)	0.34	50.2 (31.7)	66.7 (46.6)	0.35
Mean time since surgery (mths) (SD)	37.7 (27)	54.3 (26)	0.184	46.8 (29.2)	37 (23.2)	0.47
Mean diameter of femoral head (mm) (SD)	49 (4)	48 (3)	0.56	48 (3.7)	51 (2.7)	0.09

* BHR, Birmingham Hip Resurfacing

Fig. 1

Graph showing that baseline plasma cobalt levels increase with an increased angle of inclination of the acetabular component of a metal-on-metal bearing hip resurfacing.

Fig. 2

Graph showing that baseline plasma cobalt levels do not significantly change with increasing time after implantation of a metal-on-metal bearing hip resurfacing.

required. There was no significant difference in the mean number of steps taken by male or female patients (*t*-test, $p = 0.11$) or by patients with different resurfacing implants (*t*-test, $p = 0.77$) (Table II). A significant difference was noted in the mean baseline and mean peak plasma cobalt levels (paired *t*-test, $p = 0.001$). The mean rise in cobalt levels from the baseline was 4.5 nmol/l (SD 5.7) (8%). This rise was similar for both men and women (*t*-test, $p = 0.99$). Patients with a BHR resurfacing had a mean increase in cobalt levels of 3.7 nmol/l (SD 5.9) (7%), whereas patients with a Cornet 2000 resurfacing had a mean increase of 6.5 nmol/l (SD 5.1) (12%) from baseline. This difference was not significant (independent *t*-test, $p = 0.28$). Baseline plasma cobalt levels were directly corre-

lated with the inclination angle of the acetabular component ($r = 0.44$, $p = 0.404$) (Fig. 1) but not significantly correlated with time since surgery ($r = -0.08$, $p = 0.650$); Fig. 2). The exercise-related rise in cobalt levels was directly correlated with the inclination angle of the acetabular component ($r = 0.47$, $p = 0.032$; Fig. 3) and inversely correlated with time since surgery ($r = -0.5$, $p = 0.020$; Fig. 4). Multiple stepwise regression analysis showed that the inclination angle of the acetabular component was the only statistically significant predictor of baseline plasma cobalt level (Table III). In contrast, time since surgery ($p = 0.034$) and inclination of acetabular component ($p = 0.040$) were independent predictors of exercise-related cobalt rise (Table IV). Finally, we examined the results for a difference in the

Fig. 3

Graph showing that an exercise-related rise in cobalt level increases with an increased angle of inclination of the acetabular component of a metal-on-metal bearing hip resurfacing.

Fig. 4

Graph showing that an exercise-related rise in cobalt level decreases with time since implantation of a metal-on-metal bearing hip resurfacing.

Table III. Results of stepwise multivariate regression analysis of baseline plasma cobalt levels

	β	Standard error β	Standardised β
Step 1			
Constant	7.093	0.459	
Inclination angle of the acetabular component	1.26	0.584	0.44
Inclination angle of the acetabular component	0.056	0.020	0.467
Plasma cobalt levels $R^2 = 0.19$ ($p = 0.044$)			
Dependent variable: plasma cobalt levels			

exercise-related cobalt rise between the two types of implant, with time since surgery and acetabular component inclination angle as independent predictor variables. The type of prosthesis had no effect on the exercise-related cobalt rise ($\beta = 0.368$, $p = 0.416$).

In the study two patients had identical pre- and post-exercise cobalt levels, and a third patient had lower post-exercise cobalt levels than the pre-exercise level. All these patients had BHR prostheses and their time since implantation was in excess of the mean period, ranging from five to eight years. Their acetabular inclination angle was below the mean value of 40° , ranging from 29° to 70° .

Discussion

This study shows that physiological exercise in patients with a resurfacing hip prosthesis causes a significant rise in plasma cobalt levels. The mean cobalt ion levels rose by 4.5 nmol/l (8%) within one hour of completing one hour of exercise. It also shows that patients whose implant has been in place for a longer time have a smaller rise in cobalt levels in response

to exercise. In contrast, the baseline plasma cobalt levels did not decrease with a longer period of implantation. The inclination angle of the acetabular component was another important predictor of cobalt ion levels, as a greater inclination angle produced a significant increase in exercise-related and baseline plasma cobalt levels.

Wear rates have been shown to decline to a much lower level once a bearing beds in and enters a steady state.⁶⁻¹⁰ If the metal ion levels truly reflect wear rates, they should decline over time. In our study, plasma cobalt levels were not affected by the time since implantation of the resurfacing hip arthroplasty. This finding suggests that plasma cobalt levels do not mirror the pattern of wear expected from *in vitro* studies. However, the rise in exercise-related plasma cobalt level was significantly associated with time since implantation of the resurfacing arthroplasty, with an increasing time since implantation producing a smaller rise in cobalt levels. This is more consistent with the pattern of wear expected from *in vitro* studies, suggesting that the exercise-related rise in cobalt levels may be a better *in vivo* marker of wear.

Table IV. Results of stepwise multivariate regression analysis of exercise-related plasma cobalt levels

	β	Standard error β	Standardised β
Step 1			
Constant	2.92	0.33	
Time since surgery	-0.024	0.008	-0.56
Step 2			
Constant	2.6	0.427	
Time since surgery	-0.021	0.007	-0.49
Inclination angle of the acetabular component	0.056	0.020	0.467

$R^2 = 0.31$, for Step 1; and $R^2 = 0.52$ for Step 2 ($p = 0.020$)

Acetabular component inclination angle was centred to the mean

Dependent variable: exercise-related rise in cobalt levels

The rise in cobalt levels was negligible in those patients whose resurfacing hip replacement had been implanted for a longer time. This suggests that fewer wear particles were being generated in these patients and that the metal ion levels would slowly fall in the long term. As a result, the risk of cancer and cytotoxicity will also decrease as the exposure to particulate debris decreases.

A rise in metal ion levels resulting from increased activity was first detected by Gleizes et al in 1999.²⁴ We have confirmed this observation by finding a significant rise in cobalt levels following an hour of exercise. This required precise measurement of the metal ion level, as the increase may be as small as 10% of the resting value. In a previous study²² we found that there was also a rise in plasma chromium levels after exercise in patients who had no metallic implants in their bodies. Therefore, we suggest that only exercise-related cobalt levels are measured as an *in vivo* measure of metal-on-metal bearing wear.

In contrast to the present study and two earlier reports,^{22,24} two further studies^{25,26} have failed to find a significant rise in cobalt levels after strenuous activity. This may be the result of differences in the techniques of measuring the metal ion levels. Additionally, De Haan et al²⁶ collected their serum sample on the day after exercise, by which time the metal ions could have returned to their pre-exercise levels.

Higher serum cobalt levels have been reported previously in patients whose acetabular component was included more than 60°.²⁷ We found a correlation between the exercise rise in cobalt levels that extended into the normal range of acetabular inclination angle. This rise was not seen with an inclination angle below the mean value. Accordingly, we recommend implanting the acetabular component with an inclination angle of 40° or less to minimise the release of wear debris.

We found no significant difference in the exercise-related cobalt rise between patients with BHR and Cormet resurfacing prostheses, but recognise that this may be a function of the small numbers in our study.

In conclusion, we found that exercise causes a rise in plasma cobalt levels in patients who have a metal-on-metal

resurfacing hip replacement. This is greatest in the early post-operative period but decreases to an almost negligible level with time. Resting plasma cobalt levels do not show this behaviour.

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