Long-Term Changes In Blood Metal Ion Levels In Patients With Hip Resurfacing Implants: Implications for patient surveillance after ten-years follow-up

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Abstract:	Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce. Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal ion measurements were identified at two large specialist European arthroplasty centres. After excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed. Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%, chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar. Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.

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Conflict of interest

The Author(s) declare(s) that there is no conflict of interest.

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Abstract

Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce.

Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal ion measurements were identified at two large specialist European arthroplasty centres. After excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.

Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%, chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar.

Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.

Keywords: metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt

Introduction

High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip replacements although some implants have demonstrated relatively good survival in the longer-term in national joint registries (1,2) (3,4).

Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have been published (2,5–7). The main issues for following up patients with MoM hips include the risk stratification of patients, the frequency of follow-up assessments, and the actual screening methods to use. In practice, the majority of patients receive blood metal ion testing with some form of hip imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous external validation which showed patients below these defined thresholds have a low risk of adverse reaction to metal debris (ARMD) (8–10). The evidence-base for the guidelines are still limited, with clear differences in the recommendations made by each regulatory authority (2). The cost-effectiveness of these guidelines has also been questioned (11).

Most patients with their hip resurfacing (HR) still in situ are in the second decade of the implant lifetime (4,5,13–15). However, no large studies have investigated how blood metal ion levels change in the longer term, especially during the second decade after implantation. Most current surveillance guidelines have no temporal stratification (3, 6, 8). Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime are needed to clarify the specific role blood metal ion measurements play in the longer term follow-up of MoM HR patients. Specifically, more research is needed on the patients with initially acceptable metal ion levels. Patients with initially high metal ions are not an issue since these patients clearly need close surveillance, more thorough diagnostic work-up and possible evaluation for revision (20).

We assessed patients with two commonly used MoM HR implant designs (Birmingham Hip Resurfacing [BHR] and Articular Surface Replacement [ASR]) implanted at two specialist arthroplasty centres. The study aims were to determine 1) the percentage of patients with initial blood metal ion levels below previously devised thresholds whose subsequent metal ion levels were above these thresholds during the second decade, 2) the prevalence of ±2.15 parts per billion (ppb) and ±5.5 ppb changes in the long-term in serial whole blood metal ion levels, and 3) how blood metal ion levels change with time in patients with repeated metal ion measurements.

Materials

Study populations

A cohort study of patients with BHR and ASR MoM HRs implanted at two large specialist European arthroplasty centres was performed. All patients with either BHR or ASR implants and three or more blood metal ion measurements during a follow-up of more than 10 years were included for study analyses. From these patients we excluded those who had first metal ion levels higher than 7 ppb (7). Focus in our study was patients with initially acceptable metal ion levels since these patients are under frequent surveillance and in the need of repeated metal ion measurements. Patients with initially elevated ion levels are usually referred for closer follow-up and diagnostic work-up and changes in metal levels pose different kind of relevance compared to patients with well-functioning implants. If a patient with bilateral implants had undergone a unilateral revision we included only measurements taken whilst both implants were still in situ. Selection of patients was based only on initial WB metal ion levels, follow-up time and availability of measurements.

In center 1, 406 BHRs (357 patients) were implanted between January 2001 and February 2012. All patients have been referred for whole blood (WB) cobalt (Co) and chromium (Cr) measurement and clinical outcome was assessed using the Oxford Hip Score (OHS). All patients with elevated (>5 ppb) metal ion measurements or with any kind of hip related symptoms were referred for cross-sectional imaging using MRI (16). Current protocol involves follow-up every two-years, which includes WB Co and Cr, and OHS assessment. If the patient became symptomatic or metal ion levels were above the 5 ppb threshold, patients underwent cross-sectional imaging and had an appointment with a consultant orthopaedic surgeon.

Also in center 1, 497 ASR HRs (415 patients) were implanted between March 2003 and December 2009. Early surveillance and investigation of these patients has been described in detail previously (17). After early intense screening, surveillance of ASR patients was changed in 2017 to that used for BHR patients.

In center 2, there have been 3,990 BHRs (3,276 patients) implanted up until 30th April 2019. The surveillance and investigation of these patients has been described in detail previously (9–11). In summary, all symptomatic patients underwent WB metal ion sampling, radiographs and cross-sectional imaging with either MRI and/or ultrasound. Asymptomatic patients with certain factors (such as female patients, males with small BHR head sizes, bilateral MoM implants, radiographic abnormalities) also underwent blood metal ion sampling, with targeted cross-sectional imaging used if ions were raised and/or symptoms developed. All investigated patients remain under regular surveillance, typically annually. No ASRs were implanted in center 2.

Patient selection

In center 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial Wb Co or Cr above 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore excluded. Of the remaining patients, three or more blood metal ion level measurements were available for 194 BHR patients (227 hips) with follow-up of more than 10 years (Figure 1). Similarly, of 415 ASR patients (497 hips), 54 patients (68 hips) had initial Wb Co or Cr above 7 ppb, (50 of 68 [74%] hips have been revised since), and were excluded. Of the remaining patients, 216 (263 hips) have undergone three or more metal ion measurements during follow-up of more than 10 years (Figure 2).

In center 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had undergone any metal ion measurements. 418 patietns (559 hips) had more than 3 measurements and 365 patients (481 hips) had initial measurement below 7 ppb. Of these 263 patients (328 hips) have undergone three or more blood metal ion level measurements with follow-up of more than 10 years (Figure 1).

Assessment of metal ion level changes

Previous studies have established implant specific thresholds in HR patients identifying those at low risk of ARMD. The externally validated threshold for Co in unilateral patients is 2.15 ppb (11). We applied the same threshold also for Cr in this study, although acknowledge this has not been formally validated, and therefore the findings for this study should focus on the Co levels in unilateral patients. For bilateral patients externally validated threshold was 5.5 ppb for maximum of Co or Cr (11). We applied this threshold also separately for both Co and Cr values. In this study, we did two separate analyses to identify changes in metal ion measurements after 10 years or more follow-up using these thresholds. Firstly, we investigated if each repeated measurement was more than 2.15 ppb for unilateral patients while initial measurements in the first decade had been less than 2.15 ppb. In bilateral patients we assessed change from below 5.5 ppb to above 5.5 ppb. This was termed the absolute analysis since changes were assessed against the initial absolute level (Figure 3A). Secondly, we recorded relative changes or measurement-to-measurement change of more than ±2.15 ppb or ±5.5 ppb for both implant groups. This was termed the relative analysis since we only assessed changes from measurement to measurement regardless of initial metal ion level (Figure 3B). "Net change" was defined as the total sum of changes. This means that if the patient had, for example, both -2.15 ppb and +2.15 ppb changes, there was no "net change". Subgroup analysis was done in unilateral patients with a femoral head size under 50 mm.

Statistics

Continuous variables were compared using Welch´s t-test when appropriate. Comparison of continuous variables across three groups (BHRs in center 1, BHRs in center 2 and ASRs) was done with analysis of variance. Proportions across two or three groups were compared using the Chi-squared test with Yates correction. Association between time in-situ and metal ion levels was done with generalized least squares linear model with random intercepts and fixed slopes. Full description of this process is available in Supplement 1. Analysis was done with RStudio 1.2.5033.

Results

The final BHR study cohort included 359 patients with unilateral implants and 98 patients with bilateral implants totaling 457 patients with 555 hips. There was a notable difference between the institutions regarding distribution of femoral head size (Table 1). The ASR cohort included 169 patients with unilateral implants and 47 patients with bilateral implants totaling 263 hips. In total there were 2743 WB metal ion measurements, of which 1645 had been done 10 or more years after the index operation.

Absolute changes

Absolute changes in relation to established implant specific thresholds are shown in Table 2. An increase above implant specific threshold during second decade was seen in 10.8%-28.4% of the unilateral patients. In bilateral patients increase was seen in 4.3%-11.8%.

Relative changes

Table 3 shows the prevalence of ±2.15, ±5.5 ppb measurement-to-measurement changes and "net change" in metal ion levels performed after 10 years follow-up. Change of +2.15 ppb in either Co or Cr levels was seen in 3.6-10% of unilateral BHR and ASR patients overall, however "net change" was even less common. Change of +5.5 ppb were seen in 1.4-2.5% of unilateral BHR and ASR patients overall, however "net change" was again even less common. In bilateral patients, +5.5 ppb change was also rarely seen (0 to 2.1%).

Time effects

Population marginal effects are shown in Supplemental Figures 1-4. In center 1, Co levels reduced with time since index operation in patients with unilateral BHR implants and also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1A and 2A). Bilateral BHR patients also show metal ion levels reducing with time in the second decade (Supplemental Figure 4A). In center 2, metal ion levels increased with time since index operation in patients with unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1B and 2B). Bilateral BHR patients showed a plateau (Supplemental figure 4B). In the ASR patients, increasing trends in metal ion levels with time were not seen (Supplemental Table 2, Supplemental Figure 3).

Discussion

Hundreds of thousands of patients with HRs are still in the need of regular follow-up. Studies assessing the roles for blood metal ion measurements and cross-sectional imaging are urgently needed to determine if regular monitoring for all HR patients is truly needed. We aimed to assess the population level changes in blood metal ion levels into the second decade. Patients at risk of failure and in need of closer follow-up, namely those with abnormal wear due to conditions such as edge-loading, are relatively straightforward to detect with initial screening. Our focus was especially on those patients having acceptable ion levels at initial screening and no abnormalities, who have been referred for more regular follow-up.

Generally, metal ion levels remained stable during the second decade of the implant lifetime. Relative changes (measurement-to-measurement) exceeding +5.5 ppb were uncommon. Major changes were not seen even in patients with small femoral head diameter implants. In center 2, one sixth (17.2%) of BHR patients had a relative increase of more than 2.15 ppb in WB Cr but only a few percent had an increase of greater than 5.5 ppb. A change in measurement-to-measurement in Wb Co was seen in 9.1% of BHR patients in center 2. Very similar results were reported by Van Der Straeten et al. who reported 4% prevalence with an increase of more than 2.5 ppb for serum Co at ten years follow-up (18). Overall prevalence in our study with a +2.15 ppb change in WB Co was 5%.

Absolute changes in relation to fixed levels were similar to those seen in relative or measurement-to-measurement changes. We considered 2.15 ppb to be a clinically meaningful threshold for unilateral patients and 5.5 ppb for bilateral patients as per previous validation studies of these clinical thresholds (11). A change from below to above the threshold was seen in 4.3% to 28.4% and this was most common in patients with unilateral implants. Up to a quarter of BHR patients had elevation of metal ion levels above the previously established threshold by the second decade, however the clinical significance of this requires further follow-up.

Ion levels had negative association with time in one study center similar to that reported by Van Der Straeten et al, although they analyzed only unilateral patients (18). deSouza et al also reported results of serial metal ion measurements in a cohort of 53 patients with Corin HR implants (19). They reported a slightly increasing trend in metal ion levels at ten-year follow-up. We noticed a decreasing trend also in bilateral patients which is a novel finding. These temporal effects were center dependent since associations were positive in our other study center. However, it is important to see that these changes are negligible and even the upper limit of the confidence interval around these estimates remains below 5 ppb.

Differences in metal ion trends between the study centers may be related to two separate reasons. It is likely that the threshold for revision surgery due to ARMD differs between the study centers (20). Elevation in metal ion levels is always a relative indication for revision surgery but usually other factors such as symptoms and cross-sectional imaging findings are also considered as well. There are no universal criteria for ARMD revision due to heterogeneity in clinical manifestation. It is therefore reasonable to assume that metal ion levels are valued differently in decision-making between study centers and hence different population trends are observed. It is of importance, however, that regardless of these varying indications the observed trends are not important from a clinical perspective.

ASR HR has been reported to have the poorest survival of all HR implant designs (4,5). Interestingly, we observed decreasing population trends with time since index operation in metal ion levels in both unilateral and bilateral patients. Relative and absolute changes during the second decade were rare and similar to those seen in BHRs. The revision rate of ASR HRs in Center 1 has been approximately 30% at 10 years. Hence our results suggest that intense screening and high revision rates have resulted in a situation where the majority of non-revised ASR HR patients have steady state wear and metal ion trends are similar to those seen in BHRs.

The main strength of our multicenter study is the large number of patients with the largest number of analyzed metal ion measurements to date which extend into the second decade. The main limitation in our study is selection bias. All operated patients have not undergone regular metal ion measurements and some patients have only one or two measurements. In Center 2 many BHR patients have no metal ion measurements at all. This is because Center 2 have a large cohort of male BHR patients who are asymptomatic and were not included in the recall for monitoring until 2017. The BHR patients who have been monitored regularly at Center 2 are therefore the symptomatic patients, female patients and male patients with head sizes ≤46 mm, all of whom are at higher risk of ARMD than the unmonitored cohort of male asymptomatic patients who are likely to have low levels of metal ions. Metal ion trends were inferior in the BHR group which may seem counterintuitive and biased. We did not, however, aim to predict theoretical behavior of metal ion levels. It is clear that implants with poor track-record have high revision rates, such as 30% in the ASR cohort in our study. Hence our results must be seen from pragmatic view: what is the behavior of blood metal ion levels in well functioning implants not initially needing revision.

Overall our results for BHR patients show that if initial blood metal ion measurements during the first decade are acceptable, the probability is high that ion levels will remain low in the second decade. This also holds true for ASR patients, assuming a significant revision rate similar to the 30% seen in our study group. These findings have major implications for the present worldwide regular surveillance for HR patients. Regular metal ion measurements (i.e. annual) therefore do not seem reasonable if the initial values are below validated thresholds. We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for HR patients since only minor changes were seen after 10-year follow-up. Regulatory guidance stratifying implant surveillance based solely on femoral head size does not seem useful with the BHR and ASR given temporal metal ion changes.

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Table 1: Comparison study groups between institutions.

			BHR cohort			ASR cohort	p-value for three group difference
			Center 1	Center 2	p-value for difference		
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<.0001	54.3 (9.4)	<.0001
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	.30	54.3 (8.3)	0.09
	Bilateral - second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	.84	54.6 (8.4)	0.93
Gender	Unilateral	Males	110	31	<.0001	117	<.0001
		Females	51	167		52	
	Bilateral	Males	24	8	<.0001	36	<.0001
		Females	9	57		11	
Femoral diameter	Unilateral	<43mm	3	48	<.0001	2	<.0001
		44-45mm	1	0		7	
		46-47mm	28	100		25	
		48-49mm	1	0		14	
		50-51mm	51	38		24	
		52-53mm	58	11		46	
		54-55mm	19	1		26	
		56-57mm	0	0		18	
		58-59mm	0	0		5	
		≥60mm	0	0		2	
	Bilateral	<43mm	0	27		2	
		44-45mm	0	3		4	
		46-47mm	13	69		11	
		48-49mm	0	0		9	
		50-51mm	25	24		11	
		52-53mm	0	1		21	

54-55mm	14	6		19
56-57mm	0	0		9
58-59mm	14	0		7
>60mm	0	0		1

Table 2: Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	**Patients with at least one measurement above 2.15 ppb during 2nd decade**
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	**Patients with at least one measurement above 5.5 ppb during 2nd decade**
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

Table 3: Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. Small diameter means <50 mm head size.

			All BHR			Small diameter BHR			ASR	
			Overall	Center 1	Center 2	Overall	Center 1	Center 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb “net change”	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb “net change”	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
	Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)	2 (4.2%)
		-2.15 ppb change	10 (2.8%)	3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)
		+5.5 ppb change	6 (1.7%)	2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)
		-5.5 ppb change	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
		+2.15 ppb “net change”	31 (8.6%)	1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)
		+5.5 ppb “net change”	5 (1.4%)	1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)
Bilateral	Cobalt	+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)	
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb “net change”	(0%)	(0%)	(0%)				1 (2.1%)	
		+5.5 ppb “net change”	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
	Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)				2 (4.3%)	
		-2.15 ppb change	5 (5.1%)	0 (0%)	5 (7.7%)				0 (0%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				0 (0%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb “net change”	5 (5.1%)	0 (0%)	5 (7.7%)				2 (4.3%)	
		+5.5 ppb “net change”	1 (1%)	0 (0%)	1 (1.5%)				0 (0%)	

Figures

Figure 1: Flow chart for BHR patients

Figure 2: Flow chart for ASR patients

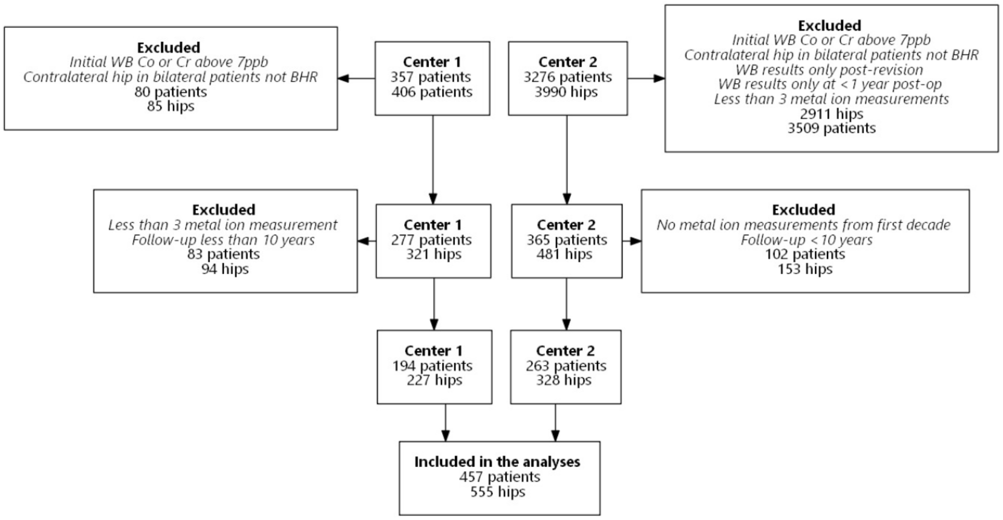
Figure 3: Explanation for A) absolute and B) relative change used in the analyses

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

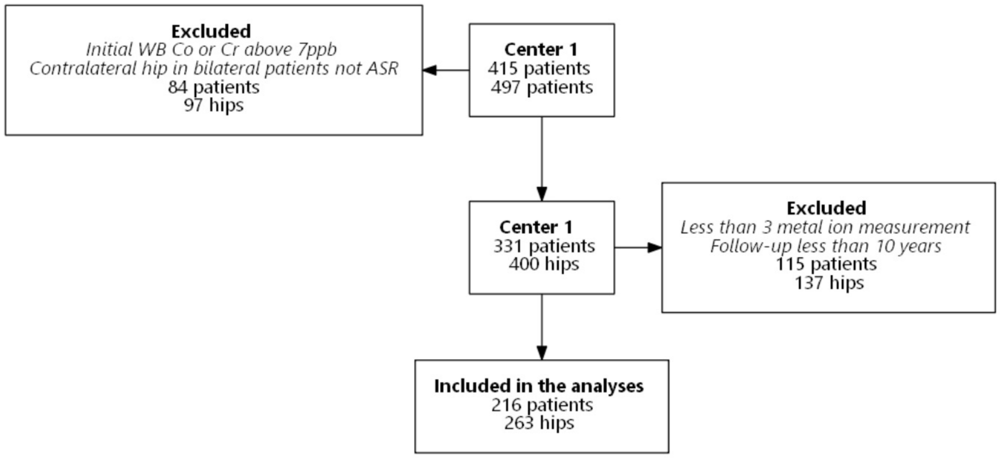
Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.



Flow chart for BHR patients

237x123mm (144 x 144 DPI)



Flow chart for ASR patients

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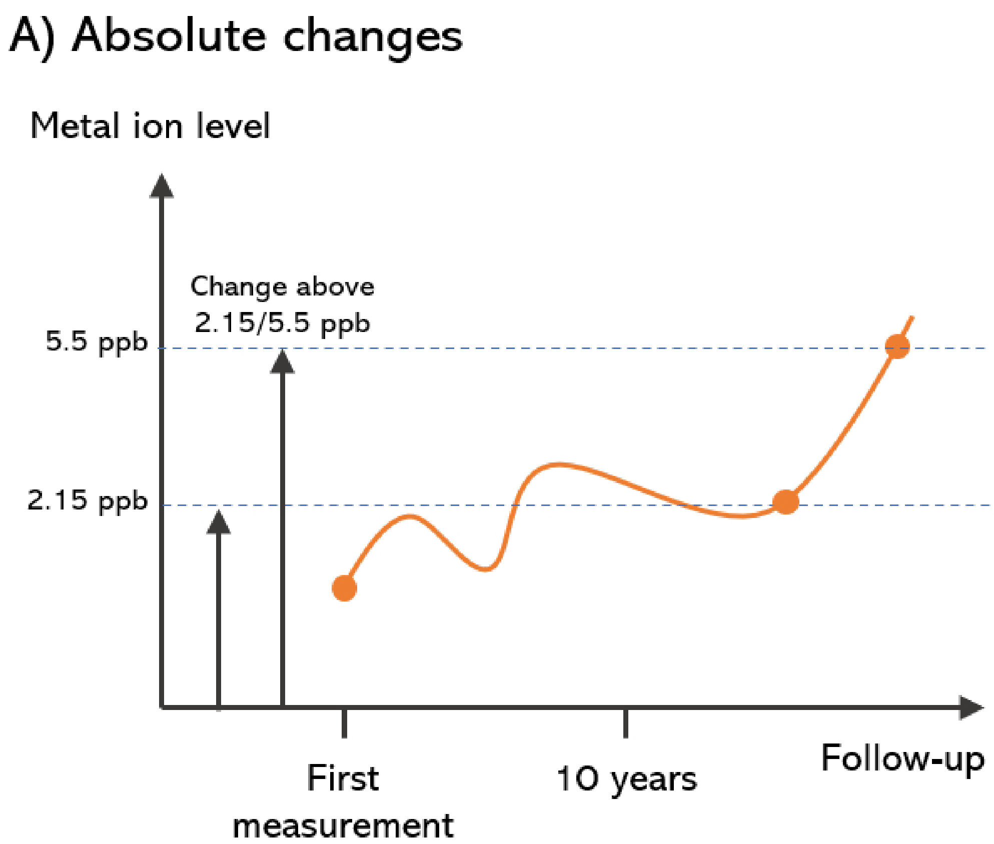
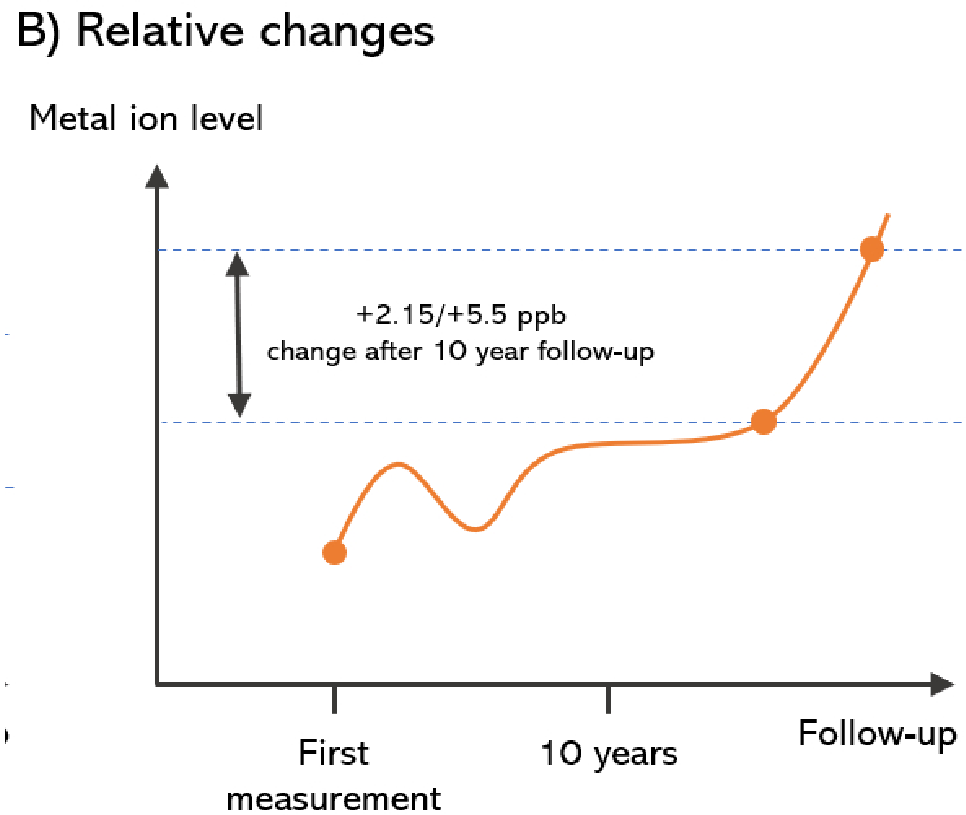


Explanation for A) absolute and B) relative change used in the analyses

266x233mm (57 x 57 DPI)



Explanation for A) absolute and B) relative change used in the analyses

273x233mm (57 x 57 DPI)

Supplemental figures and tables

Supplemental Table 1: Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in BHR patients. AIC = Akaike´s information criteria. Small diameter means <50 mm head size.

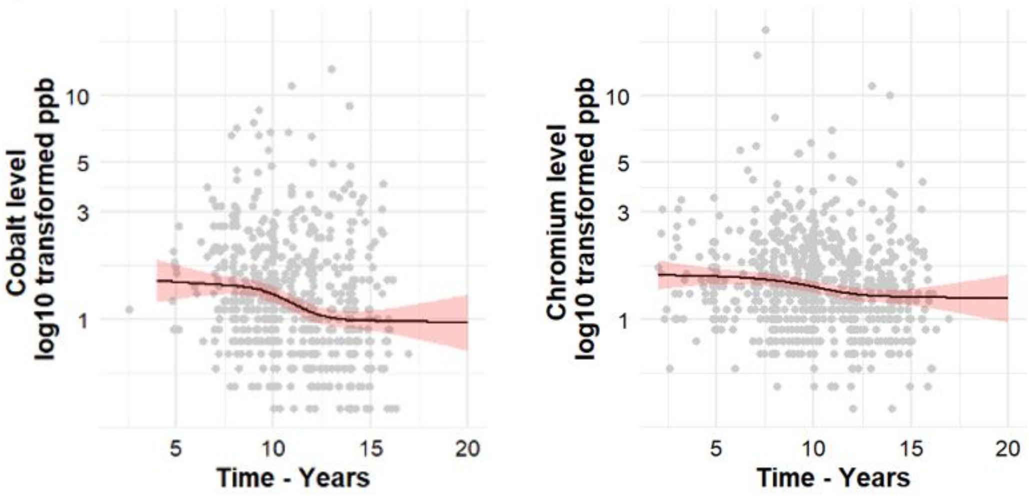
				Model 1		Model 2	
				β for time (95% CI)	AIC	AIC	p-value for nonlinearity
Center 1	Unilateral	Cobalt	All patients	-0.020 (-0.026 to -0.014)	-366.5069	-327.75	0.013
			Small diameter	-0.027 (-0.040 to -0.014)	-77.5	-86.30	0.64
		Chromium	All patients	-0.010 (-0.016 to -0.0038)	-497.271	-492.11	0.006
			Small diameter	-0.005 (-0.016 to -0.0069)	-115.34	-107.67	0.08
	Bilateral	Cobalt	All patients	-0.015 (-0.024 to -0.0054)	-103.68	-91.42	0.70
		Chromium	All patients	-0.097 (-0.021 to 0.0023)	-115.6838	-105.40	0.30
Center 2	Unilateral	Cobalt	All patients	0.0094 (0.0036 to 0.015)	-113.8499	-87.48	0.010
			Small diameter	0.011 (0.0039 to 0.018)	-86.37	-87.48	0.0007
		Chromium	All patients	0.014 (0.008 to 0.020)	-153.152	-143.485	0.063
			Small diameter	0.011 (0.004 to 0.018)	-147.172	-141.51	0.010
	Bilateral	Cobalt	All patients	0.0076 (0.0005 to 0.015)	-178.52	-199.16	0.14
		Chromium	All patients	0.0015 (-0.0071 to 0.010)	-194.29	-209.3474	0.94

Supplemental Table 2 : Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in ASR patients. AIC = Akaike´s information criteria. Small diameter means <50 mm head size.

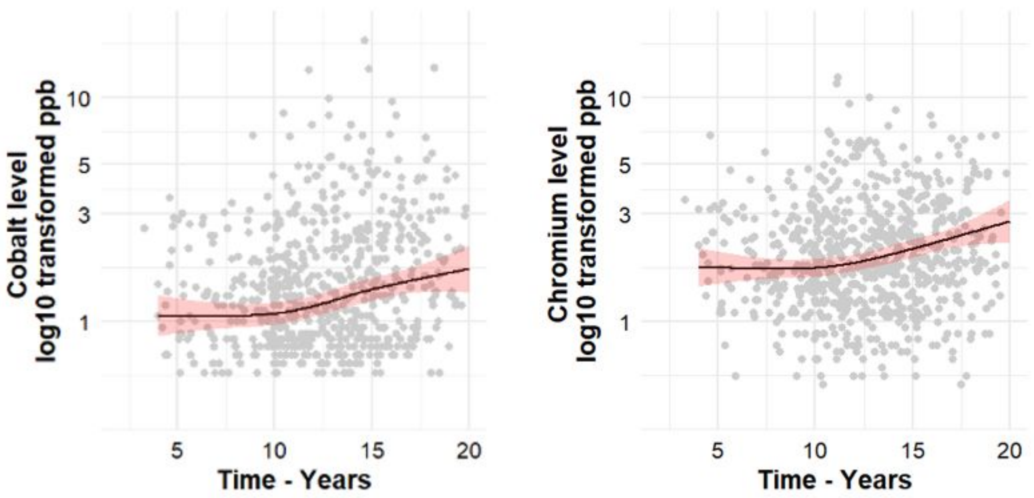
			Model 1		Model 2	p-value for model nonlinearity
			β for time (95% CI)	AIC	AIC	
Unilateral	Cobalt	All patients	-0.013 (-0.017 to -0.0090)	-179.74	-327.68	0.41
		Small diameter	-0.0036 (-0.010 to 0.0030)	-104.11	- 94.95	0.72
	Chromium	All patients	-0.0048 (-0.0079 to -0.0017)	-656.01	-625.14	0.47
		Small diameter	0.0066 (0.0010 to 0.012)	-37.52	-34.23	0.08
Bilateral	Cobalt	All patients	-0.0088 (-0.015 to -0.0030)	-144.58	-137.48	0.28
	Chromium	All patients	-0.0057 (-0.011 to -0.0005)	-225.85	-171.27	0.27

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

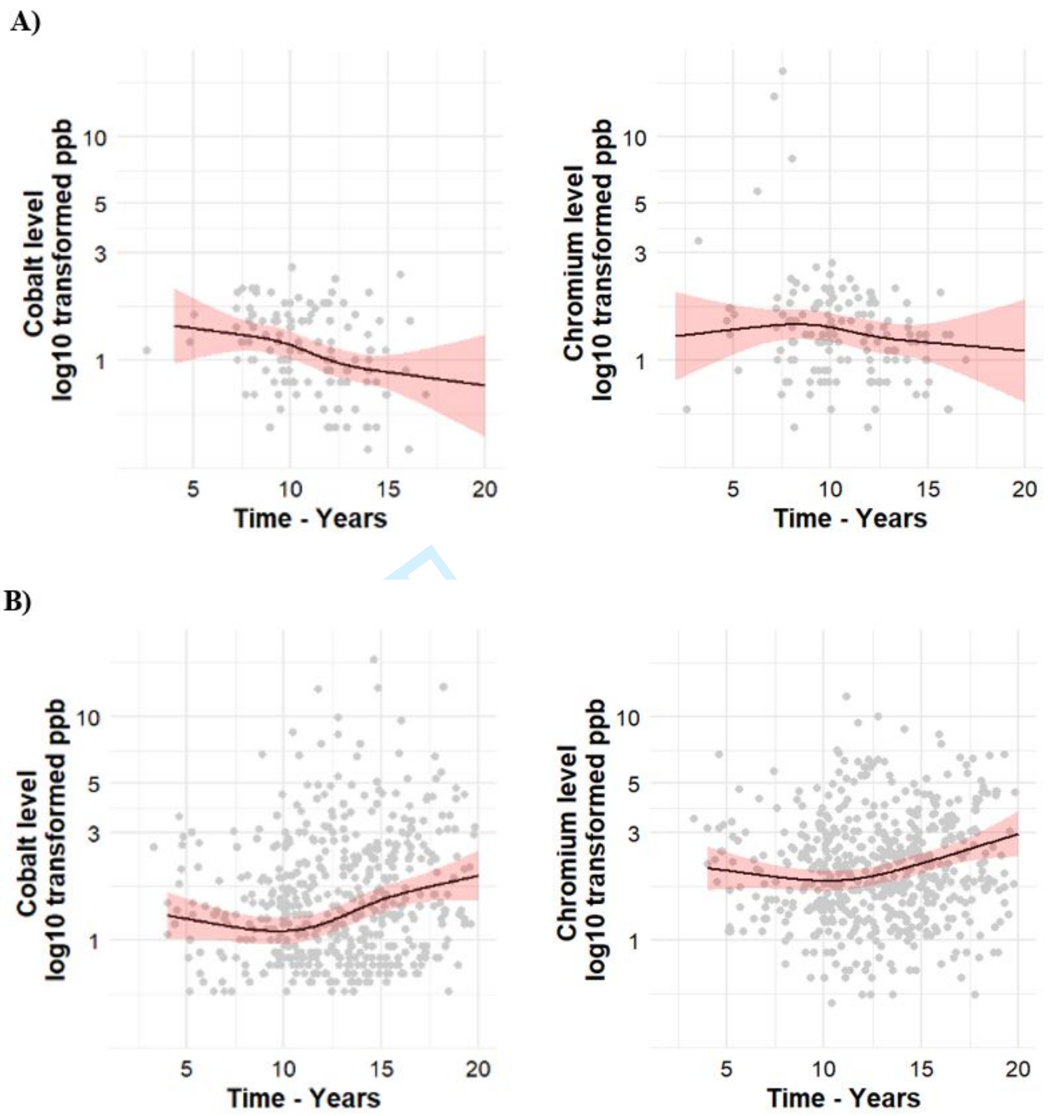
A)



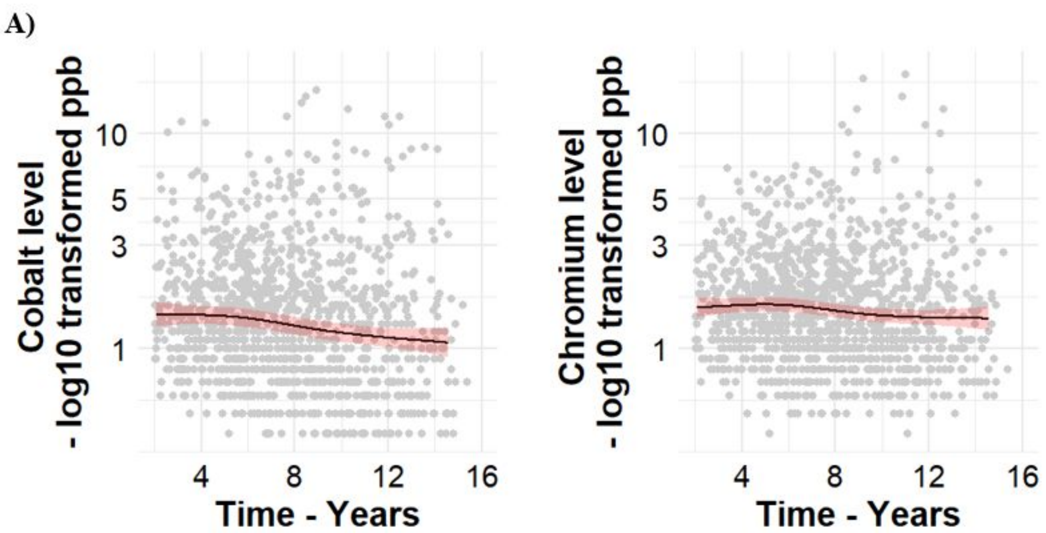
B)



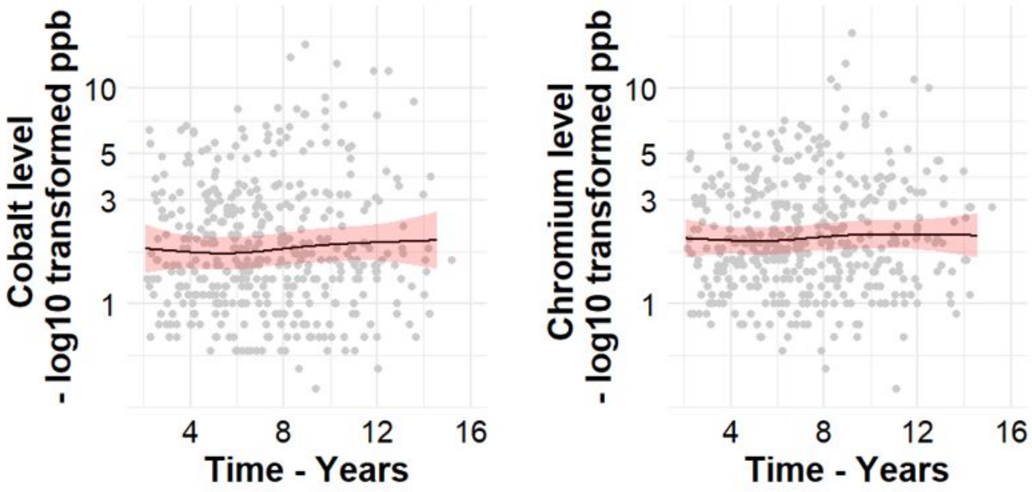
Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2



Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

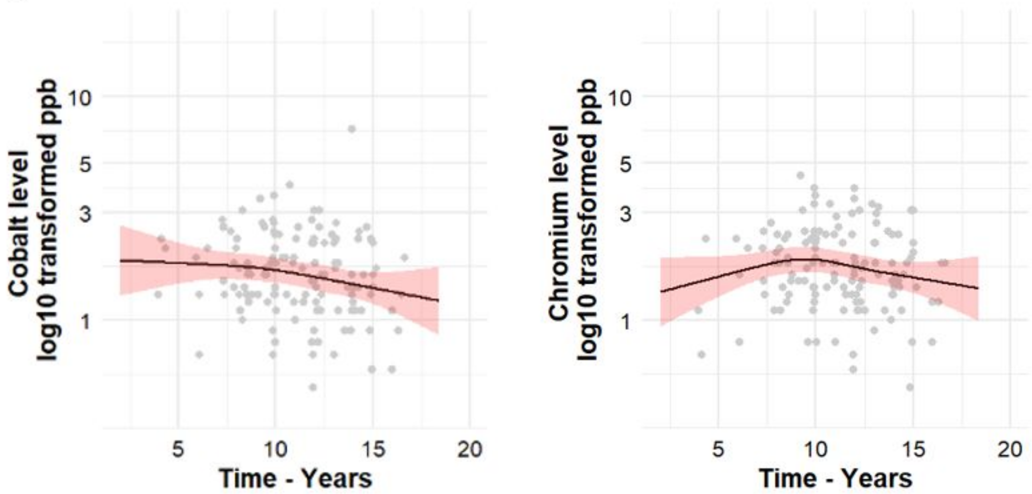


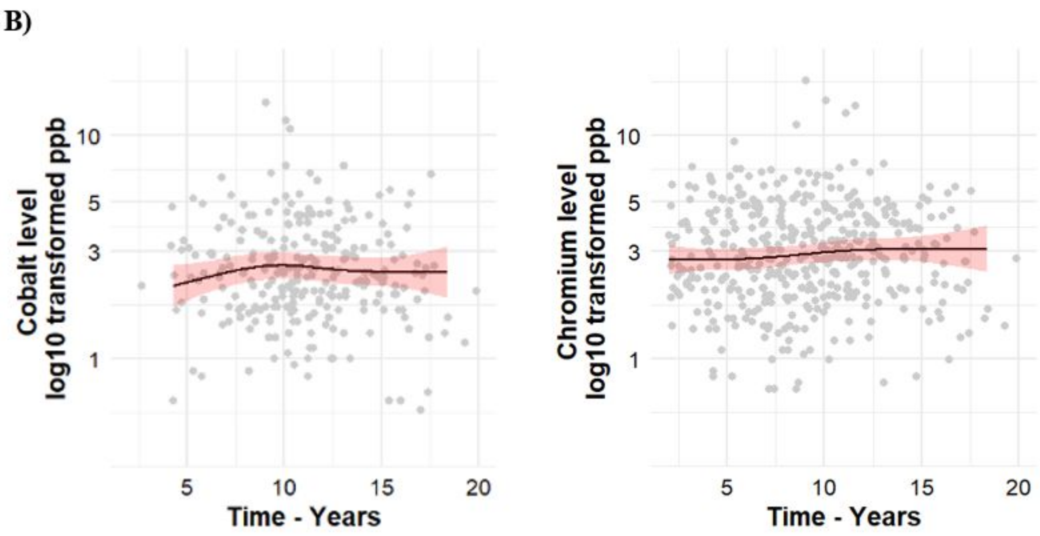
B)



Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.

A)




B)
Cobalt level
log10 transformed ppb
10
5
3
1
5
10
15
20
Time - Years
Chromium level
log10 transformed ppb
10
5
3
1
5
10
15
20
Time - Years

Long-Term Changes In Blood Metal Ion Levels In Patients With Hip Resurfacing Implants: Implications for patient surveillance after ten-years follow-up

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Abstract

Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce.

Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal ion measurements were identified at two large specialist European arthroplasty centres. After excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.

Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%, chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar.

Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.

Keywords: metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt

Introduction

High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip replacements although some implants have demonstrated relatively good survival in the longer-term in national joint registries (1,2) (3,4).

Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have been published (2,5–7). The main issues for following up patients with MoM hips include the risk stratification of patients, the frequency of follow-up assessments, and the actual screening methods to use. In practice, the majority of patients receive blood metal ion testing with some form of hip imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous external validation which showed patients below these defined thresholds have a low risk of adverse reaction to metal debris (ARMD) (8–10). The evidence-base for the guidelines are still limited, with clear differences in the recommendations made by each regulatory authority (2). The cost-effectiveness of these guidelines has also been questioned (11).

Most patients with their hip resurfacing (HR) still in situ are in the second decade of the implant lifetime (4,5,13–15). However, no large studies have investigated how blood metal ion levels change in the longer term, especially during the second decade after implantation. Most current surveillance guidelines have no temporal stratification (3, 6, 8). Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime are needed to clarify the specific role blood metal ion measurements play in the longer term follow-up of MoM HR patients. Specifically, more research is needed on the patients with initially acceptable metal ion levels. Patients with initially high metal ions are not an issue since these patients clearly need close surveillance, more thorough diagnostic work-up and possible evaluation for revision (20).

We assessed patients with two commonly used MoM HR implant designs (Birmingham Hip Resurfacing [BHR, Smith & Nephew, London, United Kingdom] and Articular Surface Replacement [ASR, DePuy/Johnson&Johnson, Leeds, United Kingdom]) implanted at two specialist arthroplasty centres. The study aims were to determine 1) the percentage of patients with initial blood metal ion levels below previously devised thresholds whose subsequent metal ion levels were above these thresholds during the second decade, 2) the prevalence of ±2.15 parts per billion (ppb) and ±5.5 ppb changes in the long-term in serial whole blood metal ion levels, and 3) how blood metal ion levels change with time in patients with repeated metal ion measurements.

Materials

Study populations

A cohort study of patients with BHR and ASR MoM HRs implanted at two large specialist European arthroplasty centres was performed. All patients with either BHR or ASR implants and three or more blood metal ion measurements during a follow-up of more than 10 years were included for study analyses. From these patients we excluded those who had first metal ion levels higher than 7 ppb (7). Focus in our study was patients with initially acceptable metal ion levels since these patients are under frequent surveillance and in the need of repeated metal ion measurements. Patients with initially elevated ion levels are usually referred for closer follow-up and diagnostic work-up and changes in metal levels pose different kind of relevance compared to patients with well-functioning implants. If a patient with bilateral implants had undergone a unilateral revision we included only measurements taken whilst both implants were still in situ. Selection of patients was based only on initial WB metal ion levels, follow-up time and availability of measurements.

In center 1, 406 BHRs (357 patients) were implanted between January 2001 and February 2012. All patients have been referred for whole blood (WB) cobalt (Co) and chromium (Cr) measurement and clinical outcome was assessed using the Oxford Hip Score (OHS). All patients with elevated (>5 ppb) metal ion measurements or with any kind of hip related symptoms were referred for cross-sectional imaging using MRI (16). Current protocol involves follow-up every two-years, which includes WB Co and Cr, and OHS assessment. If the patient became symptomatic or metal ion levels were above the 5 ppb threshold, patients underwent cross-sectional imaging and had an appointment with a consultant orthopaedic surgeon.

Also in center 1, 497 ASR HRs (415 patients) were implanted between March 2003 and December 2009. Early surveillance and investigation of these patients has been described in detail previously (17). After early intense screening, surveillance of ASR patients was changed in 2017 to that used for BHR patients.

In center 2, there have been 3,990 BHRs (3,276 patients) implanted up until 30th April 2019. The surveillance and investigation of these patients has been described in detail previously (9–11). In summary, all symptomatic patients underwent WB metal ion sampling, radiographs and cross-sectional imaging with either MRI and/or ultrasound. Asymptomatic patients with certain factors (such as female patients, males with small BHR head sizes, bilateral MoM implants, radiographic abnormalities) also underwent blood metal ion sampling, with targeted cross-sectional imaging used if ions were raised and/or symptoms developed. All investigated patients remain under regular surveillance, typically annually. No ASRs were implanted in center 2.

Patient selection

In center 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial Wb Co or Cr above 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore excluded. Of the remaining patients, three or more blood metal ion level measurements were available for 194 BHR patients (227 hips) with follow-up of more than 10 years (Figure 1). Similarly, of 415 ASR patients (497 hips), 54 patients (68 hips) had initial Wb Co or Cr above 7 ppb, (50 of 68 [74%] hips have been revised since), and were excluded. Of the remaining patients, 216 (263 hips) have undergone three or more metal ion measurements during follow-up of more than 10 years (Figure 2).

In center 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had undergone any metal ion measurements. 418 patietns (559 hips) had more than 3 measurements and 365 patients (481 hips) had initial measurement below 7 ppb. Of these 263 patients (328 hips) have undergone three or more blood metal ion level measurements with follow-up of more than 10 years (Figure 1).

Assessment of metal ion level changes

Previous studies have established implant specific thresholds in HR patients identifying those at low risk of ARMD. The externally validated threshold for Co in unilateral patients is 2.15 ppb (11). We applied the same threshold also for Cr in this study, although acknowledge this has not been formally validated, and therefore the findings for this study should focus on the Co levels in unilateral patients. For bilateral patients externally validated threshold was 5.5 ppb for maximum of Co or Cr (11). We applied this threshold also separately for both Co and Cr values. In this study, we did two separate analyses to identify changes in metal ion measurements after 10 years or more follow-up using these thresholds. Firstly, we investigated if each repeated measurement was more than 2.15 ppb for unilateral patients while initial measurements in the first decade had been less than 2.15 ppb. In bilateral patients we assessed change from below 5.5 ppb to above 5.5 ppb. This was termed the absolute analysis since changes were assessed against the initial absolute level (Figure 3A). Secondly, we recorded relative changes or measurement-to-measurement change of more than ±2.15 ppb or ±5.5 ppb for both implant groups. This was termed the relative analysis since we only assessed changes from measurement to measurement regardless of initial metal ion level (Figure 3B). “Net change” was defined as the total sum of changes. This means that if the patient had, for example, both -2.15 ppb and +2.15 ppb changes, there was no “net change”. Subgroup analysis was done in unilateral patients with a femoral head size under 50 mm.

Statistics

Continuous variables were compared using Welch´s t-test when appropriate. Comparison of continuous variables across three groups (BHRs in center 1, BHRs in center 2 and ASRs) was done with analysis of variance. Proportions across two or three groups were compared using the Chi-squared test with Yates correction. Association between time in-situ and metal ion levels was done with generalized least squares linear model with random intercepts and fixed slopes. Full description of this process is available in Supplement 1. Analysis was done with RStudio 1.2.5033.

Results

The final BHR study cohort included 359 patients with unilateral implants and 98 patients with bilateral implants totaling 457 patients with 555 hips. There was a notable difference between the institutions regarding distribution of femoral head size (Table 1). The ASR cohort included 169 patients with unilateral implants and 47 patients with bilateral implants totaling 263 hips. In total there were 2743 WB metal ion measurements, of which 1645 had been done 10 or more years after the index operation.

Absolute changes

Absolute changes in relation to established implant specific thresholds are shown in Table 2. An increase above implant specific threshold during second decade was seen in 10.8%-28.4% of the unilateral patients. In bilateral patients increase was seen in 4.3%-11.8%.

Relative changes

Table 3 shows the prevalence of ±2.15, ±5.5 ppb measurement-to-measurement changes and “net change” in metal ion levels performed after 10 years follow-up. Change of +2.15 ppb in either Co or Cr levels was seen in 3.6-10% of unilateral BHR and ASR patients overall, however “net change” was even less common. Change of +5.5 ppb were seen in 1.4-2.5% of unilateral BHR and

ASR patients overall, however "net change" was again even less common. In bilateral patients, +5.5 ppb change was also rarely seen (0 to 2.1%).

Time effects

Population marginal effects are shown in Supplemental Figures 1-4. In center 1, Co levels reduced with time since index operation in patients with unilateral BHR implants and also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1A and 2A). Bilateral BHR patients also show metal ion levels reducing with time in the second decade (Supplemental Figure 4A). In center 2, metal ion levels increased with time since index operation in patients with unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1B and 2B). Bilateral BHR patients showed a plateau (Supplemental figure 4B). In the ASR patients, increasing trends in metal ion levels with time were not seen (Supplemental Table 2, Supplemental Figure 3).

Discussion

Hundreds of thousands of patients with HRs are still in the need of regular follow-up. Studies assessing the roles for blood metal ion measurements and cross-sectional imaging are urgently needed to determine if regular monitoring for all HR patients is truly needed. We aimed to assess the population level changes in blood metal ion levels into the second decade. Patients at risk of failure and in need of closer follow-up, namely those with abnormal wear due to conditions such as edge-loading, are relatively straightforward to detect with initial screening. Our focus was especially on those patients having acceptable ion levels at initial screening and no abnormalities, who have been referred for more regular follow-up.

Generally, metal ion levels remained stable during the second decade of the implant lifetime. Relative changes (measurement-to-measurement) exceeding +5.5 ppb were uncommon. Major changes were not seen even in patients with small femoral head diameter implants. In center 2, one sixth (17.2%) of BHR patients had a relative increase of more than 2.15 ppb in WB Cr but only a few percent had an increase of greater than 5.5 ppb. A change in measurement-to-measurement in Wb Co was seen in 9.1% of BHR patients in center 2. Very similar results were reported by Van Der Straeten et al. who reported 4% prevalence with an increase of more than 2.5 ppb for serum Co at ten years follow-up (18). Overall prevalence in our study with a +2.15 ppb change in WB Co was 5%.

Absolute changes in relation to fixed levels were similar to those seen in relative or measurement-to-measurement changes. We considered 2.15 ppb to be a clinically meaningful threshold for unilateral patients and 5.5 ppb for bilateral patients as per previous validation studies of these clinical thresholds (11). A change from below to above the threshold was seen in 4.3% to 28.4% and this was most common in patients with unilateral implants. Up to a quarter of BHR patients had elevation of metal ion levels above the previously established threshold by the second decade, however the clinical significance of this requires further follow-up.

Ion levels had negative association with time in one study center similar to that reported by Van Der Straeten et al, although they analyzed only unilateral patients (18). deSouza et al also reported results of serial metal ion measurements in a cohort of 53 patients with Corin HR implants (19). They reported a slightly increasing trend in metal ion levels at ten-year follow-up. We noticed a decreasing trend also in bilateral patients which is a novel finding. These temporal effects were center dependent since associations were positive in our other study center. However, it is important to see that these changes are negligible and even the upper limit of the confidence interval around these estimates remains below 5 ppb.

Differences in metal ion trends between the study centers may be related to two separate reasons. It is likely that the threshold for revision surgery due to ARMD differs between the study centers (20). Elevation in metal ion levels is always a relative indication for revision surgery but usually other factors such as symptoms and cross-sectional imaging findings are also considered as well. There are no universal criteria for ARMD revision due to heterogeneity in clinical manifestation. It is therefore reasonable to assume that metal ion levels are valued differently in decision-making between study centers and hence different population trends are observed. It is of importance, however, that regardless of these varying indications the observed trends are not important from a clinical perspective.

ASR HR has been reported to have the poorest survival of all HR implant designs (4,5). Interestingly, we observed decreasing population trends with time since index operation in metal ion levels in both unilateral and bilateral patients. Relative and absolute changes during the second decade were rare and similar to those seen in BHRs. The revision rate of ASR HRs in Center 1 has been approximately 30% at 10 years. Hence our results suggest that intense screening and high revision rates have resulted in a situation where the majority of non-revised ASR HR patients have steady state wear and metal ion trends are similar to those seen in BHRs.

The main strength of our multicenter study is the large number of patients with the largest number of analyzed metal ion measurements to date which extend into the second decade. The main limitation in our study is selection bias. All operated patients have not undergone regular metal ion measurements and some patients have only one or two measurements. In Center 2 many BHR patients have no metal ion measurements at all. This is because Center 2 have a large cohort of male BHR patients who are asymptomatic and were not included in the recall for monitoring until 2017. The BHR patients who have been monitored regularly at Center 2 are therefore the symptomatic patients, female patients and male patients with head sizes ≤46 mm, all of whom are at higher risk of ARMD than the unmonitored cohort of male asymptomatic patients who are likely to have low levels of metal ions. Metal ion trends were inferior in the BHR group which may seem counterintuitive and biased. We did not, however, aim to predict theoretical behavior of metal ion levels. It is clear that implants with poor track-record have high revision rates, such as 30% in the ASR cohort in our study. Hence our results must be seen from pragmatic view: what is the behavior of blood metal ion levels in well functioning implants not initially needing revision.

Overall our results for BHR patients show that if initial blood metal ion measurements during the first decade are acceptable, the probability is high that ion levels will remain low in the second decade. This also holds true for ASR patients, assuming a significant revision rate similar to the 30% seen in our study group. These findings have major implications for the present worldwide regular surveillance for HR patients. Regular metal ion measurements (i.e. annual) therefore do not seem reasonable if the initial values are below validated thresholds. We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for HR patients since only minor changes were seen after 10-year follow-up. Regulatory guidance stratifying implant surveillance based solely on femoral head size does not seem useful with the BHR and ASR given temporal metal ion changes.

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Table 1: Comparison study groups between institutions.

			BHR cohort			**ASR cohort**	**p-value for three group difference**
			Center 1	Center 2	p-value for difference		
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<.0001	54.3 (9.4)	<.0001
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	.30	54.3 (8.3)	0.09
	Bilateral - second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	.84	54.6 (8.4)	0.93
Gender	Unilateral	Males	110	31	<.0001	117	<.0001
		Females	51	167		52	
	Bilateral	Males	24	8	<.0001	36	<.0001
		Females	9	57		11	
Femoral diameter	Unilateral	<43mm	3	48	<.0001	2	<.0001
		44-45mm	1	0		7	
		46-47mm	28	100		25	
		48-49mm	1	0		14	
		50-51mm	51	38		24	
		52-53mm	58	11		46	
		54-55mm	19	1		26	
		56-57mm	0	0		18	
		58-59mm	0	0		5	
		≥60mm	0	0		2	
	Bilateral	<43mm	0	27		2	
		44-45mm	0	3		4	
		46-47mm	13	69		11	
		48-49mm	0	0		9	
		50-51mm	25	24		11	
		52-53mm	0	1		21	

54-55mm	14	6	19
56-57mm	0	0	9
58-59mm	14	0	7
>60mm	0	0	1

Table 2: Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	**Patients with at least one measurement above 2.15 ppb during 2nd decade**
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	**Patients with at least one measurement above 5.5 ppb during 2nd decade**
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

Table 3: Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. Small diameter means <50 mm head size.

			All BHR			Small diameter BHR			ASR	
			Overall	Center 1	Center 2	Overall	Center 1	Center 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb "net change"	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb "net change"	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
	Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)	2 (4.2%)
		-2.15 ppb change	10 (2.8%)	3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)
		+5.5 ppb change	6 (1.7%)	2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)
		-5.5 ppb change	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
		+2.15 ppb "net change"	31 (8.6%)	1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)
		+5.5 ppb "net change"	5 (1.4%)	1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)
Bilateral	Cobalt	+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)	
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb "net change"	(0%)	(0%)	(0%)				1 (2.1%)	
		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
	Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)				2 (4.3%)	
		-2.15 ppb change	5 (5.1%)	0 (0%)	5 (7.7%)				0 (0%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				0 (0%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb "net change"	5 (5.1%)	0 (0%)	5 (7.7%)				2 (4.3%)	
		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)				0 (0%)	

Figures

Figure 1: Flow chart for BHR patients

Figure 2: Flow chart for ASR patients

Figure 3: Explanation for A) absolute and B) relative change used in the analyses

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.

Long-term changes in blood metal ion levels in patients with hip resurfacing implants: implications for patient surveillance after ten10-years follow-up

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Abstract

Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce.

Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with more than≥ 10 years follow-up and repeated blood metal ion measurements were identified at two 2 large specialist European arthroplasty centres. After excluding patients with initial metal ion levels above >7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.

Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt = 15.6%), unilateral ASR (cobalt = 13.8%), bilateral BHR (cobalt = 8.2%, chromium = 11.8%), bilateral ASR (cobalt = 8.5%, chromium = 4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar.

Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.

Keywords

Chrome, cobalt, follow-up, hip resurfacing, : metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt

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Introduction

High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip replacements although some implants have demonstrated relatively good survival in the longer-term in national joint registries.[1–4] (1,2) (3,4).

Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have been published.[2,5–7] (2,5–7). The main issues for following up patients with MoM hips include the risk stratification of patients, the frequency of follow-up assessments, and the actual screening methods to use. In practice, the majority of patients receive blood metal ion testing with some form of hip imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous external validation which showed patients below these defined thresholds have a low risk of adverse reaction to metal debris (ARMD).[8–10] (8–10). The evidence-base for the guidelines are still limited, with clear differences in the recommendations made by each regulatory authority.[2] (2). The cost-effectiveness of these guidelines has also been questioned.[11] (11).

Most patients with their hip resurfacing (HR) still *in situ* are in the second decade of the implant lifetime.[4,5,13–15] (4,5,13–15). However, no large studies have investigated how blood metal ion levels change in the longer term, especially during the second decade after implantation. Most current surveillance guidelines have no temporal stratification.[3,6,8] (3, 6, 8). Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime are needed to clarify the specific role blood metal ion measurements play in the longer- -term follow-up of MoM HR patients. Specifically, more research is needed on the patients with initially acceptable metal ion levels. Patients with initially high metal ions are not an issue since these patients clearly need close surveillance, more thorough diagnostic work-up and possible evaluation for revision.[20] (20).

We assessed patients with two 2 commonly used MoM HR implant designs (Birmingham Hip Resurfacing [BHR] and Articular Surface Replacement [ASR]) implanted at two 2 specialist arthroplasty centres. The study aims were to determine: (1) the percentage of patients with initial blood metal ion levels below previously devised thresholds whose subsequent metal ion levels were above these thresholds during the second decade; (, 2) the prevalence of ±2.15 parts per billion (ppb) and ±5.5 ppb changes in the long-term in serial whole blood metal ion levels;, and (3) how blood metal ion levels change with time in patients with repeated metal ion measurements.

Materials

Study populations

A cohort study of patients with BHR and ASR MoM HRs implanted at two 2 large specialist European arthroplasty centres was performed. All patients with either BHR or ASR implants and ≥3three or more blood metal ion measurements during a follow-up of more than 10 years were included for study analyses. From these patients we excluded those who had first metal ion levels higher than 7 ppb.[7] (7). Focus in our study was patients with initially acceptable metal ion levels since these patients are under frequent surveillance and in the need of repeated metal ion measurements. Patients with initially elevated ion levels are usually referred for closer follow-up and diagnostic work-up and changes in metal levels pose different kind of relevance compared to patients with well-functioning implants. If a patient with bilateral implants had undergone a unilateral revision, we included only measurements taken whilst both implants were still *in situ*. Selection of patients was based only on initial WB (whole blood) metal ion levels, follow-up time and availability of measurements.

In C~~c~~entre~~er~~ 1, 406 BHRs (357 patients) were implanted between January 2001 and February 2012. All patients have been referred for whole blood (WB) cobalt (Co) and chromium (Cr) measurement and clinical outcome was assessed using the Oxford Hip Score (OHS). All patients with elevated (>5 ppb) metal ion measurements or with any kind of hip~~-~~-related symptoms were referred for cross-sectional imaging using magnetic resonance imaging (MRI).[16] ~~(16).~~ Current protocol involves follow-up every ~~two~~ 2 years, which includes WB Co and Cr, and OHS assessment. If the patient became symptomatic or metal ion levels were above the 5 ppb threshold, patients underwent cross-sectional imaging and had an appointment with a consultant orthopaedic surgeon.

Also in C~~c~~entre~~er~~ 1, 497 ASR HRs (415 patients) were implanted between March 2003 and December 2009. Early surveillance and investigation of these patients has been described in detail previously.[17] ~~(17).~~ After early intense screening, surveillance of ASR patients was changed in 2017 to that used for BHR patients.

In ~~c~~Cent~~e~~re 2, there have been 3~~,~~990 BHRs (3~~,~~276 patients) implanted up until 30th April 2019. The surveillance and investigation of these patients has been described in detail previously.[9–11] ~~(9–11).~~ In summary, all symptomatic patients underwent WB metal ion sampling, radiographs and cross-sectional imaging with either MRI and/or ultrasound. Asymptomatic patients with certain factors (such as female patients, males with small BHR head sizes, bilateral MoM implants, radiographic abnormalities) also underwent blood metal ion sampling, with targeted cross-sectional imaging used if ions were raised and/or symptoms developed. All investigated patients remain under regular surveillance, typically annually. No ASRs were implanted in ~~c~~Cent~~e~~re ~~r~~ 2.

Patient selection

In C~~c~~ent~~re~~re~~er~~ 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial WB~~b~~ Co or Cr above 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore excluded. Of the remaining patients, ≥3 ~~three or more~~ blood metal ion level measurements were available for 194 BHR patients (227 hips) with follow-up ~~of more than~~> 10 years (Figure 1). Similarly, of 415 ASR patients (497 hips), 54 patients (68 hips) had initial WB~~b~~ Co or Cr above 7 ppb, (50 of 68 [74%] hips have been revised since)~~,~~ and were excluded. Of the remaining patients, 216 (263 hips) have undergone ≥3 ~~three or more~~ metal ion measurements during follow-up ~~of more than~~> 10 years (Figure 2).

[**Figure 1**. Flow chart for BHR patients.]

[**Figure 2**. Flow chart for ASR patients.]

In C~~c~~ent~~e~~re 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had undergone any metal ion measurements. 418 ~~patietns~~patients (559 hips) had ~~more than~~> 3 measurements and 365 patients (481 hips) had initial measurement ~~below~~ <7 ppb. Of these 263 patients (328 hips) have undergone ≥3 ~~three or more~~ blood metal ion level measurements with follow-up of more than≥ 10 years (Figure 1).

Assessment of metal ion level changes

Previous studies have established implant specific thresholds in HR patients identifying those at low risk of ARMD. The externally validated threshold for Co in unilateral patients is 2.15 ppb.[11] (11). We applied the same threshold also for Cr in this study, although acknowledginge this has not been formally validated, and therefore the findings for this study should focus on the Co levels in unilateral patients. For bilateral patients externally validated threshold was 5.5 ppb for maximum of Co or Cr.[11] (11). We applied this threshold also separately for both Co and Cr values. In this study, we did two 2 separate analyses to identify changes in metal ion measurements after 10 years or more follow-up using these thresholds. Firstly, we investigated if each repeated measurement was more than> 2.15 ppb for unilateral patients while initial measurements in the first decade had been less than< 2.15 ppb. In bilateral patients we assessed change from below <5.5 ppb to above >5.5 ppb. This was termed the absolute analysis since changes were assessed against the initial absolute level (Figure 3(A)). Secondly, we recorded relative changes or measurement-to-measurement change of more than ±2.15 ppb or ±5.5 ppb for both implant groups. This was termed the relative analysis since we only assessed changes from measurement to measurement regardless of initial metal ion level (Figure 3(B)). "Net change" was defined as the total sum of changes. This means that if the patient had, for example, both -2.15 ppb and +2.15 ppb changes, there was no "net change". Subgroup analysis was done in unilateral patients with a femoral head size under <50 mm.

[**Figure 3**. Explanation for (A) absolute and (B) relative change used in the analyses.]

Statistics

Continuous variables were compared using Welch´s *t*-test when appropriate. Comparison of continuous variables across three groups (BHRs in C~~c~~ent~~e~~re 1, BHRs in C~~c~~ent~~e~~re 2 and ASRs) was done with analysis of variance. Proportions across ~~two or three~~2 or 3 groups were compared using the c~~C~~hi-square~~d~~ test with Yates correction. ~~-~~Association between time *in-~~-~~ situ* and metal ion levels was done with generalis~~z~~ed least squares linear model with random intercepts and fixed slopes. Full description of this process is available in Supplement 1. Analysis was done with RStudio 1.2.5033.

Results

The final BHR study cohort included 359 patients with unilateral implants and 98 patients with bilateral implants totaling 457 patients with 555 hips. There was a notable difference between the institutions regarding distribution of femoral head size (Table 1). The ASR cohort included 169 patients with unilateral implants and 47 patients with bilateral implants totaling 263 hips. In total there were 2743 WB metal ion measurements, of which 1645 had been done ≥10 ~~or more~~ years after the index operation.

Absolute changes

Absolute changes in relation to established implant specific thresholds are shown in Table 2. An increase above implant specific threshold during second decade was seen in 10.8~~%-~~–28.4% of the unilateral patients. In bilateral patients increase was seen in 4.3–~~%-~~11.8%.

Relative changes

Table 3 shows the prevalence of ±2.15, ±5.5 ppb measurement-to-measurement changes and “net change” in metal ion levels performed after 10 years follow-up. Change of +2.15 ppb in either Co or Cr levels was seen in 3.6–~~-~~10% of unilateral BHR and ASR patients overall, however “net change” was even less common. Change of +5.5 ppb were seen in 1.4–~~-~~2.5% of unilateral BHR and ASR patients overall, however “net change” was again even less common. In bilateral patients, +5.5 ppb change was also rarely seen (0~~ to ~~–2.1%).

Time effects

Population marginal effects are shown in Supplemental Figures 1–~~-~~4. In C~~c~~ent~~e~~re 1, Co levels reduced with time since index operation in patients with unilateral BHR implants and also in patients with small headed BHR implants (Supplemental Table 1~~,~~) (Supplemental Figures 1(A) and 2(A)). Bilateral BHR patients also show metal ion levels reducing with time in the second decade (Supplemental Figure 4(A)). In C~~c~~ent~~e~~re 2, metal ion levels increased with time since index operation in patients with unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table 1)~~, ~~(Supplemental

Figures 1(B) and 2(B)). Bilateral BHR patients showed a plateau (Supplemental Ffigure 4(B)). In the ASR patients, increasing trends in metal ion levels with time were not seen (Supplemental Table 2,) (Supplemental Figure 3).

Discussion

Hundreds of thousands of patients with HRs are still in the need of regular follow-up. Studies assessing the roles for blood metal ion measurements and cross-sectional imaging are urgently needed to determine if regular monitoring for all HR patients is truly needed. We aimed to assess the population level changes in blood metal ion levels into the second decade. Patients at risk of failure and in need of closer follow-up, namely those with abnormal wear due to conditions such as edge-loading, are relatively straightforward to detect with initial screening. Our focus was especially on those patients having acceptable ion levels at initial screening and no abnormalities, who have been referred for more regular follow-up.

Generally, metal ion levels remained stable during the second decade of the implant lifetime. Relative changes (measurement-to-measurement) exceeding +5.5 ppb were uncommon. Major changes were not seen even in patients with small femoral head diameter implants. In Ccentere 2, ⅙ one sixth (17.2%) of BHR patients had a relative increase of more than> 2.15 ppb in WB Cr but only a few percent had an increase of greater than> 5.5 ppb. A change in measurement-to-measurement in WBb Co was seen in 9.1% of BHR patients in cCentere 2. Very similar results were reported by Van Der Straeten et al.[18] who reported 4% prevalence with an increase of more than >2.5 ppb for serum Co at ~~ten~~ 10 years follow-up ~~(18)~~. Overall prevalence in our study with a +2.15 ppb change in WB Co was 5%.

Absolute changes in relation to fixed levels were similar to those seen in relative or measurement-to-measurement changes. We considered 2.15 ppb to be a clinically meaningful threshold for unilateral patients and 5.5 ppb for bilateral patients as per previous validation studies of these clinical thresholds.[11] ~~(11).~~ A change from below to above the threshold was seen in 4.3~~% to~~–28.4% and this was most common in patients with unilateral implants. Up to a ¼~~quarter~~ of BHR patients had elevation of metal ion levels above the previously established threshold by the second decade, however the clinical significance of this requires further follow-up.

Ion levels had negative association with time in ~~one~~ 1 study cent~~er~~re similar to that reported by Van Der Straeten et al.~~,~~[18] although they analy~~s~~zed only unilateral patients ~~(18)~~. deSouza et al.[19] also reported results of serial metal ion measurements in a cohort of 53 patients with Corin HR implants ~~(19)~~. They reported a slightly increasing trend in metal ion levels at 10-~~ten-~~year follow-up. We noticed a decreasing trend also in bilateral patients which is a novel finding. These temporal effects were cent~~er~~re dependent since associations were positive in our other study ~~center~~centre. However, it is important to see that these changes are negligible and even the upper limit of the confidence interval around these estimates remains ~~below~~ <5 ppb.

Differences in metal ion trends between the study cent~~er~~res may be related to ~~two~~ 2 separate reasons. It is likely that the threshold for revision surgery due to ARMD differs between the study cent~~er~~res.[20] ~~(20).~~ Elevation in metal ion levels is always a relative indication for revision surgery but usually other factors such as symptoms and cross-sectional imaging findings are also considered as well. There are no universal criteria for ARMD revision due to heterogeneity in clinical manifestation. It is therefore reasonable to assume that metal ion levels are valued differently in decision-making between study centeres and hence different population trends are observed. It is of importance, however, that regardless of these varying indications the observed trends are not important from a clinical perspective.

ASR HR has been reported to have the poorest survival of all HR implant designs.[4,5] (4,5). Interestingly, we observed decreasing population trends with time since index operation in metal ion levels in both unilateral and bilateral patients. Relative and absolute changes during the second decade were rare and similar to those seen in BHRs. The revision rate of ASR HRs in CCentere 1 has been approximately 30% at 10 years. Hence our results suggest that intense screening and high revision rates have resulted in a situation where the majority of non-revised ASR HR patients have steady state wear and metal ion trends are similar to those seen in BHRs.

The main strength of our multicentere study is the large number of patients with the largest number of analyzsed metal ion measurements to date which extend into the second decade. The main limitation in our study is selection bias. All operated patients have not undergone regular metal ion measurements and some patients have only one or two1 or 2 measurements. In CenterCentre 2 many BHR patients have no metal ion measurements at all. This is because CenterCentre 2 have a large cohort of male BHR patients who are asymptomatic and were not included in the recall for monitoring until 2017. The BHR patients who have been monitored regularly at CenterCentre 2 are therefore the symptomatic patients, female patients and male patients with head sizes ≤46 mm, all of whom are at higher risk of ARMD than the unmonitored cohort of male asymptomatic patients who are likely to have low levels of metal ions. Metal ion trends were inferior in the BHR group which may seem counterintuitive and biased. We did not, however, aim to predict theoretical behaviour of metal ion levels. It is clear that implants with poor track-record have high revision rates, such as 30% in the ASR cohort in our study. Hence our results must be seen from pragmatic view: what is the behaviour of blood metal ion levels in well-functioning implants not initially needing revision.

Overall, our results for BHR patients show that if initial blood metal ion measurements during the first decade are acceptable, the probability is high that ion levels will remain low in the second decade. This also holds true for ASR patients, assuming a significant revision rate similar to the 30% seen in our study group. These findings have major implications for the present worldwide regular surveillance for HR patients. Regular metal ion measurements (i.e. annual) therefore do not seem reasonable if the initial values are below validated thresholds. We recommend less frequent blood metal-ion measurements are needed (every 3 ~~to~~ –5 years) for HR patients since only minor changes were seen after 10-year follow-up. Regulatory guidance stratifying implant surveillance based solely on femoral head size does not seem useful with the BHR and ASR given temporal metal ion changes.

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Supplemental material

Supplemental material for this article is available online.

(**Supplemental Figure 1.** Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. (A) Centre 1, (B) Centre 2.)

(**Supplemental Figure 2.** Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. (A) Centre 1, (B) Centre 2.)

(**Supplemental Figure 3.** Population marginal effect of time on log-transformed metal ion levels in (A) unilateral ASR and (B) unilateral ASR with small femoral diameter (<50 mm).)

(**Supplemental Figure 4.** Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, (A) Centre 1, (B) Centre 2 and (C) bilateral ASR patients.)

(**Supplemental Table 1.** Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in BHR patients. AIC = Akaike´s information criteria. Small diameter means <50 mm head size.)

(**Supplemental Table 2.** Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in ASR patients. AIC = Akaike´s information criteria. Small diameter means <50 mm head size.)

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Table 1~~:~~. Comparison study groups between institutions.

			BHR cohort			ASR cohort	**P~~p-~~ value for ~~three~~ 3 group difference**
			Centre~~er~~ 1	Centre~~er~~ 2	*P* ~~p~~-value for difference		
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<0.0001	54.3 (9.4)	<0.0001
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	0.30	54.3 (8.3)	0.09
	Bilateral – second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	0.84	54.6 (8.4)	0.93
Gender	Unilateral	Males	110	31	<0.0001	117	<0.0001
		Females	51	167		52	
	Bilateral	Males	24	8	<0.0001	36	<0.0001
		Females	9	57		11	
Femoral diameter	Unilateral	<43~~mm~~ mm	3	48	<0.0001	2	<0.0001
		44–45~~mm~~ mm	1	0		7	
		46–47~~mm~~ mm	28	100		25	
		48–49~~mm~~ mm	1	0		14	
		50–51~~mm~~ mm	51	38		24	
		52–53~~mm~~ mm	58	11		46	
		54–55~~mm~~ mm	19	1		26	
		56–57~~mm~~ mm	0	0		18	
		58–59~~mm~~ mm	0	0		5	
		≥60~~mm~~ mm	0	0		2	

Bilateral	<43 mm	0	27		2
	44–45 mm	0	3		4
	46–47 mm	13	69		11
	48–49 mm	0	0		9
	50–51 mm	25	24		11
	52–53 mm	0	1		21
	54–55 mm	14	6		19
	56–57 mm	0	0		9
	58–59 mm	14	0		7
	>60 mm	0	0		1

BHR, Birmingham Hip Resurfacing; ASR, SD, standard deviation.

Table 2:. Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	Patients with at least one 1 measurement above 2.15 ppb during 2nd decade
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	**Patients with at least one 1 measurement above 5.5 ppb during 2nd decade**
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

BHR, Birmingham Hip Resurfacing; ASR, Articular Surface Replacement.

Table 3~~:~~. Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. ~~Small diameter means <50 mm head size.~~

			All BHR			Small diameter BHR			ASR	
			Overall	Cent~~e~~re 1	Centre~~er~~ 2	Overall	Cent~~e~~re 1	Centre~~er~~ 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb “net change”	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb “net change”	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
	Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)	2 (4.2%)
		-2.15 ppb change	10 (2.8%)	3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)
		+5.5 ppb change	6 (1.7%)	2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)
		-5.5 ppb change	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
		+2.15 ppb “net change”	31 (8.6%)	1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)
		+5.5 ppb “net change”	5 (1.4%)	1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)
Bilateral	Cobalt	+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)	
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb “net change”	(0%)	(0%)	(0%)				1 (2.1%)	

		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)	1 (2.1%)
	Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)	2 (4.3%)
		-2.15 ppb change	5 (5.1%)	0 (0%)	5 (7.7%)	0 (0%)
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)	0 (0%)
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		+2.15 ppb "net change"	5 (5.1%)	0 (0%)	5 (7.7%)	2 (4.3%)
		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)	0 (0%)

BHR, Birmingham Hip Resurfacing; ASR, Articular Surface Replacement.

Note: Small diameter means <50 -mm head size.

Figures

Figure 1: Flow chart for BHR patients

Figure 2: Flow chart for ASR patients

Figure 3: Explanation for A) absolute and B) relative change used in the analyses

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.