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ORIGINAL ARTICLE

Metal-on-Metal Hip Joint Prostheses: a Retrospective Case Series Investigating the Association of Systemic Toxicity with Serum Cobalt and Chromium Concentrations

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Abstract

Introduction There have been concerns about prosthesis failure and the potential for systemic toxicity due to release of cobalt and chromium from metal-on-metal hip joint prostheses (MoM-HP). There is conflicting evidence on whether there is a correlation between higher cobalt and chromium concentrations and systemic toxicity.

Methods We undertook a retrospective review of consecutive patients with MoM-HP referred for outpatient review in toxicology clinics in London, UK, and in the USA recorded in the Toxicology Investigators Consortium (ToxIC) Registry from June 2011 to June 2015.

Results Thirty-one cases were identified; the median (IQR) serum cobalt concentration was 10.0 (3.8–32.8) mcg/L, and the median (IQR) serum chromium concentration was 6.9 (3.7–18.7) mcg/L. Twenty-three (74.2%) had symptoms, most commonly lethargy, hearing loss, and tinnitus. The odds ratios of symptomatic/asymptomatic patients for metal ion concentrations above/below 7 mcg/L were 1.87 (95% CI 0.37–9.57, $p = 0.45$) and 0.60 (95% CI 0.10–3.50, $p = 0.57$) for cobalt and chromium, respectively. Two (6.5%) patients with systemic cobalt toxicity had median (IQR) serum cobalt concentrations significantly higher than those without systemic features (630.4 [397.6–863.2] mcg/L versus 9.8 [2.9–16.4] mcg/L; $p = 0.017$). However, overall, there were no differences between cobalt ($p = 0.38$) or chromium ($p = 0.92$) concentrations between symptomatic and asymptomatic patients and no clinical features or investigation results correlated with cobalt or chromium concentration.

Conclusion Two (6.5%) of 31 individuals referred for assessment of MoM-HP were diagnosed with systemic cobalt toxicity. However, despite a high prevalence of reported symptoms, neither symptoms nor investigation results correlated with serum cobalt or chromium concentrations.

Keywords Metal-on-metal hip prosthesis · Chromium · Cobalt · Toxicity

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Introduction

The first total hip joint replacements date back to the late nineteenth century, constructed variously from materials such as ivory, glass, plaster, and metal [1]. From the 1930s, metal-on-metal hip joint prostheses (MoM-HP) became increasingly

common, though they became superseded from the 1960s by other materials such as polyethylene and ceramic [2, 3]. Early MoM-HP had been found to be associated with rare metal hypersensitivity reactions, thought to be predominantly due to cobalt, but also nickel and chromate [4–6]. However, they experienced a resurgence in the 1980s and 1990s, with second- and third-generation MoM-HP thought to produce less abrasive wear than their metal-on-ceramic or metal-on-polyethylene (MoC-HP and MoP-HP) counterparts and hence provide a more stable and durable prosthesis [6, 7]. Approximately one million MoM-HP have since been implanted worldwide [8, 9]. Over the past decade, however, there has been significant concern about the high failure rate of more recent MoM-HP due to tribologic wear (wear related to friction), resulting in prosthetic loosening and a subsequent increase in need for their early revision [10–14], culminating in a worldwide recall of many MoM-HP [15]. In the UK, this led to the Medicines & Healthcare products Regulatory Agency (MHRA) establishing a guideline for patients with MoM-HP in whom a concentration of cobalt or chromium of 7 mcg/L is the threshold recommended for further investigation of prosthetic failure and/or adverse local tissue reactions (10). In the USA, the Food and Drug Administration (FDA) recommends routine monitoring of those with MoM-HP, but does not provide any specific guidance regarding metal ion concentrations for further investigation [16].

There has been increasing interest in the potential for systemic toxicity associated with MoM-HP due to release of heavy metal ions, specifically cobalt and chromium, from accelerated wear [9, 17]. Cobalt, in particular, has been documented to cause endocrine, neurological, haematological, and cardiac effects [3]; the concern surrounding chromium is primarily due to its association with malignancies from inhalation of its hexavalent form, which MoM-HP do not contain [18–21]. Indeed, a recent review did not show a correlation between symptom severity and chromium concentrations, whereas it did demonstrate an association with cobalt concentrations [22].

Bradberry et al. reviewed the published cases of systemic cobalt toxicity to date [23]. They reported 18 cases published up to 2014 and described three main categories of toxicity: neuro-ocular (14 cases), cardiac (11 cases), and thyroid (9 cases). Those who had received a metal-containing revision of a previously failed ceramic prosthesis (10 cases) had a higher median peak blood cobalt concentration, 506 (range 353–6521) mcg/L, than those with primary MoM-HP (8 cases), 34.5 (range 13.6–398.6) mcg/L [23]. After reviewing the cases and proposing criteria to determine whether these patients were likely to be suffering from cobalt-related disease, they considered that the systemic features in ten of the 18 cases were likely associated with cobalt exposure; all ten had a peak blood cobalt concentration greater than 250 mcg/L; eight of these ten had had a previous ceramic prosthesis [23]. It is thought that previous ceramic implants may predispose to increased metal ion release from subsequent MoM-HP due to abrasion of the metal surfaces by microscopic ceramic debris [22–24]. Since this review, two further cases of cobalt-induced cardiomyopathy—one fatal—have been described [25, 26]. Peak cobalt concentrations were 189.0 mcg/L (in a primary MoM-HP) and 641.6 mcg/L in the fatal case (which had been a revision of a previous ceramic prosthesis). Whilst studies have variously reported serum or whole blood concentrations of cobalt and of chromium, they are not thought to be interchangeable [27, 28] and there is no consensus as to whether one is superior to the other [27, 29, 30]. Two recent studies have directly compared serum and whole blood concentrations of cobalt. One found a small mean difference between the two with an acceptable prediction error, from which they were able to derive a formula for conversion [27]; the other derived a conversion factor but the limit of agreement was less robust, although there was significantly less variability at higher cobalt concentrations [28].

The only report primarily focusing on systemic toxicity in patients with hip replacements was a case series of 39 patients referred to two specialist outpatient toxicology clinics in the USA, 26 of which were MoM-HP and 13 non-MoM-HP [31]. They found that patients with MoM-HP had an approximate tenfold increase in metal ion concentrations compared to non-MoM arthroplasties; however, there was no correlation between cobalt or chromium concentrations and the incidence of systemic symptoms [31]. Overall, data regarding systemic effects of cobalt released from MoM-HP remains limited to these case reports and small case series investigating its association with systemic toxicity [23, 25, 26, 31].

We describe here our experience from the UK and the USA of patients referred for outpatient clinical toxicology assessment of potential systemic toxicity related to metal ions released from MoM-HP.

Methods

A retrospective review of consecutive patients with MoM-HP was undertaken from two sources: a specialist outpatient clinical toxicology service in London, UK, which receives referrals from throughout the UK and the US Toxicology Investigators Consortium (ToxIC) Registry [32]. During the course of the study, the ToxIC Registry consisted of cases from 38 to 50 sites spread throughout the USA. Most of these sites practice primarily emergency and critical care inpatient toxicology. Approximately 7% of cases in the registry overall were due to clinic visits, with some sites having a more active outpatient practice than others.

The London service recorded its first case of referral for opinion of a patient with MoM-HP in June 2011; the ToxIC Metal-on-Metal Total Hip Arthroplasty Sub-Registry was

approved in 2013 and recorded its first cases in April 2014. Specific data was prospectively collected in the ToxIC database using a pre-specified computer-based data collection form. Data was collected on all cases, from the date of first referral to the London service and the date of inception of the ToxIC sub-registry until June 2015.

Case notes and clinical letters for all cases from the London service were reviewed and data extracted to align with the ToxIC Registry's Data Collection form (Appendix). Demographics, presenting symptoms and signs, and investigation results were recorded; for metal ion concentrations, the peak serum concentration was recorded. For cases in whom only a whole blood metal ion concentration was recorded, conversion to serum metal ion concentration was performed using formulae previously derived using regression analysis in paired samples from a series of 343 patients [27]: cobalt: [serum] = ([whole blood] − 0.34) / 0.88; chromium: [serum] = ([whole blood] − 0.14) / 0.58. Data was managed using Microsoft Excel 2011 (Microsoft® Corp, USA) and statistical analysis performed using SPSS electronic statistics package (Version 20.0, SPSS Inc., Chicago, IL, USA). Data were assessed for normality using the Shapiro-Wilk test: parametric data is presented as mean ± standard deviation (SD) and non-parametric data presented as median (inter-quartile range, IQR). Analysis between groups was performed using Fisher's exact test or the Mann-Whitney *U* test.

Participation in the ToxIC Registry is pursuant to participating institutions' institutional review board (IRB) approval and compliant with their policies and procedures. The registry has also been independently reviewed by the Western IRB. Data collection in the London centre is approved by the Trust Caldicott Guardian, and the Ethics Committee Chair has confirmed that analyses are exempt from formal ethical approval.

Results

Thirty-one cases were identified across the two databases: 17 from the ToxIC database (these cases were from nine separate sites across the USA; each of these nine sites contributed between one and six cases) and 14 from the outpatient clinical toxicology service in London. Patient characteristics are summarised in Table 1. Fourteen were male (45.2%) and the mean age of the entire cohort was 61.8 ± 12.7 years.

Of the 31 patients, 23 (74.2%) had unilateral MoM-HP and 8 (25.8%) had bilateral MoM-HP. All 31 had a cobalt concentration recorded: 24 in serum and 7 in whole blood; for these 7 patients, whole blood concentrations were converted to serum concentrations for statistical analysis using the method previously described by Smoulders et al. [27]. The median peak serum cobalt concentration was 10.0 (IQR 3.8–32.8) mcg/L. Chromium concentration was recorded in 25 cases, all in serum; the median peak serum chromium concentration was 6.9 (IQR 3.7–18.7) mcg/L. There was no difference in median concentration between those with unilateral versus bilateral MoM-HP for cobalt (10.0 [IQR 2.5–51.4] versus 10.2 [IQR 5.9–18.1] mcg/L; $p = 0.73$) or for chromium (9.1 [IQR 3.4–22.0] versus 6.7 [IQR 5.1–7.2] mcg/L; $p = 0.47$).

Clinical Features

Twenty-three (74.2%) patients were referred to assess whether their symptoms were related to cobalt and/or chromium toxicity. Of the remaining eight asymptomatic patients, four had a cobalt concentration above the Medicines and Health Products Regulatory Agency (MHRA) threshold concentration of 7 mcg/L and three had a chromium concentration above this threshold (Table 2). The odds ratio (OR) of symptomatic versus asymptomatic patients for metal ion concentrations above versus below 7 mcg/L were 1.87 (95% CI 0.37–9.57, $p = 0.45$) and 0.60 (95% CI 0.10–3.50, $p = 0.57$) for cobalt and chromium, respectively. Overall, there were no significant differences between cobalt or chromium concentrations between symptomatic and asymptomatic patients (Table 2). Although symptomatic patients with serum chromium concentration below 7 mcg/L had a statistically significantly higher serum chromium concentration ($p = 0.049$), this difference was small and not seen in either the group with serum chromium concentrations of greater than 7 mcg/L or in the overall combined serum chromium analysis (Table 2).

Table 1 Patient characteristics

	UK cohort ($n = 14$)	US cohort ($n = 17$)	p value	Entire cohort ($n = 31$)
Age (years); median (IQR)	61.0 (52.5–71.5)	62.5 (58.0–70.5)	0.67 ~	61.5 (56.0–71.5)
Male	7 (50.0%)	7 (41.2%)	0.72 #	14 (45.2%)
Unilateral MoM-HP	9 (64.3%)	14 (82.3%)	0.41 #	23 (74.2%)
Bilateral MoM-HP	5 (35.7%)	3 (17.7%)		8 (25.8%)
Median [IQR] peak cobalt concentration (mcg/L)	10.1 [5.4–36.1]	7.7 [2.4–23.0]	0.67 ~	10.0 [3.8–32.8]
Median [IQR] peak chromium concentration (mcg/L)	7.2 [4.5–16.7]	6.7 [1.6–20.4]	0.29 ~	6.9 [3.7–18.7]

Analysis between cohorts performed using ~ Mann-Whitney *U* test or # Fisher's exact test

Table 2 Serum cobalt and chromium concentrations in symptomatic versus asymptomatic patients

	≥7 mcg/L	<7 mcg/L	Overall
Cobalt			
Symptomatic	15, 16.4 (10.5–63.1)	8, 2.8 (2.3–4.8)	23, 10.3 (4.8–32.8)
Asymptomatic	4, 48.8 (11.2–107.0)	4, 1.9 (1.4–2.9)	8, 6.4 (1.9–30.7)
	19, $p = 1.00$	12, $p = 0.30$	31, $p = 0.38$
Chromium			
Symptomatic	8, 20.9 (9.9–63.4)	10, 4.2 (3.0–6.6)	18, 6.8 (4.0–16.7)
Asymptomatic	4, 20.4 (12.1–50.9)	3, 1.2 (1.1–2.2)	7, 10.7 (2.2–20.4)
	12, $p = 0.81$	13, $p = 0.049$	25, $p = 0.92$

Data presented as *n*, median (IQR) (mcg/L). Median cobalt/chromium concentrations of symptomatic versus asymptomatic patients; analysis performed using Mann-Whitney *U* test

Clinical features and investigation results of the patients are shown in Table 3. The most commonly reported symptoms were lethargy/malaise and hearing loss, followed by tinnitus. Overall, none of the reported features or investigation results correlated with cobalt or chromium concentration. Four patients had pre-existing malignancies (one each of melanoma, renal cell carcinoma, uterine cancer, and breast cancer), and one patient was diagnosed with carcinoid tumour during the follow-up process. Two (6.5%) patients were diagnosed with significant systemic cobalt toxicity; both were male, one each from the UK and US cohorts. Case 1 is a 56-year-old male from the UK cohort with bilateral MoM-HP who presented 7 years after his first MoM-HP with increasing hip pain and extreme lethargy; he also reported numbness in all extremities, but nerve conduction studies were negative. His peak serum cobalt concentration was 164.8 mcg/L and peak serum chromium level 100.2 mcg/L. He underwent revision of his bilateral MoM-HP with subsequent improvement in his symptoms and reduction in his heavy metal ion concentrations. At the time of last review in the specialist toxicology clinic—3 months after revision of his hips—his cobalt and chromium concentrations were 8.5 and 8.8 mcg/L, respectively. Case 2 is a 60-year-old male from the US cohort with a primary right-sided MoM-HP, who presented after 16 years with predominantly neurological symptoms, including numbness, tinnitus, and hearing and visual deficits. He had a peak serum cobalt concentration of 1096 mcg/L and was subsequently diagnosed with optic neuropathy and peripheral axonal neuropathy; he also developed polycythaemia and hypothyroidism after having his MoM-HP. He did not have a chromium concentration recorded. In these two patients with diagnosis of systemic cobalt toxicity, the median peak serum cobalt concentration was significantly higher than in those without cobalt toxicity (630.4 [IQR 397.6–863.2] mcg/L versus 9.8 [IQR 2.9–16.4] mcg/L; $p = 0.017$).

Twelve patients had joint magnetic resonance imaging (MRI), of whom two (16.7%) had evidence of adverse local tissue reactions; these were not related to serum cobalt or chromium concentrations (Fisher's exact test; $p = 0.45$ and $p = 0.18$, respectively). Of the five patients with hypothyroidism, three had this condition prior to their MoM-HP; hypothyroidism was recorded qualitatively and not quantitatively, and it is not known whether this worsened after surgery with MoM-HP. Ten patients had a full blood count performed, which showed a significant inverse correlation between cobalt and haemoglobin concentrations ($r^2 = -0.697$, $p = 0.025$). However, all recorded haemoglobin concentrations were within the laboratory reference range (median haemoglobin concentration 14.2 [IQR 13.35–15.125] g/dL). There was no correlation between serum cobalt or chromium ion concentrations and white cell count, platelet count, or haematocrit.

Discussion

The call for a robust and long-lasting prosthesis has seen the total hip joint replacement wax and wane through a multitude of guises. The newer generation of MoM-HP was hoped to be an answer to this; however, their increased rate of adverse local tissue reactions and prosthesis failure has resulted in their worldwide recall [10–15].

The release of cobalt and chromium ions into the bloodstream from wear and corrosion of MoM-HP has been described previously [33–36]; however, the significance of elevated concentrations in the asymptomatic patient remains unclear [9, 34–36]. A recent review demonstrated that whilst there was an association between symptom severity and blood cobalt concentrations, there was no association with chromium [22]. Chromium released from hip implants is preferentially distributed into serum and not red blood cells, and thus, the form of the chromium in the blood of these patients is in the non-toxic trivalent state [37]. Data from unexposed controls have shown baseline whole blood cobalt and chromium concentrations to be generally less than 0.5 mcg/L [9]. A more recent review of medically healthy patients following unilateral MoM-HP showed median peak cobalt concentrations in whole blood to range from 0.7 to 2.7 mcg/L and in serum from 0.7 to 7.5 mcg/L [35].

Comparatively, data for poorly functioning implants showed cobalt concentrations to be greater than 6 mcg/L, versus less than 3 mcg/L for well-functioning implants [30, 38]. For patients with bilateral MoM-HP, metal ion concentrations have been regarded to be higher than those with unilateral MoM-HP [30], with one study reporting cobalt concentrations of 2.45 and 1.71 mcg/L ($p < 0.001$) for bilateral and unilateral MoM-HP, respectively [39]. Another study of 139 patients with bilateral MoM-HP and 453 patients with unilateral MoM-HP also showed a significant difference between the two groups; their median serum cobalt concentrations were 4.2 and 2.4 mcg/L ($p < 0.001$), respectively. In comparison, however, our findings did not demonstrate any clinical or statistical difference in metal ion concentrations between these groups.

In the UK, the MHRA threshold for further investigation of potential prosthesis failure and/or local tissue reactions, including further blood tests and/or imaging, is a whole blood concentration of cobalt or chromium in patients with MoM-HP. Using this cut-off of 7 mcg/L, one case-control study of 176 patients with unilateral MoM-HP demonstrated a specificity of 89% and a sensitivity of 52% for detecting failure of MoM-HP [40]; failure was defined as patients awaiting revision with an unexplained failed MoM-HP, and controls were defined as patients who were satisfied with their hip replacement and who did not volunteer pain as a symptom [40]. Reducing the threshold for further investigation to 5 mcg/L improved sensitivity of identifying potential prosthesis failure to 63%, with a reduction in specificity to 86% [40, 41]. The current MHRA guidance remains unchanged [10]. In the USA, the FDA concludes that "there is insufficient evidence to recommend metal ion testing in [asymptomatic] patients with MoM hip implants… and the orthopaedic surgeon feels the hip is functioning properly" [42]. Regarding systemic features, the FDA makes no specific recommendations regarding metal ion testing or thresholds for concern; similarly, the European Commission concluded that there is insufficient evidence to establish critical cobalt or chromium values for systemic effects [8, 42]. The European Commission did, however, adopt the strategy outlined in the European Consensus Statement which recommends a range of 2–7 mcg/L for whole blood cobalt concentration as its threshold, in conjunction with clinical or radiological concern [8].

Recent reviews have demonstrated the potential for systemic toxicity [22, 23]; however, the overall number of cases remains small when considering the estimated million MoM-HP that have been implanted [8, 9]. Thus—whilst real—the incidence of cobalt/chromium-associated systemic toxicity with MoM-HP is likely, and understandably, subject to publication bias. A major issue at present is the lack of comparative data between symptomatic cases and asymptomatic controls. In one case series by Leikin et al., this was considered, demonstrating in a cohort of patients with varying types of hip joint prostheses that—whilst patients with MoM-HP had an approximate tenfold increase in metal ion levels than non-MoM arthroplasties—there was no correlation between cobalt or chromium concentrations and the incidence of symptoms [31].

Our results are consistent with these findings, with no correlation found between cobalt or chromium concentrations and any of the reported symptoms; similarly, no correlation was found with the incidence of hypothyroidism (Table 3). There were two cases of adverse local tissue reactions in our case series which, alongside one case each of cardiomyopathy and of polycythaemia, were only identified in patients with metal ion concentrations greater than the MHRA cut-off of 7 mcg/L. The patient with polycythaemia was one of the two in our case series diagnosed with cobalt-associated systemic toxicity. Prior to his MoM-HP, he was not polycythaemic; however, the clinical significance of his subsequent polycythaemia is uncertain. The two cases with adverse local tissue reactions confirmed on MRI had peak cobalt concentrations of 10.3 and 66.1 mcg/L. The subject with the cobalt concentration of 10.3 mcg/L (chromium concentration 10.7 mcg/L) was also the only subject with cardiomyopathy; however, this was reported as only mild dilatation of the right ventricle and of limited clinical significance. He also reported lethargy, night sweats, and mood swings; however, he had no objective findings of thyroid disease or neuropathy, and it was not thought that his symptoms or his right ventricular dilatation were related to his unilateral MoM-HP. Whilst no cases of adverse local tissue reactions or cardiomyopathy were found in patients with cobalt or chromium concentrations less than 7 mcg/L, identifying these pathologies using the MHRA cut-off as a reference point was not significant (Table 3); however, our numbers were small and may not have been sufficient to detect a true difference. Despite this, our results are consistent with published data for adverse local tissue reactions, which shows that whilst reported metal ion concentrations tend to be higher in those with such reactions, there remains a high degree of variability that does not follow a clear dose-response relationship [43]. Indeed, there were an equal number of asymptomatic patients who had metal ion concentrations greater than 7 mcg/L as there were those with concentrations less than 7 mcg/L. Furthermore, of these patients with cobalt concentrations greater than 7 mcg/L, the median peak cobalt concentration amongst asymptomatic patients was higher (48.8 [IQR 11.2–107.0] mcg/L) than in symptomatic patients (16.4 [IQR 10.5–63.1] mcg/L) (Table 2); this included two asymptomatic patients with peak cobalt concentrations of 85.1 and 172.9 mcg/L.

In our series of 31 patients, two males were diagnosed with cobalt-associated systemic toxicity. One (case 1) reported lethargy, whilst the other (case 2) had documented hypothyroidism, optic neuropathy, and peripheral axonal neuropathy; neither had a diagnosis of cardiomyopathy. In their review of systemic toxicity caused by cobaltism, Bradberry et al.

Table 3 Frequency of clinical features by cobalt and chromium concentration

	Number (% of 31)	Cobalt (n = 31)			Chromium (n = 25[a])		
		<7 mcg/L	≥7 mcg/L	p value[b]	<7 mcg/L	≥7 mcg/L	p value[b]
Clinical features							
Lethargy/malaise	9 (29.0)	4	5	0.70	4	2	0.64
Hearing loss	9 (29.0)	5	4	0.25	5	1	0.16
Tinnitus	8 (25.8)	4	4	0.68	2	2	1.00
Local pain or discomfort	5 (16.1)	2	3	1.00	2	2	1.00
Numbness/paraesthesiae	5 (16.1)	0	5	0.13	0	2	0.22
Rash	3 (9.7)	2	1	0.54	1	0	1.00
Weakness	3 (9.7)	0	3	0.26	0	2	0.22
Peripheral neuropathy	2 (6.5)	1	1	1.00	1	0	1.00
Asymptomatic	8 (25.8)	4	4	0.68	3	4	0.67
Investigations							
Hypothyroidism	5 (16.1)	3	2	0.35	2	2	1.00
Adverse local tissue reaction, on MRI	2 (6.5)	0	2	0.51	0	2	0.22
Cardiomyopathy	1 (3.2)	0	1	1.00	0	1	0.48
Polycythaemia	1 (3.2)	0	1	1.00	0	0	1.00

[a] Chromium concentration not performed in six patients

[b] Fisher's exact test

described three categories of toxicity: neuro-ocular, cardiac, and thyroid [23]. They found that all ten cases considered to have systemic toxicity had peak blood cobalt concentrations of greater than 250 mcg/L; this is similar to the 300 mcg/L concentration that Paustenbach et al. described as the concentration above which thyroid effects—in their review, the most sensitive of effects of elevated cobalt concentration, alongside polycythaemia—secondary to cobalt were possible [3]. One of our patients (case 2) who was diagnosed with systemic cobalt toxicity had a peak cobalt concentration greater than these values (1096 mcg/L); the other patient (case 1) had a peak cobalt concentration below these values (164.8 mcg/L). Two other patients in our series had cobalt concentrations of the same magnitude as case 1 but did not have systemic toxicity nor significant symptoms; one of these was completely asymptomatic. Case 1 was referred due to symptoms of lethargy and occasional paraesthesia in his feet and hands; he had normal nerve conduction studies and had previously had an echocardiogram, which was normal, and an MRI of his hips, which showed no associated adverse local tissue reaction. Having been referred by his orthopaedic surgeon for opinion of elevated cobalt and chromium concentrations, subsequent revision of his bilateral MoM-HP resulted in the decrease in both his symptoms and his cobalt concentrations, from 164.8 mcg/L pre-revision to 8.5 mcg/L 3 months post-revision. Of the two most recent case reports of cobalt-induced cardiomyopathy, there were similarly diverse cobalt concentrations of 189.0 and 641.6 mcg/L [25, 26]. Using the criteria proposed by Bradberry et al. [23]—that objective findings of known effects of cobalt occur after a MoM-HP and in conjunction with raised cobalt concentrations—both our case (cobalt concentration 164.8 mcg/L) and the non-fatal case of cardiomyopathy (cobalt concentration 189.0 mcg/L) [26] should be considered to have systemic features associated with cobalt toxicity.

The results of our study highlight the current difficulty in the interpretation of metal ion concentrations in the context of MoM-HP for both adverse local tissue reactions and systemic toxicity [44, 45]. In an asymptomatic patient, what is the significance of elevated metal ion concentrations? And at what metal ion concentrations should we be significantly concerned? Clearly, monitoring of metal ion concentrations alone is not sufficient to include or exclude pathology, and the need for a clear consensus for their detection remains lacking. Neither does there appear to be a correlation between those with adverse local tissue reactions and systemic features or vice versa. A previous review of the literature proposed an algorithm for evaluation of both asymptomatic and symptomatic patients with MoM-HP in an attempt to simplify the investigative process [19]. However, adding to the complexity in evaluating these patients is the difference in type and size of prostheses, duration of implants, and whether unilateral or bilateral prostheses are present.

Previous data has observed patients with MoM-HP implanted following a previously failed ceramic prosthesis had higher median peak blood cobalt concentrations than those with primary MoM-HP [23]. However, no patients in our cohort had previous ceramic implants and the highest recorded

cobalt concentration was significantly elevated at 1096 mcg/L. What is clear, at least from our series and the current literature, is that systemic toxicity appears to be a rare occurrence. Our experience in London and in the USA from 4 and 2 years, respectively, of referrals to specialist toxicology services highlights this, with only two cases identified during this period. With an increasing focus on the potential for systemic effects of cobalt from MoM-HP, a higher index of suspicion may lead to identification of more cases of cobalt-associated systemic toxicity. However, whether a causal relationship exists remains unclear. Further studies will help to determine the true prevalence of this rare entity and to develop the current monitoring guidelines for potential adverse effects, both local and systemic, associated with MoM-HP [46].

Limitations

This study is subject to several limitations, the first being the small number of patients. As a result, it may be underpowered to identify those with symptoms or positive investigation results based on the MHRA cut-off of 7 mcg/L. As described above, the use of this figure as the threshold for interpreting results is itself problematic as the discussion surrounding the ideal concentration to pique concern over potential for local or systemic effects of MoM-HP continues. Further, there is no consensus as to whether serum or whole blood concentrations should be used when measuring metal ion concentrations. Whilst they are not interchangeable, their mean difference has been shown to be small [27], of a magnitude that is unlikely to represent a clinically significant difference.

As this was a retrospective study drawing data from more than one outpatient cohort, there was no a priori time point for measuring cobalt and chromium concentrations. Indeed, as data is from specialist referral toxicology centres, initial measurement and referral, and therefore inclusion in this series, were at the discretion of the referring doctor; this introduces another potential bias. Whilst in most cases repeated metal ion concentrations were taken and the peak recorded for this study, it is possible that the peak concentrations were missed or occurred prior to the first measured concentrations. With the establishment of guidelines for monitoring metal ion concentrations, it is likely that future studies will have more consistent timing of measurements. Finally, the diagnosis of whether symptoms related to systemic metal toxicity was based on the treating toxicologist's opinion—as there are no formal diagnostic criteria, there is the potential for bias in this diagnosis; however, the toxicologists involved are all experienced medical (clinical) toxicologists associated with specialist toxicology units.

Conclusion

In this series of 31 individuals referred for assessment of potential systemic toxicity from cobalt and chromium associated with MoM-HP, there was a high prevalence of reported symptoms. Only two (6.5%) individuals were diagnosed clinically with systemic cobalt toxicity; their cobalt concentrations were significantly higher than those of individuals not diagnosed with systemic toxicity. Overall, however, reported symptoms and investigation results did not correlate with peak serum cobalt or chromium concentrations.

Sources of Funding There was no specific funding for this project.

Compliance with Ethical Standards

Conflicts of Interest Jerrold B. Leikin has been a paid consultant of DePuy Companies, which makes metallic hip prostheses since March 2011. Jeffrey Brent was a paid consultant of DePuy Companies from 2012 to 2013 and since 2016 has been a consultant for Stryker Corporation and Smith and Nephew, both of whom make metallic hip prostheses. The other authors report no declarations of interest.

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