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BIOMATERIALS

Cobalt-induced cardiomyopathy – do circulating cobalt levels matter?

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Elevated levels of circulating cobalt ions have been linked with a wide range of systemic complications including neurological, endocrine, and cardiovascular symptoms. Case reports of patients with elevated blood cobalt ions have described significant cardiovascular complications including cardiomyopathy. However, correlation between the actual level of circulating cobalt and extent of cardiovascular injury has not previously been performed. This review examines evidence from the literature for a link between elevated blood cobalt levels secondary to metal-on-metal (MoM) hip arthroplasties and cardiomyopathy. Correlation between low, moderate, and high blood cobalt with cardiovascular complications has been considered. Elevated blood cobalt at levels over 250 µg/l have been shown to be a risk factor for developing systemic complications and published case reports document cardiomyopathy, cardiac transplantation, and death in patients with severely elevated blood cobalt ions. However, it is not clear that there is a hard cut-off value and cardiac dysfunction may occur at lower levels. Clinical and laboratory research has found conflicting evidence of cobalt-induced cardiomyopathy in patients with MoM hips. Further work needs to be done to clarify the link between severely elevated blood cobalt ions and cardiomyopathy.

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Keywords: Cobalt, Cardiomyopathy, Metal-on-metal, Hip, Arthroplasty

Article focus

- A review of the link between elevated blood cobalt ions and cardiomyopathy.
- A summary of the relevant case reports.
- Analysis of recent clinical and laboratory studies.

Key messages

- Elevated blood cobalt levels greater than 250 µg/l appears to be a risk factor for cardiomyopathy.
- It is not clear if there is a cut-off value and cardiac dysfunction can occur at lower levels of circulating cobalt.
- Cobalt-induced cardiomyopathy is an infrequent but serious complication of metal-on-metal hip arthroplasty.

Strengths and limitations

- A review of case reports and retrospective studies.
- Clinical and laboratory research has found conflicting evidence for cobalt as a risk factor for cardiomyopathy in patients with metal-on-metal hip arthroplasties.
- Further studies required to clarify link between elevated blood cobalt ions and cardiomyopathy.

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Introduction

Metal-on-metal (MoM) hip arthroplasties are known to have higher failure rates than metal-on-polyethylene (MoP) or ceramic-on-ceramic (CoC) total hip arthroplasties (THAs).[1] As a consequence MoM hip arthroplasties accounted for less than 1% of hip arthroplasties performed in the UK last year,[2] down 20% from their peak in 2005.[3] When MoM hips fail they release cobalt and chromium ions into the local tissues and the bloodstream. Detection of these ions in samples of whole blood plays an important role in the screening for failing MoM hips.[4] Elevated levels of circulating cobalt ions have been linked with a wide range of systemic complications including neurological, endocrine, and cardiovascular symptoms.[5,6] There have been isolated case reports of patients with elevated blood cobalt ions suffering considerable cardiovascular complications including cardiomyopathy. However, clinical

and laboratory research has found conflicting evidence of cobalt induced cardiomyopathy in patients with MoM hips. Here we present an up-to-date review of the evidence linking elevated blood cobalt ions to cardiomyopathy.

Metal-on-metal ion levels. MoM arthroplasties release cobalt and chromium ions which can cause local tissue damage and are absorbed into the blood stream.[7] Laboratory values for metal ions in the blood are given as either parts per billion (ppb) or micrograms per litre (µg/l) and these values are equivalent and interchangeable. Normal blood cobalt levels for the unaffected population are below 0.51 µg/l,[8] and well-functioning MoM hips have blood cobalt levels of up to 2 µg/l.[9] Higher metal ion levels in the blood reflect a poorly functioning MoM implant[10] with an increased risk of complication,[11] and the Medicines and Healthcare products Regulatory Agency (MHRA) guidance recommends using whole blood ion levels of 7 ppb (7 µg/l) as a screening tool for failing MoM arthroplasties.[4,7] This figure was derived from a 2009 study by Hart et al,[12] which analyzed the effect of cobalt and chromium ions on T lymphocytes in well-functioning MoM hips and was later shown to have a specificity of 89% and sensitivity of 52% for detecting an unexplained failing MoM implant.[13] Further studies have attempted to validate this figure with various ion levels being suggested as more sensitive or specific screening tools.[9,14-16] Implant-specific ion levels have been proposed,[17] but the heterogeneity of MoM implants makes this an impractical screening tool. While the MHRA recommends using whole blood to report cobalt levels, serum has been used in most clinical trials.[18] While similar, these values are not interchangeable and care should be taken when interpreting values.[19,20]

Mechanism of cobalt cardiotoxicity. Cobalt is a widespread trace metal, which is the metallic component of Vitamin B12 but can be acutely cytotoxic in larger doses.[21] Cobalt-induced cardiomyopathy is a dilated cardiomyopathy similar to idiopathic, non-ischaemic cardiomyopathy,[22] and is diagnosed by demonstration of biventricular dilatation and systolic dysfunction in the presence of elevated blood or tissue cobalt and the subsequent normalization of cardiac structure and function when cobalt levels return to normal.[23] It has a rapid onset and progression and a high short-term mortality rate, but survivors can experience complete cardiac and clinical recovery once cobalt has been removed from their system.[23]

The cardiotoxic effects of cobalt have been proposed to be due to cobalt-induced alterations in cardiac calcium handling.[21] Cobalt is a divalent cation similar to calcium (Ca^{2+}) and has been shown to interfere with the binding of calcium to sarcolemmal proteins, and the transport of Ca^{2+} into cardiac myocytes. Several proteins dedicated to transporting divalent cations including Ca^{2+} into cardiac cells have been considered as a means of cobalt entry and it has been hypothesized that Co^{2+} may mimic Ca^{2+} and use similar transport routes.[24] Transient receptor potential (TRP) channels belonging to the TRP superfamily of Ca^{2+} permeable channels have been suggested as a means of cobalt entering cardiac cells.[25] Cobalt may also affect Ca^{2+}-dependent intracellular proteins and enzymes that are pivotal to healthy cardiac function. One possible target for the cardiotoxic effects of cobalt could be calcium-/calmodulin-dependent protein kinase II (CaMKII). This Ca^{2+}-dependent enzyme is a key mediator of healthy cardiac function but sustained activation results in adverse cardiac remodelling, inflammation, and dysfunction.[26,27] As such it has been highlighted as a promising target for pharmacological inhibition in the treatment of heart disease. If Co^{2+} can directly or indirectly affect CaMKII activation, then it could exert a broad spectrum of detrimental effects on the heart via this well-recognized route. In addition to altering Ca^{2+} signalling, cobalt also interrupts the citric acid cycle and the generation of ATP by aerobic cellular respiration.[23] It inhibits the activity of respiratory chain enzymes and ATP production in mitochondria,[28] producing a net result of depressed cardiac function and altered cardiac cell structure.[23,29] The toxic effects of cobalt are reversible as it does not change mitochondrial function[30] or cardiac contractility.[31]

Historical papers. Cobalt induced cardiomyopathy was first described at a March 1965 cardiology conference in Belgium.[32] The effects of cobalt were reported in North American beer drinkers who developed acute cardiomyopathy after cobalt was added as a foam stabilizer to their beer of choice.[33,34] The amount of cobalt consumed by these patients was less than regularly prescribed nutritional supplements of the time. However, the individual patient's length of alcohol excess prior to exposure to cobalt[35] and their general nutritional deficit, specifically a lack of protein, zinc, and thiamine,[34] were bigger predictors of a fatal outcome than the actual dose of cobalt they were exposed to. Cobalt-induced cardiomyopathy has also been reported in patients on haemodialysis receiving cobalt supplementation for anaemia,[36] and in patients who handled powdered cobalt in their industrial occupation.[37]

Cardiomyopathy associated with metal-on-metal implants. Cobalt-induced cardiomyopathy secondary to cobalt chrome hip arthroplasties has been described in case reports (Table I), most of which were summarized in a recent review article.[38] Cases of cobalt-induced cardiomyopathy have been reported from primary MoM hip arthroplasties,[39-51] revision MoM arthroplasty,[39-41] and revision MoP hip arthroplasties following a fracture of a ceramic articulation.[52-61] Patients have presented between two months[56] and ten years[48] postoperatively with a range of cardiac symptoms including dyspnoea,[39-44,46,47,49,53,55,58,59,61] heart failure,[48,50,51,57] orthopnoea,[47,53] fatigue,[45,52,53,59,60] and cardiomegaly.[62] Blood cobalt levels have also varied greatly, with symptomatic patients having a serum cobalt level as low as 13 µg/l[42] and as high as 6,521 µg/l.[52] Echocardiographs most commonly demonstrated a decreased left ventricular ejection fraction[42,43,45-47,49-51,53,57-59,61] but also a dilated atrium,[42] diastolic dysfunction,[39-41,47] left ventricular hypertrophy,[53,56,62] and a pericardial effusion.[52,53] Outcomes have varied from full recovery after revision

Table I. A summary of cases reporting cobalt-induced cardiomyopathy. The normal recorded values for left ventricular ejection fraction were 55% to 70%.

Cardiac presentation	Implant	Sample	Cobalt (µg/l)	Length of follow-up	Echocardiogram results	Outcome
Dyspnoea, neurotoxicity[39-41]	Primary MoM arthroplasty	Serum	122	18 months	Diastolic dysfunction	Revision, symptoms resolved
Dyspnoea[39-41]	Revision MoM arthroplasty	Serum	23	43 months	N/A	Revision, symptoms resolved
Dyspnoea, chest pain[42]	Primary MoM arthroplasty	Serum	13	6 years	Dilated atrium, decreased LVEF (21%)	Revision, LVEF (45%)
Exertional dyspnoea, cough[43]	Primary bilateral MoM resurfacings	Serum	287	4 years	Decreased LVEF (10%)	Heart transplant, hip revision
Cardiomyopathy[62]	Failed CoC revised to MoM	Serum	506	N/A	Left ventricular hypertrophy	Chelation therapy, revision, symptoms improved
Dyspnoea[44]	Primary MoM resurfacing	Serum	258	3 years	N/A	Revision surgery, symptoms resolved
Exertional chest tightness, fatigue[45]	Primary bilateral MoM arthroplasties	Whole blood	189	11 months	Decreased LVEF (30%)	Heart transplant, bilateral hip revisions
Dyspnoea[46]	Primary bilateral MoM arthroplasties	Did not specify	200 to 300	2 years	Decreased LVEF (10% to 15%)	Death
Fatigue[52]	Failed CoC revised to MoP	Whole blood	6,521	6 months	Pericardial effusion	Death
Dyspnoea, fatigue[53]	Failed CoC revised to MoP	Serum	489	6 years	Left ventricular hypertrophy, pericardial effusion, decreased LVEF (13%)	Chelation, revision normal LVEF (58%).
Dyspnoea, orthopnea[53]	Failed CoC revised to MoP	Serum	112	6 years	Decreased LVEF (24%), pericardial effusion	Revision surgery, chelation, heart transplantation
Cardiogenic shock[54]	Failed CoC revised to MoP	Serum	652	N/A	N/A	Heart transplant
Cardiomyopathy[56]	Failed CoP revised to MoP	Serum	625	2 months	Left ventricular hypertrophy	Revision surgery, symptoms resolved
Dyspnoea[55]	Failed CoC revised to MoP	Whole blood	641	10 months	LVEF 15% to 20%	Death
Dyspnoea, orthopnoea[47]	MoM	Whole blood	246	4 years	Diastolic dysfunction, decreased LVEF (20%)	Revision surgery, symptoms resolved, LVEF 45% to 50%
Heart failure[48]	MoM	Serum	169	10 years	N/A	Heart transplantation, revision surgery
Exertional dyspnoea[49]	Bilateral MoM	Did not specify	156	2 years	Dilated cardiomyopathy with decreased LVEF (20%)	LVAD inserted, no improvement, bilateral hip revisions 1 year later, symptoms resolved
Heart failure[50]	Bilateral MoM	Serum	120	N/A	Decreased LVEF (36%)	Bilateral revision surgery, LVAD
Heart failure[51]	MoM	Serum	200 to 300	N/A	Decreased LVEF (14%)	Death
Heart failure[57]	Failed CoC revised to MoP	Whole blood	780	2 years	Decreased LVEF (25%)	Chelation therapy, revision surgery, LVEF 40%
Dyspnoea, chest tightness[58]	Failed CoC revised to MoP	N/A	45	8 years	Dilated cardiomyopathy, reduced LVEF (28%)	Revision surgery, symptoms resolved
Dyspnoea, fatigue[59]	Failed CoC revised to MoP	Serum	373	3 years	Dilated cardiomyopathy, severe left ventricular dysfunction, LVEF (20%)	Death
Fatigue, tachycardia[60]	Failed CoC revised to MoP	Did not specify	788	8 years	N/A	Revision surgery, symptoms resolved
Dyspnoea[61]	Failed CoC revised to MoP	Did not specify	397	N/A	Decreased LVEF (25%)	Chelation therapy, revision surgery, symptoms resolved

CoC, ceramic-on-ceramic; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MoM, metal-on-metal; MoP, metal-on-polyethylene; N/A, not available.

Table II. A summary of case reports according to documented blood cobalt level. The normal recorded values for left ventricular ejection fraction were 55% to 70%.

Blood cobalt levels (µg/l)	Patients, n	Mean blood cobalt levels, µg/l (range)	Cardiac presentation	Implants	Echocardiography results	Outcome	References
> 250	11	1,049 (258 to 6521)	Cardiogenic shock (1 case), cardiomyopathy (2 cases), dyspnoea (5 cases), fatigue (4 cases), exertional dyspnoea and cough (1 case),	CoC revised to MoP (7 cases), CoP revised to MoP (1 case), primary MoM resurfacing (1 case), bilateral primary MoM resurfacings (1 case)	Decreased LVEF (5 cases), mean LVEF reported was 17% (range 10% to 25%), pericardial effusion (2 cases), LVH (3 cases)	Death (27%, 3 cases), chelation and revision resolved symptoms (27%), revision resolved symptoms (27%), heart transplantation (18%, 2 cases)	43,44,52-56,59-61
200 to 300	2	Unknown	Dyspnoea, heart failure	Primary bilateral MoM resurfacing, primary MoM resurfacing	Decreased LVEF, mean LVEF 13%	Death (100%, both cases)	46,51
< 250	10	119.5 (13 to 246)	Heart failure (2 cases), dyspnoea (5 cases), exertional chest pain (3 cases), orthopnoea (1 case)	Bilateral primary MoM arthroplasties (3 cases), primary MoM arthroplasties (4 cases), CoC revised to MoP (2 cases), revision MoM arthroplasty (1 case)	Decreased LVEF (7 cases), mean LVEF reported was 24% (range 10% to 36%), diastolic dysfunction (2 cases), dilated cardiomyopathy (2 cases), pericardial effusion (1 case)	Heart transplantation and revision (30% 3 cases), revision resolved symptoms (60% 6 cases), LVAD and revision (10%, 1 case)	39-41,45,47-50,53,58

CoC, ceramic-on-ceramic; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MoM, metal-on-metal; MoP, metal-on-polyethylene.

surgery[39-42,44,47,53,56,58,60] or chelation therapy,[53,57,61,62] to left ventricular assist device implantation,[49,50] to cardiac transplantation[43,45,48,53,54] or death.[46,51,52,55,56,58]

Discussion

The case reports have shown a correlation between blood cobalt levels and cardiovascular complications[63] and mortality (Table II). There is no clear cut-off cobalt level above which risks of complications increase, however an analysis of the published case reports available in 2014 found that ten patients had systemic complications attributable to elevated cobalt and all ten had blood cobalt levels above 250 µg/l.[5] Another review of the medical and toxicology literature suggested a cut-off level for blood cobalt of 300 µg/l above which otherwise healthy individuals risk developing serious systemic complications,[64] and they suggested that patients with nutritional deficiencies such as a hypoalbuminaemia were at risk of systemic complications below 300 µg/l.

A review of the literature suggests that patients with blood cobalt of all levels are at risk of cobalt-induced cardiomyopathy, however there has been no consistency of findings between clinical studies (Table III). The case reports compiled in this present review demonstrate that reversible cardiac complications confirmed on echocardiogram can be present in patients with blood cobalt levels as low as 13 µg/l.[42] Asymptomatic patients with lower levels of circulating cobalt can still suffer cardiac damage. A comparison of patients with and without MoM hip resurfacings using echocardiography and blood tests found a reduced cardiac ejection fraction and increased end diastolic cardiac volume in the MoM patients (mean blood cobalt level of 1.75 µg/l) at a mean of eight years postoperatively. There were no such changes in the control group.[65] A separate cohort of MoM patients were assessed by cardiac MRI eight years postoperatively and asymptomatic patients with minimally elevated metal ion levels were found to have statistically significant but clinically insignificant mild cardiac changes. This suggests that adverse cardiac processes may be at work in asymptomatic MoM patients, even when they have normal or minimally elevated blood cobalt levels.[66] Population-wide studies have demonstrated cardiac complications in MoM patients without studying individual blood cobalt levels. A retrospective cohort study of the Australian Government Department of Veterans' Affairs demonstrated that men with an ASR XL THA had a statistically significant higher rate of hospitalization for heart failure than men with a MoP THA. This higher rate of complications was not demonstrated in women or in men with other types of MoM implants.[67] The French health insurance database was used to identify all MoP, ceramic-on-polyethylene (CoP), MoM, and CoC

Table III. A summary of published research into cardiovascular complications of metal-on-metal hip arthroplasties.

Reference	Study design	Study group	Control group	Study group blood cobalt, µg/l	Findings
Prentice et al[65]	Cross-section associational study	Aymptomatic patients with MoM hip resurfacings	Age- and sex-matched patients with non-MoM hip arthroplasties	Whole blood cobalt 1.75 µg/l compared to 0.38 µg/l in control group	Cardiac ejection fraction reduced and end diastolic volume increased in MoM group
Lodge et al[69]	Single centre, non-randomized, observational study	Patients with MoM hip arthroplasties in 3 groups, separated by cobalt levels	Age-matched controls with non-MoM hip arthroplasties	Plasma cobalt in 3 study groups 14.6 µg/l, 7.8 µg/l, and 1.3 µg/l compared to 0.6 µg/l in control group	Increasing cobalt values associated with increased heart volume but not with cardiac dysfunction and no clinical difference between groups was demonstrated
Berber et al[70]	Prospective, single centre, blinded trial	MoM bearing with elevated blood cobalt ions	MoM bearing with low blood cobalt ions and CoC bearing	Whole blood cobalt 30 µg/l and 2.47 µg/l in respective MoM groups compared to 0.17 µg/l in control group	No relationship between cobalt levels and ejection fraction. No differences between groups in the left atrial or ventricle size, B-type natriuretic peptide level, or troponin level, and all values were within normal ranges
van Lingen et al[71]	Longitudinal cohort study	10 asymptomatic MoM patients with highest cobalt levels out of a population of 643 MoM patients	None	Whole blood cobalt 18 to 153 µg/l (mean 46.8 µg/l)	No signs or symptoms of cardiomyopathy could be identified
Gillam et al[67]	Observational cohort study from Australian Government Department of Veteran's Affairs health claims database	63 men with an ASR XL THA	1,502 men with MoP THA, 199 men with other MoM THAs, 2,044 women with MoP, 58 women with ASR XL THA, and 153 women with other MoM THAs	Not recorded	Men with an ASR XL THA had a statistically significant higher rate of hospitalization for heart failure than men with a MoP THA. This higher rate of heart failure was not demonstrated in women or in men with other types of MoM implants
Lassalle et al[68]	Cohort study in the French National Health Insurance Databases	11,298 patients with MoM hips	93,581 patients with MoP, 58,095 patients with CoP, 92,376 patients with CoC	Not recorded	Small increase in heart complications in metal bearing surfaces compared to non-metal surfaces was identified after controlling for confounding factors, most pronounced in MoM vs CoC in women and men over 75 years of age
Goodnough et al[72]	Analysis of the Standard Analytics Files database in the USA	29,483 patients with MoM hips	24,175 patients with non-MoM hips	Not recorded	At 5 years there was no difference in cardiac complications such as cardiac failure, arrhythmia, acute myocardial infarction, or cardiomyopathy
Sabah et al[73]	Linkage study between the National Joint Registry, Hospital Episodes Statistics and records of the Office for National Statistics on death	53,529 patients with MoM hips	482,247 patients with non-MoM hips	Not recorded	At 7 years the risk of cardiac failure was lower in the MoM cohort compared with the non-MoM cohort. When the groups were matched their risk of cardiac failure was similar.
Juneau et al[66]	Cross-section study using cardiac magnetic resonance	20 MoM resurfacing patients, 10 bilateral, 10 unilateral	10 case-matched non-MoM total hip arthroplasty patients	Mean serum cobalt 1.3 µg/l in study group compared to 0.18 µg/l in control group	None of the MoM patients showed clinically significant cardiac functional abnormality. The MoM patients had larger end diastolic volumes. There was a small decrease in T2 time in the MoM patients. Higher metal ion levels were associated with larger LV volumes and with shorter T2 time.

CoC, ceramic-on-ceramic; CoP, ceramic-on-polyethylene; LV, left ventricular; MoM, metal-on-metal; MoP, metal-on-polyethylene; THA, total hip arthroplasty.

THAs performed in France between 2008 and 2011 and follow them up until 2015. All new diagnoses of dilated cardiomyopathy or heart failure in that time were included in the study. Due to the heterogeneity of implants in such a large study the authors performed two separate comparisons: soft-bearing THA MoP versus CoP, and hard-bearing implants MoM versus CoC. A small increase in heart complications in metal bearing surfaces compared to non-metal surfaces was identified after controlling for confounding factors and this was

most pronounced in MoM versus CoC in patients over 75 years of age.[68] These studies represent a range of different experimental designs including cross-sectional observational studies[65,66] and population-based cohort studies,[67,68] and they find broadly similar results.

Other studies have failed to reproduce negative cardiac effects in patients with elevated blood cobalt levels or across MoM populations despite using similar methodology to the previously described research. A total of 95 MoM patients with previously recorded serum cobalt levels of > 7 µg/l were compared to 15 age- and comorbidity-matched patients without a MoM prosthesis. Plasma cobalt levels were rechecked and used to divide the study patients into three groups with mean serum cobalt levels of 14.6 µg/l, 7.8 µg/l, and 1.3 µg/l, respectively. The control group had a mean serum cobalt level of 0.6 µg/l. All patients underwent echocardiography measurements, which found that increasing cobalt levels were associated with increased heart volume but not with cardiac dysfunction, and no clinical difference between groups could be demonstrated.[69] No clinically significant correlation between blood ion levels and any cardiac tests were demonstrated when patients with MoM implants with elevated blood ion levels (mean 30 µg/l), MoM implants with low blood ion levels (mean 2.47 µg/l), and CoC implants (mean 0.17 µg/l) were assessed using cardiac MRI and echocardiography.[70] Ten Dutch patients with large head MoM hip arthroplasties and a mean whole blood cobalt level of 46.8 µg/l were followed up for a mean of 4.2 years without any signs or symptoms of cardiomyopathy.[71] These studies were variously described as a single centre, non-randomized, observational study,[69] a prospective, single centre, blinded trial,[70] and a longitudinal cohort study,[71] but they were all fairly analogous to the cross-sectional observational studies described above and were unable to demonstrate similar findings. Similarly, population-based studies performed in the USA[72] and the UK[73] did not have similar findings to the Australian[67] and French[68] studies. An analysis of the Standards Analytics Files database in the USA compared every patient who had undergone a MoM hip arthroplasty between 2005 and 2012 to an age- and sex-matched cohort who had undergone a non-MoM hip arthroplasty in the same period. They found that at five years there was no difference in cardiac complications such as cardiac failure, arrhythmia, acute myocardial infarction, or cardiomyopathy.[72] A retrospective analysis of over half a million hip arthroplasty patients in the UK's National Joint Registry, including 53,529 MoM patients, demonstrated no association between a MoM implant and cardiac failure at seven years postoperatively.[73] While there were subtle differences in methodology, none of the population-based studies selected patients for their cobalt levels. Despite the wide range of study designs, none have as yet recreated or studied the population described in the case reports: patients with elevated cobalt over 250 µg/l.

There is a clear requirement for future experimental study design to take a more focused approach with stringent inclusion/exclusion criteria around cobalt levels being considered. Elevated cobalt at levels over 250 µg/l have been shown to be a risk factor for developing systemic complications,[5] and published case reports document cardiac transplantation[43,45,48,53,54] and death[46,51,52,55,59] in patients with severely elevated blood cobalt ions. Currently it is unclear whether there is a hard cut-off value and cardiac dysfunction may occur at cobalt levels less than 250 µg/l (Table II). However, none of the experimental research conducted to date has specifically studied patients with blood cobalt levels over 250 µg/l (Table III). This may account for the inability of previous experimental studies to reproduce the severity of cardiac complications described in the case reports outlined here. Interestingly, a number of animal-/cell-based studies have used higher levels of cobalt to examine potential cardiotoxic effects.[24] While these studies may not exactly recreate clinical levels of cobalt, they demonstrate the severe impact that high levels of cobalt may have on cardiac viability and function. Future experimental design needs to include studies that focus only on examining patients with high (> 250 µg/l) cobalt levels. An important aspect of cobalt-induced cardiomyopathy is that the awareness of this phenomenon is low. There may be patients with cardiomyopathy in which the link to failing MoM hip implants has not been acknowledged. This present review presents 24 case reports of cobalt-induced cardiomyopathy following MoM hip arthroplasty, and this is a small proportion of the millions of MoM hips implanted worldwide. Future studies should focus on identifying those patients at risk. In order to do this, cardiac MRI and current biomarkers for cardiac injury, such as Troponin-T and Brain Natriuretic Peptide biomarkers, should be performed to assess for cardiomyopathy in all patients with elevated blood cobalt levels > 250 µg/l. Indeed, cardiologists and orthopaedic surgeons should consider investigating for cardiomyopathy in MoM patients with elevated blood cobalt of all levels. To overcome the design weaknesses in the experimental studies performed to date, and analyze the true incidence of this rare but devastating complication in more detail, future studies should aim to capture all patients in a defined MoM population with cobalt levels greater than 250 µg/l. Due to the small numbers involved this should be on a regional or national basis.

In conclusion, despite a growing number of cases reported in the literature, it remains unclear from experimental studies whether circulating levels of cobalt correlate directly with cardiac dysfunction. Further work needs to be done to clarify the link between elevated blood cobalt above 250 µg/l and cardiomyopathy. Cobalt-mediated effects on cardiac Ca^{2+} handling proteins should be studied to identify specific cellular changes that occur prior to clinical dysfunction. All

patients with blood cobalt levels over 250 µg/l should have thorough, routine cardiological investigation.

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