Cobalt-related cardiomyopathy: A real concern! A review of published evidence

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Abstract

Background: Cobalt (Co) toxicity-related cardiomyopathy (CMP) in hip arthroplasty has recently been reported in the literature. The purpose of this review was to identify and assess available published evidence of CMP in hip arthroplasty patients and to derive recommendations for management. Methods: We evaluated 23 cases reported till October 2018 and stratified into three categories, based on pre-existing risk factors for CMP, histological confirmation and evidence of systemic signs of Co toxicity. Results: Co toxicity was considered to be the definite cause of CMP in 8 cases and probably contributory in 13 cases. Two cases were considered to have developed CMP secondary to pre-existing risk factors. Majority of the patients had good recovery of cardiac function after hip revision and cardiac management, but five cases deteriorated and died. Conclusion: Although Co-related CMP has been reported in a small number of cases of hip arthroplasty, a delay or missed diagnosis may lead to significant morbidity and mortality. Timely diagnosis, removal of causative implant and avoidance of metal articulations in revision for fractured ceramic implants may help in effective management.

Keywords
cardiomyopathy, cobalt, hip arthroplasty, metal-on-metal, toxicity

Introduction

Cobalt (Co) toxicity has been reported in the literature as an occupational hazard in hard metal industry, diamond polishing and mineral assay industry. Hip arthroplasty-related Co toxicity with significant morbidity and mortality has been highlighted recently in the literature, which generated some media attention. Among other clinical manifestations of Co toxicity, cardiomyopathy (CMP) has been reported in some cases. Medical and Healthcare products Regulatory Agency (MHRA) has recently been recommended surveillance guidelines of patients with metal-on-metal hip arthroplasty to identify any local or systemic signs of metal toxicity.¹

Hip prosthesis bearing surfaces may be made of metals, such as Co, chromium (Cr), stainless steel or non-metal materials, such as ceramic or polyethylene. Metal ions, such as Co and Cr, are generated from corrosion of fixed and modular components of the prosthesis, abrasion between bearing surfaces of prosthesis and micromovements of failing components of the modular implant. The Co bivalent ions are predominantly responsible for systemic and local tissue reactions, whereas Cr trivalent ions are reduced rapidly in biological systems.²

High systemic concentration of Co ions leads to a specific form of CMP, along with other systemic effects like...
neurological symptoms, hypothyroidism and polycythemia. This particular type of CMP was first reported in individuals with a high intake of Co containing beer and its features were distinctive from previously known features of this condition. Recently, this type of CMP has been reported in patients with hip arthroplasty.

The purpose of this review was to evaluate all published case reports of Co-related CMP in patients with hip arthroplasty. Our aim was to identify the scale and discuss salient features and management of this condition.

Methods

A search of PubMed and Embase databases was conducted to identify relevant studies using terms “CMP and Co or metal and hip or replacement or arthroplasty” till October 2018. Two reviewers (MU and MFK) independently screened articles, assessed for quality and extracted data from 21 articles, which described 23 cases of CMP in patients with metal hip arthroplasty implants (Table 3).

Data collection included patient demographics, potential risk factors for CMP (Table 1), type of hip implants, presentation of CMP, serum Co levels, systemic Co toxicity features (Table 1) and outcomes.

The selected cases were categorised into three subgroups (Table 2), based on histopathology evidence, systemic Co toxicity features and presence/absence of risk factors of CMP.

Definite group (Co toxicity likely cause of CMP):

- Patients with confirmed Co-related CMP on a histopathological study of cardiac tissue and have evidence of systemic features of Co toxicity (Table 1).
- No pre-existing risk factors for CMP (Table 1).

Probable group (Co toxicity may have contributed towards CMP):

- Patients with confirmed Co-related CMP on a histopathological study of cardiac tissue OR patients with systemic features of Co toxicity (Table 1).
- Have pre-existing risk factors for CMP (Table 1) before hip replacement.

Non-causal group (Co toxicity unlikely to be the cause of CMP):

- Have pre-existing risk factors for CMP (Table 1) before hip replacement.
- No evidence of systemic or cardiac Co toxicity.

Results

The cases were categorised into metal-on-metal (MoM, n = 12) and non-MoM group (n = 11). Non-MoM group included metal-on-ceramic (n = 1) and metal-on-polyethylene (n = 10). Interestingly, all cases in non-MoM group had implants as a revision procedure after fractured primary ceramic components.

The mean age was 58 years in the 12 cases of MoM compared to 56 years in 11 cases of non-MoM group (Table 4). The mean time to presentation with symptoms of CMP following hip procedure was comparable (MoM: 2.5 years vs. non-MoM: 2.6 years). In MoM group, the mean blood Co level was lower compared to non-MoM group (322 μg/L vs. 1041 μg/L; Table 5).

Thirteen cases presented with systemic signs of Co toxicity of which four patients did not recover from hearing loss and visual loss. Most of non-MoM cases (8/11) showed systemic Co toxicity signs, whereas, in MoM group, only one-third (4/12) reported such features. Mean blood Co concentration was higher in patients with systemic signs (937 μg/L vs. 312 μg/L).

Twenty-one cases had their hips revised and a majority (n = 18) had reported extensive local tissue signs of metallosis, such as discoloration, degeneration, fluid collections...
Table 3. Summary of cases of cardiomyopathy in patients with hip arthroplasty.

| Reference        | Age/sex | Risk factors                  | Implant | Time   | Blood / cardiac Co (μg/L) | Presentation                                                                 | Outcome                                                                 |
|------------------|---------|-------------------------------|---------|--------|--------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Tilney et al.12  | 40/M    | NR                            | MoM     | 4 years | 246/NR                   | Exertional dyspnoea, palpitations, orthopnoea, LV failure with hypotrophy, pericardial effusion, LVEF decreased to 20% with advanced diastolic dysfunction – no ischaemia | Hip revised (severe metallosis) – improved in 5 months (LVEF = 45–50%) |
| Martin et al.11  | 64/F    | NR                            | MoM     | 2 years | 192/4.75                 | Hip pain with impaired shortness of breath and impaired renal function. Poor cardiac function with LVEF 10–15% and delayed enhancement on MR | Hip revised (severe metallosis) – deteriorated – CVA – died |
| Moniz et al.13   | 58/F    | NR                            | MoM     | 10 years | 169/NR                   | Heart failure with non-ischaemic dilated cardiomyopathy and severe biventricular dysfunction. Idiopathic fibrosing on MR. Advanced multiorgan failure lead to cardiac transplant | Cardiac transplantation – 2 years later hip revision (extensive metallosis) – metal levels and cardiac function normalised |
| Tower et al.8    | 49/M    | NR                            | MoM     | 11 months | 122/NR                   | Dyspnoea, hip pain, anxiety, headaches, irritability, fatigue, tinnitus, hearing loss, hand tremors, lack of coordination, cognitive decline, depression. Visual changes with optic nerve atrophy. Diastolic dysfunction on echo | Hip revised – systemic symptoms improved |
| Tower et al.8    | 49/M    | NR                            | MoM     | 1 year   | 23/NR                    | Cognitive impairment, vertigo, hearing loss, groin pain, rashes and dyspnoea | Hip revised (severe metallosis) – satisfactory recovery of systemic symptoms |
| Charette et al.14| 46/M    | AVN hip                       | MoM     | 2 years | 1556/NR                  | Dyspnoea on exertion, increased abdominal girth, dilated cardiomyopathy with LVEF 20%. | Repeated admissions for heart failure – LVAD – no improvement – BL hip revisions (severe metallosis) – good recovery clinically |
| Machado et al.15 | 75/M    | DM II, renal impairment, high BMI, hypercholesterolemia, CA prostate | MoM     | 6 years | 11.96/NR                 | Dilated cardiomyopathy, LVEF 21% – no ischaemia, worsening failure – AF | Hip revised – marked improvement – LVEF 45% |
| Mosier et al.16  | 54/M    | Obesity                       | MoM – bilateral | 11 months | 189/NR                   | Exertional chest tightness, fatigue, diaphoresis, non-ischaemic diastolic dysfunction with LVEF 30%, mild renal impairment, lower limb paraesthesia | BL hip revisions (extensive metallosis) – good hip outcome with reduced metal ion levels – cardiac status worsened – LVAD – cardiac transplant |
| Samar et al.17   | 54/M    | MoM – bilateral               | NR      | 120/NR  |                          | Worsening heart failure, biventricular dysfunction – LVEF 36% – cobalt cardiomyopathy on MR | Bilateral hip revision – metal levels improved but cardiac function remained poor – LVAD inserted |
| Khan et al.18    | 69/F    | Hypertension, mild renal impairment, bilateral THR | MoM     | 2 years | 200–300/NR              | CCF, LVEF 25–30%, pericardial effusion, normal angiography, dilated cardiomyopathy | Failed medical treatment – repeated admissions – decreasing LVEF 14% – cardiogenic shock – advanced heart failure support – biventricular assist device – hip revised – haemorrhagic stroke – died |

(continued)
| Reference       | Age/sex | Risk factors                   | Implant          | Time  | Blood / cardiac Co (µg/L) | Presentation                                                                                                                                                                                                                                                                                                                                 | Outcome                                                                                                                                                                                                                          |
|-----------------|---------|--------------------------------|------------------|-------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allen et al.7   | 59/F    | Polyarthritis                  | MoM – bilateral  | 3 years | 398.6/NR                  | Heart failure with exertional dyspnoea, oedema, fatigue, cardiomegaly, pulmonary oedema. LVEF 25% then 10%, pericardial effusion. Hypothyroidism secondary to amiodarone, worsening cataract. Histo – abnormal mitochondrial forms with electron dense deposits – cobalt cardiomyopathy. Deterioration of cardiac function – cardioverter defibrillator – cardiac transplant – hip revised (extensive metallosis) – good resolution of metal ions (11.8) and LVEF 38%                                                                 |                                                                                                                                                                                                                                  |
| Giampreti et al.19 | 75/M    | NR                             | MoM              | 5 years | 352.6/NR                  | Hip pain, metallosis, asthenia, dilated cardiomyopathy with global hypokinesis and LVEF 32%. Pericardial effusion, raised pulmonary pressure (43 mmHg). Hip revision followed by chelation therapy – significant improvement clinically                                                                                                                                        |                                                                                                                                                                                                                                  |
| Apel et al.20   | 65/M    | Obesity, hypercholesterolemia, hyper tension, DM, THR | CoC – fractured head – MoC | 5 years | 393.5/NR                  | Pericardiomyopathy, generalised malaise, paroxysmal atrial fibrillation, hypothyroidism, PE, bulbar palsy, motor axonopathy, worsening vision. Hip revised – improved metal ions and systemic improvement                                                                                                                                                                                                 |                                                                                                                                                                                                                                  |
| Pelcova et al.21 | 56/M    | High BMI, hypertension, DM     | CoC – fractured liner – MoP | 20 months | 930/NR                   | Paraesthesia, walking difficulties, weight loss, bilateral sensory-neural hearing loss, pericardial effusion and hypertrophic cardiomyopathy, hypothyroidism, sensory motor peripheral polyneuropathy all four limbs. Chelation therapy – revision hip (severe metallosis) – systemic symptoms improved except deafness                                                                 |                                                                                                                                                                                                                                  |
| Choi et al.22   | 52/M    | Hypertension, alcohol, AVN of femoral head | CoC – fractured head – MoP | 2 years | 489.5/NR                  | Dilated cardiomyopathy, dyspnoea on exertion, progressive inefficiency, fatigue, dysesthesia, paraesthesia, proximal muscle weakness and bilateral sensorineural hearing loss. Echo showed LV wall thickness with LVEF 13% with pericardial effusion. Hip pain. Chelation – revision THR – normal LVEF 58% and improved heart function – normal everyday function                                                                 |                                                                                                                                                                                                                                  |
| Choi et al.22   | 46/M    | Hypertension, CKD 3, AVN of femoral head | CoC – fractured head – CoP – fractured head – MoP | 6 years | 111.98/NR                  | Dyspnoea, orthopnoea with LVEF 24% and pericardial effusion. Progressed to advanced heart and kidney failure. Histo – non-specific degeneration and fibrrosis with negative congo-red stain. Electron microscopy of explant showed cobalt toxicity with dense osmophilic intra-mitochondrial particles. Medical management – deteriorated – continuous hemodynamic support – hip revision – chelation therapy – cardiac transplantation – good recovery of cardiac and everyday function                                                                 |                                                                                                                                                                                                                                  |
| Oldenburg et al.3 | 55/M    | No                             | CoP – fractured head – MoP | 2 months | 625/NR                   | Progressive inefficiency, poor concentration, fatigue, hypothyroidism, headaches, convulsions, peripheral paraesthesia, weight loss, nail discolouring, eczema, lingual film, dysgeusia, progressive hearing loss. Reduced LV function with LV hypertrophy. Hip revision (severe metallosis) – improvement of systemic symptoms in 5 months – metal levels improved                                                                 |                                                                                                                                                                                                                                  |
| Zywiel et al.6  | 46/M    | NR                             | CoC – fractured liner – MoP | 6 months | 6521/3.85                  | Severe fatigue, anorexia, weight loss, hypothyroidism, hip pain, HO, SOB – dilated cardiomyopathy with LV failure and pericardial effusion – cardiogenic shock – renal, hepatic and respiratory failure. Histo – autopsy – cobalt toxicity – cardiac mitochondria contained abnormal electron dense deposits with significant interstitial fibrosis. Effusion drained – cardiac ICU management – hip revision (extensive metallosis) – chelation therapy – worsening cardiac function (<10%) – not suitable for cardiac transplant – LVAD support – died 18 months post-exposure                                                                 |                                                                                                                                                                                                                                  |
Table 3. (continued)

| Reference | Age/sex | Risk factors | Implant | Time | Blood / cardiac Co (µg/L) | Presentation | Outcome |
|-----------|---------|--------------|---------|------|---------------------------|--------------|---------|
| Fox et al.10 | 60/F | NR | CoC – fractured liner – MoP | 10 months | 817/2.5 | Hip pain, progressively worsening dyspnoea, bilateral PE, weight loss, loss of appetite due to dysgeusia with metal taste, worsening hearing loss, HO, cardiomyopathy with LVEF 15–20%, worsening fatigue, weakness, difficulty ambulating, worsening CCF – Co-related dilated cardiomyopathy, respiratory failure | After initial cardiac improvement – deteriorated – chelation therapy started and revision THR planned – respiratory failure – CCF – metabolic acidosis – continuous renal replacement therapy (CRRT) – cardiac arrest – died |
| Peters et al.23 | 71/M | DM, multiple myeloma | CoC – fractured liner – MoP | 2 months | 596.5/NR | Hypothyroidism, asymmetrical hearing loss, visual impairment, vertigo, weight loss, cerebrovascular accident | Revision planned – CVA – chelation therapy – deteriorated – died |
| Dahms et al.9 | 55/M | NAD, B/L THR | CoC – fractured implant – MoP | 2 years | 780/NR | Severe heart failure – LVEF 25% – cardiomyopathy. Severe visual and hearing loss, pyrexia of unknown origin, hypothyroidism, reflux oesophagitis. Lymphadenopathy | Chelation therapy – revision THR – cardioverter defibrillator – clinical improvement at 14 months – LVEF 40% – slight recovery of hearing and vision loss |
| Vasukutty et al.24 | 40/M | Haemochromatosis | CoC – fractured liner – MoP | 8 years | 45/NR | Dyspnea, chest discomfort, reduced LVEF (28%), dilated cardiomyopathy, debilitating cognitive impairment with intermittent confusion, forgetfulness, mood swings, encephalomyelitis, and pain and restricted movement in his right hip | Hip revised (extensive metallosis) – good clinical and metal ion level recovery |
| Weber et al.25 | 66/F | DM, coronary artery disease, myocardial hypertrophy | CoC – fractured implant – MoP | 2 years | 412/NR | Bilateral vision loss, paraesthesias in her hands and feet, imbalance, bilateral vestibular loss, bilateral hearing loss, cardiomyopathy, recurrent depression, fatigue, and decreased appetite with weight loss | Hip revision (extensive metallosis) – good recovery of hip function – some improvement in cardiac function – limited improvement in visual and hearing symptoms |

MoM: metal-on-metal; MoP: metal-on-polyethylene; MoC: metal-on-ceramic; LVAD: left ventricular assist device; NR: not reported; time: time to presentation with cardiomyopathy following hip arthroplasty; blood/cardiac Co: highest reported blood and cardiac cobalt levels.
and pseudotumour formation. Cardiac function recovered in 15 cases following hip revision. However, in nearly one-quarter cases ($n=6$), cardiac function remained significantly impaired despite the improvement of Co levels. Three of these “poor responders” had further deterioration of cardiac function and developed fatal multisystem failures. Two patients had left ventricular assist device implanted and one patient had cardiac transplant.

Eight cases of Co toxicity-related CMP were confirmed in definite group5–11 (Table 3) based on confirmed histopathology features of Co toxicity of cardiac tissue and systemic signs of Co toxicity and no pre-existing risk factors of CMP. This group had the highest mean blood Co level of $1217 \text{ mg/L}$ with a range of $122–6521 \text{ mg/L}$.

Chelation therapy was initiated in seven cases upon a diagnosis of Co toxicity, which led to a reduction in serum Co concentrations but required additional measures for clinical improvement including hip revision and cardiac function support. Different types of therapies used include N-acetyl-cysteine,19 2,3-dimercaptopropane-1-sulfonate 21 and ethylenediaminetetraacetic acid.22

Five reported cases died of progressive deterioration of clinical presentation. In all of these cases, cardiac Co toxicity was confirmed either on biopsy or autopsy. Cerebrovascular accident was cause of death in three cases and other two died of multisystem failure. Three patients had revision of hip replacements but other two were not fit enough for any surgical procedure. Three of these patients received chelation therapy for Co toxicity.

### Discussion

Several million MoM implants have been used worldwide since the emergence of second-generation arthroplasty implants. However, 23 cases of metal-induced CMP are reported in the literature, currently, suggest either low incidence or lack of awareness in medical community. Recent MHRA guidelines have strongly suggested regular long-term surveillance of patients with MoM implants.

**Co-related metallosis**

Majority of the reported cases (18) described extensive tissue metallosis at the time of revision hip surgery. In MoM group, four articles reported a potential link between MoM hip implant malpositioning and metallosis. Charette et al.14 and Martin et al.11 reported excessive anteversion of acetabular components as a potential cause of excessive metal wear.

In majority of patients with revision non-MoM implants for fractured primary ceramic implants resulted in severe abrasions and destruction of metal head components secondary to retained ceramic components, leading to third body wear. This may support the reason for significantly high serum Co concentrations in comparison to cases with primary MoM. In a recent review article, Rambani et al.26 have recommended against the use of metal articulations in revision procedures for fractured ceramic components, and we endorse this recommendation.

### Histopathology of Co-related CMP

Histopathology of myocardial tissue demonstrated myocardial hypertrophy and interstitial fibrosis in all reported cases, where either biopsy or autopsy was performed. These were generic features for any CMP. In our review, some studies also reported Co toxicity specific features, including increased vacuolation and lipofuscin,11,12 myofiber disarray13,16 and abnormal mitochondrial forms with

### Table 4. Mean age, gender distribution and time to presentation – categorized into MoM and non-MoM groups.

| Number of cases | Mean age | Time to presentation (years) |
|-----------------|----------|-------------------------------|
| MoM             | 12       | 58                            |
| F               | 4        | 63                            |
| M               | 8        | 55                            |
| Non-MoM         | 11       | 56                            |
| F               | 2        | 63                            |
| M               | 9        | 54                            |
| Grand total     | 23       | 57                            |

MoM: metal-on-metal; M: male; F: female.

### Table 5. Mean blood cobalt levels categorized by implant type and further stratified in three categories according to criteria in Table 2 (described in “Materials and methods” section).

| No of cases | Average of blood cobalt ($\mu$g/L) |
|-------------|-----------------------------------|
| MoM         | 12                                |
| Definite    | 4                                 |
| Probable    | 7                                 |
| Non-causal  | 1                                 |
| Non-MoM (MoP/MoC) | 11                            |
| Definite    | 4                                 |
| Probable    | 6                                 |
| Non-causal  | 1                                 |
| Grand total | 23                                |

MoM: metal-on-metal; MoP: metal-on-polyethylene; MoC: metal-on-ceramic.
electron-dense deposits.\textsuperscript{6,7,10,22} Myocardial biopsy may help in diagnosis of Co CMP in suspected cases.

**Role of chelation therapy**

The chelating agent is a chemical, which binds metal (Co) and aids its renal excretion, thus reducing metal ion load in the body. In our review, different substances were used as chelating agents in seven cases. Although all such cases reported good outcome in terms of blood Co levels, all the authors suggested chelation therapy as an adjunct in management. Removal of the causative implant remains the recommended treatment, although chelation therapy can help to normalise Co levels while waiting for surgery or in patients who are not fit for any surgical intervention. If chelation therapy is initiated, patients kidney function should be monitored as it relies on renal excretion and Co toxicity that can lead to renal impairment.

**Managing Co-related CMP**

Lack of awareness in medical community has led to delay in timely diagnosis of metal-induced CMP. In one reported case, diagnosis of Co toxicity-related CMP was not made upto 4 years after initial presentation. However, in majority of reported cases, patients recovered from CMP after the removal of causative implant and with appropriate medical treatment.

Although a recent observational study by Lodge et al.\textsuperscript{27} has not shown a significant increase in cardiac dysfunction in patients with MoM hip arthroplasty, Lassalle et al.\textsuperscript{28} following a review of the French national health insurance database (255,350 patients) have recommended regular monitoring of cardiac function in patients with metal head hip arthroplasties, particularly with MoM articulation in women and older patients.

**Recommendations**

We recommend, based on the analysis of the above literature and MHRA guidelines, establishing a local framework for robust and cost-effective surveillance programme for the selected group of patients with hip implants, including MoM implants and all patients revision hip implants for fractured ceramic components.

If patient gives a history of new onset features of Co toxicity or cardiac symptoms and serum cobalt levels are above MHRA acceptable threshold for metal hips (7 ppb),\textsuperscript{1} cardiology review is advised to exclude cobalt-related CMP.

Diagnosis of CMP may be aided by investigations, including cardiac tissue biopsy, cardiac tissue cobalt levels and contrast-enhanced cardiac magnetic resonance scan.

Once a diagnosis of Co toxicity is established, the patient will benefit from the removal of causative implant and debridement of affected tissues to lower systemic Co concentration. Management of cardiac and systemic symptoms will be according to the clinical presentation. Chelation therapy can play a role in certain cases, where surgery is either delayed or not possible.

**Conclusion**

Co-related CMP has been reported in relatively very low number of cases of metal hip arthroplasty, however, a delay in diagnosis may lead to significant morbidity and mortality. All patients with MoM hip replacement and patients with a history of fractured ceramic components should be offered long-term surveillance for clinical, biochemical...
and/or echocardiographic features of Co toxicity. Timely diagnosis, removal of causative implant and avoidance of metal articularations in revision for fractured ceramic implants may help in effective management.

Limitations
This review only includes case reports. However, to our knowledge, this is the largest review study on Co-related CMP in hip arthroplasty patients.

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