Systematic review
Cobalt cardiomyopathy in hip arthroplasty

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Abstract

Background: Cobalt toxicity-related cardiomyopathy in hip arthroplasty has recently been reported in the literature. The purpose of this review is to identify and assess available published evidence of cardiomyopathy in hip arthroplasty patients and to derive recommendations for management.

Methods: We evaluated 23 cases reported until October 2018 and stratified them into 3 categories, based upon pre-existing risk factors for cardiomyopathy, histological confirmation, and evidence of systemic signs of cobalt toxicity.

Results: Cobalt toxicity was considered to be the definite cause of cardiomyopathy in 8 cases, and probably contributory in 13 cases. Two cases were considered to have developed cardiomyopathy secondary to pre-existing risk factors. Majority of the patients had a good recovery of cardiac function after hip revision and cardiac management, but 5 cases deteriorated and died.

Conclusions: Although cobalt-related cardiomyopathy 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 an effective management.

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Introduction and background

Cobalt toxicity has been reported in the literature as an occupational hazard in the hard metal industry, diamond polishing, and mineral assay industry. Hip arthroplasty-related cobalt toxicity has been associated with significant morbidity and mortality and has been highlighted recently in the literature, which generated some media attention. Among other clinical manifestations of cobalt toxicity, cardiomyopathy (CMP) has been reported in some studies [1,2]. Medical and Healthcare products Regulatory Agency (MHRA) has recently recommended surveillance guidelines of patients with metal-on-metal (MoM) hip arthroplasty to identify any local or systemic signs of metal toxicity [3].

Hip prosthesis bearing surfaces may be made of metals such as cobalt, chromium, stainless steel, or non-metal materials such as ceramic or polyethylene. Metal ions, such as cobalt and chromium, are generated from corrosion of fixed and modular components of the prosthesis, abrasion between bearing surfaces of prosthesis, and micro-movements of failing components of the modular implant. The cobalt bivalent ions predominantly are responsible for systemic and local tissue reactions, whereas chromium trivalent ions are reduced rapidly in biological systems [4].

High systemic concentration of cobalt ions leads to a specific form of CMP, along with other systemic effects like neurological symptoms, hypothyroidism, and polycythemia [5]. This particular type of CMP was first reported in individuals with high intake of cobalt-containing beer and its features were distinctive from previously known features of this condition [6]. Recently, this type of CMP has been reported in patients with hip arthroplasty.
The purpose of this review is to evaluate all published case reports of cobalt-related CMP in patients with hip arthroplasty. Our aim is to identify the scale and discuss salient features and management of this condition.

**Material and methods**

A search of PubMed and Embase databases was conducted to identify relevant studies using terms (cardiomyopathy and [cobalt or metal] and [hip or replacement or arthroplasty]) until October 2018 (1965-2018). We removed duplicates and screened references for case reports of CMP in metal hip implant patients (Fig. 1). Two reviewers (M.U., M.F.K.) independently screened articles and assessed for quality. We excluded articles which did not state that the patient had cobalt-related CMP (Appendix 1). A total of 21 articles which described 23 cases of CMP in patients with metal hip arthroplasty implants were included in this study (Appendix 2).

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

The selected cases were categorized into 3 sub-groups (Table 2), based on histopathology evidence, systemic cobalt toxicity features, and presence/absence of risk factors of CMP.

- **Definite group (cobalt toxicity likely cause of CMP)**
  - Patients with confirmed cobalt-related CMP on a histopathological study of cardiac tissue AND have evidence of systemic features of cobalt toxicity (Table 1) AND
  - No pre-existing risk factors for CMP (Table 1)

- **Probable group (cobalt toxicity may have contributed toward CMP)**
  - Patients with confirmed cobalt-related CMP on a histopathological study of cardiac tissue OR patients with systemic features of cobalt toxicity (Table 1) AND
  - Have pre-existing risk factors for CMP (Table 1) before hip replacement

- **Non-causal group (cobalt 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 cobalt toxicity

**Results**

The cases were categorized as 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 the 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 the MoM group, mean blood cobalt level was lower compared to the non-MoM group (322 ppb vs 1041 ppb) (Table 4).

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

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, and pseudo-tumor formation. Cardiac function recovered in 15 cases following hip revision. However, in nearly one-fourth of the cases (n = 6), cardiac function remained significantly impaired despite improvement in cobalt levels. Three of these “poor responders” had further deterioration of cardiac function and developed fatal multi-system failures. Two patients had left ventricular assist device implanted and 1 patient had cardiac transplant.

Eight cases of cobalt toxicity-related CMP were confirmed in the definite group [7-13] (Appendix 1) based on the following...
combination of histopathology features: cobalt toxicity of cardiac tissue, systemic signs of cobalt toxicity, and no pre-existing risk factors of CMP. This group had the highest mean blood cobalt level of 1217 ppb (range 122-6521).

Thirteen cases were included in the probable group [13-23] based on the presence of either cardiac histopathology or cobalt systemic toxicity features and evidence of pre-existing risk factors for CMP (Table 3). Mean blood cobalt level was 425 ppb (range 112-1556).

The 2 cases [24,25] in the non-causal group had pre-existing risk factors of CMP and no evidence of cardiac or systemic cobalt toxicity features (Table 4). Blood cobalt levels in these cases were 45 ppb and 14 ppb.

Chelation therapy was initiated in 7 cases upon a diagnosis of cobalt toxicity which led to a reduction in blood cobalt concentrations, but required additional measures for clinical improvement including hip revision and cardiac function support. Different types of therapies used include N-acetyl-cysteine [26], 2,3-dimercaptopropane-1-sulfonate [18], and ethylene diamine tetra-acetic acid [17].

Five reported cases died of progressive deterioration of clinical presentation. In all of these cases, cardiac cobalt toxicity was confirmed either on biopsy or autopsy. Cerebrovascular accident was determined as the cause of death in 3 cases and multi-system failure was the cause of death in the additional 2 patients. Three patients had revision of hip replacements, but other 2 were not fit enough for any surgical procedure. Additionally, 3 of these patients received chelation therapy for cobalt toxicity.

**Discussion**

Several million MoM implants have been used worldwide since the emergence of second-generation arthroplasty implants. However, only 23 cases of metal-induced CMP are reported in the literature, currently, which suggests 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.

**Cobalt-related metallosis**

Majority of the reported cases (18) described extensive evidence of adverse local tissue reaction at the time of revision hip surgery. In the MoM group, 4 articles reported a potential link between MoM hip implant malpositioning and metallosis. Charette et al [21] and Martin et al [13] reported excessive anteversion of acetabular components as a potential cause of excessive metal wear.

A majority of patients with non-MoM implants for fractured primary ceramic implants, evaluated in this review, had 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 blood cobalt concentrations in comparison to cases with primary MoM, although this is speculation due to a lack of causal evidence to support. In a recent review article, Rambani et al [27] have recommended against the use of metal articulations in revision procedures for fractured ceramic components, and we endorse this recommendation.

**Histopathology of cobalt-related cardiomyopathy**

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 cobalt toxicity-specific features including increased vacuolation and lipofuscin [13,15], myofiber disarray [16,23], and abnormal mitochondrial forms with electron dense deposits [8,9,12,17]. Myocardial biopsy may help in the diagnosis of cobalt CMP in suspected cases.

**Role of chelation therapy**

The chelating agent is a chemical which binds metal (cobalt) and aids its renal excretion, thus reducing metal ion load in the body. In our review, different substances were used as chelating agents, in 7 cases. Although all such cases reported good outcome in terms of blood cobalt 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 normalize cobalt levels while waiting for surgery or in patients who are not fit for any surgical intervention. If chelation therapy is initiated, patient’s kidney function should be monitored as it relies on renal excretion and cobalt toxicity can lead to renal impairment.

**Table 1**

Risk factors for cardiomyopathy, features of cobalt-related cardiomyopathy, and systemic features of cobalt toxicity.

| Risk factors for cardiomyopathy | Features of cobalt-related cardiomyopathy | Systemic/local features of cobalt toxicity |
|--------------------------------|------------------------------------------|------------------------------------------|
| - Protein deficiency          | - Exertional dyspnea                      | - Elevated myocardial cobalt levels      |
| - Thiamine deficiency         | - Palpitations                            | - Polycythemia                           |
| - Heavy alcohol consumption   | - Orthopnea                               | - Hypothyroidism                         |
| - Obesity                     | - Pericardial effusion                    | - Loss of hearing                        |
| - Renal impairment            | - Dilated cardiomyopathy                  | - Loss of vision                         |
| - Hypercholesterolemia        | - Reduced LVEF                            | - Paraesthesia                           |
| - Diabetes                    | - Absence of ischemia and other common causes of cardiomyopathy like amyloidosis and autoimmune conditions | - Groat or thigh pain                    |
| - Malnutrition                |                                           | - Soft tissue swelling                   |

**Table 2**

Three categories of cases with reported cardiomyopathy based on cobalt toxicity as cause of presentation.

| Risk factors of CMP | Systemic features of cobalt toxicity | Histopathology confirmation of cobalt toxicity |
|---------------------|-------------------------------------|-----------------------------------------------|
| Definite            | No                                  | Yes                                           |
| Probable            | Yes                                 | Yes (maybe)                                   |
| Non-causal          | Yes                                 | No                                            |

**Table 3**

Mean age, gender distribution, and time to presentation: categorized into MoM and non-MoM groups.

|                  | Number of cases | Mean age | Time to presentation (y) |
|------------------|-----------------|----------|--------------------------|
| MoM              | 12              | 58       | 2.5                      |
| Female           | 4               | 63       | 2.0                      |
| Male             | 8               | 55       | 2.8                      |
| Non-MoM          | 11              | 56       | 2.6                      |
| Female           | 2               | 63       | 1.4                      |
| Male             | 9               | 54       | 2.8                      |
| Grand total      | 23              | 57       | 2.5                      |
Managing cobalt-related cardiomyopathy

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

Although a recent observational study by Lodge et al[28] has not shown a significant increase in cardiac dysfunction in patients with MoM hip arthroplasty, Prentice et al[29] found potentially deleterious effects on left ventricular function in their cross-sectional study at 8 years after implantation of MoM hip prosthesis. Similarly, Lassalle et al[30] following a review of 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 program for selected group of patients with hip implants including MoM implants and all patients with revision hip implants for fractured ceramic components. If a patient gives a history of new onset features of local or systemic cobalt toxicity or cardiac symptoms [Table 1], and blood cobalt levels are above MHRA acceptable threshold for metal hips (7 ppb)[3], a cardiology review is advised to exclude cobalt-related CMP.

Diagnosis of CMP may be aided by investigations including echocardiography, cardiac tissue biopsy, cardiac tissue cobalt levels, and contrast-enhanced cardiac magnetic resonance scan. Echocardiography can be a very effective tool, as the progenitor of symptomatic cardiac cobalistis is diastolic dysfunction that is easily graded with echocardiography. Moreover, it is readily available and a very cost effective investigation, when compared with cardiac magnetic resonance imaging.

Once a diagnosis of cobalt toxicity is established, the patient will benefit from removal of causative implant and debridement of affected tissues to lower systemic cobalt 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.

Limitations

This review only includes case reports (level IV evidence). However, to our knowledge, this is the largest review study on cobalt-related CMP in hip arthroplasty patients. Further research is needed to properly evaluate this important issue.

Conclusions

Cobalt-related CMP has been reported in a relatively very low number of cases of metal hip arthroplasty. However, it may be the tip of the iceberg, as for every published case report, there are likely hundreds of similar severity unrecognized or recognized and not reported cases. A delay in diagnosis may lead to significant morbidity and mortality. All patients with MoM hip replacement and patients with history of fractured ceramic components should be offered long-term surveillance for clinical, biochemical, and/or echocardiographic features of cobalt toxicity. Timely diagnosis, removal of causative implant, and avoidance of metal articulations in revision for fractured ceramic implants may help in an effective management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.artd.2019.04.010.

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Table 4

Mean blood cobalt levels categorized by implant type and further stratified into 3 categories according to criteria in Table 2 (described in the Material and methods section).

| No of cases | Average of blood cobalt (ppb) |
|-------------|-----------------------------|
| MoM         | 12                          | 322                          |
| Definite    | 4                            | 222                          |
| Probable    | 7                            | 422                          |
| Non-causal  | 1                            | 14                           |
| Non-MoM (MoP/MoC) | 11 | 1041                      |
| Definite    | 4                            | 2212                         |
| Probable    | 6                            | 427                          |
| Non-causal  | 1                            | 45                           |
| Grand total | 23                           | 666                          |

MoC, metal-on-ceramic; MoM, metal-on-polyethylene.
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