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ORIGINAL STUDY

Cobalt related cardiomyopathy in hip arthroplasty is a complication of concern. A review of published evidence

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Cobalt toxicity related cardiomyopathy in hip arthroplasty has recently been reported in the literature. Purpose of this review was to identify and assess available published evidence of cardiomyopathy in hip arthroplasty patients and to derive recommendations for management.

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

Cobalt toxicity was considered to be the definite cause of cardiomyopathy in 8 cases, and probably contributory in 13 cases. 2 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.

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.

Keywords : Cardiomyopathy ; cobalt ; metal on metal ; hip arthroplasty ; toxicity.

INTRODUCTION

Cobalt toxicity have been reported in literature as occupational hazard in hard metal industry, diamond polishing and mineral assay industry. Hip arthroplasty related cobalt toxicity with significant morbidity and mortality have been highlighted recently in literature, which generated some media attention. Among other clinical manifestations of cobalt toxicity, cardiomyopathy (CMP) has been reported in some cases. Medical and Healthcare products Regulatory Agency (MHRA) has recently recommended surveillance guidelines of patients with Metal-on-Metal hip arthroplasty to identify any local or systemic signs of metal toxicity*(15)*.

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Hip prosthesis bearing surfaces may be made of metals such as cobalt (Co), chromium (Cr), 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 micromovements 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 *(14)*.

High systemic concentration of cobalt ions lead to a specific form of cardiomyopathy, along with other systemic effects like neurological symptoms, hypothyroidism and polycythemia *(6)*. This particular type of cardiomyopathy was first reported in individuals with high intake of cobalt containing beer and its features were distinctive from previously known features of this condition *(17)*. 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 cobalt related cardiomyopathy 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 "(cardiomyopathy and (cobalt or metal) and (hip or replacement or arthroplasty))" till October 2018. Two reviewers (MU, MFK) independently ; screened articles, assessed for quality and extracted data, from 21 articles which described 23 cases of cardiomyopathy in patients with metal hip arthroplasty implants (table III).

Data collection included patient demographics, potential risk factors for cardiomyopathy (table I), type of hip implants, presentation of cardiomyopathy, serum cobalt levels, systemic cobalt toxicity features (table I) and outcomes.

The selected cases were categorised into three sub-groups (table II), based on histopathology evidence, systemic cobalt toxicity features and presence/absence of risk factors of cardiomyopathy.

Definite Group (cobalt toxicity likely cause of cardiomyopathy) :

○ Patients with confirmed cobalt related cardiomyopathy on a histopathological study of cardiac tissue AND have evidence of systemic features of cobalt toxicity (table I)

AND

Table I. — 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 features of cobalt toxicity
○ Protein deficiency ○ Thiamine deficiency ○ Heavy alcohol consumption ○ Obesity ○ Renal impairment ○ Hypercholesterolemia ○ Diabetes ○ Malnutrition	○ Exertional dyspnoea ○ Palpitations ○ Orthopnoea ○ Pericardial effusion ○ Dilated cardiomyopathy ○ Reduced LVEF ○ Absence of ischaemia and other common causes of cardiomyopathy like amyloidosis, autoimmune conditions	○ Elevated myocardial Co levels ○ Polycythemia ○ Hypothyroidism ○ Loss of hearing ○ Loss of vision ○ Paraesthesias

Table II. — Three categories of cases with reported cardiomyopathy based upon cobalt toxicity as cause of presentation

	Risk factors of CMP	Systemic features of Co toxicity	Histopathology confirmation of Co toxicity
Definite	No	Yes	Yes
Probable	Yes	Yes	Yes (may be)
Non-causal	Yes	No	No

Table III. — Summary of cases of cardiomyopathy in patients with hip arthroplasty

Reference	Age/Sex *Risk Factors*	Implant	Time	Blood / Cardiac Co (ug/L)	Presentation	Outcome
Tilney et al.*(24)*	40/M *NR*	MoM	4yr	246 / NR	Exertional dyspnoea, palpitations, orthopnoea, LV failure with hypertrophy, pericardial effusion, LVEF decreased to 20% with advanced diastolic dysfunction – no ischaemia *Histo - Perivascular fibrosis and vacuolation of cardiomyocytes*	Hip revised (severe metallosis) – improved in 5 months (LVEF=45-50%)
Martin et al.*(13)*	64/F *NR*	MoM	2yr	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. *Histo - Co toxicity*	Hip revised (severe metallosis) – deteriorated – CVA - DIED
Moniz et al.*(16)*	58/F *NR*	MoM	10yr	169 / NR	Heart failure with non-ischaemic dilated cardiomyopathy and severe biventricular dysfunction. Idiopathic fibrosing on MR. Advanced multiorgan failure lead to cardiac transplant *Histo - Cardiomyocyte dis-array*	Cardiac transplantation – two years later hip revision (extensive metallosis) – metal levels and cardiac function normalised
Tower et al.*(25)*	49/M *NR*	MoM	11m	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.*(25)*	49/M *NR*	MoM	1yr	23 / NR	Cognitive impairment, vertigo, hearing loss, groin pain, rashes and dyspnoea	Hip revised (severe metallosis) – satisfactory recovery of systemic symptoms
Charette et al.*(3)*	46/M *AVN hip*	MoM	2yr	1556 / NR	Dyspnoea on exertion, increased abdominal girth, dilated cardiomyopathy with LVEF 20%. *Histo – No cobalt toxicity, no amyloidosis*	Repeated admissions for heart failure – LVAD – no improvement – BL hip revisions (severe metallosis) – good recovery clinically
Machado et al.*(12)*	75/M *DM II, renal impairment, high BMI, Hypercholesterolemia, CA Prostrate*	MoM	6yr	11.96 / NR	Dilated cardiomyopathy, LVEF 21% - no ischaemia, worsening failure - AF	Hip revised – marked improvement – LVEF 45%
Mosier et al.*(18)*	54/M *Obesity*	MoM - Bilateral	11m	189 / NR	Exertional chest tightness, fatigue, diaphoresis, non-ischaemic diastolic dysfunction with LVEF 30%, mild renal impairment, lower limb paraesthesia *Histo - Cobalt cardiomyopathy – myocyte hypertrophy with interstitial fibrosis. Scattered myofibres with large cytoplasmic vacuoles*	BL hip revisions (extensive metallosis) – Good hip outcome with reduced metal ion levels – cardiac status worsened – LVAD – cardiac transplant
Samar et al.*(23)*	54/M	MoM - Bilateral	NR	120 / NR	Worsening heart failure, biventricular dysfunction – LVEF 36% - cobalt cardiomyopathy on MR *Histo - Negative for amyloidosis*	Bilateral Hip Revision – metal levels improved but cardiac function remained poor – LVAD inserted

Khan et al.*(9)*	69/F *Hypertension, mild renal impairment, Bilateral THR*	MoM	2yr	200 -300 / NR	CCF, LVEF 25-30%, pericardial effusion, normal angiography, dilated cardiomyopathy *Histo - Myocyte hypertrophy with interstitial fibrosis*	Failed medical treatment – repeated admissions – decreasing LVEF 14% - cardiogenic shock – advanced heart failure support – Biventricular assist device – Hip revised – haemorrhagic stroke - Died
Allen et al.*(1)*	59/F *Polyarthritis*	MoM - Bilateral	3yr	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 58%
Giampreti et al.*(8)*	75/M NR	MoM	5yr	352.6 / NR	Hip pain, metallosis, asthenia, dilated cardiomyopathy with global hypokinesis and LVEF 32%. Pericardial effusion, raised pulmonary pressure (43mmHg)	Hip revision followed by Chelation therapy – significant improvement clinically
Apel et al.*(2)*	65/M *Obesity, Hypercholesterolemia, hypertension, DM, THR*	CoC - fractured head - MoC	5yr	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
Pelclova et al.*(20)*	56/M *High BMI, Hypertension, DM*	CoC – fractured liner – MoP	20m	930 / NR	Paraesthesia, walking difficulties, weight loss, bilateral sensory-neural hearing loss, pericardial effusion and hypertrophic cardiomyopathy, hypothyroidism, sensory motor peripheral polyneuropathy all 4 limbs	Chelation therapy – Revision Hip (severe metallosis) – systemic symptoms improved except deafness
Choi et al.*(4)*	52/M *Hypertension, Alcohol, AVN of femoral head*	CoC – fractured head – MoP	2yr	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.*(4)*	46/M *Hypertension, CKD 3, AVN femoral head*	CoC – fractured head – CoP – fractured head – MoP	6yr	111.98 / NR	Dyspnoea, orthopnoea with LVEF 24% and pericardial effusion. Progressed to advanced heart and kidney failure *Histo - Nonspecific degeneration and fibrosis 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 thearpy – Cardiac transplantation – good recovery of cardiac & everyday function
Oldenburg et al.*(19)*	55/M *No*	CoP – fractured head – MoP	2m	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 *Histo - Interstitial fibrosis*	Hip revision (severe metallosis) – improvement of systemic symptoms in 5 months – metal levels improved

Zywiel et al.*(28)*	46/M *NR*	CoC – fractured liner – MoP	6m	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 mohts post exposure
Fox et al.*(7)*	60/F *NR*	CoC – fractured liner – MoP	10m	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 *Histo - Autopsy – Co in heart muscle cells*	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.*(21)*	71/M *DM, Multiple Myeloma*	CoC – fractured liner – MoP	2m	596.5 / NR	Hypothyroidism, asymmetrical hearing loss, visual impairment, vertigo, weight loss, cerebrovascular accident *Histo - Hypertrophic heart on autopsy with no coronary disease*	Revision planned – CVA – Chelation therapy – deteriorated - Died
Dahms et al.*(5)*	55/M *NAD, B/L THR*	CoC – fractured implant – MoP	2yr	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. *(26)*	40/M *Haemochromatosis*	CoC – fractured liner – MoP	8yr	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.*(27)*	66/F *DM, Cornory artery disease, Myocardial hypertrophy*	CoC – fractured implant - MoP	2yr	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 *Histo - cardiomyocytic degeneration, vacuolation, atrophy, as well as mild fibrosis*	Hip revision (extensive metallosis) – good recovery of hip function – some improvement in cardiac function – limited improvement in visual and hearing symptoms

NR = not reported. Time = time to presentation with cardiomyopathy following hip arthroplasty. Blood/Cardiac Co = highest reported blood and cardiac cobalt levels

○ No pre-existing risk factors for cardiomyopathy (table I)

Probable Group (cobalt toxicity may have contributed towards cardiomyopathy) :

○ Patients with confirmed cobalt related cardiomyopathy on a histopathological study of cardiac tissue OR Patients with systemic features of cobalt toxicity (table I)

AND

○ Have pre-existing risk factors for cardiomyopathy (table I) before hip replacement

Non-causal Group (cobalt toxicity unlikely to be the cause of cardiomyopathy) :

○ Have pre-existing risk factors for cardiomyopathy (table I) before hip replacement

○ No evidence of systemic or cardiac cobalt toxicity

RESULTS

The cases were categorised in to Metal on Metal (MoM) (n=12) and non-MoM group (n=11). Non-MoM group included Metal on Ceramic (MoC) (n=1) and Metal on Polyethylene (MoP) (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 IV). The mean time to presentation with symptoms of cardiomyopathy following hip procedure was comparable (MoM :2.5 years vs non-MoM :2.6 years). In MoM group, mean blood cobalt level was lower compared to non-MoM group (322 mg/L vs 1041 mg/L) (table V).

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

21 cases had their hips revised and a majority (n=18) had reported extensive local tissue signs of metallosis such as discolouration, degeneration, fluid collections and pseudo-tumour formation. Cardiac function recovered in fifteen cases following hip revision. However, in nearly one-fourth cases (n=6), cardiac function remained significantly impaired despite improvement of cobalt levels. Three of these "poor responders" had further deterioration of cardiac function and developed fatal multisystem failures. Two patients had LVAD (Left ventricular assist device) implanted and one patient had cardiac transplant.

8 cases of cobalt toxicity related CMP were confirmed in definite group *(1,5,7,13,19,25,28)* (table III) based on confirmed histopathology features of cobalt toxicity of cardiac tissue and systemic signs of cobalt toxicity and no pre-existing risk factors of cardiomyopathy. This group had the highest mean

Table IV. — Mean age, gender distribution and time to presentation – categorised in to MoM and Non MoM groups

	Number of cases	Mean Age	Time to Presentation (yrs)
MoM	**12**	**58**	**2.5**
F	4	63	2.0
M	8	55	2.8
Non MoM	**11**	**56**	**2.6**
F	2	63	1.4
M	9	54	2.8
Grand Total	23	57	2.5

Table V. — Mean blood cobalt levels categorised by implant type and further stratified in three categories according to criteria in table II (described in materials and methods)

	No of cases	Average of Blood Cobalt (mg/L)
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**

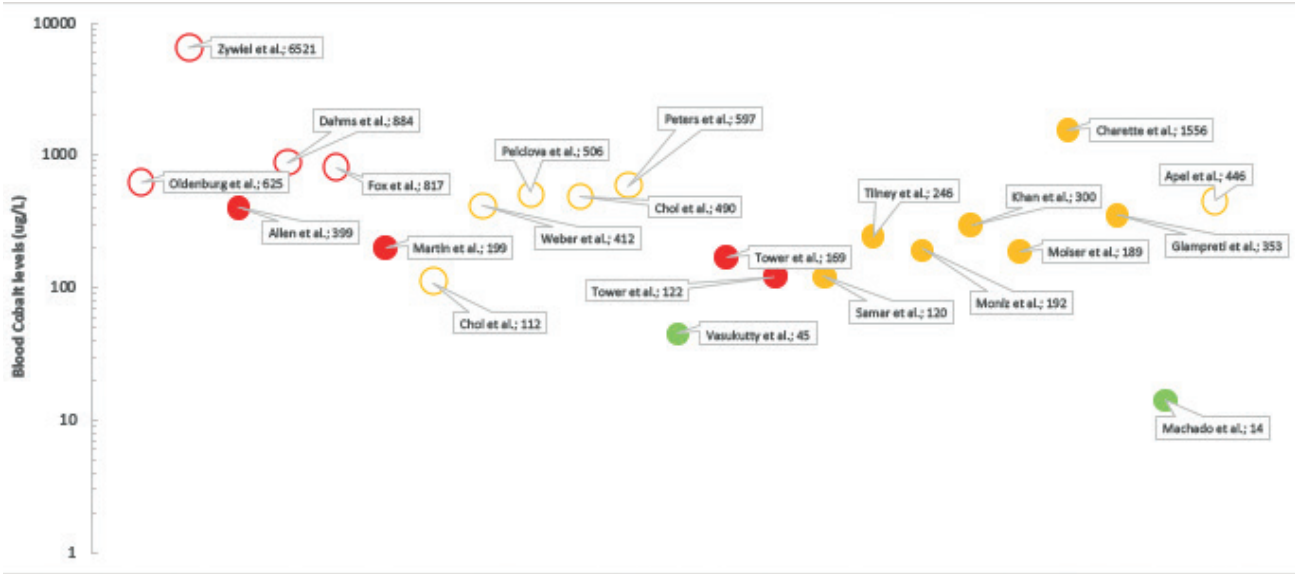

Figure I. — Blood cobalt levels of all studies

Key : Colour shows categories with reference to cobalt toxicity as cause of CMP - Red: Definite ; Yellow : Probable ; Green : Non-causal. Shape shows type of implant - Solid Circle : MoM ; Empty Circle : Non MoM (MoP or MoC).

blood cobalt level of 1217 mg/L with a range of 122 mg/L to 6521 mg/L.

Thirteen cases were included in the probable group *(2,3,4,8,9,13,16,18,20,21,23,24)* based on the presence of either cardiac histopathology or cobalt systemic toxicity features and evidence of pre-existing risk factors for cardiomyopathy (table IV). Mean blood cobalt level was 425 mg/L with a range of 112 to 1556 mg/L.

The two cases *(12,26)*, in non-causal group, had pre-existing risk factors of cardiomyopathy and no evidence cardiac or systemic cobalt toxicity features (table V). Blood cobalt levels in these cases were 45 mg/L and 14 mg/L.

Chelation therapy was initiated in seven cases upon a diagnosis of cobalt toxicity which led to a reduction in serum cobalt concentrations but required additional measures for clinical improvement including hip revision and cardiac function support. Different types of therapies used include N-acetylecysteine (NAC) *(8)*, 2,3-Dimercaptopropane-1-sulfonate (DMPS) *(20)* and Ethylene diamine tetra-acetic acid (EDTA) *(4)*.

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 cause of death in three cases and other two died of multi system failure. Three patients had revision of hips replacements but other two were not fit enough for any surgical procedure. Three 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, 23 cases of metal induced cardiomyopathy are reported in the literature, currently, suggests either low incidence or lack of awareness in medical community. Recent MHRA guidelines has strongly suggested regular long-term surveillance of patients with MoM implants.

Majority of the reported cases (eighteen) 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. *(3)* and Martin et al. *(13)* 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 cobalt concentrations in comparison to cases with primary MoM. In a recent review article, Rambani et al. *(22)* has recommended against the use of metal articulations in revision procedures for fractured ceramic components, and we endorse this recommendation.

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 cardiomyopathy. In our review, some studies also reported cobalt toxicity specific features including increased vacuolation and lipofuscin *(13,24)*, myofiber disarray *(16,18)* and abnormal mitochondrial forms with electron dense deposits *(1,4,7,28)*. Myocardial biopsy may help in diagnosis of cobalt cardiomyopathy in suspected cases.

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 seven 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 normalise cobalt 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 cobalt toxicity can lead to renal impairment.

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

Although a recent observational study by Lodge et al. *(11)* has not shown a significant increase in cardiac dysfunction in patients with MoM hip arthroplasty, Lassalle et al. *(10)* 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.

We recommend, based on the analysis of above literature and MHRA guidelines, establishing local framework for robust and cost-effective surveillance programme for 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 cobalt toxicity or cardiac symptoms, and serum cobalt levels are above MHRA acceptable threshold for metal hips (7ppb) *(15)*, a cardiology review is advised to exclude cobalt related cardiomyopathy.

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

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.

Cobalt related cardiomyopathy 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 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 .

This review only includes case reports. However, to our knowledge, this is the largest review study on cobalt related cardiomyopathy in hip arthroplasty patients.

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