SPECIALTY UPDATE
Systemic cobalt toxicity from total hip arthroplasties

REVIEW OF A RARE CONDITION PART 1 - HISTORY, MECHANISM, MEASUREMENTS, AND PATHOPHYSIOLOGY

Recently, the use of metal-on-metal articulations in total hip arthroplasty (THA) has led to an increase in adverse events owing to local soft-tissue reactions from metal ions and wear debris. While the majority of these implants perform well, it has been increasingly recognised that a small proportion of patients may develop complications secondary to systemic cobalt toxicity when these implants fail. However, distinguishing true toxicity from benign elevations in cobalt ion levels can be challenging.

The purpose of this two part series is to review the use of cobalt alloys in THA and to highlight the following related topics of interest: mechanisms of cobalt ion release and their measurement, definitions of pathological cobalt ion levels, and the pathophysiology, risk factors and treatment of cobalt toxicity. Historically, these metal-on-metal arthroplasties are composed of a chromium-cobalt articulation.

The release of cobalt is due to the mechanical and oxidative stresses placed on the prosthetic joint. It exerts its pathological effects through direct cellular toxicity.

This manuscript will highlight the pathophysiology of cobalt toxicity in patients with metal-on-metal hip arthroplasties.

Take home message: Patients with new or evolving hip symptoms with a prior history of metal-on-metal hip arthroplasties warrant orthopaedic surgical evaluation. Increased awareness of the range of systemic symptoms associated with cobalt toxicity, coupled with prompt orthopaedic intervention, may forestall the development of further complications.

Cite this article: Bone Joint J 2016;98-B:6–13.

Cobalt is a trace metal element which is essential for normal cellular metabolism, but at high levels may lead to cellular apoptosis, 1–3 necrosis, 3–5 and oxidative DNA damage. 5,6 Historically, cobalt toxicity became a recognised clinical problem following industrial exposure, as well as iatrogenic toxicity following treatment of anaemia with cobalt-chloride tablets. 7,13 It has been used in a foam-stabilising agent in the beer industry, 14–16 which led to an increase in low-output cardiomyopathy that resolved when cobalt was removed from the manufacturing process.

Recently, there has been increased recognition of local and systemic adverse events associated with the release of cobalt ions and nanoparticles from total hip arthroplasties (THA). In the last 15 years, the introduction and use of large-diameter metal-on-metal (MoM) THAs and hip resurfacing arthroplasties, has been associated with a rise in reports of metal-related local adverse events. 17–20 In June 2012, the United Kingdom’s Medicines and Healthcare Products Regulatory Agency (MHRA) published a report which recommended annual lifetime orthopaedic follow-up and measurement serum cobalt and chromium ions, for all patients with MoM arthroplasties. This was further supported by the Scientific Committee on Emerging and Newly Identified Heath Risks in September 2014. 22 The United States Food and Drug Administration (FDA) also acknowledged the risk of cobalt toxicity and its associated signs and symptoms, in these arthroplasties. 23 However, the FDA has cautioned that currently no standard exists for accurate and reproducible measurement of cobalt and suggests further research. Similarly, the American Association of Hip and Knee Surgeons and the American Association of Orthopaedic Surgeons (AAOS) have issued similar advisory statements on metal-related adverse reactions, 24,25 although they note that most patients have well-functioning implants. In the United States, MoM articulations were used in approximately 35% of hip arthroplasties in 2006, but usage has since declined rapidly worldwide. 26,27 The
increased level of clinical vigilance has shown that adverse events are more common than previously thought, and patients may develop, potentially, systemic symptoms. This is not limited to only MoM articulations, but also other component parts of modular THAs may be implicated.

The development of systemic cobalt toxicity from hip arthroplasty appears to be very rare. Only 18 cases have been reported, ten involving MoM articulations. However, it is estimated that one million MoM hip arthroplasties had been performed in the United States and 60 000 in the United Kingdom. The large numbers of potential patients at risk, coupled with the insidious and varied presentation of cobalt toxicity, suggests that all medical specialties should be aware of the possibility of cobalt toxicity.

Although a variety of metal ions (e.g. cobalt, vanadium, and chromium) are released from prostheses and have been implicated in the development of systemic symptoms, this review will focus on cobalt toxicity. Specifically, in this article, we will review the use of cobalt alloys in THA, highlighting the following topics: historical context of cobalt in THA; mechanisms of ion release; and the pathophysiology of toxicity.

**Historical context of the use of cobalt alloys in hip arthroplasty**

While modern THA has been used for approximately half a century, the earliest designs were developed in the late 19th century. Hip arthroplasties are subjected to considerable dynamic mechanical loading in a saline environment. This requires mechanical and material stability, biocompatibility, and long-term wear resistance. Cobalt–chromium (Co–Cr) alloys were found to have one of the best combinations of high material toughness and yield strength (resistant to breakage and deformation), ductility (deformation rather than breakage), hardness, wear and corrosion resistance, within the human body, and are highly compatible with other implant metals.

Approximately 350 000 THAs are performed annually in the United States alone, and survivorship > 90% is consistently reported at 15 to 20 years with established designs. Owing to the advantageous mechanical and metallurgical properties, most contemporary THAs include components made of Co–Cr alloys. Stainless steel (another material used in femoral head and femoral component manufacture) continues to be used, particularly in Europe. Stainless steel components contain very little cobalt in comparison, and are not to be confused with Co–Cr bearings mentioned below. It is important to note that there are a large number of different implant designs available from a variety of manufacturers. For a single bearing couple, there can be considerable differences in clinical behaviour as a consequence of design differences. As a result, while there may be a ‘class-effect’ defined by the presence of a given material or articular couple (e.g. MoM), large variability exists in the risk and magnitude of metal ion release between specific implant designs, the specifics of which will be discussed in further detail below.

**Mechanisms of cobalt ion release**

Cobalt does not occur in the elemental state in vivo, but, exists as either a bi-valent (2+) or tri-valent (3+) cation that can complex with other extra- or intra-cellular molecules to form cobalt oxides, organophosphates, and chlorides. THA ion release ultimately occurs from oxidation-reduction reactions with the surrounding environment that liberate cobalt ions from metal surfaces (i.e. corrosion). This can occur on any Co–Cr component surfaces, or through oxidative particle breakdown generated by mechanical wear. Metal wear particles are smaller than the debris generated by other THA materials such as polyethylene, (measured in nanometres rather than micrometres). Because they are similar in size to typical cellular components and proteins, nanoparticles may enter the intra-cellular environment more efficiently when compared with larger debris particles and can directly affect gene transcription, or be involved in direct DNA damage. Nanoparticles are likely to have a different cytotoxicity profile than larger-sized particles.

Mechanical wear and the generation of metal particles, can occur through contact between the intended bearing surfaces; surfaces contaminated with abrasive debris (third-body wear); two non-bearing surfaces; or one intended and one unintended bearing surface. The first three mechanisms are particularly relevant to understanding abnormal cobalt ion release in hip arthroplasty, which is an inevitable consequence in all arthroplasties.

Corrosion is an electro-chemical process of oxidation-reduction reactions resulting in the release of cobalt and other ions from surfaces of cobalt-alloy implants. Like wear, it is an inevitability in all arthroplasties. Corrosion and wear occur simultaneously and may be synergistic giving rise to the term ‘tribocorrosion’. Tribocorrosion incorporates both electro-chemical (corrosion) and mechanical (tribological) behaviour of metals used in many engineering applications, including joint arthroplasty. Important tribocorrosion processes lead to significant amounts of debris include fretting corrosion of metal/metal modular junctions and the degradation of bearing surfaces in MoM THA and hip resurfacing devices.

Articulation between unintended bearing surfaces can be a source of metal particle generation. Virtually all contemporary hip arthroplasties are modular, which allows variable implant choices for patients. However, micro-motion can sometimes occur at the non-articular interface of the different components (most commonly the taper junction of head and neck). Micro-motion can initiate events resulting in localised loss of protective surface oxide layers, at the points of contact and movement, with subsequent corrosion and cobalt ion release. Recently, large-diameter femoral heads, as used in certain MoM arthroplasty designs have shown increased risk of this type of wear. Additionally, some THAs, which include additional modular junctions at the neck-stem interfaces, have shown similar increased wear. These non-articulating junctions are
sensitive to micro-motion and associated cobalt ion release. This has led to the recall of these designs by manufacturers.65

While cobalt ion release occurs in all Co-Cr components, systemic ion accumulation is limited by renal excretion, which regulates homeostasis between ion generation and loss.58-60

Abnormal wear and/or corrosion of a Co-Cr component through any mechanism can result in ongoing metal wear particles and/or cobalt ion generation. Wear particles collect peri-articularly, and can be disseminated widely in the body through the bloodstream and the lymphatic system.61

The highly acidic environment of intra-cellular phagosomes may actually promote intra-cellular corrosion of phagocytosed particles, resulting in additional cobalt ion release.62

Many factors can cause abnormal wear and/or corrosion which generate high cobalt ion levels that overwhelm the body’s ability to sequester effectively, transport, and excrete them. While certain implant materials or designs are at higher risk for these mechanisms, there is a complex interplay of implant and patient factors, which modulates risks for cobalt ion generation and toxicity.

**Pathophysiology of cobalt toxicity**

Early in vitro studies examining cytotoxicity of heavy-metal alloys used in arthroplasties demonstrated that cobalt can induce gross tissue necrosis and macrophage toxicity.53,64 Recent studies suggest that the cytotoxic effects of cobalt impair function in macrophages, fibroblasts, and osteoblasts through free radical formation and aneuploidy.65-67 This effect depends on nanoparticles dose, size, and shape as released by articular surface wear, rather than direct metal ion release alone.68 Particles which infiltrate mitochondria and macrophages may undergo rapid intracellular corrosion, producing soluble cobalt ions, which activate extrinsic and intrinsic apoptotic pathways.

Cobalt can cause apoptosis and necrosis through multiple mechanisms such as DNA fragmentation and reactive oxygen species generation.69,70 At lower doses, it leads to cellular apoptosis, while at higher doses, it leads to cellular necrosis and initiation of inflammatory cascades.

It should be noted that hip arthroplasties may cause both local and systemic effects. Systemic toxicity occurs through diffusion and transport of soluble cobalt ions generated in the peri-articular space, or the transport of metal wear particles through the lymphatic and vascular system with subsequent deposition at remote sites. Locally, solid or cystic peri-articular reactions known as ‘pseudotumours’ may form secondary to local tissue reactions. The topic of adverse local reactions has been reviewed elsewhere,71-73 so we will focus on systemic effects of implant-associated cobalt toxicity, distant to the peri-articular milieu.

**Cardiac**

Most of our understanding of cobalt-induced myocardial toxicity is derived from occupational exposure, oral treatment of anaemia or recreational consumption of beer produced using a foam-stabilising agent containing cobalt sulphate or cobalt chloride.74,75 Both the atria and the ventricles may be affected.76 Patients with cardiac cobalt toxicity typically present with shortness of breath, palpitations, and exertional chest tightness, often leading to low-output, dilated cardiomyopathy. The cardiomyopathy may induce atrial fibrillation or be complicated by pericardial effusion.

The exact pathophysiological mechanism of cobalt cardiotoxicity remains unknown. One theory proposes that cobalt interferes with cardiac myocyte uptake of oxygen through inhibition of alpha-lipoic acid sulphydryl groups in the citric acid cycle, and transmembrane transport system disruption, leading to increased intracellular calcium and inhibition of sympathetic tone.77

Various histopathological changes have been described for cobalt-related cardiac toxicity. Light microscopy reveals myofibrillar hypertrophy, interstitial fibrosis, and muscle fibre degeneration which may be vacuolar, granular, or present with myofibril dissolution.74 Loss of myofibrils, sarcoplasmic reticulum glycogen deposition, and intramyofibril deposits consistent with cobalt particles are found on electron microscopy.78 However, calcified fibrils or other deposits within myofibrils are often absent, differentiating cobalt-induced cardiomyopathy from other toxic aetiologies.

Alexander74 reported on cobalt toxic effects on myocardium in 28 beer drinkers who presented with acute-onset left ventricular failure, acidosis, and cardiogenic shock following ingestion up to 10 mg/day of cobalt in beer. Pre-disposing factors, such as inadequate protein and vitamin intake, and micronutrient deficiency may have increased patient susceptibility for this condition. Barborik and Dusek79 reported on a fatal case of dilated cardiomyopathy following four years of industrial exposure to cobalt. At autopsy, cobalt content of cardiac tissue was substantially above normal at 140 μg/100 g of the heart’s dry weight.

Recently, there have been ten reports of suspected cobalt-induced cardiac toxicity following THA.28,32,36,80-85 Gilbert et al80 reported on a fatal case of cobalt-induced dilated cardiomyopathy 14 months following revision of a ceramic-on-ceramic THA to a Co-Cr metal-on-polyethylene articulation, owing to ceramic liner fracture. The high whole blood cobalt concentration of 6521 μg/L found was reported to result from third-body abrasive wear of the Co-Cr components by residual debris from the fractured ceramic liner. Tower,35 reporting on two patients, found echocardiographic evidence of diastolic dysfunction and pericardial effusion associated with serum cobalt of 122 μg/L in a 49-year-old man who underwent MoM THA approximately three years previously. The second patient, who had a serum cobalt of 23 μg/L, did not present with cardiac symptoms. In a subsequent report of five patients by the same author (including the previous two patients), three of the five patients with ‘arthro-prosthetic’ cobaltsim following MoM THA, had evidence of cardiomyopathy.
secondary to elevated blood cobalt levels.\textsuperscript{36} Unfortunately, the author did not clearly describe the cobalt blood levels associated with cardiac dysfunction.

Despite these reports of cobalt-induced cardiomyopathy, in most cases, a direct cause-and-effect relationship with the magnitude of blood cobalt levels cannot be clearly established. It is worth noting that cardiac symptoms have almost exclusively been reported in patients with markedly elevated cobalt levels, with only one report of an afflicted patient with cobalt < 100 \textmu g/L. In addition, some of the patients appeared additionally to have poor nutritional status and/or other underlying disease states such as severe alcoholism or renal compromise,\textsuperscript{66} which could have further increased cobalt ion levels and/or contributed to the cardiac dysfunction. Lack of clear evidence, or alternative possible explanations for symptoms in these patients, suggests that it is difficult to assert that high cobalt concentrations are the single factor responsible for symptoms. However, two of the reports of cardiac dysfunction were in patients who had extremely high serum cobalt levels (> 5000 \textmu g/L) as a result of unrecognised malfunctioning hip arthroplasties. The data strongly suggest that these cobalt levels were important contributing factors to these patients’ symptoms.\textsuperscript{37,81}

**Thyroid**

Much of what is known about the thyrotoxic effects of cobalt comes from its use in the treatment of anaemia and from industrial exposure to cobalt-containing dyes.\textsuperscript{87} Patients with cobalt toxicity may develop signs and symptoms such as goitre, lassitude, lethargy, weakness, poor concentration, and diminished reflexes suggestive of hypothyroidism.\textsuperscript{1}

Cobalt can inhibit both iodine uptake and thyroperoxidase (tyrosine iodinase) activity, thereby preventing oxidation of iodide and subsequent incorporation of iodine into thyroxine.\textsuperscript{5,79}

Biopsy specimens show large, irregular follicles with a columnar, rather than cuboidal appearance, consistent with decreased activity.\textsuperscript{80} There is also epithelial hypertrophy, sparse, highly vaculated colloid (which normally contains highly iodinated thyroglobulin) and multiple papillary intra-follicular projections.\textsuperscript{80}

It is debatable whether low-level occupational exposure leads to clinically obvious hypothyroidism. The risk of hypothyroidism correlates directly with the level and duration of cobalt exposure, with high exposure levels (5 mg/day to 10 mg/day) being implicated.\textsuperscript{8} However, previous reports demonstrate that several weeks following the cessation of cobalt therapy, both hypothyroidism and goitre resolve.\textsuperscript{1} In contrast, Christensen and Poulsen,\textsuperscript{88} in their study on health effects of exposure to cobalt compounds in Danish pottery painters, found no inhibitory effects on thyroid function. They found that the ratio of T4 to T3 increased, suggestive of some interference with thyroid metabolism with cobalt exposure.

In the past years, there have been nine reports concerning hypothyroidism that potentially developed as a result of high serum/plasma levels of cobalt following THA, with cobalt levels > 250 \textmu g/L in all of these cases.\textsuperscript{32,37,80,81,84,85} Apel et al\textsuperscript{81} found gradual development of a multisystem illness over five years involving hypothyroidism, motor weakness, paroxysmal atrial fibrillation, and declining vision in a 65-year-old man following revision of a ceramic-on-ceramic prosthesis with a Co-Cr head after ceramic head fracture. The plasma cobalt level was 7567 nmol/L, with a blood chromium level of 894 nmol/L. Following re-revision with a metal head arthroplasty, there was a marked decrease in serum cobalt level, as well as general health, cardiac, and thyroid functional improvement.

Currently, no direct evidence exists which supports the cause-and-effect relationship of blood cobalt concentration < 250 \textmu g/L and thyroid dysfunction after Co-Cr THA. However, at very high serum cobalt levels (> 4000 \textmu g/L; n = 2 cases) a reversible hypothyroidism has been reported in patients with a malfunctioning THA.

**Haematology**

Historically, cobalt was used as a treatment for anaemia beginning in 1952, particularly in patients requiring haemodialysis.\textsuperscript{4-7} Cobalt-induced polycythaemia can also occur and is speculated to occur by two main mechanisms. Cobalt impairs oxidative phosphorylation.\textsuperscript{76} The resulting tissue hypoxaemia stimulates erythropoietin production by upregulating the production of Hypoxia-Inducible Factor 1 (HIF-1).\textsuperscript{89} HIF-1 is a nuclear factor that activates transcription of erythropoietin. Cobalt chloride can activate erythropoietin production directly through induction of HIF-1.\textsuperscript{89} Mutations in the HIF-1 binding site disrupt hypoxia-inducible transcription and explains why some patients do not develop secondary polycythaemia despite toxic cobalt levels. In addition, cobalt can affect cell-mediated immunity, lymphocyte reactivity, and chemokine secretion.

There is only one reported case of polycythaemia occurring as a result of cobalt toxicity following THA.\textsuperscript{80} Gilbert et al\textsuperscript{80} found that a 52-year-old patient developed fatal multisystemic illness including polycythaemia (haemoglobin 190 g/l) 14 months following hip revision to a metal-on-polyethylene articulation for ceramic liner fracture. Serum cobalt levels were found to be substantially higher than normal at 6251 \textmu g/L (N: 0.032 \textmu g/L to 0.29 \textmu g/L) following revision. There is limited evidence available to suggest a direct cause-and-effect relationship between elevated cobalt levels following THA and development of haematological abnormalities such as polycythaemia. In addition, little is known about the reversibility of the potential haematological consequences of cobalt toxicity following THA revision.

**Neurological**

Cobalt toxicity can involve a number of neurologically-related organ systems including the auditory, ocular, central, and peripheral nervous systems causing progressive...
deafness, visual loss, short-term memory loss, cognitive changes, fatigue, depression, loss-of-concentration, headaches, impaired reflexes, and vibration/position sense, as well as limb paraesthesias.80

Animal studies have shown that the neurotoxic effects of cobalt are mediated through depletion of neurotransmitters such as dopamine, noradrenaline, and serotonin80 and pre-synaptic blockade of calcium channels.86 In addition, cobalt ions induce the formation of reactive oxygen species such as hydroxyl radicals that increase oxidative stress and decrease glutathione levels. This can result in demyelination and axonal loss, and toxic damage to oligodendrocytes, which are particularly sensitive to oxidative stresses.

Case series of cobalt neurotoxicity were documented in the mid-1900s, when cobalt was used as a treatment for anaemia. Tinnitus was described after four to 16 weeks of treatment in four patients, while one patient developed sensorineural deafness after 12 weeks.82 Other patients developed paraesthesia and ataxia, associated with hypo-reflexia and impaired vibration sense.6 All symptoms resolved within three to four months of cessation of cobalt therapy. Another case described markedly decreased visual acuity when cobalt was used in the treatment of pancytopenia and hypercellular bone marrow.89 Investigations revealed reduced visual acuity bilaterally, with findings of optic disc pallor, suggestive of optic atrophy and possibly impaired choroidal perfusion. The total dose of cobalt-chloride received over three years amounted to 73 g, almost half of which was given four months before the patient's visual symptoms. While symptoms did not resolve following discontinuation of cobalt treatment, they did not progress.

Of the 18 cases of cobalt toxicity that have been described, 13 had evidence of neurotoxic manifestations.30-36,81,85,92 Of these cases, none developed symptoms of neurological dysfunction with cobalt levels below 20 μg/L, and only three had reported peak cobalt concentrations of < 100 μg/L.35,36,92 The most common neurological symptoms were paraesthesia, tinnitus, and visual loss. Peripheral nerve conduction studies were reported in three cases, with variable findings. One study identified sensorimotor abnormalities,32 one reported absent sensory, but near-normal motor function,30 while the third described mild amplitude reductions only.31 Audiometry testing demonstrating sensorineural hearing loss, has been reported in six patients.30,32,36 In all cases, neurological impairment appeared to improve over several months following revision THA, although the magnitude of improvement was variable.

Although abnormally high concentrations of serum cobalt can potentially increase the risks of progressive ocular, audio-vestibular, and cognitive impairment, it is not known whether these toxic effects are completely reversible. There have only been a limited number of cases of cobalt-induced neurotoxicity in patients with high cobalt levels following malfunctioning THAs, and symptoms have been reported over a range of ion levels.

Hepatic

Hepatotoxicity is an uncommon manifestation of cobalt toxicity because of a high toxicity threshold. The liver is the first site of cobalt accumulation causing reduced glutathione levels.44 In a population study of 582 patients, involving inhaled cobalt particles, 56% of hard metal workers experienced mild-to-moderate liver enzyme elevation, while others experienced hepatomegaly. One patient died of hepatic congestion, although the authors postulated this as secondary to congestive heart failure rather than primary hepatic pathology.87

Gross pathology demonstrated significant hyperaemia and inflammation, while light microscopy demonstrated central vein displacement, condensation of hepatocyte cytoplasm, steatosis, increased inflammatory infiltrate, and destruction of mitochondrial cristae.87 In animal studies, a dose-response relationship has been reported between elevated liver enzymes and cobalt ingestion.87 To date, there has been only one report of hepatotoxicity, as evidenced by elevated liver enzymes or serum bilirubin levels, associated with elevated serum cobalt levels following a Co-Cr containing THA. This patient had extreme blood cobalt levels (6521 μg/L), and ultimately died secondary to multi-organ failure.

Carcinogenicity and genotoxicity

The possible role of cobalt compounds in inducing carcinogenesis and genotoxicity was evaluated by the International Agency for Research on Cancer in 2003.88 They concluded that cobalt was possibly carcinogenic. There is in vitro evidence that cobalt ions can interfere with DNA repair mechanisms,80 and cobalt containing compounds have been shown to have the capacity to cause direct DNA damage.90 Sufficient evidence has been reported to support carcinogenic effects of cobalt sulphate and cobalt metal powder in animals. Human studies, however, are limited to hard metal workers exposed to cobalt dust and evaluated the subsequent development of lung cancer. This makes extrapolation of data to metal ion exposure in THA difficult. Recent evidence from the United Kingdom has shown the presence of DNA damage (aneuploidy and chromosomal translocations) in patients having cobalt-containing implants.37 Nevertheless, convincing in vivo evidence in humans is lacking.

Tharani et al,93 studied 110 792 total hip and 29 800 total knee arthroplasties, and found no causal link between arthroplasties and cancer development. They found that the total number of observed cases of cancer was 12 052 in patients who had undergone THAs, compared with 12 435 expected cases of cancer in the general population in the same time period (risk ratio (RR), 0.97, 95% confidence interval (CI) 0.95 to 0.99). In a similar study, Visuri et al94 evaluated the occurrence of cancer in patients who had undergone MoM THA compared with the general population. They found no difference in the incidence of the cancer in both groups (RR = 0.95, 95% CI 0.79 to 1.13). Similarly, a recent study using data from the National Joint Registry for England, Wales and Northern Ireland evaluated the risk
of cancer in 11,540 patients who underwent THA between 2003 and 2010. The authors stratified patients into three cohorts: MoM THA, hip resurfacing arthroplasty, and THA with other bearing surfaces. The authors demonstrated a similar cancer risk in patients with resurfacing (RR = 0.69; 95% CI 0.39 to 1.22) and THA with other bearing surfaces (RR = 0.96; 95% CI 0.64 to 1.43) compared with individuals who received MoM THA.\(^9\) Multiple Scandinavian database studies demonstrated that the cancer risk in patients who had MoM hip arthroplasties was similar to the general population.\(^4\)\(^,\)\(^9\)\(^4\)\(^-\)\(^10\)

In summary, THA remains a successful procedure for the treatment of end-stage degenerative hip disease. However, concerns have been raised about the impact of metal debris and ion release on patient morbidity and decreasing implant longevity in cobalt containing MoM articulations. Although patients who have prostheses with Co-Cr bearing surfaces, or who have implants revised to a Co-Cr component following fracture of a ceramic component, are theoretically at increased risk for systemic cobalt toxicity, this is a rare phenomenon.

There is no one symptom that is pathognomonic of cobalt toxicity, but rather it is a constellation of systemic symptoms often associated with hip pain. Given the frequently insidious nature of symptoms associated with this phenomenon, and the non-specific nature of systemic symptoms, clinicians should be aware of this rare, but potentially devastating condition, and be familiar with a systematic approach to its diagnosis. The presence of new or evolving hip symptoms in a patient with a prior history of THA warrants orthopaedic surgical referral. There has been considerable variation in the symptoms, signs, and cobalt levels associated with implant-related cobalt toxicity reported to date. Increased awareness of the range of symptoms associated with cobalt toxicity, and early orthopaedic intervention when these symptoms do occur, may forestall the development of further complications.

Author contributions:
A. C. Cheung: Writing, Literature Review, Critical Revision.
S. Banerjee: Writing, Literature Review, Critical Revision.
F. Wong: Writing, Literature Review, Critical Revision.
J. Butany: Writing, Literature Review, Critical Revision.
C. Gilbert: Writing, Literature Review, Critical Revision.
C. Overgaard: Writing, Literature Review, Critical Revision.
M. G. Zyviel: Writing, Literature Review, Critical Revision.
J. J. Jacobs: Writing, Literature Review, Critical Revision.
M. A. Mont: Writing, Literature Review, Critical Revision.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by D. J. Johnstone and first proof edited by G. Scott.

References