Mini Review

Jonathon R. Campbell and Mathew P. Estey*

**Metal release from hip prostheses: cobalt and chromium toxicity and the role of the clinical laboratory**

**Abstract**

Individuals with advanced hip disease suffer from pain, impaired hip function, and decreased quality of life. Roughly one million metal-on-metal (MoM) hip prostheses have been implanted worldwide in order to ameliorate these issues. While most MoM hip replacements are successful, some patients suffer from serious adverse effects secondary to the release of metal debris due to implant wear and corrosion. MoM hip prostheses are comprised predominantly of cobalt and chromium, and the serum concentration of these metal ions has been shown to correlate with both implant wear and the accumulation of metal debris in the periprosthetic tissue. Consequently, measurement of cobalt and chromium concentrations may be useful in the assessment of implant function and the potential for adverse effects in the follow-up of patients with MoM hip prostheses. The purpose of this Mini Review is to describe the adverse biological consequences of metal release from hip prostheses, provide an overview of the clinical utility of cobalt and chromium measurement and the current recommendations for testing, and alert laboratorians and physicians to the many challenges associated with measuring these metal ions.

**Keywords:** chromium; cobalt; hip prosthesis; metal-on-metal; metal toxicity.

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**Introduction**

In simplistic terms, the hip can be thought of as a ball and socket joint, in which the femoral head (the ball) rotates within the acetabulum (the socket). Several conditions, such as osteoarthritis, trauma, dysplasia, and osteonecrosis, can impair the function of the hip joint, resulting in loss of motion and pain. Hip function can be restored through hip replacement, in which the diseased ball and socket are replaced with synthetic components. These implants are classified according to their composition as metal (ball) on plastic (socket), ceramic-on-ceramic, or metal-on-metal (MoM). While each implant type has its own pros and cons, it remains unclear which is the most successful [1].

MoM implants are composed predominantly of cobalt and chromium. Two types of hip replacements can be performed with these prostheses [1]. In MoM total hip replacement, the patient’s femoral head is removed and replaced with a stemmed femoral component. In MoM resurfacing, the patient’s femur is preserved and capped with a metal component. MoM hip prostheses are thought to exhibit increased toughness, decreased wear, and a lower susceptibility to dislocation compared to other types of hip prostheses [2]. However, excess release of metal debris from some MoM hip implants has proven to be a serious problem.

**The problem with MoM hip prostheses**

Continuous motion of a MoM hip prosthesis causes wear of the acetabular-femoral head junction, resulting in the release of metal microparticles [2]. This metal debris can become incorporated into the periprosthetic tissue or undergo corrosion and enter the bloodstream. Corrosion of the metal prosthesis itself has also been documented [3]. As a result, patients with metal hip prostheses have higher blood cobalt and chromium concentrations than unexposed individuals [4]. It is important to note that in individuals with well-functioning metal hip prostheses, these concentrations are not thought to be toxic. However,
several studies have described patients with poorly functioning metal hip prostheses who had markedly elevated cobalt and chromium concentrations in the joint synovial fluid and blood. This was associated with several adverse biological effects (see adverse biological consequences of metal release from hip prostheses).

Several factors influence the function of metal hip prostheses, and thus the likelihood of excess metal release. Suboptimal surgical positioning and orientation of the prosthesis are correlated with elevated blood cobalt and chromium concentrations [5, 6]. Certain implant designs such as the DePuy Articular Surface Replacement (ASR) resurfacing and ASR total hip replacement are more prone to accelerated wear, especially at the bearing surfaces [7, 8]. In addition, mixing of components from different manufacturers [9] and different types of hip prostheses [10] is also thought to impede proper function. Increased physical activity, bilateral MoM hip replacement and impaired renal function may also contribute to the accumulation of metal debris in the body [1].

Adverse biological consequences of metal release from hip prostheses

Numerous studies have demonstrated that excess metal debris from hip replacements can cause periprosthetic soft tissue reactions, ultimately leading to implant failure requiring revision surgery [11–17]. In rare cases, floridly elevated blood cobalt and chromium concentrations have been documented, which were associated with severe systemic symptoms [10, 18–24].

Local effects

Metal debris can become integrated into the periprosthetic tissue, triggering local inflammatory reactions and the formation of soft tissue masses and fluid collections [11, 13, 16]. These reactions can cause tissue necrosis [14, 15] and osteolysis [17], ultimately leading to early failure of the hip prosthesis and the requirement for revision surgery. Adverse reaction to metal debris (ARMD) is a general term used to describe these harmful biological responses to metal particles. In the majority of cases, these responses are thought to represent a toxic reaction to excess release of metal particles. However, some cases of ARMD may represent a hypersensitivity of the individual to a normal amount of metal debris [16]. Patients with ARMD present with various symptoms including the presence of a palpable lump, pain, spontaneous dislocation, and nerve palsy [13, 16]. Five-year hip failure rates secondary to ARMD have been estimated to be <1% in patients with normal bearing surface wear; however, this figure is much higher (9.8%) in patients with a DePuy ASR [12].

Systemic effects

Metal debris released from hip prostheses can also enter the bloodstream. Multiple reports [10, 18–24] have described patients with metal hip prostheses who presented with serious systemic symptoms (Table 1). These include neurological symptoms such as auditory impairment/deafness [10, 18, 20–24], visual impairment/blindness [10, 22, 23], peripheral neuropathy/dysesthesia of the extremities [10, 18, 20–22, 24], and poor concentration/cognitive decline [20, 23, 24]. Other symptoms include cardiomyopathy [19–21, 23] and hypothyroidism [18, 20–22]. All patients had floridly elevated cobalt and/or chromium concentrations in their blood, serum, plasma, and/or urine, suggesting that these systemic symptoms may be due to metal toxicity as a result of excessive implant wear. Consistent with this notion, revision surgery to remove the defective metal hip prostheses resulted in lowered blood concentrations of cobalt and chromium and improved symptoms. It should be noted, however, that neurological symptoms persisted in some patients.

In an effort to understand the basis of neurological cobalt and chromium toxicity, Ikeda et al. [18] performed a sural nerve biopsy of a patient presenting with polyneuropathy (including dysesthesia of the extremities, difficulty walking, and hearing impairment). They found both evidence of axonal degeneration and elevated concentrations of cobalt and chromium in the sural nerve. This suggests that cobalt and/or chromium may induce axonopathy of the peripheral nerves, thus leading to dysesthesia of the extremities and difficulty walking. Interestingly, many of the cases of cobalt and chromium toxicity in patients with metal hip prostheses have documented elevated concentrations of these metal ions in cerebrospinal fluid (CSF) [10, 21–23]. Therefore, it seems feasible that cobalt and/or chromium may also induce axonal degeneration of cranial nerves, thus leading to visual and auditory impairment and cognitive decline. Consistent with this notion, blindness and deafness have been documented after industrial exposure to cobalt [25]. Similar symptoms were observed in patients receiving 60cobalt radiotherapy for acute lymphocytic leukemia [26], and cobalt chloride for treatment of anemia [27]. In addition, in vitro studies have demonstrated that cobalt induces cell toxicity and death [28].
Cardiomyopathy due to cobalt ingestion was described in the 1960s, when several heavy beer drinkers were hospitalized [29]. They presented with severe myocardial failure, with a mortality rate between 40% and 50%. Extensive investigations revealed that these patients drank a particular brand of beer, to which cobalt had been added as a foam stabilizer [30]. While cobalt was believed to be the essential factor that caused cardiomyopathy in these patients, other factors (such as poor nutrition and myocardial damage due to alcoholism) likely also contributed. Cardiomyopathy as a result of industrial exposure to cobalt has also been described [31].

Cobalt-induced hypothyroidism was described in the 1950s [32]. Patients treated with cobalt chloride for anemia developed thyroid hypofunction and hyperplasia as a result of impaired iodine uptake by the thyroid. Cobalt-induced goiters were also observed in some of the heavy beer drinkers described above [30]. The exact mechanism by which cobalt impairs iodine uptake by the thyroid remains unclear.

It should also be noted that concern has been raised regarding the mutagenic and carcinogenic potential of metal debris released from hip prostheses [1]. This remains an active area of research.
Recommendations regarding cobalt and chromium testing in patients with MoM hip prostheses

It has been demonstrated that serum cobalt and chromium concentrations are increased in patients with metal debris accumulation in the periprosthetic tissue (referred to as metallosis). In addition, the serum concentration of these metal ions increases with the degree of implant wear [33]. Consequently, some have suggested that measurement of cobalt and chromium concentrations should be part of the routine follow-up of patients with metal hip prostheses, as a means of assessing implant function and the risk of adverse biological consequences [33, 34]. However, this view is not universally accepted.

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK recently issued updated recommendations for managing patients with MoM hip replacements [34]. According to these recommendations, any symptomatic patient with a MoM hip replacement should be followed up annually for the lifetime of the implant. This includes both imaging [metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) or ultrasound] and blood cobalt and chromium testing. Patients with certain types of MoM implants (stemmed total hip replacements with a femoral head diameter ≥36 mm, or any type of DePuy ASR total hip replacement) should be followed up annually in the same manner, even in the absence of symptoms. Whole blood metal ion concentrations >7 parts per billion (119 nmol/L cobalt or 134.5 nmol/L chromium) suggest potential for soft tissue reaction, and should be re-assessed after a 3-month period. Abnormal imaging results and/or increasing blood metal ion concentrations should prompt consideration of the need for revision surgery. However, recommendations on what constitutes a clinically significant increase in cobalt or chromium concentrations have not been established.

In contrast to the recommendations of the MHRA, the US Food and Drug Administration (FDA) ‘currently believes there is insufficient evidence to correlate the presence of localized lesions, clinical outcomes, and/or the need for revision with specific metal ion levels for individual patients’ [35]. However, the FDA does acknowledge that increasing metal ion concentrations over time may indicate significant and/or ongoing implant wear, which may necessitate revision surgery. They suggest that monitoring of serial metal ion concentrations be considered in instances where clinical and imaging assessments imply an adverse reaction to metal debris. However, cobalt and chromium concentrations should be interpreted in the context of the complete clinical picture when contemplating further actions. According to the FDA, ‘the utility of routine screening of asymptomatic patients using diagnostic soft tissue imaging and/or blood metal ion testing has not been established’ [35].

Assessment of cobalt and chromium concentrations in biological specimens

Both inductively coupled plasma mass spectrometry (ICP-MS) and graphite furnace atomic absorption spectrometry (GFAAS) have been used to determine cobalt and chromium concentrations in biological specimens. However, ICP-MS allows for simultaneous assessment of both cobalt and chromium and has a lower limit of detection when compared to GFAAS [1]. Consequently, ICP-MS is the method of choice for assessing cobalt and chromium concentrations in patients with metal hip prostheses. It is important to note that significant pre- and postanalytical challenges exist when measuring these metal ions (Table 2).

Preanalytical challenges

Biological specimens are extremely susceptible to contamination, both from the environment and from products used in the specimen collection process. Chromium concentrations in airborne dust are up to 10,000-fold greater than normal blood chromium concentrations [2]. Consequently, extreme care must be taken to avoid exposure of specimens to room air. In addition, the majority of blood

<table>
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<td>High risk of environmental contamination</td>
<td>No universally accepted cut-offs that are indicative of local or systemic toxicity</td>
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<tr>
<td>High risk of contamination from specimen collection products</td>
<td>Unclear what constitutes a clinically significant increase in concentration</td>
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<tr>
<td>Unclear which specimen type is optimal</td>
<td>Concentration differences in various blood fractions (especially chromium)</td>
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<td></td>
<td>Results may vary between laboratories due to lack of standardization</td>
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</table>

Table 2 Challenges associated with the measurement of cobalt and chromium.
collection tubes contain both chromium and cobalt in the rubber stopper or O-ring, as does the black rubber plunger of many syringes [2]. Given the minute concentrations of cobalt and chromium in normal biological specimens, it is crucial that blood collection tubes and syringes that are certified for trace metal testing are used when obtaining specimens for measurement of the metal ions.

Measurements of both whole blood and serum metal ion concentrations are used in clinical practice. Two recent studies assessed whether cobalt and chromium concentrations in different blood fractions are interchangeable. Smolders et al. assessed the concentration of cobalt and chromium in matched whole blood and serum specimens from over 300 patients with MoM hip prostheses up to 24 months postoperatively [36]. They found that on average cobalt concentrations were slightly higher in whole blood compared to serum, whereas chromium concentrations were higher in serum compared to whole blood. Newton et al. performed a similar study on matched whole blood and EDTA plasma specimens from approximately 200 patients who had a MoM hip prosthesis implanted 8 months to 12 years beforehand [37]. Similar to the findings of Smolders et al., they concluded that chromium concentrations were significantly higher in EDTA plasma compared to whole blood. However, Newton et al. found that whole blood cobalt concentrations exhibit a 1:1 correlation with EDTA plasma cobalt concentrations. It should be noted that the median EDTA plasma cobalt concentration in the Newton et al. study was nearly double the median serum cobalt concentration in Smolders et al. study. Consequently, it is possible that the slight difference between whole blood and serum cobalt concentrations observed by Smolders et al. is simply not evident at higher cobalt concentrations. However, the possibility that differences exist between serum and EDTA plasma cobalt concentrations cannot be ruled out. Given the differences in cobalt and chromium concentrations in different blood fractions, it is critical that the same specimen type is always used when serially monitoring the concentrations of these metal ions in a given patient.

It remains controversial which specimen type is optimal for assessing cobalt and chromium concentrations. Whole blood requires less processing compared to serum, and may therefore be less susceptible to contamination. It should be stressed that the MHRA cut-off of 7 parts per billion (119 nmol/L cobalt or 134.5 nmol/L chromium) is based on metal ion concentrations in whole blood [34]. Research demonstrating a correlation between cobalt and chromium concentrations and implant wear was performed using serum samples [33]. As a result, others have recommended the measurement of serum cobalt and chromium concentration to assess MoM implant wear [2, 33].

### Postanalytical issues

There is currently no universally accepted cut-off that defines elevated cobalt or chromium concentrations in patients with metal hip prostheses. However, several threshold concentrations have been proposed (Table 3). De Smet et al. measured serum metal ion concentrations in patients scheduled for revision surgery, and found that cobalt concentrations above 19 μg/L (323 nmol/L) and chromium concentrations above 17 μg/L (327 nmol/L) were indicative of metallosis [33]. These cut-offs were derived from the lower value of the interquartile range of serum metal ion concentrations in patients with metallosis. As discussed above, the MHRA recommendations state that whole blood metal ion concentrations >7 ppb (119 nmol/L cobalt or 134.5 nmol/L chromium) suggest potential for soft tissue reaction and warrant further investigation [34]. In a study investigating the utility of cobalt and chromium concentrations in identifying failed MoM hip replacements, Hart et al. [38] suggested that the optimal cut-off is 4.97 ppb (84.5 nmol/L cobalt or 95.5 nmol/L chromium).

While the above thresholds may be useful in identifying local adverse effects of metal release from hip prostheses, patients presenting with systemic symptoms typically had much higher cobalt and/or chromium concentrations (Table 1). However, specific threshold concentrations that cause or are indicative of adverse systemic effects have not been established.

### Clinical utility of cobalt and chromium measurement

Several recent studies have assessed the utility of cobalt and chromium concentrations in identifying adverse events associated with metal hip prostheses (Table 4). Hart et al. performed a case control study to elucidate

<table>
<thead>
<tr>
<th>Study</th>
<th>Cut-off, ppb*</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Smet et al. [33]</td>
<td>Serum Co: &gt;19; Serum Cr: &gt;17</td>
<td>Metallosis</td>
</tr>
<tr>
<td>MHRA [34]</td>
<td>Whole blood Co: &gt;7; Whole blood Cr: &gt;7</td>
<td>Potential for soft tissue reaction</td>
</tr>
<tr>
<td>Hart et al. [38]</td>
<td>Whole blood Co: &gt;4.97; Whole blood Cr: &gt;4.97</td>
<td>MoM hip replacement failure</td>
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</tbody>
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Table 3 Suggested cobalt and chromium concentration cut-offs for patients with MoM hip prostheses. *Conversion factor to nmol/L: Co: ×17; Cr: ×19.2.
the sensitivity and specificity of whole blood cobalt and chromium concentrations for predicting MoM hip replacement failure [38]. They measured whole blood metal ion concentrations in patients with an unexplained failed hip prosthesis and an equal number of matched controls with a well-functioning hip prosthesis. The MHRA cut-off of 7 ppb (specimen classified as positive if either cobalt or chromium were above this threshold) yielded a sensitivity of 52% and a specificity of 89% for detecting unexplained MoM hip replacement failure. Receiver operating characteristic (ROC) curve analysis showed that a cut-off of 4.97 ppb (84.5 nmol/L cobalt or 95.5 nmol/L chromium) provided the optimal balance between sensitivity (63%) and specificity (86%). The authors concluded that whole blood cobalt and chromium concentrations are useful in discriminating between poorly functioning and well-functioning MoM hip prostheses. However, they pointed out that metal ion concentrations should be used as an adjunct to clinical assessment and other investigations.

Macnair et al. measured serum cobalt and chromium concentrations in patients with Depuy ASR hip resurfacings or total hip replacements, and performed MARS MRI to detect soft tissue reactions [39]. Using the MHRA cut-off of 7 ppb, serum chromium detected soft tissue reactions with a sensitivity of 56% and a specificity of 83%, whereas serum cobalt had a sensitivity of 56% and a specificity of 76%. The authors concluded that cobalt and chromium concentrations are not sufficient as a screening tool for the detection of soft tissue reactions, and advocated for MARS MRI imaging in all patients. Several limitations of this study should be noted, most of which were raised by the authors. First, the MHRA cut-off of 7 ppb is intended for whole blood specimens. Since this study assessed the concentration of cobalt and chromium in serum, it is likely that the MHRA cut-off is not optimal. This is particularly the case for chromium, whose concentrations are significantly higher in serum compared to whole blood [36]. Second, nearly one third of the hips assessed in this study were of one of bilateral MoM hip replacements. Patients with bilateral implants are known to have higher metal ion concentrations compared to those with unilateral hip prostheses. Lastly, the utility of cobalt and chromium concentrations in detecting soft tissue reactions were assessed independently of one another. It would have been interesting to simultaneously consider both cobalt and chromium concentrations when determining the sensitivity and specificity (i.e., classify a specimen as positive if either cobalt or chromium were above the 7 ppb threshold).

Malek et al. measured plasma cobalt and chromium concentrations in a cohort of symptomatic patients with unilateral MoM hip prostheses, and performed MARS MRI to identify ARMD [40]. Plasma cobalt or chromium above 7 ppb identified ARMD with a sensitivity of 57% and a specificity of 65%. Once again, the authors emphasized that metal ion concentrations should not be used as the only screening test for ARMD, but should be considered in combination with symptoms and imaging results.

Griffin et al. assessed whether cobalt and chromium concentrations can predict soft tissue damage in a cohort of patients who underwent revision surgery [41]. Whole blood cobalt and chromium concentrations were measured preoperatively and the presence of metallosis and/or soft tissue damage was noted during revision surgery. Using the MHRA cut-off of 7 ppb, whole blood chromium predicted soft tissue damage with a sensitivity of 29% and a specificity of 75%, whereas whole blood cobalt had a sensitivity of 65% and a specificity of 56%. Based on these results, the authors concluded that metal ion concentrations are not reliable predictors of soft tissue damage, and therefore should not be used in isolation as a trigger for surgical intervention. They suggest that patient history, physical examination, metal ion concentrations and imaging results should all be taken into account before considering revision surgery. Limitations of this study should also be noted. Cobalt and chromium concentrations were measured by several different laboratories, so the results may have been affected by laboratory specific

<table>
<thead>
<tr>
<th>Study</th>
<th>Cobalt Sensitivity</th>
<th>Cobalt Specificity</th>
<th>Chromium Sensitivity</th>
<th>Chromium Specificity</th>
<th>Cobalt or chromium Sensitivity</th>
<th>Cobalt or chromium Specificity</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart et al. [38]</td>
<td>49%</td>
<td>90%</td>
<td>38%</td>
<td>92%</td>
<td>52%</td>
<td>89%</td>
<td>MoM hip replacement failure</td>
</tr>
<tr>
<td>Macnair et al. [39]</td>
<td>56%</td>
<td>76%</td>
<td>56%</td>
<td>83%</td>
<td>ND</td>
<td>ND</td>
<td>Soft tissue reactions</td>
</tr>
<tr>
<td>Malek et al. [40]</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>57%</td>
<td>65%</td>
<td>ARMD</td>
</tr>
<tr>
<td>Griffin et al. [41]</td>
<td>65%</td>
<td>56%</td>
<td>29%</td>
<td>75%</td>
<td>ND</td>
<td>ND</td>
<td>Soft tissue damage</td>
</tr>
</tbody>
</table>

Table 4: Clinical utility of cobalt and chromium concentrations (using the MHRA 7 ppb cut-off).

ND, not determined. *Macnair et al. used serum specimens. †Malek et al. used plasma specimens. All others used whole blood specimens.
biases. As in the Macnair et al. study, the utility of cobalt and chromium concentrations in predicting soft tissue damage were only assessed independently of one another. Curiously, the mean whole blood cobalt concentration of the 23 patients without metallosis was 174 μg/L (289 nmol/L). This is several-fold higher than the median serum cobalt concentration of 3.2 μg/L (54.4 nmol/L) observed by De Smet et al. in a cohort of 16 patients without metallosis [33]. In fact, the highest serum cobalt concentration observed by De Smet et al. in a patient without metallosis was only 14 μg/L (238 nmol/L). While cobalt concentrations may be slightly higher in whole blood compared to serum [36], the reasons for the large disparity in cobalt concentrations between these studies is not clear.

Conclusions

In some patients with MoM hip prostheses, release of excess metal debris causes periprosthetic soft tissue reactions, ultimately leading to implant failure and the need for revision surgery. In rare cases, severe systemic symptoms, including neurological impairment, cardiomyopathy, and hypothyroidism, have also been reported. Cobalt and chromium concentrations may be useful in assessing implant function, potential for soft tissue reactions, and the likelihood of systemic metal ion toxicity. However, there are significant pre- and postanalytical challenges associated with their measurement. Most studies agree that cobalt and chromium concentrations should not be used in isolation when assessing a patient with a MoM hip prosthesis; they must be interpreted in the context of the complete clinical picture.

Conflict of interest statement

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