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Systemic toxicity of metal ions release from specific types of implanted medical devices: Systemic review of clinical studies

Henryk Matusiewicz [1,*] and Magdalena Richter [2]

[1] *Faculty of Chemical Technology, Poznan University of Technology, Poznań, Poland.*
[2] *Department of Orthopedics and Traumatology, Poznan University of Medical Sciences, Poznań, Poland.*

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Abstract

There is public concern over the long term systemic health effects of metal released from implanted medical devices that use metal alloys. Systemic toxic side effects have been associated with excessive metal ion release from implants into human biological specimen's circulation, in which cobalt and chromium plays an important role. Cobalt intoxication has become more frequent due to the wide use of metallic medical implants. Despite the technological improvements in replacement metallic medical implants, wear and corrosion products associated with the metal compounds of these implants may result in systemic reactions and toxicities. The current review encompasses a literature of the systemic toxicity studies concerning the effect of metallic wear debris released from wear and corrosion of specific types of implanted medical devices, resulting in a postoperative increase in metal ion levels in bodily fluids and at different organ sites. Release of metallic debris is mainly in the form of particles and ions of different valences, and oxides composed of cobalt and chromium. Toxicological, clinically significant, data regarding "potential hazards" of circulating metals after systemic chronic exposure to the metal ions from metals have been included. This review further highlights some of the clinical features of cobalt toxicity.

Keywords: Systemic toxicity; Systemic health effects; Cobalt toxicity; Metallic medical implants; Metal ion release; Biological fluids

1. Introduction

Metal and their compounds have long been recognized as important toxic agents, causing acute and chronic poisoning cases in occupational settings and in environmental high-exposure situations. Exposure can be a result of metal release from implanted medical devices. Metal ions released from an implanted metallic device can produce local adverse effects at the site of implantation and/or systemic effects at sites distant to the implant if the ions or debris are carried by the bloodstream or lymphatic system. Systemic toxicity refers to adverse effects (other than systemic sensitization, genotoxicity, and carcinogenicity) that occur in tissues other than those at the site of local contact between the body and the device. The development of systemic toxic effects typically requires the release of chemical compounds from the device and distribution of these compounds to distant target tissue sites where deleterious effects are produced. The ability of metals released from implanted devices to produce adverse toxicological effects, and the challenges associated with assessing these effects, are best illustrated by examining issues associated with the release of metals from specific types of implanted devices. These include implanted orthopedic, cardiovascular, and spinal devices. In addition, there are unique issues that should be addressed when estimating the risk posed by exposure of patients to metals released from implanted metallic devices, notably the need to account for the form (particles *vs*. ions) and valence of the compound released from the device, the ability to estimate the dose of the compound released from the device

* Corresponding author: Henryk Matusiewicz
Faculty of Chemical Technology, Poznan University of Technology, Poznań, Poland.

using biomonitoring data, and the need to account for systemic adverse effects on target organs distant to the implant [1].

This review presents an overview of going research regarding the potential related adverse biological effects associated with systemic toxicity attributed to elevated trace metal ions released from metallic medical implants, based on the available *in vivo* and *in vitro* clinical studies. This article further aims to describe the exposure, uptake, dissemination and biological activity of metal ions and metallic wear debris released from specific types of implanted medical devices. Toxicological, clinically significant, data regarding "potential hazards" of circulating metals after systemic chronic exposure to the metal ions from metals have been included. Toxicological data regarding potential adverse events after local exposure to metals have not been included; detailed reviews are given in several papers [2-5].

2. Clinical observations of systemic responses to implanted medical devices

Toxic systemic effects of compounds released from the device materials are among the most important endpoints to be assessed in a biological evaluation of an implanted metallic device or biomaterial. The toxic effects associated with implanted metallic devices are typically related to the release of metal ions, particular wear debris, or both, from the device. Therefore, an important part of the process of evaluating the biocompatibility of a device or biomaterial in an assessment of the likelihood that metal ions or wear debris released from alloys will produce adverse toxicological responses systemically after transport of the metal ions or nanoparticles to target tissues distant from the implant. The extent to which metal ions or wear debris are released from the device typically determines the severity of the toxic response to the implanted device. Implanted metallic devices undergo corrosion that can lead to the release of metal ions or the generation of wear debris. Corrosion can result in the release of metal ions or wear debris from the device, with the potential for adverse toxicological consequences or functional failure of the device.

Toxicity is often viewed at the cellular and systemic levels. Inflammatory and immunological responses can result in toxic effects at the cellular level, which is usually known as cytotoxicity. However, excessive or severe inflammatory and immunological responses, together with direct chemical toxicity of wear, corrosion and degradation products, may cause systemic toxicity. Systemic toxicity may be readily detected due to the damage to target organs, which reveals apparent signs and symptoms; however, this is not always the case. Degradation products of implant materials are one of the typical factors that cause both no immune and immune systemic toxicity. Information regarding metal-induced toxicity is based on limited amounts of epidemiological and experimental studies involving *in vitro* and *in vivo* models.

2.1. Metallic orthopedic implants

A wide range of orthopedic devices are made from metal, but few implanted metallic orthopedic devices have attracted as much public and scientific interest as metal-on-metal (MoM) hip prostheses. Unfortunately, very a few well-conducted epidemiological studies have assessed the incidence or prevalence of adverse systemic effects in patients with MoM hip prostheses [6-8]. Cobalt and chromium ions can elute from metallic debris particles, and so gain access to the systemic circulation (and distant body tissues). Systemic ion levels, therefore, parallel the peri-prosthetic burden of metal debris and are a marker for bearing performance. However, even in patients with a well-performing MoM prosthesis, the average cobalt and chromium ion levels exceed those in patients with metal-on-plastic hips.

Two recent investigations systematically looked into potential systemic sequelae of MoM hip arthroplasty: Chen et al. [9] and Prentice et al. [10]. Chen et al. [9] studied 32 consecutive patients with a large-head MoM THA and compared their results to a matched cohort of 32 patients with MoP THA with a mean follow-up of two years postoperatively. Serum metal ion levels, liver and kidney function and host immunologic immune responses were evaluated throughout the observation period. Mean Co and Cr levels in the LH-MoM implant group were 4.33- and 1.95-fold higher than those in the control group. Clinical scores as well as liver and kidney function parameters did not show any difference between the groups, CD3+, CD4+ and CD8+ cell levels in the LH-MoM implant group were significantly decreased, the INF-y level was increased. Although this study revealed that subtle immunological changes can occur after MoM implantation, it is doubtful if these abnormalities are able to compromise host defense mechanisms which may play a role in foreign body reaction to metal products. Prentice at al. [10] performed a detailed cross-sectional health screening in 35 asymptomatic patients with MoM HRA eight years after implantation and compared the results to a matched cohort of 35 asymptomatic patients after conventional THA with a non-metallic bearing. They found an increase of body bone mineral density by 5% and a decrease of bone turnover by 14% in the MoM group. The cardiac ejection fraction was 7% lower (mean absolute difference 25%, P=0.04) and left ventricular end-diastolic diameter was 6% larger (mean difference 27 mm, P=0.007) in the resurfacing group. There was no evidence of difference in neuropsychological, renal tubular, hepatic or endocrine function between the two cohorts. The authors concluded that chronic exposure to metal concentrations in patients even with well-functioning MoM hip arthroplasty may have systemic effects.

While overt implant-related metal toxicity is rare, elevated serum/blood metal levels represent one of the most frequently reported adverse reactions with potential systemic effects. Even well-performing MoM arthroplasties can result in elevated blood/serum Co and Cr levels [11,12]. A systematic review of 11 randomized controlled trials (RCTs) and 93 epidemiological studies on metal ion levels (Co, Cr, Mo, Ni, Ti) in 9,957 patients with metal-containing hip implants identified elevated metal ion levels (whole blood, serum, plasma, erythrocytes, urine) in patients with MoM hip bearings [13]. A summary of the six reviewed studies that reported metal ion concentrations with regard to MoM implant performance showed that cases with malfunctioning implants with "adverse local tissue reactions" (ALTRs) had higher Co levels compared to those with well-functioning implants. Differences in total body bone mineral density and bone turnover as well as some cardiac functions were found in patients with well-functioning MoM hip resurfacing *vs.* conventional hip replacements, suggesting that chronic exposure even to relatively low elevated metal ions may have systemic effects [10]. On the other hand, ALTRs may develop in MoM hip patients without elevated serum metal ion levels [14].

van Lingen et al. [15] performed screening for systemic health effects in ten hip implant asymptomatic patients with very high Co levels of 18-153 μg L^{-1} (mean 46.8 μg L^{-1}) at a mean follow-up time of 4.2 years after implantation of LH-MoM arthroplasty. Extensive neurological and cardiological investigations as well as laboratory assessment of renal and thyroid function have been performed. The authors could not identify any signs or symptoms of neurological dysfunction, cardiomyopathy, or renal or thyroid dysfunction in a cohort of 10 asymptomatic patients who had received a MoM total hip replacement but, unlike the Prentice et al. [10] study, they found no evidence of cardiomyopathy in patients with MoM hip replacement.

Leikin et al. [16] described a large case series of blood Co levels and systemic symptoms in MoM *vs.* non-MoM patients. The authors performed an observational study of 39 hip arthroplasty patients (26 of them having MoM THA), who were investigated at two outpatient medical toxicology clinics. The median blood Co level in the MoM group (14.1 μg L^{-1}) was about 10-fold higher than that of the non-MoM group (1.5 μg L^{-1}). Twelve patients were symptom-free, nine complained of fatigue and two other patients had been previously diagnosed with fibromyalgia. A major complaint was tinnitus/hearing loss in 12 patients, but no difference between the incidence of this symptom in MoM and non-MoM implant patients could be observed. Of three patients with provisional diagnosis of demyelinating neuropathy, one patient experienced marked improvement after revision surgery. Overall, 20 patients underwent revision surgery of their THA and surgery was associated in a decrease of metal ion levels. The patients' subjective complaints, however, did not correlate with Co and Cr ion levels. A recent study used an extensive battery of auditory and vestibular tests to examine the ototoxic effects of MoM hips in a group of 20 MoM hip patients and a group of non-implanted controls matched for age, gender and noise-exposure [17]. Small changes were found in the high frequency hearing function in the MoM group but no differences in the vestibular outcomes were found. Although, there was no association with the circulating cobalt levels, the authors suggested that the hearing changes may reflect cobalt-induced damage, citing previous findings on drug-induced ototoxicity and recent animal experiments. Recently, a case was reported of a man who had extreme wear of a Co-Cr-Mo femoral head (metal-on-ceramic THA) and increased concentrations of Co in the serum (398 μg L^{-1}) and cerebrospinal fluid (3.2 μg L^{-1}). He suffered loss of vision, hearing impairment, numbness of the feet and dermatitis [14]. Ophthalmogical examination showed toxic atrophy of the optic nerve and retinopathy with malfunction of the macula, which recovered with time. Audiometry revealed that his hearing was returning. The numbness of the feet and the dermatitis also disappeared with time [18].

Metal-on-metal implants have typically been contraindicated for patients with chronic kidney disease because of the concern that the metal ions would not be cleared efficiently and would therefore accumulate *in vivo*. In several cross-sectional surveys evaluating kidney function after MoM THA and HRA, the authors did not report any clinically relevant impairment even after long follow-up times [19-22]. The question of whether chronic exposure to Co and Cr ions leads to kidney problems was addressed in a retrospective study of serum creatinine levels are urine renal markers in 31 patients who had received MoM hip resurfacing arthroplasties 10 years or more prior. A group of age- and gender-matched subjects without known kidney problems or metal exposure acted as controls. No elevation in renal markers was detected in the HRA patients [23]. In patients with chronic kidney failure and MoM-THA, only minor elevation of cobalt and normal chromium values have been documented [24].

Metals modulate the activities of immunocompetent cells by a variety of immunostimulatory or immunosuppressive mechanisms. With regard to orthopedic metal ions, the effects generally include altered function of T-cells, ß-cells and macrophages, modified cytokine release, the formation of immunogenic compounds and direct immunotoxicity. A significant reduction in circulating lymphocytes, in particular $CD8^*$ T-cells has been observed in patients with MoM articulations, although this did not form a linear correlation with serum metal (Co, Cr) concentrations. There was no evidence that their patients suffered as a result of this reduced level of $CD8^*$ T-cells [25]. However, a threshold value of 5 μg L^{-1} combined Co and Cr was identified, under which no significant reduction was observed. An inverse correlation

between the concentration of Cr and the numbers of circulating $CD4^+$ T-cells and $CD20^+$ ß-cells has been reported in patients with metal-on-polyethylene (MoP) articulations, while myeloid cells and $CD8^*$ T-cells were consistently decreased regardless of metal levels. These data suggest that the presence of Cr ions released from prosthesis components may be associated with lymphocyte subpopulations changes in patients with loosening of joint prostheses [26]. Other investigation of aseptically failed MoM hip joints found histological lymphocyte accumulations associated with implant failure. Hart et al. [27] conducted a cross-sectional study aiming to evaluate the relationship between MoM replacements, the levels of Co and Cr ions in whole blood and the absolute numbers of circulating lymphocytes. Laboratory-defined T-cell lymphopenia was present in 15% ($CD8^+$ lymphopenia) and in 13% ($CD3^+$ lymphopenia) with unilateral MoM hips. A significant reduction in the absolute $CD8^+$ T-lymphocyte subset counts for the MoM groups compared with each control group was noted but also some reduction in $CD19^+$ (ß-cell) counts.

2.2. Metallic spinal implants

It is being recognized that spinal implants are associated with adverse tissue responses, mediated by degradation products. There have been very few subsequent studies assessing the short-, medium- and long-term sequel of implant-derived systemic metal dissemination [28-30].

Cundy et al. [28] reported that serum concentrations of Ti ion were increased in patients who had spinal implants. This rapid rise in the serum Ti level was further investigated by the authors [28] and seems to be associated with a release of metal during the implantation, but an elevated Ti level in intraoperative fluids was reported in only two patients.

In the case of fracture fixation devices, such as intramedullary nails, an elevation of the serum Ti level was observed in patients with implants made of Ti-6Al-4V alloy [29].

Recently, Savarino et al. [30] reported metal concentrations, in pediatric and adult subjects implanted with stainless steel posterior spinal instrumentation, that serum Cr levels were higher than levels measured in controls more than 4 years after surgery. This study has failed to detect elevated amounts of circulating Cr or Ni from stainless steel scoliosis rod fixation systems.

2.3. Metallic cardiovascular implants

A number of implanted medical devices with cardiovascular indications are made either entirely or in part from metallic components. Such devices include bare metal stents intended to maintain the patency of blood vessels and occlusion devices that repair cardiac defects. Similar to other metallic devices, cardiovascular devices can undergo corrosion by the mechanisms outlined previously and can release metal ions and/or wear debris particles from the device. The severity of local and systemic effects that may occur after implantation of cardiovascular metallic devices is largely dependent on the rate at which metal ions and wear debris are released from the device by various corrosion mechanisms. Nickel release from cardiovascular devices made from the alloy, Nitinol, is of particular interest from a safety perspective. Nitinol is an alloy composed of 55% nickel and 45% titanium. The alloy has thermoelectric properties that make it ideal for use in certain cardiovascular device applications. Nitinol is used for the manufacture of various cardiovascular devices, including cardiovascular stents and those that occlude congenital cardiac defects, such as atrial septal defect, and patent ductus arterious. However, because of the potential for nickel to be released from these devices if not properly manufactured, concerns have been expressed about the possible health effects following the release of nickel from the devices.

The time course of nickel release from these devices is important to consider when assessing the potential toxicological effects that may be associated with nickel release. Serum levels of nickel increase dramatically in patients shortly after Nitinol occluders are inserted to correct atrial septal defects [31,32] and remain elevated for period up to 1 month before returning to baseline levels. The reduction of metal levels in serum after an initial peak is caused by passivation of the alloy by a layer of calcium-phosphate on the device or by endothelialization of the device. The release kinetics of nickel from the device should be kept in mind when assessing the potential toxicological risks associated with the nickel release from these types of Nitinol devices. Tsuji and Bogen [33] developed a biokinetic model to estimate the dose of nickel released from implanted metallic cardiovascular devices, and implementation of this approach provides a practical way to address this challenge.

3. Systemic health effects

Systemic toxicity refers to adverse effects (other than systemic sensitization, genotoxicity, and carcinogenicity) that occur in tissues other than those at the site of local contact between the body and the device. The development of systemic toxic effects typically requires the release of chemical compounds from the device and distribution of these to

distant target tissue sites where deleterious effects are produced. Systemic toxicity is included as a recommended endpoint in the biological evaluation of devices depending on the nature and duration of device contact with the patient. Furthermore, the likelihood of certain ARMD may be also affected by implant-related constituent metals (e.g. Co/Cr *vs.* Ni or Ti) as well as predominant wear debris type (e.g. particles *vs.* ions). Implant-related metallic debris may cause systemic effects, mostly due to blood and lymphatic dissemination.

Systemic toxicity testing can be designed to evaluate both local and systemic responses to implanted medical devices, but this review will focus only on systemic evaluations.

3.1. Cardiovascular system

Cardio toxic effects have been described in relation to cobalt and are usually in the form of cardiomyopathy and impairment of left ventricular function. Treatment of Co toxicity is primarily supportive. Specifically, in 1966 the syndrome "beer drinker's cardiomyopathy" appeared in Quebec City, Canada, and was characterized by pericardial effusion, elevated hemoglobin concentrations and congestive heart failure [34]. Among other clinical manifestations of Co toxicity, in a 2020 three identical reviews (exactly this same text, references, tables and figures) [35 a,b,c], toxicity-related cardiomyopathy (CMP) has been reported in some cases. Several cases of CMP were reported in patients with a MoM hip implant [36-46]. In most of these cases, necropsy revealed severely elevated Co levels in the myocardial tissue. Furthermore, echocardiography has shown a moderately to severely reduced left ventricular systolic function and left ventricular or atrial hypertrophy [36-38,43]. One patient presented with paroxysmal atrial fibrillation [38], and three fatal cases of Co-induced cardiomyopathy have been reported [40,42,43]. The cobalt intoxication is an increasingly recognized and life-threatening problem [40]. A few studies have reported increased Co concentrations in the liver, kidney and heart of patients with Co-containing hip prostheses [42,47,48]. However, data relating measured Co blood concentrations in MoM patients to other target tissue concentrations patients are scarce.

Based on the available data most MoM patients with well functioning implants would not be expected to experience an increased risk for systemic health effects as the estimated inorganic Co concentration in key tissue such as the kidney, heart, and liver are appreciably less than the critical Co concentration associated with systemic health effects such as polycythemia and cardiomyopathy. The possibility of diagnosis should always be in the forefront of clinicians' minds when confronted with a patient with MoM and systemic symptoms that cannot be attributed to other more common systemic diseases.

3.2. Cardiotoxicity

There are a number of case reports describing Co-induced cardiotoxicity [12] with possible permanent myocardial damage [49] after implantation of a metal implant.

A fatal Co-induced cardiomyopathy was recently described in a female patient with fractured ceramic hip implant who was revised to a MoP articulation and ten months post-revision, developed hip pain, dyspnea (difficulty breathing), worsening hearing loss, metallic dysgeusia (sense of taste), and weight loss [50]. The causative role of Co toxicity in this case was evidenced from the increased Co levels in whole blood and urine, as well as the autopsy-based Co levels in the heart tissue and periprosthetic effusion [43].

A recent the Australian Government Department of Veterans' Affairs health cohort study found that men with MoM (ASR XL) hip prostheses had a higher rate of hospitalization for heart failure compared to men with MoP hip prostheses (HR = 3.2; 95% CI: 1.6-6.5). Of the 4,019 patients with no prior history of heart failure, men with one type of MoM total hip were found to have a higher rate of hospitalization, but no such associated was found for the other types of MoM total hip or for women with that particular implant. No statistically significant difference in mortality was observed for any of the MoM bearings compared to MoP total hips. The authors of the study pointed out that causality between the MoM implant and heart failure could not be established but suggested that their observations warranted further monitoring of MoM patients for long-term cardiac complications [50].

While the majority of patients included in the above study had stemmed total hips, one group selected to examine patients with well-functioning MoM hip resurfacings. Magnetic Resonance Imaging (MRI) imaging was used to compare liver and heart tissue features and cardiac structure and function, and the findings were correlated with metal ion (Co, Cr) levels in a group of 10 unilateral and 10 bilateral MoM resurfacing patients and a group of 10 patients with non-MoM total hips. The MoM HRA patients had slightly larger indexed right and left end diastolic volumes and a small decrease in T2 time that were associated with higher metal ion levels [51]. Similarly, metallic head THAs, especially MoM hips in women and older patients were associated with the slightly increased risks for dilated cardiomyopathy and heart failure in a cohort study based on the French national health insurance databases [52].

Berber et al. [53] evaluated 90 patients with either ceramic on ceramic, MoM hips with low ion levels, and MoM hips with high ion levels (>7 μg L^{-1}). In this study, there was no difference in cardiac MRI results. There was no difference in ejection fraction between any of the three groups. The authors concluded that their study "excludes any clinically important association" between moderate metal ion levels and cardiotoxicity.

The one case of MoM total hip arthroplasty cobalt toxicity of cardiac tissue was confirmed that has led to patient death. The pathology report demonstrated elevated cardiac and serum Co levels in their patient. Her cardiac biopsy sample revealed a Co level 25 times higher than the normal limits [54].

3.3. Systemic cobalt toxicity

During the past decade, the initial popularity of MoM hip implants has shown a progressive decline due to increasingly reported implant failure and revision surgeries. Local as well as systemic toxic side effects have been associated with excessive metal ion release from implants, in which cobalt plays an important role. Medical exposure to Co is a growing concern, especially in patients implanted with a MoM hip prosthesis, who are subjected to the most invasive Co exposure route. The toxic reactions to Co exposure primarily depend on its chemical form. In the medical setting (e.g. MoM hip implants), exposure to Co nanoparticles as well as Co ions occurs [55]. Systemic toxic reactions may arise when Co ions enter the blood and lymphatic circulation and subsequently disseminate to different organs. *In vitro* experiments demonstrated that ionized cobalt (Co^{2+}) is the primary toxic form for systemic toxicity [37] and more specifically the unbound (free) Co^{2+} ions, which are more bioavailable than their albumin-bound counterparts to interact with various cellar receptors, in channels and biomolecules. Consequently, a shift in the distribution of free *vs.* bound cobalt towards a larger portion of free Co^{2+} ions is expected to increase the risk assessment for toxic effects. Systemic Co toxicity manifests as a clinical syndrome with a variable presentation of cardiovascular symptoms, depending on the systemic Co levels (blood/urine).

Toxic effects in response to metallic orthopedic implants are frequently described, in the literature, to cobalt and are referred to as cobaltism [56,57]. The rare condition of systemic cobaltism seems to manifest as a clinical syndrome with cardiac, endocrine, and neurological symptoms. In most cases described in the literature, revision surgery and the subsequent drop in blood Co level led to (partial) alleviation of the symptoms, suggesting a causal relationship with Co exposure [56,57]. They reviewed at least 18 published case reports where a THA device was associated with systemic cobalt toxicity; cobalt metal ion toxicity has been attributed to the use of Co-Cr alloys in hip arthroplasty. Of these cases, the great majority reported more pronounced toxicity at serum Co levels exceeding 100 μg L^{-1}; however, multisystem involvement was found in all examined cases, with neurological, cardiac, and thyroid effects seen more commonly. Zywiel et al. [56] concluded that the large majority of cases of systemic symptoms were associated with cobalt levels greater than 100 μg L^{-1} and that systemic toxicity is extremely unlikely in the context of low cobalt levels, even in the presence of hip pain or radiographic abnormalities. Zywiel et al. [56] noted that no definitive cobalt level threshold is available to suggest increased systemic health risks in patients with Co-Cr containing THAs which likely reflect the rarity of reported systemic health effects. Taken together, the weight of evidence from the available toxicological information and case reports suggests limited concerns for systemic Co toxicity in the vast majority of patients with HRA or THA devices. From these reports, it seems evident that CoCr nanoparticles and metal cobalt ions released from MoM THA implants have toxic effects *in vivo* and may pose a health risk to patients [12,40,58-60]. Case reports suggest that adverse systemic effects seen in patients with implanted orthopedic devices can be attributed to the release of metal ions or wear debris from the devices [60]. However, it remains unclear whether metals released from these devices cause adverse systemic effects in patients [61].

In an extensive review of the orthopedic literature up to February 2014, Bradberry et al. [62] reported that there were 18 individual cases of systemic toxicity related to total hip prostheses. The greatest risk of systemic cobalt toxicity seems to result from accelerated wear of a cobalt-containing revision of a failed ceramic prosthesis, rather than from primary failure of a MoM prosthesis. Using a slightly broader search strategy, a systematic review of 25 patients identified several organ systems involved with the cardiovascular system (55%) being the most frequently affected, followed by central nervous system. The mean time to presentation or revision in this population was 41 months, and the mean serum cobalt level 324 μg L^{-1}, although they reported symptoms in patients with levels as low as 20 μg L^{-1} [63]. In both reviews, rare cases of cardiotoxicity were attributed to cobalt rather than chromium toxicity, based on known clinical effects of cobalt. Although MoM hip patients were among the reported cases, the most severe instances involved massive wear of metallic femoral heads that were inserted in revisions for fractured ceramic bearings. Extremely high blood cobalt levels (for example 300 to 600 μg L^{-1}) were documented and clinical symptoms included blindness, deafness, neuropathy, cardiomyopathy, fatigue, and headaches. Lower cobalt levels (20 μg L^{-1}) have been associated with symptoms of cobaltism in one report [60]. In nearly all reported cases, cobalt levels were documented to fall following revision of the worn implants and usually, but not always, with an accompanying decrease or resolution in symptom

severity [62]. Applying these observations on the published cases of "arthroprosthetic cobaltism", reviewed by Cheung et al. [12], Zywiel et al. [56], and Gessner et al. [63], there are some contradictions. Zywiel et al. [56] concluded that neurological (72%), cardiovascular (55%) and endocrine (50%) effects are most commonly seen in this condition, of which the former two also occurred for Co levels much lower than 700 μg L^{-1} and in several cases even below 300 μg L^{-1}. Consequently, no consensus has been achieved regarding the "threshold" Co concentration for systemic health effects, which warrants the need for controlled clinical studies in the future. However, there is also an observed dose-response relationship between serum cobalt level and severity of symptoms, which may make this a good screening tool with levels >7 μg L^{-1}, warranting observation of cardiac and neurologic function and levels >20 μg L^{-1} as an indication for revision surgery to alternative bearing surfaces [59,63].

Van Der Straeten et al. [64] collected questionnaires, validated to detect cobaltism in occupationally exposed individuals, in a MoM hip implant population. They found a significant correlation between increasing Co levels and the prevalence of several toxicity symptoms, and concluded that patients with repeated high blood or serum Co concentrations exceeding 20 μg L^{-1} are at risk for systemic toxicity, as an indication for revision surgery to alternative bearing surfaces. Likewise, a recent systematic review of the published cases of probable systemic Co toxicity from MoM hip arthroplasty reported a significant association between the Co concentration and a quantitative measure of overall symptom severity [63]. However, the measured Co levels covered an extensive range of 10-1085 μg L^{-1}. Approximately half of these cases showed Co levels above 100 μg L^{-1}, of which the majority had a fractured ceramic head before implantation of the MoM bearing. The higher Co concentrations in this subgroup probably result from abrasion of the metal surface by residual ceramic fragments [36].

Devlin et al. [65] reviewed 10 cases of suspected prosthetic hip-associated cobalt toxicity and reported that these patients have had severe systemic side effects, findings consistent with cobalt toxicity. Furthermore, a cross-sectional study of patients with resurfacing MoM THA hip arthroplasties identified reduced cardiac ejection fraction in asymptomatic patients who had cobalt levels above the cobalt levels in patients in a matched reference group, but below what was previously thought to be the threshold concentration for prosthesis malfunctions [10].

Based on the available data most MoM patients with well functioning implants would not be expected to experience an increased risk for systemic health effects as the estimated inorganic Co concentration in key tissues such as the kidney, heart, and liver are appreciably less than critical Co concentration associated with systemic health effects such as polycythemia and cardiomyopathy.

Metal ions can be generated not only at the junction between the femoral head and socket, but also at the junction of the head and stem of the femoral component [66]. Use of large-head MoM bearing surfaces in THA has created new and unique modes of failure for this type of articulation; that of the wear at the trunnion of the prosthesis. The excessive Co debris has been linked to "trunnionosis" [67,68], i.e. the phenomenon whereby wear particles are produced due to corrosion at the head-neck junction (trunnion) in modular hip replacements [69,70]. However, potential systemic toxicity due to high Co levels is not limited to trunnionosis or MoM prostheses in general [60].

A wide range of adverse systemic health effects in patients have been attributed to the release of cobalt ions from MoM hip implants. Hip arthroplasty-related Co toxicity with significant morbidity and mortality has been highlighted recently in the literature. Among other clinical manifestations of Co-induced systemic toxicity cardiomyopathy have been reported in some cases [38,40,41,49,54,62,71-76]. Some patients have reported multiple symptoms that have been attributed to the release of cobalt from MoM hip prostheses. In the last years, a new condition derived from the implantation of MoM hip prostheses has emerged: arthroprostatic cobaltism, which represents an intoxication of the patients [45,46,60].

Literature comparison of cases of cobalt systemic toxicity-related cardiomyopathy and arthroprostetic cobaltism in patients with metal hip arthroplasty are presented in Table 1.

The majority of patients with well-functioning MoM hip implants have cobalt blood concentrations ranging between 0.2 and 10 μg L^{-1} [77]. In another study performed by De Smet et al. [78] serum levels have been used to estimate the MoM HAs wear at the bearing surfaces over time, based on the positive correlation that exists between the wear measurements and the serum Co ion level measurements. Patients with metallosis had significantly higher serum cobalt-ion concentrations (>19 μg L^{-1}) and significantly greater amounts of femoral component wear.

Table 1 Literature comparison of cases of cardiomyopathy and arthroprostetic cobaltism in patients with MoM hip arthroplasty

Prosthesis type	Follow-up	No. patients	Body fluid analyzed	Metal ion(s) measured	Concentration (μg L^{-1})		Median (μg L^{-1})	Clinical outcomes	Refs.
					MoM	Control			
Hip	6 y	1	blood	Co	11.96			Dilated cardiomyopathy, hip revised, marked improvement	[38]
Hip bilateral	n/a	1	blood	Co				Catastrophic failure: cardiac failure, dilated cardiomyopathy, liver failure	[40]
Hip	n/a	1	serum	Co	156	0.1-04		Dilated cardiomyopathy, pericardial effusion	[41]
Hip/THA	2 y	1	blood	Co	156	<0.2		Dilited cardiomyopathy, severe metallosis, good recovery clinically	[45]
Hip	18 m	1	serum	Co Cr	122 63			Progressive pain and noise at the prosthetic hip, cardiomyopathy	[46]
Hip bilateral	11 m	1	blood	Co	189			Progressive cardiomyopathy, exertional chest tightness, extensive metallosis, cardiac transplant	[49]
Hip/THA	2 y	1	blood	Co Cr	192 77	<1 <1		Hip pain, poor cardiac function, severe metallosis, deteriorated, died	[54]
Hip/THA	4 y 5 y	1 1	serum serum	Co Cr Co Cr	15.1 5.1 24 12.5	 <1.1 <5.1		Neurological symptoms, mild groin pain Bone loss around the acetabular	[58]
Hip	1 y	2	serum joint fluid	Co Co	23 - 122			Hip pain, hearing loss. Hip revised - systemic	[60]

					3200 - 3300			symptoms improved	
Hip	10 m	8	blood/ serum	Co Cr	>250 >80		34.5(13.6 -398.6) 48(4.1-221)	Cobalt cardiomyopathy, neurological damage	[62]
Hip/THA	3 y	1	blood	Co	398.6			Heart failure, cardiomegaly, deterioration of cardiac function, cobalt cardiomyopathy, cardiac transplant - hip revised (extensive metallosis)	[71]
Hip bilateral	n/a	1	serum	Co Cr	120 108.8	<1 <1.4		Worsening heart failure, cobalt cardiomyopathy, cardiac function remained poor	[72]
Hip	2 y	1	serum	Co Cr	200-300 80.3	<1.0 <1.0		Dilated cardiomyopathy, hip revised - haemorrhagic stroke - died	[73]
Hip/THA	5 y	2	blood	Co Cr	352.6 7			Hip pain, metallosis, dilated cardiomyopathy. Hip revision followed by chelation therapy - significant improvement clinically	[74]
Hip/THA	4 y	1	blood	Co	246	<1		Pericardial effusion, Hip revised (severe metallosis) - improved in 5 months	[75]
Hip/THA	10 y	1	serum	Co Cr	169 31			Heart failure with dilated cardiomyopathy, cardiac transplantation. Hip revision (extensive metallosis) - cardiac function normalized	[76]

Results are reported as "mean/median concentration, range (in parentheses)"; n/a - data not available; m-month; y-year

Despite above mentioned evidence for systemic Co toxicity from MoM implants, there is a current lack of uniform criteria concerning blood Co concentrations to guide physicians in the detection and management of this condition. Cobalt levels are not useful in defining toxicity and thresholds vary substantially from one study to the next. In addition, levels may be measured from serum, whole blood, or erythrocytes and there is no conversion factor for these values as the intracellular and extracellular compartments act independently of each other. Cobalt and chromium levels, or cobalt levels alone, may be used to identify patients at risk of adverse reactions to metal debris.

Different organizations attempted to define threshold values for the identification of patients with adverse reaction to metal debris that require clinical follow-up or intervention. According to the European multidisciplinary consensus statement on the use and monitoring of MoM bearings, while Co values < 2 μg L^{-1} are probably devoid of clinical concern, the range of 2-7 μg L^{-1} represents the threshold value for clinical concerns in unilateral MoM hip replacements [79]. The Mayo Clinic stated that Co serum levels above 10 μg L^{-1} indicate significant implant wear, whereas values between 4 and 10 μg L^{-1} reflect good condition of the MoM implant device [80]. The Medicines and Healthcare products Regulatory Agency identified the value of blood Co level as the threshold of 7 μg L^{-1} for toxicity related to prosthesized patients, who demonstrated only a modest sensitivity (57%) and specificity (65%) [81].

In summary, it is clear that metal ion levels should be interpreted carefully and serve as an adjunct to clinical and radiographic evaluation, for which different clinical algorithms have been proposed [61,81,82]. Additionally, (highly) elevated Co concentrations have been related to certain systemic manifestations of Co toxicity [83,84]. In any patient care or monitoring algorithm, caution should be exercised when identifying specific blood or serum cobalt levels to serve as thresholds for clinical decision-making, since interlaboratory variability may exist in reported values [85]. In addition, the assessment of pain, function, and imaging findings should be very seriously considered when determining the course of treatment for any patient, along with metal levels in the blood or serum.

4. Conclusion

The purpose of this review was to summarize the present status of the systemic biological response to metallic implant wear debris, with emphasis on the toxicology of CoCr alloy wear debris. Research into possible role of other metals than cobalt and chromium such as titanium and vanadium, in view of the inconsistency in relationship between the clinical outcome and Co/Cr metal ion levels is necessary. It is important to realize that, although some regulatory agencies have begun to assess the potential for cobalt and chromium toxicity associated with metallic implant devices, there are no universally accepted criteria for what constitutes a toxic cobalt and chromium level, nor are there consistent guidelines surrounding the measurement of cobalt and chromium in whole blood, serum, or erythrocytes. Similarly, there has been considerable variation in the symptoms, signs, and cobalt levels associated with implant-related cobalt toxicity reported to date. Clinical vigilance is needed to diagnose and manage cobalt toxicity in patients who have undergone total hip arthroplasties in the past. An increased awareness of the range of symptoms of cobalt toxicity, and the role of early orthopedic, spinal, or cardiovascular intervention when these symptoms do occur, may forestall the development of further complications. In addition, there are unique issues that should be addressed when estimating the risk posed by exposure of patients to metals released from implanted metallic medical devices, notably the need to account for the form (particles *vs*. ionic) and valence of the compound released from the device, the ability to estimate the dose of the compound released from the device using biomonitoring data, and the need to account for systemic effects on target organs distant to the implant. The physical and chemical form of the metal released from a metallic implant, in particulate form or as metal ions, can have a significant impact on the toxicity of the compound. Consequently, it is important to take this factor into account when assessing the risk posed by patient exposure to metals released from metallic implants. Direct evidence for effects of chronic exposure to metal on systemic organ function in patients with well-functioning implants is needed to inform appropriate endpoints for the studies now required of manufacturers, and to inform the appropriate clinical monitoring of patients.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare no conflicts of interest associated with this manuscript.

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