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Periarticular metal hypersensitivity complications of hip bearings containing cobalt–chromium

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- Hip joints with bearings composed of cobalt–chromium alloy (metal-on-metal bearings) have been one of the most widely used implants in joint replacement arthroplasty. Unfortunately, these implants can contribute to a complication called aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), a type IV metal hypersensitivity response around the joint.
- Consistent with such bearings, increased metal debris can be found in the surrounding fluids and in remote tissues and organs, due to wear and corrosion. It is hypothesized that metal ions released from the prosthesis (including Co^{2+}) can potentially form haptens with proteins such as serum albumin in synovial fluid that in turn elicit ALVAL.
- Generally, elevated cobalt and chromium levels in synovial fluids may indicate implant failure. However, such measurements cannot be used as a reliable tool to predict the onset of ALVAL. To detect ALVAL, some diagnostic tests, questionnaires and imaging techniques have been used clinically with some success, but a standardized approach is lacking.
- At present, guidelines for implant usage and patient management are ambiguous and inconsistent across health care authorities. To reduce and better manage the development of ALVAL, further research into the precise molecular mechanism(s) by which ALVAL develops is urgently needed.
- Identification of diagnostic and prognostic biomarkers for ALVAL is required, as are more standardized guidelines for surgery and patient management.

Keywords

- metal-on-metal implant
- metal ion release
- hip replacement
- ALVAL
- immunology

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Introduction

Bearing partners for artificial joint implants are usually composed of ceramic, high-quality plastic or durable metal and are used to replace the damaged joint(s) (i.e. hip, knee, shoulder, ankle and elbow joints). Among a variety of materials used in such prostheses, cobalt–chromium (CoCr)-based devices (consisting of 30–60% Co and 20–30% Cr) became outstandingly popular in the early 2000s due to excellent mechanical properties, biocompatibility and corrosion resistance, with a promising survivorship (1). CoCr alloys have been widely used in metal-on-metal (MoM) hip replacements, femoral component of total knee replacements (TKR) as well as in the ball portion of shoulder replacements. For example, in mid-2000s, approximately 35% of hip arthroplasty (HA) procedures involved MoM implants, and over 1 million MoM HAs have been performed worldwide so far (2, 3).

However, the usage of CoCr alloys in MoM bearings is related to the initiation of a series of complications, including a severe inflammatory response called aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), pseudotumor, metallosis, cell death and peri-prosthetic soft tissue/bone necrosis as well as other health-related concerns (4). Due to high complication rates, their usage in joint arthroplasty (JA) has sharply declined, especially in MoM total hip replacements (THR) where CoCr alloys are not legally marketed in USA and MoM hip resurfacing of CoCr-based devices has been approved in only a limited number of centers (5, 6). Although the usage of CoCr-based devices has been largely decreased, many individuals still live with these implants (7, 8).

ALVAL is a metal hypersensitivity associated with the formation of metal–protein complexes in the surrounding synovial fluid, accompanied by macrophagic infiltration. Joint effusion, bone and soft tissue damage and osteolysis

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are pronounced features in ALVAL patients (9), with most experiencing persistent pain (especially groin pain in hip JA patients) around the joint (10). Notably, ALVAL is thought to occur in 0.6% of patients with MoM hip bearing; this number was obtained from a pooled estimation consisting of 13,898 MoM hips, with females at greater risk of developing hypersensitivity than males (11). In hip resurfacing, the prevalence of ALVAL is estimated to be at 0.3% in Birmingham hip resurfacings (BHR) and 1.2% in articular surface replacements (ASR) (12, 13). Additionally, the prevalence of failure of MoM THRs secondary to ALVAL has been suggested to be over 30% at 6 years (14). In TKR, the prevalence of severe ALVAL (or pseudotumors) has been reported to reach over 7% at revision surgeries (15). These patients present a typical type IV hypersensitivity (T-lymphocyte-mediated reaction), accompanied with lymphocyte filtration and cytokine expression (16). However, the most important mechanism underlying ALVAL is still largely unknown. In the present review, we outline recent progress made in understanding the by-products released from CoCr alloy prostheses, especially nanoparticles and metal ions, a summary of what is known concerning the immunogenic aspects of ALVAL and an evaluation of the hypothesis that cobalt–human serum albumin (HSA) complexes in some cases may serve as immunogens to elicit ALVAL. Finally, we also provide a perspective on the challenges relating to ALVAL diagnosis and implant management.

Increased cobalt and chromium concentrations are associated with wear and corrosion

Despite some excellent aspects of CoCr bearings, normal usage can generate by-products including wear debris, metal–protein particles and metal ions via wear and corrosion, triggering local and/or systematic adverse conditions (17, 18). Albeit it is well acknowledged that elevated metal concentrations are associated with CoCr-based implants (particularly in MoM hip replacement and TKR), comprehensive studies about debris properties such as size, diameter and wear volume are mainly focused on MoM implants. Therefore, here, we demonstrated an example of by-products released from MoM hip implants (Fig. 1). Generally, in a MoM hip replacement, wear debris is caused by wear and corrosion (e.g. tribocorrosion) at the head–cup interface and head–stem taper junction (19, 20), and nanocrystal metal–protein particles form on the surface due to the damage of the passive film (21). These particles can damage local tissues and accelerate the release of metal particles and ions (22). In a well-functioning MoM hip prosthesis, the volumetric particle wear rate is <1 mm^3 per million cycles compared with >100 mm^3 per million cycles in a failure device (23). The sizes of released metal particles are typically 1 nm–1 μm in diameter, with a mean size <50 nm (9, 24). Such particles are small enough to be ingested by macrophages, dendritic cells, osteoblasts or osteoclasts or be disseminated throughout the body via the circulatory or lymphatic systems, triggering immune reactions. In addition, released metal ions, either via wear/corrosion or subsequent cell lysis, can dispense into the surrounding fluids and local tissue, with some being able to reach the circulatory system and remote organs. The major metal ions released from CoCr-based implants are Co^{2+} and Cr^{3+} (25).

Elevated cobalt and chromium concentrations in different fluids and tissues have been reported in patients who have undergone CoCr JA, and abnormal metal ion concentrations are associated with lymphocyte-dominated responses, albeit it is not a positive and causative relationship, due to other factors such as genetics, gender and age also playing significant roles in metal hypersensitivity. Langton *et al*. found that severe ALVAL was related to the elevations of cobalt and chromium concentration in joint fluids (26). A positive association between blood metal ion concentrations and ALVAL was also noted in failed MoM HA (27, 28). A systematic review of 104 studies including 9957 HA patients reported that concentrations of these metals were found to be increased in whole blood, serum, plasma, erythrocytes and urine following implantation (25). In some extreme cases, the serum cobalt level was >200 μg/L (29). High levels of metal ions were also found in TKRs, as critically high levels of mean serum cobalt (16.3 μg/L) and chromium (9.5 μg/L) were observed in patients with CoCr modular hinged TKRs (30). In Table 1, we summarize whole-blood/serum cobalt and chromium levels of patients who underwent JAs (including THR, hip resurfacing, TKR and shoulder replacement). Notably, different devices are contributed to different effects on cobalt and chromium levels and failure rates. However, high levels of metal content were more common in MoM hip bearing than those found in knee and shoulder arthroplasties, and no abnormal metal concentrations were found in patients who underwent shoulder replacement procedures in this review. With respect to metal content in patients with MoM hip bearing, a large-scale study conducted to compare metal ion levels from patients who underwent MoM THR and hip resurfacing showed that whole-blood cobalt and chromium concentrations were higher in the THR group than the hip resurfacing group (31). In addition, ASR THR and ASR hip resurfacing have high failure rates of 48.8% and 25%, respectively, at 6 years (14, 32). The National Joint Registry reported a failure rate of 30.3% for ASR hip resurfacing at 15 years, as compared to 10.6% of BHR (33). According to the European Commission, MoM hip implants with a large femoral head have the highest incidence of local reactions and should be avoided due to the high failure rate (34). Similarly, different serum metal ion levels were associated with usage of different systems

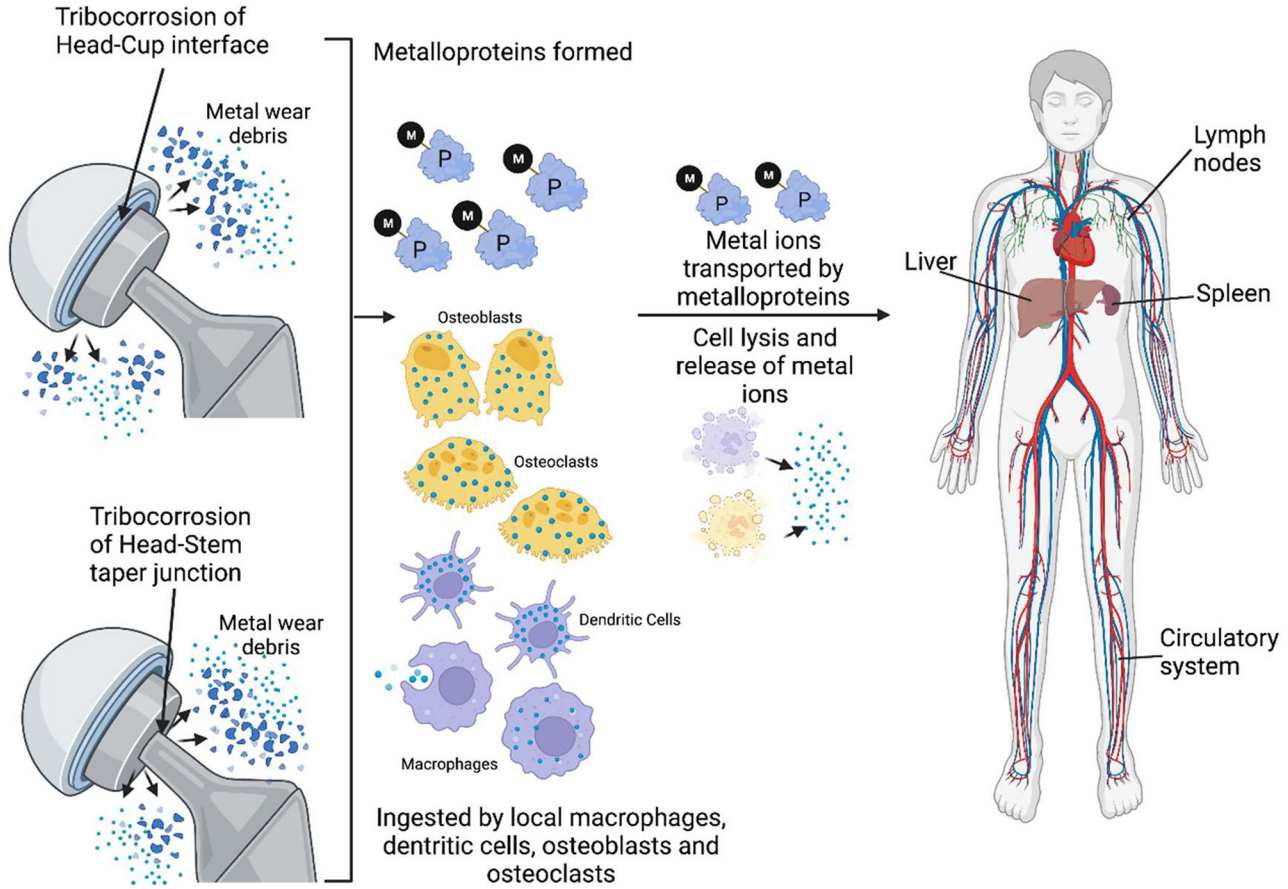

Figure 1

By-products released from MoM hip implants due to wear and corrosion (e.g. tribocorrosion). By-products including metal wear debris, nanoparticles and free ions can be generated from the head/cup interface and the head/stem taper junction. Either nano- or ionic forms of by-products may form complexes with local proteins or be ingested by local cells including macrophages, dendritic cells, osteoclasts and osteoblasts. As a result, metal ions either transported by metalloproteins or released from cells can be disseminated to distant organs and tissues. Created with BioRender.com.

in TKR, as results demonstrated that megaprosthesis devices contributed to 25 and 9 times higher serum cobalt and chromium levels than standard rotating-hinge knee, respectively (35).

Accumulative metal ions are excreted through urine, and their clearance rates are relatively high. Urine cobalt and chromium were reported to dramatically increase by 35.1-fold and 17.4-fold, respectively, after MoM device implantation (36). Furthermore, whole-blood cobalt and chromium levels decrease to 50% in 2–3 months after implant removal (37). If implants are not removed, metal concentrations in urine remained high (7.8 μg/day for cobalt and 3.9 μg/day for chromium) at 6 years, implying that a relatively high concentration of metal ions circulate in the body due to continuous release of metal debris from the prosthesis (38). Without prompt clearance, metal particles can also be detected in tissues and organs, such as the liver, spleen and lymph nodes (39). Notably, cobalt has now been classified as a hazardous, mutagenic and toxic substance as well as a carcinogen by the European Chemical Agency and the French Competent Authority (40, 41). However, it has not been definitively proven that CoCr-based implants lead to cancer (42).

Although elevations in cobalt and chromium concentrations are associated with ALVAL, there is no unified 'safe' threshold for baseline concentrations for these metal ions in the blood. In well-functioning HA cases, serum cobalt concentrations should be <1 μg/L and not >2 μg/L (34, 43). According to the Medicines and Healthcare Products Regulatory Agency in the UK, patients with MoM hip bearing need to be followed-up when total cobalt concentration in serum is >7 μg/L (44). Additionally, there is controversy as to whether elevated metal levels are useful tools to predict failure of functioning prosthesis or ALVAL and how to understand the role of partitioning of metals in different fluids (serum, whole blood and synovial fluid (SF)). It has been reported that volumetric wear is associated with serum or whole-blood cobalt and chromium levels (which

Table 1 Comparison of blood cobalt and chromium levels in CoCr JAs.

Reference	Medium	Device type	Patients, *n*	Duration	Co	Cr
Total hip replacement						
Lainiala *et al.* (31)	Whole blood	CoCr	1335	Measurement lasts for 12 years	2.5 (0.1;192)	1.7 (0.1;115)
Pozzuoli *et al.* (105)	Whole blood	Group 1 ($n=34$): CoCr (cup and head)	68	Group 1 follow-up: 7 years	1.2 (0.6;13.6)	0.8 (0.1;7.3)
		Group 2 ($n=34$): Ti-6Al-4V (cup)-ceramic (head)		Group 2 follow-up: 7 years	0.6 (0.6;2.5)	0.3 (0.1;2.5)
Civinini *et al.* (106)	Serum	Modular dual-mobility	37	Mean 5.1 years (2–10) after surgery	1.99 (0.07;16.05)	2.08 (0.02;11.8)
Kim *et al.* (107)	Serum	Bearing (28 mm Metasul, Zimmer); Stem (Wagner Cone, Zimmer ($n=52$); CLS Spotorno, Zimmer ($n=19$))	71	Follow-up: 5 years	4.14 (0.13;4.14)	6.89 (0.40;6.89)
				Group A ($n=62$) follow-up between 5 years and the minimum 10 years (10–18.6 years)	(0.01;1.01)	(0.20;1.82)
				Group B ($n=9$) follow-up between 5 years and the minimum 10 years (10–18.6 years)	18.97	19.37
Lehtovirta *et al.* (108)	Whole blood	CoCr	69	Follow-up: 30 months	11.0 (0.6;108.5)	3.7 (0.4;29.9)
Ahmed *et al.* (109)	Whole blood	36 mm CoCr Pinnacle (Corail THA System)	55	Follow-up: 3– 9 years	24 ± 29	13.2 ± 13.3
Ando *et al.* (110)	Whole blood	Magnum group (femoral head between 38 mm and 52 mm)	116	Magnum group ($n=62$) follow-up: 5 years	1.16 ± 1.32	1.2 ± 1.9
		Conventional group; (28 mm or 32 mm femoral head)		Conventional group ($n=54$) follow-up: 5 years	3.77 ± 9.8	2.6 ± 4.9
Hip resurfacing						
Lainiala *et al.* (31)	Whole blood	CoCr	890	Measurement lasts for 12 years	1.2 (0.1;225)	1.4 (0.1;125)
Lehtovirta *et al.* (108)	Whole blood	CoCr	13	Follow-up: 30 months	3.9 (1.5;16.2)	3.9 (1.5;7.2)
Ahmed *et al.* (109)	Whole blood	ASR, BHR, Cormet (Stryker), Corin (Cirenchester, UK)	50	Follow-up: 3–9 years	28.2 ± 44.2	19.6 ± 29.5
Grammatopoulos *et al.* (27)	Serum	BHR ($n=26$); conserve hip resurfacing ($n=12$)	38	Follow-up: 11 months (0-37)	4.3 (0.7;67.1) (17.6)	9.1 (1.2;69.5) (15.6)
Underwood *et al.* (32)	Whole blood	ASR ($n=66$)	130	Mean follow-up: 35 months (7-59)	13.5 (0.5;167)	9.8 (0.2;11.9)
		BHR ($n=64$)		Mean follow-up: 49 months (10-121)	10.2 (0;167)	4.8 (0.4;183)
Total knee replacement						
Lons *et al.* (111)	Whole blood	Posterior stabilized TKRs CoCr (Fem) Ti (Tib)	66	Preoperative (mean (min; max))	0.23 (0.03;1.18)	0.48 (0.02;1.7)
				1-year follow-up (mean (min; max))	1.34 (0.20;2.91)	1.23 (0.1;2.81)
Lützner *et al.* (112)	Plasma	CoCr – Columbus Knee System; Standard – Not coated ($n=59$); Coated- AS coating (Cr layer, CrN–CrCN layers and ZrN layer) ($n=61$)	120	Standard preoperative	0.67 ± 0.54	0.50 ± 0.42
				Standard 1-year follow-up	0.50 ± 0.44	0.35 ± 0.31
				Coated preoperative	0.53 ± 0.33	0.54 ± 0.60
				Coated 1-year follow-up	0.45 ± 0.37	0.31 ± 0.15
Savarino *et al.* (113)	Serum	Group I – Stable TKRs ($n=24$) (CoCr (Fem+ Tib) = 7; CoCr (Fem) and Ti (Tib)=17); group II – Failed TKRs ($n=35$) (CoCr (Fem + Tib) = 15; CoCr (Fem) and Ti (Tib): 20)	59	Group I: Mean follow-up in months (range): 39 (10 to 108)	0.44 (0.08;4.65)	0.24 (0.06;1.39)

(*Continued*)

Table 1 Continued.

Reference	Medium	Device type	Patients, *n*	Duration	Co	Cr
				Group II – Mean follow-up in months (range) 30 (8–74)	1.10 (0.08;8.80)	0.45 (0.06;1.44)
Reiner *et al.* (114)	Whole blood	PFC Sigma; CoCr (Fem); Ti (Tib)	22	Preoperative	0.006 (0.005;0.141)	0.251 (0.052;1.297)
				1-year follow-up	0.243 (0.122;0.615)	0.268 (0.000;1.984)
Luetzner *et al.* (115)	Serum	Foundation Knee System CoCr (Fem+ Tib): Unilateral TKR ($n=23$), Bilateral TKR ($n=23$)	41	Unilateral : Mean follow-up in 59 months (median 66 months)	3.28 (1.40;4.50)	0.92 (0.73;1.32)
				Bilateral: Mean follow-up in 59 months (median 66 months)	4.28 (2.10;5.40)	0.98 (0.38;1.64)
Garrett *et al.* (116)	Serum	Profix : CoCr (Fem) ($n=23$); OxZr (Fem) ($n=14$)	37	CoCr (nmol/L): Mean follow-up in 66 months	3.00 (0.00;91.00)	9.00 (3.00;85.00)
				OxZr (nmol/L): Mean follow-up in 48 months	2.50 (1.00;10.00)	8.0 (1.00;12.00)
Masoumiganjgah et al (117)	Whole blood (Cr), Serum (Co)	Triathlon Knee System CoCr ($n=11$) – ACS Knee System CoCr with titanium nitride coating ($n=11$)	22	Triathlon mean follow-up: 50 months (nmol/L)	4 (2;9)	16 (10;19)
				ACS mean follow-up: 50 months (nmol/L)	5 (3;9)	15.5 (10;23)
Gupta *et al.* (118)	Serum	Attune Knee System CoCr (Fem+Tib)	1	17 months after the primary TKR	2.4 (0.08;0.5 reference)	>1000 (0.06;0.93 reference)
Ho *et al.* (119)	Serum	Vanguard System – Custom titanium alloy (Ti-6Al-4V)	1	24 months after the primary TKR	0.3	0.4
Kenny *et al.* (120)	Whole blood	AGC Total Knee System, Modular Design	1	84 months after the primary TKR	8.65	2.35
Liu *et al.* (121)	Whole blood	Loosened ($n=20$)- 4 Ti-6Al-4V+16 CoCr; stable ($n=20$) - 5 Ti-6Al-4V+16 CoCr; Control ($n=20$) – no implant	60	Loosened	116.1 ± 49.2	108.1 ± 40.7
				Stable	0.9 ± 0.9	10.1 ± 2.9
				Control	0.8 ± 0.5	5.8 ± 2.6
Shoulder replacement						
Reiner *et al.* (122)	Whole blood	TSA group anatomic TSA: TESS (The Total Evolutive Shoulder System; Biomet): 11 Simpliciti (Tornier, Bloomington, MN, USA)): 6, Aequalis Anatomical (Tornier): 3 RSA group reverse TSA: Aequalis Reversed Shoulder Prosthesis (Tornier): 20	40	Control ($n=23$)	0.11 (0.03–0.19)	0.14 (0.04–0.99)
				TSA mean follow-up: 29.5 (8-52) months ($n=20$)	0.15 (0.03–0.48)	0.31 (0.09–1.26)
				RSA mean follow-up: 25.7 (19-37) months ($n=20$)	0.18 (0.1–0.66)	0.48 (0.17–2.41)
Pareek *et al.* (123)	Whole blood	Stryker ReUnion	72	Preoperative	0.38 ± 0.43	0.31 ± 0.43
				1-year follow-up	0.45 ± 0.49	0.31 ± 0.47

Co and Cr concentration in µg/L or ng/mL; AGC, anatomic graduated component; ASR, articular surface replacement; BHR, Birmingham hip resurfacing; Co, cobalt; CoCr, cobalt–chromium; Cr, chromium; CrN-CrCN, chromium nitride–chromium carbonitride; Fem, femoral component; JA, joint arthroplasty; OxZr, oxidized zirconium; PFC, press-fit condylar; RSA, reverse shoulder arthroplasty; THA, total hip arthroplasty; Ti-6Al-4V, titanium alloy; Tib, tibial tray; TKR, total knee replacement; TSA, total shoulder arthroplasty; ZrN, zirconium nitride.

are reliable indicators of performance of MoM-bearing surfaces) and recommended that a level of whole-blood cobalt at 4.5 µg/L should be used as a detection tool for identifying abnormal wear (only recommended for hip resurfacing cases) (45). A cobalt:chromium joint fluid ratio >1 indicates severe ALVAL in hip replacement, and an elevated whole blood:serum chromium ratio can assist to detect ALVAL and abnormal wear processes (46). However,

these baseline values are only considered as potential criteria for MoM HA according to current guidelines. No consensus thresholds of metal levels indicating ALVAL or prosthesis failure are available for TKR or other joint replacements using CoCr-based implants. Therefore, it is not known whether these guidelines may be implied following knee and shoulder replacements using CoCr-based implants.

Immunology of ALVAL

The most accepted mechanism for the development of ALVAL is lymphocyte-mediated hypersensitivity to metal debris, also known as the type IV or delayed-type hypersensitive response. Here metal debris released from CoCr implants can potentially bind to peri-prosthetic or plasma proteins to form complexes that become haptens. These are then presented to T-cell receptors (TCRs) on the surface of helper T-cells (generally purported to be the CD4+ T_{H-1} subtype) by antigen-presenting cells (APCs). After activation, CD4+ T_{H-1}-cells proliferate and excrete cytokines, including interleukin-1 (IL-1), IL-2, tumor necrosis factor-α and interferon-γ (IFN-γ) to stimulate macrophages and heighten inflammatory responses (Fig. 2) (47).

The involvement of T-cells in metal hypersensitivity has been well documented, but the effect of increased metal ion concentrations on which types and subtypes of T-cells is ambiguous. Revell *et al*. analyzed CD4+ T-cell subtypes and inducible co-stimulator (ICOS) surface expression in peripheral blood (PB) and SF of patients with failed MoM hip replacement by flow cytometry. ICOS is a homodimeric protein expressed specifically on the surface of T-cells, which enhances T-cell proliferation and antigen presentation. It also aids lymphokine secretion, promotes cell–cell interactions and boosts B-cell expression (48). They found that although the percentage of CD4+ T-cell subtypes was similar in PB, their subtype distribution was altered between PB and SF. In the SF, CD4+ T-central memory and T-naïve cells decreased, while T-effector memory cells that can enter inflamed sites rapidly increase in number in addition to increased cytokine release. Moreover, ICOS was increased on the surface of CD4+CD28+ T-cells in PB and SF (49). A randomized study also found the percentages of HLA-DR+CD4+ and HLA-DR+CD8+ T-cells were positively correlated with the concentrations of cobalt and chromium (28, 50). Paradoxically, some studies reported that T-cell lymphopenia was associated with cobalt release from CoCr devices. Hart *et al*. determined that CD3+ and CD8+ T-cell subset counts were significantly reduced in patients that underwent MoM hip replacement surgeries (51). A previous study also showed that cobalt and chromium concentrations in blood were associated with CD8+ T-cell reduction in asymptomatic patients with well-fixed MoM hip resurfacing (52).

However, knowledge of exactly how T-cells participate in ALVAL is still elusive. Some DQA1/DQB1 haplotypes presented with a high predicted affinity to serum albumin were more common in ALVAL patients (53). HLA sequencing showed that DQA1*02:01, DQB1*02:02 and DRB1*07:01 were significantly positive with ALVAL. Additionally, DQA1*02:01–DQB1*02:02 had the highest affinity binding to the N-terminal sequence of albumin, while DQA1*01:01–DQB1*05:01 exhibited the lowest binding affinity, which was found in patients without ALVAL in a high frequency (54). Another study showed that in patients with MoM bearings, CD86 and HLA-DR molecule expression on the surface of APCs is increased, strongly implying the presence of an immune response (55).

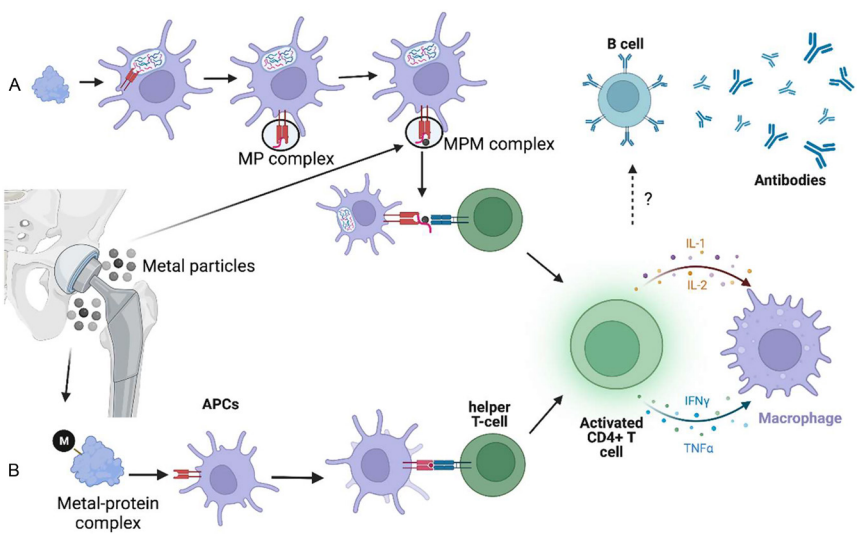

Figure 2

Mechanisms for metal presentation to helper T-cells. (A) Antigen-presenting cells (APCs) digest endogenous or exogenous proteins, and the digested peptides can compete for the binding groove of major histocompatibility complex (MHC) molecules forming a MHC:peptide (MP) complex, which are then transported to the cell surface. Released metal ions from the implant can cross-link the MP complex (forming MHC:peptide:metal (MPM) complex) with T-cell receptors (TCRs), leading to helper T-cell activation; (B) Preformed metal–protein complexes are presented by APCs and recognized by TCRs, resulting in helper T-cell activation. Activated T-cells excrete cytokines that can recruit and activate macrophages. However, involvement of B-cells and antibodies in ALVAL has not been determined. Created with BioRender.com.

Despite the involvement of T-cells, cytokines are known to be significant contributors in the activation of immune reactions related to arthroplasty failure. Hallob *et al*. reported that patients who underwent MoM THRs exhibited a higher concentration of IFN-γ and IL-2 but significantly lower lymphocyte proliferation than individuals without implants (56). Dapunt *et al*. quantified cytokine gene expression in patients with MoM bearing and found that IL-1β, IL-8, MIP2α, MRP-14 and IP-10 genes from peri-prosthetic tissues were more highly expressed than in samples taken from more distant tissues (57). Furthermore, cytokine levels including IL-6, IL-8 and IP-10 and VEGF in peri-prosthetic fluid positively correlate with the severity of ALVAL (58). The involvement of cytokines implies that local inflammatory responses may occur after implantation. Furthermore, this also suggests that metal implants elicit cell-mediated metal hypersensitivity in these patients and that cytokines play a role.

ALVAL may occur due to activation of the endothelium by cobalt or chromium released from CoCr implants (and thus not relate to the formation of metal–protein (auto)antigens (59). Laboratory studies suggested that the release of IL-8, MCP-1 and ICAM-1 is involved in the process of lymphocyte transendothelial migration from PB to inflammatory sites (60, 61). Activated endothelial cells can release IL-8 and MCP-1 which can trigger a transition in circulating lymphocytes to the adhesion state. ICAM-1 helps lymphocytes migrate through the endothelial layer to inflammatory locations. It was suggested that Co^{2+} ions may play a role in the activation of endothelium cells and in the upregulation of IL-8, MCP-1 and ICAM-1 release (59, 62). In addition, Co^{2+} promoted the adhesion of lymphocytes to endothelium cells and transendothelial migration.

Toll-like receptors (TLRs) are also reported to be involved in the development of ALVAL. TLR4 is a receptor that binds bacterial lipopolysaccharide and plays a crucial role in regulating dendritic cell functioning and initiation of immune response (63, 64). Similarly, Co^{2+} ions can activate TLR4. Co^{2+} may bind to residues His456 and His458 which could facilitate TLR4 dimerization, the initial step for TLR4 receptor activation (62). Increased expression of IL-6, MCP-1, IL-8, CCL20 and CXCL10 through activation of TLR4 by Co^{2+} has been observed *in vitro* (65, 66, 67, 68, 69). These cytokines can recruit and direct inflammatory cells and lymphocytes to the site of inflammation.

Other adverse reactions related to abnormal metal concentrations

In addition to ALVAL, there are other conditions related to the abnormally high concentrations of metals associated with CoCr implants. However, the boundaries between disorders and conditions related to metallic wear debris are ambiguous. For example, diffuse lymphocytic infiltrate accompanied by extensive tissue necrosis is frequently observed in some patients (70). In addition, a macrophage-dominated histology is frequently found in ALVAL (71). Intriguingly, a macrophage response predominantly induced by larger wear debris was characterized by histocyte accumulation on the surface of local soft tissues, while ALVAL mainly induced by smaller volumes of metal debris was seen in deeper locations, such as fat and muscle (70, 72). Therefore, it has been suggested that the term ALVAL could be altered to adverse local tissue reactions (ALTR) in cases where it is important to collectively classify and describe a cohort of adverse reactions associated with artificial CoCr implants, including when vasculitis is absent and/or adverse reactions to metal debris (ARMD) (4).

There are three major features of ALTR/ARMD (including pseudotumor, metallosis and cell death and peri-prosthetic tissue necrosis), regarding histopathological examinations of peri-prosthetic soft tissue and bone (4). Pseudotumor(s) is a generic term to describe peri-prosthetic soft tissue masses formed with variable size and content in joint replacement, associated with high levels of cobalt and chromium in blood (73). The term ‘pseudotumor’ is frequently misused as a synonym of ALVAL. However, the most distinctive feature of pseudotumors is the cell composition of inflammatory infiltrate, rather than the presence of lymphocyte-dominated reactions that are predominantly featured in ALVAL. The incidence of pseudotumor development in MoM implant hip replacement surgeries is reported to be high; around 28% of patients who received BHR hip resurfacing were found to develop pseudotumors and 28.6% of cases with small-head (28 mm) MoM THRs developed pseudotumors (74, 75). However, the incidence of pseudotumors may be underestimated due to asymptomatic cases and incidental discovery (73). Additionally, female gender, age and implants with a large head are high risk factors for pseudotumor development (76, 77). In histological studies, both non-specific inflammatory responses and hypersensitivity reactions in response to metal wear were seen in the pseudotumor cases. This suggests that it is not only macrophages that participate in the process of pseudotumor formation but also lymphocytes (72, 78).

Metallosis is a term used to describe the accumulation of metal debris around joint fluid, peri-prosthetic tissues and/or bone marrow, potentially leading to toxic effects on various organs and systems triggered by high metal levels in blood (79, 80). It is reported to be a rare complication with a prevalence of around 5% in MoM hip replacements (79). However, it cannot be used as a diagnostic terminology to define implant failure as it fails to distinguish the complexity of metallic wear debris generated by various mechanisms, devices and positions (4). Additionally, metallosis is only a descriptive term that infers the presence of a variable amount of metal wear

debris but does not offer any measurable threshold of the content. Therefore, it is necessary to substitute and/or expand metallosis with specific wear in addition of other histopathologic diagnose to offer a better understanding and management of ALTR/ARMD.

Cell death, predominantly found in macrophages, is one the major features of ALTR/ARMD. Shed metal particles are initially phagocytosed mainly by macrophages, leading to the release of cytokines and other inflammatory components into the surrounding environment. Phagocytosed wear debris is oxidative reactive and can induce cytotoxicity, resulting in cell death and lysis (81, 82). *In vitro*, induction of cell death either via apoptosis or via necrosis of macrophages is dependenton metal ion levels and incubation time (83). Additionally, the degree of cell death is correlated with the presence of metal debris as compared with non-metal wear (84). Notably, macrophagic death results in re-release of wear debris, leading to a vicious cycle of macrophagic recruitment and death, aggregating inflammatory reactions and surrounding tissue damage (85). Necrosis and inflammation of peri-prosthetic soft tissue is also seen in ALTR/ARMD. In a MoM hip resurfacing study, substantial necrosis and inflammation was observed in the peri-prosthetic connective tissue in response of metal particles, accompanied with macrophage and lymphocyte infiltration (86). However, more research should be performed to elucidate the different effects of metal particles on mechanisms and subtypes of necrosis.

Metal–protein complexes as immunogens?

Metal hypersensitivity: nickel–HSA complex as a model

Some metal ions, such as Ni^{2+}, Be^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Cd^{2+}, and Hg^{2+}, are reported to be related to skin hypersensitivity, and some can even induce autoimmune diseases (87). Nickel-induced contact hypersensitivity is perhaps the most studied of such conditions. Released Ni^{2+} ions are allergens which can induce the production and release of different kinds of cytokines and chemokines. The resultant molecules can activate APCs and nickel-specific T cells, which eventually cause complex immune responses in the body (88). The dominant form of nickle in the body is the Ni^{2+}–HSA complex. HSA is the primary transporter of Ni^{2+}, binding to the first three residues of the N-terminus (Asp1, Ala2 and His3) (89). The Ni^{2+}–HSA complex is considered as an inducer to activate T cells and promote transient contact between TCRs and APC-exposed HLA (90). Although nickel-induced hypersensitivity is well established, the content of nickel in a CoCr device is low (only 1%), compared to the levels of cobalt and chromium (37). Regarding Cr^{3+}, transferrin (not HSA) is the preferred binding protein in plasma (91).

Co^{2+}–HSA complex: binding properties and a potential immunogen

HSA is the predominant protein in plasma (ca. 600–700 μM) and SF (around 66% of total protein in SF) (92, 93, 94). HSA was described as the main carrier of Co^{2+} in the blood, with two major binding sites located at N-terminal sequence (NTS and site B) and one located at the interface between domains I and II (site A) identified so far (91). NTS was previously proposed to be the primary Co^{2+}-binding site (95, 96, 97, 98). However, current evidence indicates that site B (partially composed of His9 and Asp13) is more likely the principal binding site for Co^{2+} rather than NTS (99, 100). Although NTS is not the primary (or even secondary) binding site for Co^{2+}, it still can in theory bind to Co^{2+} if these are present at sufficiently high levels. Furthermore, patients with an HLA class II genotype that encodes a protein with peptide-binding grooves possessing greater affinity for the N-terminal sequence of HSA have a greater risk of developing delayed-type hypersensitivity (54). Therefore, although yet to be proven, cobalt–HSA complexes are considered to be potential immunogens which can elicit ALVAL (101).

Follow-up guidelines of patient management

Some authorities and regulatory bodies have published guidelines for MoM HAs and patient management. However, there remains no single consensus with different regulatory agencies providing different guidelines. This is far from ideal and leads to uncertainty for surgeons and other health care professionals. Some current guidelines are summarized below.

The American Food and Drugs Administration (FDA)

Long-term follow-up of patients with MoM hip implants every 1–2 years is recommended by FDA. Patients with higher risk of developing ALTR/ARMD are advised to take closer follow-up. These include patients with bilateral implants or with resurfacing systems with small femoral heads (≤44 mm), female patients, those receiving high doses of corticosteroids and those with renal insufficiency, suppressed immune systems, evidence of suboptimal alignment of device components, suspected metal sensitivity (e.g. cobalt, chromium, nickel), severe obesity (body mass index (BMI) > 40) or high levels of physical activity. Routine long-term follow-up of asymptomatic patients (every 1-2 years) is recommended. However, with respect to symptomatic patients with MoM hip implants, follow-up should occur at least every 6 months, and metal ion testing is also needed. Additionally, metal artifact reduction sequence (MARS)-MRI is recommended to detect potential ALTR/ARMD (102).

The European SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks)

For asymptomatic patients with MoM hip implants, regular follow-up is suggested, but time intervals and tools of investigation are dependent on implant category and local protocols. With respect to symptomatic patients, annual follow-up is necessary for all implants, especially for large-head MoM THR (≥36 mm) and hip resurfacing. For the latter, annual follow-up is recommended for the first 5 years and can be changed to local protocols if metal ion levels are not significantly increased. However, annual follow-up for the life of implants is recommended for some patients with MoM hip resurfacing, with higher risk including small component size, female gender and so on. For patients with abnormal clinical and/or radiographic examination or dramatically elevated metal ion levels, ultrasound, CT and/or MRAS-MRI are recommended. Cobalt levels in whole blood between 2 and 7 μg/L can be treated as a threshold value for necessitating further investigation (34).

Medicines and Healthcare Products Regulatory Agency

An annual follow-up is compulsory for certain patients with or without symptoms. These include all patients with a larger femoral head size (≥36 mm) in stemmed THRs, all patients with DePuy ASR hip resurfacing devices, female patients with hip resurfacing systems or male patients with small femoral head resurfacing systems (≤48 mm). In addition, annual follow-up is necessary for symptomatic patients with MoM hip resurfacing (male and femoral head diameter >48 mm) and small-head MoM THR (femoral head diameter <36 mm). Whole-blood cobalt and/or chromium levels ≥7 ppb are indicator for closer follow-up and cross-sectional imaging. MARS-MRI or ultrasound are recommended to all symptomatic cases and/or patients with elevated metal ion levels (103).

European multidisciplinary consensus statement

Systematic follow-up is recommended for all patients with MoM THRs and hip resurfacing. For asymptomatic patients with small-head THRs, follow-up should be occurred as frequent as conventional THRs, but annual follow-up is necessary for large-head THRs. In the case of hip resurfacing, annual follow-up is recommended for the first 5 years and may be changed to local protocols based on metal ion levels. However, patients with higher risk such as those with small-size femoral components (<50 mm), female gender and low coverage arc, annual follow-up is recommended for the life of the implant. During follow-up, x-ray examination is recommended for all patients, and additional imaging including ultrasound, CT and MARS-MRI should be applied in case of clinical/radiographic abnormality and/or excessive metal ion levels. Particularly, cobalt levels within the range of 2–7 μg/L is of clinical concern (104).

Conclusions

Current evidence indicates that metal debris levels are generally increased in the surrounding fluids. This is likely to contribute to ALVAL in patients who have received such implants. ALVAL is associated with lymphocyte infiltration around the joint and is accompanied by macrophage infiltration, along with destruction of local tissues, including bone, muscle and neurovascular structures. Current studies have suggested that a metal–protein complex (possibly the cobalt–HSA complex) acts as a hapten that elicits ALVAL. However, further work is needed to support this hypothesis, and, if confirmed, how such a complex presents to T-cells and immune components such as APCs and B cells that participate in this response. HSA is the predominant metal ion carrier in the plasma. However, knowledge of other potential proteins in SF which can bind metal ions and act as haptens that elicit metal hypersensitivity should be investigated. Although some techniques discussed above are useful to diagnose ALVAL, there are still no tools to predict which patients are at most risk of developing ALVAL. A novel genetic predisposition (HLA-DQ haplotypes) test has been proposed to guide implant selection and inform on postoperative management. Additionally, an annual physical examination and metal ion concentration test could be useful for early diagnosis of such complications. Finally, there are no fully standardized guidelines available relating to the use of CoCr implants. More precise and standard criteria (e.g. peri-prosthetic tissue sampling for histopathological analysis) should also be established between clinics and regulatory agencies for revision surgery (4).

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