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Systemic and local toxicity of metal debris released from hip prostheses: A review of experimental approaches

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Abstract

Despite the technological improvements in orthopedic joint replacement implants, wear and corrosion products associated with the metal components of these implants may result in adverse local tissue and perhaps systemic reactions and toxicities. The current review encompasses a literature review of the local and systemic toxicity studies concerning the effect of CoCrMo wear debris released from wear and corrosion of orthopedic implants and prostheses. Release of metallic debris is mainly in the form of micro- and nano-particles, ions of different valences, and oxides composed of Co and Cr. Though these substances alter human biology, their direct effects of these substances on specific tissue types remain poorly understood. This may partially be the consequence of the multivariate research methodologies employed, leading to inconsistent reports. This review proposes the importance of developing new and more appropriate *in-vitro* methodologies to study the cellular responses and toxicity mediated by joint replacement wear debris *in-vivo*.

Keywords

Total joint replacement; Wear particles; CoCrMo; Toxicity; Systemic; Hip-simulator

Joint replacement surgery is the standard treatment option for patients with end-stage joint diseases.[1–4] The most commonly replaced joint is the knee, followed by the hip. Currently,

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around 300,000 Total Hip Replacements (THRs) are annually performed in US, and this is expected to increase to 572,000 by 2030.[5] Table S1 (see supplementary data) describes different joint arthroplasties and the materials used for manufacturing these implants.

A modern hip prosthesis is a modular system consisting of a femoral and acetabular component (similar to a ball (head) and socket (cup) joint). Subsequently, these can be assembled from two or more components each. Commonly, the femoral component is constructed of a stem and a head. The elongated part of the stem will be inserted in femoral stem and top part has a tapered neck that connects with the head (ball). The neck and head connections are known as modular taper junctions. Likewise, the acetabular component is modular (consisting of multiple interchangeable parts). A typical acetabular modular construct will include a metal shell perhaps fixed to the pelvis bone with screws, and a polyethylene liner that articulates with the femoral head. Currently, the components of artificial hip replacements include highly cross-linked ultra-high molecular weight polyethylene, cobalt chromium molybdenum alloys, titanium alloys, zirconium–niobium alloy, stainless steel, tantalum, ceramics, or metal–ceramic structures.[6] The manufacturing methods and materials used to make these devices have been heterogeneous. The metals employed in these device components can be either cast, wrought, or 3D printed. Different combinations of materials have been employed at the articulation (head and cup), such as the metal-on-metal (MOM) hip implants introduced in 1950s, and metal-on-polyethylene (MOP) implants introduces during the 1960s. Many MOM devices were recalled due to a reported high rate of implant failures as indicated by revision surgery numbers.[7,8] MOP implants are currently in use with uncertain limitations on their long-term survival. Ceramic on metal (COM), ceramic on ceramic (COC) and ceramic on polyethylene (COP) are other combinations available in the market. An emerging issue is the morbidity of biological and immunological responses[9] caused by implant degradation products.

Irrespective of the nature of the bearing couple (MOP, MOM, COC or COP), the degradation products released from the implants, in the form of metal, polymer or ceramic nano- and micro-particles, and metal ions, are disseminated into the surrounding tissue as well as to remote locations in the body. The adverse effects of these processes are becoming apparent and were critical to the failure of many MOM designs.[6,9–11] Substantial scientific evidence has been reported regarding the toxicity of these metal particles and ions by *in vitro* and *in vivo* studies.[12–19] In-depth studies regarding the toxicity mechanisms of the independent metal particles with regard to fibroblasts,[12,15] macrophages,[20,21] lymphocytes,[13] and osteoblasts[22] have been reported. In addition, toxicity of the degradation products from different types of prosthetic component constructs, such as Co, Cr, Ti, Al, V, polymeric and ceramic debris has been studied by toxicologists, pathologists, and clinical researchers.[17,23,24]

Considering the increase in number of total joint replacement (TJR) surgeries to date, as well as thousands of new surgeries anticipated to be performed in future, the risk of toxicity from corrosion and wear particles is of great concern. Also, since there is a trend for younger patients to undergo joint replacement, this increases the expectation for implant manufacturers to develop implant components with enhanced performance and durability leading to a low risk of periprosthetic as well as systemic toxicity over the time.

From the robust evidence observed by different researchers, it was established that the degradation products (DPs) of the implants materials are complex, and they may present as metal–protein complexes, free metallic ions, inorganic metal salts or oxides and as organic storage form such as hemosiderin.[11] In addition, there were substantial studies clearly depicting that the bioactivity of the DPs varies based on the physicochemical characteristics, which in turn vary depending on the technique adopted to generate the particles for particular studies.[25–29] The particles characterized from the peri-prosthetic tissues of retrieved implants vary in their geometrical shapes and dimensions. These particles may be round, oval, needle, spike, etc., of varying sizes.[26,30–33] However, there are disparities in the analysis of physicochemical characteristics of the degradation products from tissue samples due to the variation in isolation methodologies adopted by the researchers. Different isolation techniques have specific impact on the characteristics of the particles. Hence, the disparities on the reported physicochemical characteristics of the DPs and the toxicity associated with them are not consistent. It is important to consider the changes in characteristics of these products which occur during their transportation through the circulatory systems before reaching the site where they induce toxicity. Scharf et al demonstrated the macrophage mediated mechanism of formation of ions from Co and Cr nanoparticles. The study also suggested that several cellular pathways and functions could be compromised due to the interaction of metal ions with several important cellular proteins.[34] Evaluation of such evolution of the wear products is highly complex. Moreover, unfortunately, some of the reported studies have simulated degradation products using commercially available materials, which may be very far from the chemical states of the *in vivo* DPs generated from joint replacement implants. This may lessen the relevance of such toxicology studies. Recently, *in vitro* hip-simulator studies provided substantial evidence to prove that the debris generated using serum (simulated synovial fluid) has similar characteristics to that of patient tissue samples.[31]

This review focuses on the overall evaluation of cobalt–chromium–molybdenum alloy (CoCrMo) implant degradation, the characteristics of the wear products, *in vivo* and *in vitro* studies concerning the interaction of CoCrMo wear debris with different cellular environments and the potential toxicity in the human body. The study also offers some understanding of the challenges and perspectives of implant wear debris-mediated toxicity studies.

Search strategy

A Medline bibliographical search (from 1988 up to 2017) was carried out. The following search items were explored: “metal implant” AND “wear”, “wear” AND “toxicity”, “CoCr wear particles” AND “toxicity”, “Co/Cr ions” AND “toxicity”, “Co/Cr particles” AND “cell toxicity”, “genotoxicity” AND “metal particles/ions”, “toxicity mechanism” AND “metal particles”, “clinical reports”, AND “hip implant”, “neurotoxicity”, “DNA damage AND metals”, “Cardiotoxicity AND metals” OR “renal toxicity” AND “metals”, liver toxicity” AND “metals”. The inclusion criteria were: *in vitro* studies; meta-analysis; randomized controlled trials; perspective cohort studies published in English. The search was limited to total hip replacements and cobalt CoCrMo-based orthopedic devices. Nano- and micro-particles composed of cobalt and chromium were also included although particles mixed

with other metals or components were excluded in this study. Articles not involving of toxicity of cobalt–chromium debris were also excluded. The title and abstract of the identified articles were preliminarily evaluated based on the inclusion criteria. The evaluation of the appropriateness of articles was independently carried out by of the authors (Bijukumar and Segu). The search resulted in 220 papers; 37 did not fit the inclusion criteria resulting in 183 articles, which were selected for review for this report.

Degradation of structural materials

CoCrMo, Ti and its alloys and stainless steel (SS) are commonly used metals in implant design. Each of these materials has its advantages and disadvantages. CoCrMo alloys are known for their rigidity and long-term corrosion resistance, but one of the major disadvantages of this metal is the cost of fabrication because of its high rigidity.[35] On the other hand, Ti alloys are of relatively low density and show excellent corrosion resistance and biocompatibility. However, Ti alloys have a relatively low shear strength, low wear resistance and high cost. Lastly, stainless steel has a relatively high elastic modulus and good corrosion and fatigue resistance in short term application, but tends to corrode in long-term application. In addition, it has a relatively high proportion of Ni, which is potentially immunogenic, thereby making it less desirable in permanent implant applications. An ideal implant material should have the modulus elasticity of bone, high corrosion and wear resistance and excellent biocompatibility. To attain the maximum efficiency and durability of an implant the manufacturers use different materials for different parts of an implant. For example, CoCrMo is used for the femoral head in total hip replacements and the femoral component of total knee replacements as it has excellent strength and wear resistance. The femoral stem of total hip replacements and the tibial tray of total knee replacements are typically fabricated from Ti-alloy (high strength with a modulus of elasticity closer to bone) and finally the acetabular cup and the tibial articulating surface are made of UHMWPE. Hence, CoCrMo alloy is widely used in both total hip and total knee replacments, which makes the research on toxicity of CoCrMo degradation products more imperative for patient safety and implant longevity.

Corrosion plays a major role in the release of metal ions,[36] however, both wear (mechanical) and corrosion (chemical) act synergistically (tribocorrosion) in the presence of protein rich synovial fluid. This interaction results in the generation of complex degradation products. When two metals come in contact with each other and undergo tribological process (sliding or fretting), wear debris will be released from their interface. These are mechanical wear particles or corrosion products and/or metal ions. In general, tribocorrosion is an irreversible process resulting in transformation/degradation of the material with a resultant change in the mechanical function of the device.[37] This is due to the synergistic interaction of sliding, abrasion, fretting, crevice and galvanic corrosion mechanisms leading to the mechanical alteration of the implant.[38]

Tribocorrosion behavior mainly depends on (i) the properties of the contacting materials, (ii) the mechanics of the tribological contact, and (iii) the physicochemical properties of the environment. These aspects are strongly interrelated—either synergistic or antagonistic,

which can have beneficial or deleterious influence over the performance of the tribological system.[38]

In a femoral component of a hip implant, there are three interfaces; head–cup (sliding–corrosion),[37–39] head–neck or trunnion (modular junction–galvanic corrosion, fretting–corrosion)[40,41] and stem–bone (fretting–corrosion)[42] (Figure 1). In an ideal implant, the head–cup interface should have smooth tribological motion, produce no debris and be biologically inert. The other two interfaces should not have any movement and should be biologically inert. However, these interfaces may experience micro-motion during the *in vivo* performance of the implant (physical activities under loading), which finally results in fretting–corrosion process. Fretting–corrosion is a type of tribocorrosion phenomenon that occurs during repeated cyclic micro-motion. This can lead to severe damage on the contacting surfaces.[43] Recently, there have been concerning clinical reports regarding the performance of modular junctions.[44–48] In fact, all component interfaces can lead to generation of wear particles and/ or metal ions. In certain cases local, and possibly systemic, biological reactions have occurred resulting in pain and local tissue damage that require revision surgery.[9,11,16,49]

When sliding/fretting occurs in the setting of a crevice geometry (as is present at the head/neck junction of a femoral component of a total hip replacement), a synergistic degradation by wear and corrosion takes place to cause metal ion and particle release at an unexpected high level.[39] Wear process can be accelerated based on the corrosion processes such as pitting[50] or intergranular corrosion.[47,51–53] This is directly related to the properties of the material and the alloy microstructure.[6,37,50] Crevice corrosion can occur at any implant interface where the gap between the contacting surface is very minimum, leading to oxygen depletion and low pH levels creating a highly acidic environment.[54,55]

Degradation products (DPs) are generated and released from orthopedic implants and prostheses due to wear and corrosion during daily functional performance.[56] Major components of the complex degradation products (DPs) are wear particles composed of polymers, ceramics or metals modified by the environment.[11] The release of metallic debris from CoCrMo-based prostheses (weight percentage compositions are approximately 68% Co, 28% Cr and 7% Mo) is mainly in the form of micro/nanoparticles and metal ions of different valences and reactivities. These particles can cause adverse local tissue reactions (ALTR, which includes aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), necrosis, osteolysis and so-called pseudotumors) and systemic toxicity (including cardiomyopathy, polycythemia, hypothyroidism, and neurological disorders).[57–64] The bioactivity of the nano-scale metal particles is higher than that for micro-sized due to the large surface area per mass.[24,65] According to Doorn et al, the wear rate of MOM articulation is approximately 20 times lower than that of MOP articulation. Also, the released metal particles are significantly smaller than polyethylene particles.[30]

Toxicity to peri-prosthetic tissues

After THR surgery using CoCrMo-based orthopedic prosthesis, an increase in the level of Co and Cr ions in serum and synovial fluid[66] has been reported. Periprosthetic tissues

become potential sites of local toxicity due in part to the presence of wear particles released from the prosthetic materials. The degradation products (DPs) generated from the implant due to wear and corrosion cause an ALTR mediated by monocytes, macrophages, and lymphocytes as illustrated in Figure 2. Ricciardi et al described macrophage predominant, mixed lymphocytic–macrophagic cell infiltrates with or without hypersensitivity reactions, and with sarcoid-like granulomas.[67] The wear debris activate endothelial cells at the implant–tissue interfaces and in turn express the adhesion molecules such as P-selectin, ICAM-1, VCAM and CD44.[68–70] Granulocytes, macrophages, monocytes and lymphocytes are attracted by these adhesion molecules towards the tissue interfaces. Macrophages activated by the phagocytosis of the wear particles trigger the secretion of pro- inflammatory cytokines (IL-8, IL1-β, IL-6), chemokines, growth factors, prostaglandins, degradative enzymes, reactive oxygen species and other factors.[71–75] Additionally, multinucleated giant cells and osteoclasts generated by the fusion of the macrophages, adhere to the metal surface of the bone-metal interface, triggering osteolysis which may lead to aseptic loosening of the implant.[76–79]

Debris induced aseptic loosening and osteolysis depends on the physico-chemical characteristics of the tribocorrosion debris, which in turn influenced by the chemical composition of the prosthesis.[80] According to Doorn et al, the size of the CoCr wear particles isolated from surrounding tissues of the failed implant is in the range of 6-834 nm in the case of MOM implant.[30] However, the size CoCr wear particles may vary from 0.07 to 12.2 μm in the case of MOP implants.[31,33] Moreover, Davies et al reported that the inflammation pattern exhibited by the anatomical layers of neocapsule formed around the implant varies with type of articulation.[81] More ulcerated tissue samples were obtained from MOM hip prosthesis than from other types. Far less surface ulceration was observed on MOP prostheses. Those implants exhibited aseptic loosening with no clear evidence of ulceration and lymphocytic and plasma cells infiltrations and the loosening is mainly attributed to the involvement of histiocytes (a stationary phagocytic cell present in the tissue/organ).[81]

Another ALTR associated with wear debris is so-called pseudotumor formation. The prevalence of pseudotunor following metal-on- metal THA is 1%-39%.[82–85] However, asymptomatic pseudotumor was a supplementary finding in 57%-78% of cases[83,86–88] even though THA revision surgery due to symptomatic psuedotumor was only 1.7%-5.6%.[86,89] Characteristic features of pseudotumors include lymphocytic infiltration, lymphoid aggregates and prominent necrotic pattern with macrophages. The condition can be destructive and sometimes painful, and patients may require revision surgery. Though the etiology of this abnormal condition is not yet clearly understood, serum levels of Co, and Cr in patients with pseudotumors are elevated in comparison to patients without pseudotumors.[90] In turn, elevated metal levels correlate with excessive wear debris generation.

Systemic toxicity of cobalt and chromium

Systemic toxicity of the CoCrMo wear debris is also of conern in orthopedic surgery. Table S2 (See supplementary data) summarizes relevant toxicity studies reported previously. Several clinical reports reveal a clear correlation between CoCr-based hip prosthesis and

systemic cobalt toxicity.[91–96] In addition, the deposition of the metal wear debris found in distant organs has also been reported.[23,92,95,96]

Nano-scale metal and polymeric particles or metal ions can circulate systemically via lymphatics to lymph nodes, bone marrow, liver, and spleen. In addition, the metal particles are reported to enter the bloodstream, and concentrated inside the erythrocytes.[97] Erythrocytes containing metal then circulate throughout the body and further enhance the cytotoxic, genotoxic and immunological effects.[30,95,98]

Intracellular transport of metal particles mainly occurs by diffusion or endocytosis through the plasma membrane of the cell and receptor-mediated mechanisms.[26] Large sized particles are taken up by the cells via the pinocytosis and phagocytosis processes of macrophages.[15] Hence, the debris released by the implants, regardless of their composition, are capable of disseminating into the bloodstream and entering into different tissue compartment depending on the size regime.

The role of cobalt and chromium particles and /or ions in inducing cytotoxicity has been studied using different cell types[99–101] as shown in Table S2 (See supplementary data). *In vitro* studies also demonstrated that Co^{2+} and Cr^{3+} ions and nano-particles can induce apoptosis and necrosis and inflammatory responses in macrophages and pneumocytes.[14,102] In addition, the Co^{2+} can influence iron metabolism by binding with apotransferrin, which might affect normal hematopoietic tissue metabolism.[103] However, few studies have been reported in relation to implant wear debris and iron metabolism. One study revealed that Co nano-particle at a concentration of 25 and 100 ppm had toxic effect on the human hematopoietic progenitor cells derived colonies.[104]

Dose-dependent toxicity of cobalt and chromium nano-particles of size at 30-60 nm and their respective ions was investigated for macrophages by Kwon et al. It was found that cobalt nanoparticles at 1×10^{12} particles/ml and Co^{2+} ions at 1000 μM (589 ppm) concentration exhibited various levels of toxicity to the macrophages whereas Cr^{3+} failed to produce any toxicity at this concentration. Nevertheless, Catelas and coworkers reported Co^{2+} and Cr^{3+} at 8-10 μg/ml (8-10 ppm) and 350-500 μg/ml (350-500 ppm) respectively as toxic concentrations.[14,20,105] A significant level of toxicity has also been demonstrated by studies using several different sizes of cobalt and chromium particles as well as ions with different valences (Table S2, See supplementary data). Using commercially available cobalt–chromium wear debris (DePuy international, Leeds, UK), a significant increase in uptake of ions and apoptosis gene up-regulation was demonstrated at concentrations of 0-5 mg/10^6 in monocyte-like U937 cells.[106] More importantly, the study demonstrated clear evidence of an increase in wear particle-mediated toxicity after revision surgery by comparing wear particle toxicity of ion pretreated cells versus that of non-pretreated cells.[106,107]

Apart from *in vitro* studies, clinical reports analyzed the relationship between serum metal concentration and circulating immune cells counts and suggested that released Cr^{3+} ions may cause changes in lymphocyte subpopulations in THR patients.[108]

Deposition of wear debris in distant organs is another concern. Even though cobalt–chromium alloy particles accumulated within the liver macrophages and kidney,[23,109] toxic

effect was not detected by histologic analysis.[110] However, there is a correlation between wear debris accumulation and upregulation of metalloprotein I/II, which can result in the alteration of xenobiotic metabolism by liver. Despite the low level of immediate toxicity of metal particles in the liver,[95,96] in the long-term, there is still a possibility of diffusion of ions and transferring of metal particles to other organs similar to iron deposition. An *in-vivo* study demonstrated that an intramuscular CoCrMo device, implanted for a period of nine months, resulted in metal accumulation in liver and kidney tissue. This indicated that after long term exposure metal particle and ions are released from an implant even under non-functional conditions.[109]

Concerning clinical complications, involvement of metals such as Ni, Al, and Co in parkinsonian dementia, dialysis encephalopathy and Alzhemeir's disease[111–113] etc. has been reported. Oxidative stress-mediated toxicity of cobalt can be reversible by pretreatment of cells with α-estradiol.[114] However, the correlation with patients who had undergone joint replacement was limited. Recently, there have been clinical reports of visual and hearing impairments as well as numbness of the feet.[63] For instance, retinal pathology has been linked to a high level of serum cobalt and chromium by several clinical reports.[57,62,63,115,116] Clinical studies have also reported polyneuropathy with progressive sensory disturbance and hearing loss with sural nerve biopsy indicating axonopathy and cardiomyopathy.[59,64,93,94] Mortality due to cardiac failure with clear evidence of Co deposition into the patient's heart tissue (cardiomyocytes) was reported recently,[136] highlighting the need for research in this field.

Genotoxic effect of nano-debris

Genotoxicity as the result of metal debris has also been extensively investigated. Nanoparticles are major constituents of wear debris and hence the understanding of the effect of nanoparticles at the molecular level is very important. Through the evolution of nano-toxicology, several investigators have studied the cellular response to metal particles at the nano-scale, starting from uptake to molecular activity and genotoxicity. Humans have a basic tolerance to various nano-particles at a certain concentration. However, the quantum properties of nano-materials make them unpredictable in developing carcinogenicity *via* genotoxicity. The major reason for the toxicity is their small size, allowing them to penetrate the cells and different organelles and the capability to generate an excess amount of reactive oxygen species (ROS). The physical and chemical properties of nano-materials cannot be predicted based on the bulk composition and their physicochemical properties will vary according to the surroundings. The consequences of interaction between metallic nano- or micro-particles with intracellular biological components cause oxidative stress, protein conformational changes, mutations and alterations in signaling pathways (Figure 3).[117–119]

In vitro studies have demonstrated that cobalt nano-particles have well-known genotoxic effect. In comparison to chromium, cobalt is considered less toxic, and the mechanism of action of each is critically different. Carcinogenicity was also detected in their ionic form. Several previous studies have shown a strong interest in the mutagenic and genotoxic effects of Co^{2+} and Cr^{3+} (Table S2, See supplementary data). The major mechanism of genotoxicity of cobalt includes single strand breaks (Fenton-type reaction),[120] cross-linking

(topoisomerase poison),[121] sister chromatid exchanges, aneuploidy and ineffective DNA repair properties (damage to the zinc-finger domains of repair proteins)[122–124] (Figure 4). Colognato et al studied the genotoxicity of cobalt micro-particle at a size scale at 0.1-0.5 μm and showed increases in the tailing of DNA.[125] Moreover, single and double stranded breaks mediated by cobalt nano-particles have also been reported in further studies.[125,126] In fact, the role of chromium in inducing DNA damage is mainly attributed to the reactive oxygen species once Cr^{4+} undergoes reduction to Cr^{3+}. Another peculiarity of Cr^{3+} is its ability to form stable Cr-DNA adducts.[127] Also, it can cause DNA damage through single and double stranded breaks as well as cross-linking.[128] A comparative investigation of the distinct toxic response of mouse fibroblast to cobalt particles and $CoCl_2$ solution showed that $CoCl_2$ primary caused DNA damage while cobalt particles induced neoplastic transformation and genotoxicity[129] (Table S2, See supplementary data). In addition, it was concluded that cobalt particles are more toxic than $CoCl_2$.[126,129]

Peripheral lymphocyte analysis of patients with MOM implants, showed increased lethal and non-lethal aneuploidy and chromosomal translocations[130] that correlated with metal ion levels; detectable genetic damage was reduced following revision to a MOP device.[131,132] A recent study on the toxicity of soluble (cobalt chloride hexahydrate) and particulate cobalt metal to the lung cells showed that soluble cobalt was more genotoxic than particulate cobalt, even though the isolated intracellular ionic concentrations using ICP-MS were higher in particulate than the soluble form.[133] Co^{2+} and Cr^{3+}ions have the ability to break DNA as reported in several studies (Table S2, See supplementary data).[101,134,135]

While short-term in vitro investigations into exposure of cells to individual particles or ions have been reported, the long-term effect of particles and ions on cells has not been elucidated. Moreover, apart from ions or particles, evaluation on the toxicity of the metal–protein complexes or with phosphates and sulfates formed during exposure into the *in vivo* environment needs to be considered.

Current limitations in implant-based toxicity evaluation: challenges and perspectives

The outcome of the toxicity studies of metal debris reported in this review demonstrates the importance and clinical significance of research into the development of new prosthetic devices. Notwithstanding, several aspects related the methodology used to assess degradation products (DPs) of orthopedic implants and prostheses should be meticulously evaluated in order to determine clinical failures pathways. The objective should be the development of standardized physical–chemical characterization techniques for evaluation of the toxicity of prosthetic functional wear debris based on morphology and material composition.

Physicochemical properties of the wear particles will vary with the composition of the implant materials, the extant of degradation processes and possibly the patient's state of health (which may affect the surrounding fluid properties). Attention should be paid to each of these variables in evaluating the toxicity of wear debris (Figure 5). However, elucidation of precise *in vivo* physicochemical properties of wear debris is difficult due to the limitations

in methodologies for isolation and characterization (such as enzymatic, alkaline digestion for LC-MS analysis).

Morphology and content of wear debris

Characterization of metallic wear particulates in the periprosthetic tissues of retrieved MOP and MOM implants demonstrated varying morphologies: round, oval, needle and spike-like.[31,32] Moreover, the size of the particles varies significantly based on the type of implant. As reported by Doorn et al, the particles from MOM implants ranged from 6 nm up to 0.83 μm.[30] Campbell et al also reported a similar size range, varying from 18 nm up to 0.47 μm. For MOP prostheses, the particle size reported ranged from 7 nm up to 6.3 μm, which is significantly larger than those recorded for MOM.[26,33] These investigators emphasized the limitations in the characterization of particles smaller than 0.4 μm, which indicates the apparent inconsistency in observations available in the literature. In addition, the concentration of Co and Cr species in the samples were dissimilar in crystalline and amorphous areas of the particle.[30] A high Co content was detected in crystalline areas; high Cr and oxygen content was detected in the amorphous areas. According to Campbell et al, the periprosthetic tissue analysis demonstrated a higher content of CoCr based particles and a lesser amount of Cr oxide particles. There are very few reports addressing the properties of wear particles from synovial fluid. The available reports using different isolation and characterization techniques[137,138] show dissimilar material properties. In addition, there are no studies reported clearly depicting the surface area of the wear particles generated *in vivo*, other than the size measurements described above. Ogunwale et al showed the surface area of 4 nm sized CoCr particles generated by spark discharge method as 185 m^2g^{-1}.[139] Again, one may question the clinical relevance of such particles. Surface charge of the CoCr wear particles has significant influence on their bioactivity. CoCr particles of 30 nm (generated by pin-on-plate tribometer) and 80 nm (generated by thermal plasma techniques) showed a surface charge of −14 mV and −12 mV respectively. The study also showed differences in metal ion release by particles prepared by these two different methods. Specifically, 80 nm particles generated by thermal spray technique released 7 times more Co and Cr ions in comparison to thermal plasma, even though there was no significant difference in their surface charge. It might be difficult to measure the surface charge of particles from the periprosthetic milieu due to binding of proteins on the surface. It was also speculated by Simoes et al that the strong dissolution of Mo from CoCrMo alloy nanoparticles in the presence of bovine serum albumin (BSA) is due to the similarity of their surface charge to that of the isoelectric point of BSA.[140,141] Overall, these studies provide very little and inconclusive information about the surface characteristics of the CoCr wear particles *in vivo*, leaving a large gap in this research field.

Limitations in the evaluation of physico-chemical properties

There are disparities in reports of the physico-chemical characteristics of the wear particles from patient samples. This is primarily due to methodology chosen for evaluation of the samples. Metal particle analysis is a complex process, with different steps including digestion, isolation, morphological characterization and chemical analysis. Investigators can choose different protocols for each step based on expediency.[142] Previous studies have reported different methods to separate and isolate particles for physical–chemical

characterization.[30,143–146] For example, enzymatic digestion can be accomplished in three different ways, namely: (1) Papain and Proteinase K, (2) Papain and Proteinase K with NaOH wash, (3) Papain and Proteinase K with yeast lytic enzyme and zymolase. Each technique has its own effect on defining the characteristic properties of the material and might lead to disparate results.

Materials commonly used for the some of the previous *in vitro* studies are summarized in Table S2 (See supplementary data). The majority of studies tested $CoCl_2$, $CrCl_3$, Cr_6O_2, Cr_3O_4 or $K_2Cr_2O_7$ (potassium dichromate) as the source of Co and Cr ions. In addition, commercially available CoCr-based nano- and micro-particles were also used to evaluate the cytotoxicity of wear particles from orthopedic implants and prostheses. The above-mentioned particles from different sources have varying degrees of clinical relevance. There is no standard method for generating particles for *in-vitro* and *in-vivo* studies. To accurately model the biological impact of wear debris, it is important to simulate the in vivo degradation products, both particles and ions, as closely as possible. Moreover, it is understood that wear debris *in vivo* may consist of metal–protein complexes, free metallic ions, inorganic metal salts or oxides and as organic storage form (e.g. hemosiderin[11]). In fact, the bioactivity of the degradation products varies significantly based on their physicochemical properties and biological environment.[25–29] However, previous reports have not considered these facts when performing toxicity evaluation within their experimental designs. Instead, commercially available metal particles were used to study the toxic effect of wear debris. For example, some reported studies addressed the toxicity of CoCr alloy particles (metal ion valence: Co^{2+}, Cr^{3+}, Cr^{6+}) and Ti ions *in vitro* on fibroblasts,[12,147] macrophages,[20,21] lymphocytes,[13] osteoblasts[22] and osteoclasts.[22] However, the particles used in these studies may have very different surface properties than the wear particles generated *in vivo*.[148–153] Nonetheless, those studies are a helpful first-order approximation. The toxicity of wear debris *in vivo* is a cumulative effect of all the different forms of debris that are generated. In addition, the toxicity of the organometallic species[154] generated in the synovial fluid may be unique (and possibly less toxic) than its ionic form. It was also reported that the albumin can enhance the dissolution of Co ions from wear debris.[155] These findings suggest a fruitful area of investigation that is currently poorly understood.

Second generation of toxicity evaluation

To potentially mimic the *in vivo* joint conditions, 2nd generation toxicity evaluation researchers used a hip wear simulator for generating wear debris. Many studies have shown that *in vitro* simulator testing is an accurate methodology to predict the performance of joint replacements.[154,156–158] Moreover, Catelas et al carried out a comparative evaluation of the physicochemical properties of wear particulate extracted from tissue samples of patients who underwent CoCrMo implant revision surgery in comparison to wear particles generated from the hip simulator. It was revealed that the particles generated in the simulator were comparable to those found in the periprosthetic patient samples with regards to the chemical composition, size and shape.[159] However, the characterstics of wear particles generarated from pin-on-disk/plate may be influenced by the contact bearing surfaces and the testing lubricant solution.[31] Researchers in this field are now aware of the pitfalls in the physical–chemical characterization methodologies used to isolate and quantify particles from the

simulator as well as from patient tissue samples. In addition, there are very in limited *in vivo* studies utilizing particles from hip simulators with clinically relevant joint fluid for toxicity evaluation.[160] Therefore, the reported studies on the wear debris generated from hip simulator may have limited applicability to the actual *in vivo* scenario.

The type of cells used for toxicity evaluation is equally important. Generally, immortalized cells are considered for such evaluations due to their unlimited number of cell division to grow in unlimited quantities. However, the use of immortalized cells for such investigations has been questioned due to their genetic modification, which alters their morphological, molecular and phenotypic characteristics in comparison to native cells.[161] In short, the major challenges in the current cytotoxicity studies of CoCrMo wear particles include i) particle source, ii) physico-chemical properties, iii) dosage, iv) static nature of the *in vitro* cell culture studies compared to the dynamic nature of the in vivo scenario, and iv) type of cells used for toxicity studies. In order to address these challenges, a uniform *in vitro* methodology, optimally simulating *in vivo* conditions, should be established to study the cellular responses and toxicity caused by wear debris.

Important points that need to be considered before undertaking toxicity studies of wear debris include: 1) using clinically relevant dosing, preferably with wear debris generated in a hip simulator with simulated joint fluids; 2) using wear debris with clinically relevant physico-chemical properties; and 3) using clinically relevant primary tissue specific cells.

Concluding remarks

The purpose of this review was to summarize the present status of the systemic and local biological response to implant wear debris, with special emphasis on the toxicology of CoCr alloy wear debris. *In vitro* studies addressing the effect of metal particles and ions on different cells/cell lines are numerous, although the experimental methodology varies substantially in the extant literature. While previous studies have provided a good basis for the understanding of the mechanism of action for various degradation products, due to the non-uniformity of the methodologies used in these studies there are many gaps in our knowledge. In addition, the cumulative effects of the products of wear and corrosion may be different from their individual components in terms of both the mechanism of action and the intensity of the response. To develop an accurate risk assessment of wear debris in implant patients, experimental models should be developed using wear debris, cells, culture media and environmental milieu which more closely simulate *in vivo* conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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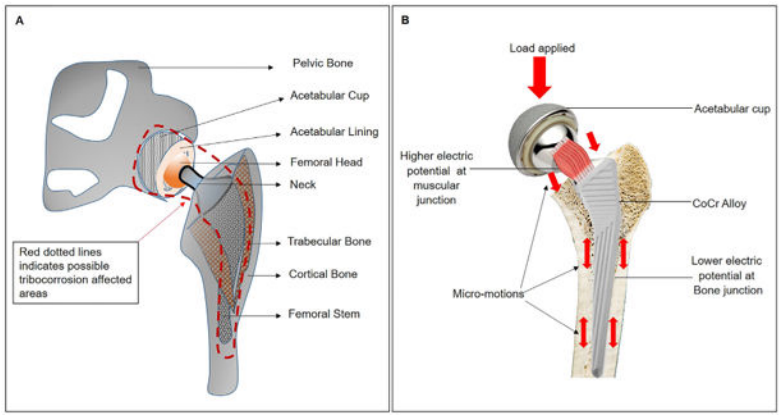

Figure 1.

(**A**) Components of a total hip implant. Red dotted line indicating the area around the implant with possibilities of tribocorrosion. (**B**) Showing the sites of micromotion on a total hip implant during physical activity. The load generated at the head region will transferred to the stem through neck and possible site of micromotion during physical activity are clearly spotted with direction of micromotion (red arrows).

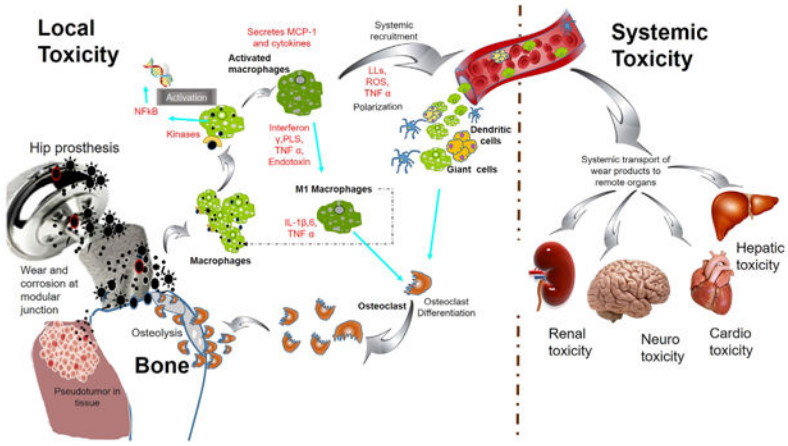

Figure 2.

Schematic of adverse tissue reaction cascade at peri-prosthetic tissue region and systemic toxicity leading to osteolysis. Wear particles generated from implant, particularly from the modular junctions induce macrophages mediated inflammatory reactions. The wear debris uptaken by the macrophages via phagocytosis, diffusion and membrane mediated transport mechanism will activate periprosthetic macrophages and lead to systemic recruitment and polarization of systemic macrophages, giant cells and dendritic cells towards periprosthetic region. Particulate debris via circulatory system can cause toxicity to distal organs.

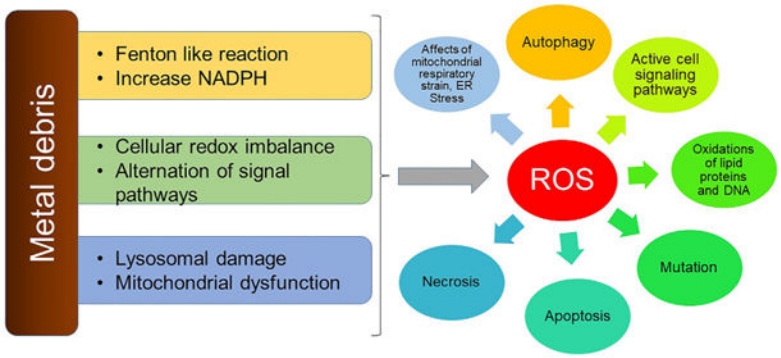

Figure 3.

Depicting the ROS mediated cellular toxic mechanism due to metal particles and ions. Metal particles can cause Fenton-like reaction as wells as cellular and molecular changes. Most of the cellular damage is due to ROS species.

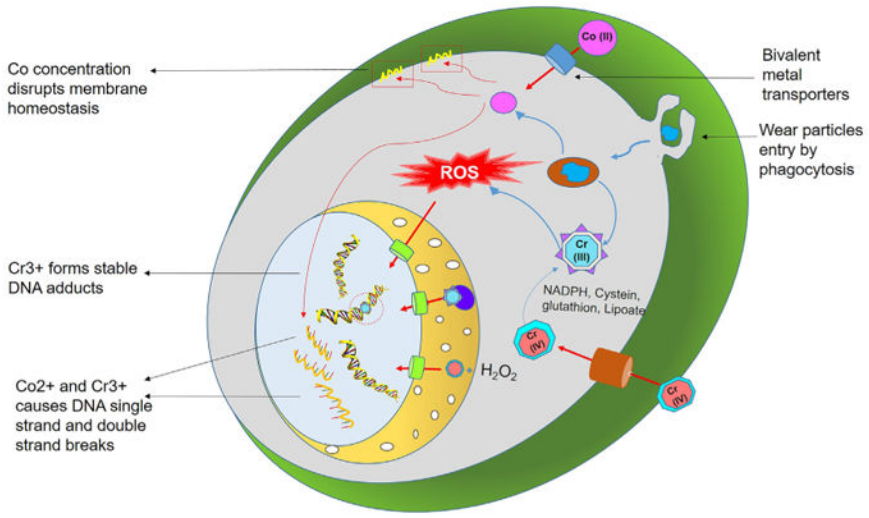

Figure 4.

Schematic representation of transport of Co and Cr ions inside the cells and nucleus leads to genotoxicity. The metal ions can cause direct DNA damage by causing single and double stranded breaks in DNA as well as indirect damage via ROS mediated genetic alterations leading to abnormal gene expression.

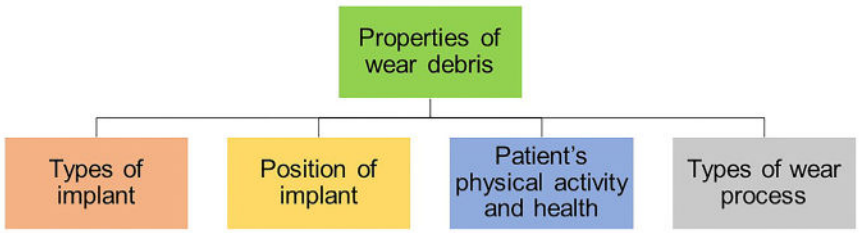

Figure 5.
Summary of different variables influencing the property of wear particles *in vivo*.