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■ REVIEW ARTICLE

Orthopaedic metals and their potential toxicity in the arthroplasty patient

A REVIEW OF CURRENT KNOWLEDGE AND FUTURE STRATEGIES

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The long-term effects of metal-on-metal arthroplasty are currently under scrutiny because of the potential biological effects of metal wear debris. This review summarises data describing the release, dissemination, uptake, biological activity, and potential toxicity of metal wear debris released from alloys currently used in modern orthopaedics. The introduction of risk assessment for the evaluation of metal alloys and their use in arthroplasty patients is discussed and this should include potential harmful effects on immunity, reproduction, the kidney, developmental toxicity, the nervous system and carcinogenesis.

Total hip replacement (THR) and resurfacing arthroplasty have become some of the most successful elective surgical procedures in modern medicine, restoring mobility and quality of life to hundreds of thousands of patients annually. In 2004, a total of 48 987 hip procedures were carried out in England and Wales alone.[1] Between 2002 and 2004 the number of patients aged 50 years or less receiving primary hip replacement in Sweden increased by 6.0%.[2,3] In Canada, the number of hip replacements carried out in patients aged less than 45 years during 2002 rose by 11.0% compared with 1994.[4] This increasing number of younger patients exposed to orthopaedic metal alloys (Table I) has caused concern about the long-term biological effects.[5] The population is regularly exposed to a variety of metals through food, water, occupation and the environment and the potential risk from exposure is assessed and forms the basis of regulatory guidelines imposed to protect the health of individuals. Risk assessment includes a framework for gathering data and evaluating their sufficiency and relevance.

This paper aims to describe the exposure, uptake, dissemination and biological activity of metals released from orthopaedic materials. Toxicological data regarding potential adverse events after systemic exposure to metals have been included. We also introduce a framework for the risk assessment of orthopaedic implants and discuss areas in which our knowledge needs to be expanded.

Prosthesis-derived metal wear debris

Wear debris is generated by mechanical wear, surface corrosion or a combination of both, and consists of both particulate and soluble forms.[6,7] Metal-on-metal articulations generate approximately 6.7×10^{12} to 2.5×10^{14} particles every year, which is 13 500 times the number of polyethylene particles produced from a typical metal-on-polyethylene bearing.[8] Despite this, the actual volumetric wear of a metal-on-metal articulation is lower because of the nano-scale size of the particles (generally < 50 nm)[8] when compared with polyethylene particles, which are rarely less than 0.1 μm.[9] Corrosion can occur at all metal surfaces, resulting in either the formation of a protective passive layer[10-12] or dissolution of the bulk metal alloy.[13] Cobalt (Co(II)), titanium (Ti(V)), aluminium (Al(III)), iron (FE(III)), nickel (Ni(II)) and chromium (Cr(III)) have all been detected in solution during the corrosion of metal alloys.[13-16] Despite evidence supporting the release of Cr(VI) from the CoCrMo (molybdenum) alloy, this remains controversial.[16,17] Corrosion products predominantly consist of metal oxides (Cr_2O_3, CoO, TiO_2, Al_2O_3, etc) and hydroxides ($Cr(OH)_3$, $Co(OH)_2$, etc) within the synovial environment.[18] The deposition of calcium phosphate and the subsequent formation of metal phosphates ($CrPO_4$, $Co_3(PO_4)_2$, etc) occur in non-synovial environments.[19] This may significantly alter the biological and chemical properties of free particulate metals outside the effective joint space.

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Table I. Approximate weight percent of the constituents of different metals used in orthopaedic implants.[116] Alloy compositions are standardised by the American Society for Testing and Materials (ASTM vol. 13.01)

Alloy*	Ni	N	Co	Cr	Ti	Mo	Al	Fe	Mn	Cu	W	C	Si	V
Stainless steel														
(ASTM F138)	10.0 to 15.5	< 0.5	†	17.0 to 19.0	†	2.0 to 4.0	†	61.0 to 68.0	†	< 0.5	< 2.0	< 0.06	< 1.0	†
CoCrMo alloys														
(ASTM F75)	< 2.0	†	61.0 to 66.0	27.0 to 30.0	†	4.5 to 7.0	†	< 1.5	< 1.0	†	†	< 0.35	< 1.0	†
(ASTM F90)	9.0 to 11.0	†	46.0 to 51.0	19.0 to 20.0	†	†	†	< 3.0	< 2.5	†	14.0 to 16.0	< 0.15	< 1.0	†
Ti Alloys														
CPTi														
(ASTM F67)	†	†	†	†	99.0	†	†	0.2 to 0.5	†	†	†	< 0.1	†	†
Ti-6A1-4V														
(ASTM F136)	†	†	†	†	89.0 to 91.0	†	5.5 to 6.5	†	†	†	†	< 0.08	†	3.5 to 4.5

* Ni, nickel; N, nitrogen; Co, cobalt; Cr, chromium; Ti, titanium; Mo, molybdenum; Al, aluminium; Fe, iron; Mn, manganese; Cu, copper; W, tungsten; C, carbon; Si, silicon; V, vanadium

† indicates < 0.05%

Prosthesis-derived metal wear products are found extensively within the synovial fluid and peri-prosthetic tissues of arthroplasty patients.[20] At post-mortem further accumulation has been identified in the regional lymph nodes, liver and spleen.[21,22] Because metal particles are very small (nano scale) the true extent of dissemination is not yet known. Free or phagocytosed wear particles are transported within the lymphatic system.[21,22] Metallic debris may additionally distribute through the vascular system as ions or particles.[23,24] In occupational biomonitoring, blood and urine metal concentrations are used as biomarkers to assess exposure.

In many instances, the mean metal levels identified in exposed workers and joint replacement recipients are comparable. For example, mean whole blood levels of chromium of 5.98 μg L^{-1} average have been found in chrome-electroplaters[25] which is comparable to the mean whole blood Cr levels (4.6 μgL^{-1} or 6.5 μgL^{-1} depending on the implant type) in metal-on-metal patients four years post-operatively.[26] Biological and atmospheric guidance values have been assigned for Cr and Co by health and safety organisations such as the Health and Safety Executive and the Deutsche Forschungsgemeinschaft. Specifically, exposure equivalents of carcinogenic substances (EKA values) corresponding to the workplace exposure limits,[27] in the United Kingdom for Co are 5.0 μgL^{-1} and 60 μgL^{-1} in whole blood and urine, and for Cr are 17 μgL^{-1} and 20 μgL^{-1} in erythrocytes and urine respectively.[28] Several studies in the field of orthopaedics have observed patients with biological metal levels greater than one or more of these values.[26,29,30] The range of methods used to assess metal levels in orthopaedic studies, such as analytical technique, specimen, and time of collection etc, make reliable comparisons difficult between studies and, in general, relatively few studies investigating metal levels are currently available. It is clear, however, that patients with joint replacement, most notably those with metal-on-metal articulations, are likely to experience elevated metal levels throughout the life of the prosthesis.

Cellular uptake and biological responses to metal wear debris

The uptake of metal nanoparticles (< 150 nm) by cells occurs by endocytotic processes, particularly non-specific receptor-mediated endocytosis and pinocytosis.[31] Larger particles (> 150 nm) can stimulate phagocytosis in specialised cells such as macrophages.[32] Once internalised, metal particles can induce cytotoxicity,[33] chromosomal damage[34] and oxidative stress.[35] The toxicity of particles is modified by passivation[14] and particle size.[34] These factors both influence the dissolution of metal from the surface, which may account for biological activity. Evidence of cell damage, such as irregular cell membranes and enlarged mitochondria, may be induced by the physical properties of the particles themselves.[36]

The uptake of Cr(VI) occurs readily through anionic channels because of the structure of the chromate anion while Cr(III) accumulates at the plasma membrane.[37] Cr(VI) is rapidly reduced to Cr(III), with the transient formation of Cr(V) and Cr(IV), and distributed throughout the cell bound to peptide and/or protein ligands.[38] Divalent metal transporter ((DMT)-1)), expressed in a range of tissues, and natural resistance-associated macrophage protein (NRAMP)1, located on the phagosomal membrane, may facilitate the uptake of Co(II) and Ni(II).[39,40] Transferrin-bound Fe(III), A1(III), Cr(III) or vanadium(V) can be internalised by cell-surface transferrin receptors.[41-43] Metal ions released from orthopaedic implants induce apoptosis and/or necrosis in a range of cells, with Co(II) and V(III) among the most cytotoxic.[44,45] Corrosion products, including CoO, Cr_2O_3 and $CrPO_4$ also show moderate cytotoxicity.[46] Within the nucleus, Cr(III) can cause mutagenesis by form-

ing adducts with DNA[47] and DNA-DNA cross-links.[48] Cr, Ni, Co and Ti are redox metals and can generate reactive oxygen species, such as the superoxide radical ($O_2^{\cdot}$) and the hydroxyl radical ($^{\cdot}OH$) via a Fenton-driven reaction with hydrogen peroxide (H_2O_2).[49] Reactive oxygen specie can induce oxidative damage to DNA,[50] proteins,[51] and lipids.[52] Inhibition of DNA repair, altered signal transduction and gene expression have all been documented in response to a range of orthopaedic metal ions, notably Ni(II), Cr(VI) and Co(II).[53,54]

Local tissue reactions

Aseptic loosening and osteolysis remain the major cause of failure of an implant, despite the re-introduction of metal-on-metal bearings as an alternative to metal-on-polyethylene articulations.[1] In patients with metal-on-polyethylene bearings aseptic loosening is thought to be due to the response of macrophages to particulate wear debris. By contrast, particles from metal-on-metal bearings have a limited capacity to activate macrophages and may cause osteolysis by some immunological reaction involving hypersensitivity.[55,56] The pattern of inflammation in the peri-prosthetic tissue of loose metal-on-metal articulations is significantly different to that of metal-on-polyethylene articulations, and is characterised by perivascular infiltration of lymphocytes and the accumulation of plasma cells.[57] Experimental data suggest that orthopaedic metals induce immunological effects which support a cell-mediated hypersensitivity response.[58]

Systemic toxicology

Information regarding metal-induced toxicity is based on a limited amount of epidemiological and experimental studies involving *in vitro* and *in vivo* models. Unfortunately, there are few data available on the systemic effects of metal in arthroplasty patients. At present, the following toxic responses have been documented:

The blood. Both A1 and Cr(VI) can induce changes in haemoglobin and haematocrit values which are linked to their ability to disrupt cellular iron utilisation.[59,60] In renal patients, the effect of impaired A1 clearance is associated with the development of microcytic anaemia.[61] No significant effect of Ni(II) has been identified *in vivo*, although *in vitro* oxidative effects, predominantly lipid peroxidation, at high concentrations have been reported.[62]

The immune system. Metals modulate the activities of immunocompetent cells by a variety of immunostimulatory or immunosuppressive mechanisms. With regard to orthopaedic metal ions, the effects generally include altered function of T-cells, B-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 metal-on-metal articulations, although this did not form a linear correlation with serum metal concentrations.[63] However, a threshold value of 5 ppb 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 $CD20^+$ B-cells has been reported in patients with metal-on-polyethylene articulations, while myeloid cells and $CD8^+$ T-cells were consistently decreased regardless of metal levels.[64] These effects have not been recreated in experimental animals exposed to metal alloy solutions, although lymphoid populations were significantly altered.[65]

The liver. Hepatocellular necrosis often occurs in response to very high levels of metal in the body, as observed after acute ingestion of Cr(VI) in humans.[66] Portal inflammation and oxidative stress have been observed after exposure to A1,[61] although pathological changes were not evident in experimental animals.[67]

The kidney. Cr is concentrated in the epithelial cells of the proximal renal tubules and can impair renal function, induce tubular necrosis and cause marked interstitial changes in experimental animals and humans.[68,69] Indicators of tubular dysfunction have been identified in human subjects exposed to Cr(VI) through occupation.[70] Al, Ni and Co are all rapidly excreted by the kidney, hence renal toxicity tends to require significantly larger doses.

The respiratory system. The effects of exposure to Co, Ni and Cr on the respiratory system are well documented[71] because of the frequency of occupational exposure and include an increased incidence of asthma and inflammatory conditions. These effects are often observed in stainless-steel welders, who are repeatedly exposed to metal fumes containing Cr and Ni.[72] Toxic responses of the respiratory system are largely related to inhalation exposure and are therefore difficult to extrapolate to a vascular route.

The nervous system. Several neurological manifestations have been attributed to A1 intoxication in humans, including include memory loss, jerking, ataxia and neurofibrillary degeneration.[61] The development of some neuropathological conditions, including amyotrophic lateral sclerosis, Parkinsonian dementia, dialysis encephalopathy and senile plaques of Alzheimer's disease, may be related to the accumulation of A1 in the brain.[61] A1 is generally associated with changes which may reduce nerve conductivity, promote neuronal degeneration and increase Fe-induced oxidative damage.[73] In relation to Alzheimer's disease, A1 has significant effects on the formation and aggregation of associated proteins such as β-amyloid, the secretion of which is increased *in vitro* by Co(II).[74] Oxidative stress may be significant in the development and/or progression of neurodegenerative disorders, particularly in response to Fe.[75] Markers of oxidative damage have been identified in the brains of experimental animals exposed to Cr(VI) and V(V).[76,77] Significant alterations in visuospatial ability and attention span have been observed in male workers with a mean serum level of 14.4 ppb of V resulting from occupational exposure.[78]

The heart and vascular systems. The accumulation of Co in the myocardium can induce cardiomyopathy, which was particularly evident after the 1966 episode of 'beer-drinkers' cardiomyopathy', during which Co was used as a foam-stabilising agent in beer.[79] Altered left ventricular function relaxation was evident in a small series of cobalt production workers exposed to an average of 0.40 mg Co $year^{-1}$, although clinically significant cardiac dysfunction was absent.[80] Ni and V were thought to have contributed to changes in cardiac function in experimental animals after the inhalation of fine ambient particulate matter was shown to significantly increase the mortality to cardiovascular disease.[81]

The musculoskeletal system. Deposition of A1 in the bone occurs as a consequence of chronic exposure and has been linked to osteomalacia, bone pain, pathological fractures, proximal myopathy and the failure to respond to vitamin D_3 therapy.[82] Orthopaedic metal particles and soluble metal compounds adversely affect osteoblast function, which may in turn influence bone remodelling.[83]

The endocrine system. A1, Cr(II), Co, Ni and V can all bind to cellular oestrogen receptors, which may contribute to aberrant oestrogen signalling.[84] Ni(II), Cr(VI), A1 and Co(II) have the capacity to alter the production or circulation of sex hormones in experimental models, which is normally due to a direct effect on the reproductive cells, as in the case of Cr(VI).[85] Co(II) prevents the uptake of iodine into the hormone thyroxine by its inhibition of the enzyme tyrosine iodinase, which can induce hypothyroidism.[86] Occupational exposure in a small series of Danish pottery painters showed no effect on normal thyroid function despite evidence indicating an altered thyroid metabolism.[87] A1 is known to disrupt parathyroid hormone levels, which may account for A1-induced bone disorders in dialysis patients.[82]

The visual and auditory systems. A1, Co, and Ni can cause severe retinal degeneration at high concentrations in experimental animals.[88,89] Recently, a case was reported of a man who had extreme wear of a CoCrMo femoral head and increased concentrations of Co in the serum (398 $\mu g\ l^{-1}$) and cerebrospinal fluid (3.2 $\mu g\ l^{-1}$).[90] He suffered loss of vision, hearing impairment, numbness of the feet and dermatitis.[90]

The skin. Metal-induced skin reactions can include contact dermatitis, urticaria and/or vasculitis.[91] The incidence of dermal reactions and positive skin-patch testing to Co, Ni and Cr in patients with total joint replacement, with stable and loose prostheses increases by 15% and 50% respectively, above those of the general population.[92]

The reproductive system. Chronic exposure to Cr(VI) induces numerous effects detrimental to fertility in experimental animal models.[93,94] These include decreased sperm count, epithelial degradation, abnormalities of the sperm, a reduced number of follicles and ova, and an increased number of atretic follicles. A large epidemiological study in stainless-steel workers found no significant causal link between exposure to Cr and reduced sperm quality,[95] but workers in chromium sulphate manufacturing had a significant positive correlation between the incidence of morphologically abnormal sperm and blood Cr levels.[96] Exposure to Ni(II), V, A1 and Co(II) has been shown to induce some limited reproductive toxic effects in male experimental animals, such as abnormal histopathology and spermatogenesis.[97-100] However, there seems to be a distinct lack of data relating to the effects of these metals in female animals.

Developmental toxicology. An increase of Co and Cr has recently been described in the cord blood in a study of ten women with metal-on-metal resurfacing, who became pregnant following surgery, suggesting that orthopaedic metals may translocate from the maternal to the fetal circulation.[101] Experimental animal studies suggest that several metals, including Cr, Co, Ni, V and Al, may induce developmental toxicity.[102] For example, Cr(VI) exposure in male and/or female mice either before or during gestation can affect the number of implantations and viable fetuses resulting from conception.[94] Many metals can also induce teratogenic malformations, including Cr, Ni, and V.[102] Transgenerational carcinogenesis, which refers to the transmission of the risk of cancer to the untreated progeny of parents exposed to carcinogens before mating, has been observed in response to some metals, such as Cr(III).[103] In addition to the transplacental route, the passage of metals from the mother to the developing offspring may occur during lactation, as has been suggested in a study with V.[104] In one large study, the incidence of congenital malformations and cancer in the children of male stainless-steel workers was not significantly increased,[95] but follow-up investigation revealed a significantly increased risk of spontaneous abortion among the partners of these male workers.[105] Epidemiological studies have also found a relationship between parental occupational exposure and an increased risk of childhood cancer, but the exact aetiological agent remains unknown.[106] In a very limited study of 13 female arthroplasty patients, the incidence of pregnancy-related complications did not differ from that in the general population.[107]

Carcinogenesis. An increased incidence of chromosomal aberrations has been found in the peripheral lymphocytes of both arthroplasty patients, and welders.[108,109] The significance of this finding and its relationship to an increased risk of cancer remains unknown, but there is a growing consensus that metal-induced DNA damage may lead to carcinogenesis. Occupational metal exposure such as to Cr, has been linked to an increased risk of cancer.[110] Studies in Norway on patients with THR have identified a small but significant excess in the incidence of haematopoietic, prostate and endometrial cancer and malignant melanoma.[111,112] The International Agency for Research on Cancer, which publishes information on the risks posed by chemicals on the development of human cancers,[113] has classified Cr(VI) and Ni(II) as carcinogenic, metallic Ni and soluble Co as possibly carcinogenic, and metallic Cr, Cr(III)

compounds and implanted orthopaedic alloys as unclassifiable.

Conclusions

The European Food Safety Authority and the World Health Organisation have recently discussed the use of risk assessment in the evaluation of genotoxic and carcinogenic substances in food.[114] Data obtained from approved *in vitro* and *in vivo* models and human epidemiological studies form the basis of standard risk assessment. Dose-response analysis allows quantification of the no adverse effect level and the low adverse effect level calculated against the experimental uncertainty. This allows potential human risk to be classified according to exposure and for informed decisions regarding risk management to be made in conjunction with other considerations including socio-economic and technical factors.

Risk assessment of orthopaedic metals in THR must comprise a structured risk/benefit analysis, assessing the direct benefits of THR to the patient and the risks related to outcomes, failure of the implant and prosthesis-derived metals. THR has revolutionised the treatment of osteoarthritis and other crippling conditions, with most patients noticing a signifcant improvement in their quality of life.[115] Most available survivorship and mortality data have been obtained from select series and misrepresent current clinical trends. Over the coming years however, as longer follow-ups become available, initiatives such as the Swedish Hip Register and the National Joint Registry (NJR) for England and Wales will become an invaluable data source relating to joint replacement outcomes. Risk assessment of prosthesis-derived metal requires estimation of exposure to the patient, which should be based on numerous factors including the type of prosthesis, patient activity, the potential length of exposure and the likelihood of increased metal release through implant loosening. The last is a complex situation since the relationship between elevated steady-state metal levels and loosening is unknown, as is the ideal interval between patient discomfort and clinical intervention. Associated risk also depends on the type of articulation and the alloy used in the components.

This review has outlined the 'potential hazards' of circulating metals based on the available information. However, without detailed characterisation of both the physical and chemical properties of wear debris, particularly once the metal has left the effective joint space, the risk posed by orthopaedic metals is difficult to assess. In addition, toxicology data obtained from animal studies are limited by protocols which cannot easily be extrapolated to the clinical situation. From the limited studies consulted in this review, several areas have been identified which deserve investigation, including immunity, reproduction, the kidneys, developmental toxicity, the nervous system and carcinogenesis. The mechanism behind altered peripheral lymphocyte populations needs to be elucidated since this may be indicative of specific prosthesis-derived metal-induced toxicity. The incidence of metal-induced toxicity in the kidney can be clarified by renal monitoring of arthroplasty patients. In the light of current International Agency for Research on Cancer classification of metals, in particular Co and Cr, monitoring of the incidence of cancer in patients must remain a high priority. This should include evaluation of the possible relationship between metal-induced chromosomal aberrations, genotoxicity and carcinogenesis. Relatively few studies have addressed the potential effects of prosthesis-derived metals on the reproductive system. This is particularly important in males and should begin with analysis of sperm to determine whether prosthesis-derived metal has an effect on fertility. It is improbable that female fertility would be affected by circulating metal although this should not be dismissed. Epidemiological monitoring of arthroplasty patients, female partners and offspring would indicate any increases in stillbirth, spontaneous abortion, birth defects and childhood cancer. Cognitive testing may help to uncover potential neurotoxic effects occurring from prosthesis-derived metal. Liver-function tests and cardiac monitoring would clarify any possible toxicity within patients and may be worthwhile, but should not take priority. At present, elucidation of the exact mechanism behind aseptic loosening has been the main focus in orthopaedic research and continues to provide information regarding tissue and cellular responses to metal debris, although the role of oxidative stress and chronic immune-driven damage should perhaps receive attention in the future.

Finally, it is imperative that we continue to support initiatives such as the Swedish National Hip Arthroplasty Register and the National Joint Register in England and Wales since they will give a sophisticated, patient-based risk assessment and provide the scope for continuous improvements in the field of orthopaedics. The benefits of orthopaedic surgery are proven, but the risks are theoretical or uncertain. Therefore any decision on the use of orthopaedic metal alloys, particularly in articulations, should not be taken lightly and must be the product of further research and careful consideration of risk *versus* benefit.

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