

# The effects on bone cells of metal ions released from orthopaedic implants. A review

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## Summary

**The increasing use of orthopedic implants and, in particular, of hip and knee joint replacements for young and active patients, has stimulated interest and concern regarding the chronic, long-term effects of the materials used. This review focuses on the current knowledge of the adverse biologic reactions to metal particles released from orthopaedic implants *in vivo* and *in vitro*. More specifically, the purpose of this article is to provide an overview of the current literature about the adverse effects of metal particles on bone cells and peri-implant bone.**

**KEY WORDS:** orthopaedic implants; metal ions; adverse effects; bone cells; osteolysis.

## Introduction

Over the last 30 years, orthopaedic surgery has immeasurably improved the lives of millions of people, restoring their mobility, bringing pain relief and ultimately giving them a better quality of life. The main orthopaedic implants currently in use are prostheses for replacing arthritic joints, and devices for fixing fractures and stabilizing the spine. Joint replacement, and in particular knee and hip replacement, has arguably seen the greatest advances in terms of investment, research and clinical results. Prosthetic joint replacement has proved to be a highly reliable treatment even in the long term (1). However, in spite of the success of this type of surgery, there still remains the need for further progress; average life-expectancy is rising which necessitates ever more long-lasting implants, and complications and adverse effects are not infrequent (1) and often require the substitution of the prosthesis. Furthermore, it is generally accepted that within 15-20 years after surgery, aseptic loosening of the implants is almost inevitable. If infection is excluded, the most frequent complication associated with joint replacement is the deterioration of the prosthetic components and the resulting biological response of the body to the material released by the implant.

Thus the generation of wear debris and the subsequent tissue reaction to this debris, have a fundamental effect on the longevity of total joint arthroplasties. Although adverse reactions to implants are relatively rare, if we take into account the huge number of prostheses implanted to date and the hundreds of thousands of new prostheses implanted each year, the problem could potentially be huge. The situation has become more urgent with the increasing number of reports of adverse effects related to metal ion release from certain types of hip prosthesis, in particular those which have direct contact between two metal joint components (MoM: metal-on-metal). As these prostheses have mechanical characteristics which are particularly attractive, they have been widely used over the last few years, particularly in younger patients.

Whilst adverse reactions to metals have been studied for many years by pathologists, toxicologists, company doctors and dermatologists, research has begun relatively recently in Orthopaedics, and therefore the results are limited. The toxicokinetics of small metal wear particles and associated corrosion products remain unclear, and data are particularly scarce regarding the effect of metal ions on bone cells and bone resorption (osteolysis). In light of this lack of data and the emerging problems in the field of orthopaedic implants, we have carried out a review of the literature on the adverse effects of metal ion release. The purpose of this review is to provide a comprehensive update on the effects of metal ions on bone cells and bone resorption after a surgical orthopaedic implant.

## Orthopaedic biomaterials

The principal characteristic required by biomaterials if they are to be used in orthopaedic surgery is that they are resistant to repeated mechanical stress. Only metals, ceramics and polymers meet this fundamental requirement (Table 1).

## Metals

Amongst the orthopaedic biomaterials currently in use, only metals provide a combination of additional advantages: high strength, ductility, tenacity, hardness, fracture toughness, corrosion resistance, formability and biocompatibility. Although initial prosthetic designs used stainless steel, over the years the metal alloys developed in the aeronautical and naval industries were adopted for use in Orthopaedics.

The three main metal alloys used in the production of joint prostheses are the following: stainless steel based alloys; cobalt alloys; and titanium alloys. Each of these alloys has its own particular strength, rigidity and ductility properties. However, their high resistance to corrosion has made them particularly suitable for use in the manufacture of orthopaedic implants.

## Current technology in total hip and knee arthroplasty

The vast majority of joint arthroplasties are performed either in the hip or the knee. The materials used for the prosthetic components are more or less similar for the two joints. Currently, hip prostheses tend to comprise a titanium or cobalt-chromium alloy femoral

Table 1 - Orthopaedic biomaterials.

	Material	Use
<b>Metals</b>	Titanium alloys (Ti-6%, Al-4%V)	Plates, screws, prosthetic components
	Cobalt-chromium-molybdenum alloys (Co-Cr-Mo)	Prosthetic components
	Stainless steel	Plates, screws, cerclage wire, prosthetic components
<b>Polymers</b>	Polymethyl methacrylate (PMMA)	Bone cement
	Ultra-high-molecular-weight-polyethylene (UHMWPE)	Prosthetic inserts
<b>Ceramics</b>	Aluminium oxide (AlO <sub>2</sub> )	Prosthetic surfacing
	Zirconium (ZrO <sub>2</sub> )	Prosthetic surfacing

stem, either cemented with PMMA or press fitted, which is connected to a cobalt-chromium alloy or ceramic head. The head articulates with a UHMWPE or ceramic or cobalt-chromium cup liner, which is cemented, screwed or press fitted into the acetabulum. In younger patients the preferred design is ceramic-on-ceramic or metal-on-metal (MoM) due to the greater longevity of these implants. The most widely-used metal implants are chromium-cobalt-molybdenum and cobalt-nickel-chromium-molybdenum, then titanium alloys, and recently new zirconium and tantalum alloys. This may account for the fact that there are many more studies published about the effects of chromium and cobalt than those regarding the effects of other ions.

### Orthopaedic biomaterial degradation

Orthopaedic biomaterials are associated with local and remote adverse tissue responses. Generally, these adverse effects are mediated by the degradation products of implanted materials, which are primarily generated by wear and corrosion. This debris can be present in different forms: free metallic ions; colloidal complexes; inorganic metal salts or oxides; organic forms (such as hemosiderin); and finally, wear particles.

Particulate debris has a very large surface area with which to interact with surrounding tissues, and this is confirmed by the chronically elevated levels of metal content in serum and urine found in patients who have received a metal implant. The particulate debris that is generated by wear, fretting and fragmentation, and which is unavoidable when a prosthesis is implanted, can induce an inflammatory reaction in some circumstances. This, at a certain point, promotes a foreign-body granulation tissue response that is able to invade the interface between bone and implant. This results in progressive local osteolysis that threatens the fixation of the hardware (2).

Whilst polyethylene degrades through wear alone, the metal alloys used in orthopaedic implants also degrade due to corrosion, or a combination of wear and corrosion (3, 4).

### Wear

Two materials placed together under load develop electrorepulsive and atomic binding interactions in the area of contact. When the surfaces slide across each other, these reactions are disrupted, and particles of material (wear debris) are generated. These particles may attach to the counter face, remain between the two surfaces or disperse into the system of the host.

The rate of wear depends largely on the contact force between the two surfaces and the sliding distance, and thus increases with physical activity, weight gain, larger implants and the roughness of the implant surface (5). Every step that a patient takes creates

a loading cycle that can potentially cause wear of the bearing surfaces, even in an optimally designed and implanted prosthesis.

### Corrosion

All metallic surfaces undergo electrochemical corrosion that reduces the structural integrity of the implant and releases products of degradation that are potentially toxic to the host. The mechanism of corrosion is essentially the galvanic effect, based on the thermodynamic driving forces which cause an oxidation/reduction reaction. Every metal has its own reactivity to oxidation and the exposure of metal to synovial or organic fluids produces a gradient-based exchange of electrons and ions (cations) from the metal to the solution, whereas oxygen anions from the watery solution tend to migrate into the implant.

### Results of metal degradation

The main products of metal degradation are metal oxides (i.e. CoO) and hydroxides [i.e. Cr (OH)<sub>3</sub>] that can be found within the synovial environment, and metal phosphates (i.e. CrPO<sub>4</sub>) that are generally deposited in the extra-synovial tissues. Compared with polyethylene debris, metal particles are markedly smaller (<50nm vs. >0.1 μm) and more numerous (up to 13,500 times more in MoM hip arthroplasties) (6). Moreover, particle size and shape changes with the severity of wear and the passage of time, as corrosion is a continuous process (7, 8). As the size of the particle decreases, the cumulative surface area increases, with more atoms exposed and a greater biological activity per given mass compared to larger particles (7).

Owing to their small size, nanoparticles are ingested by macrophages or disseminate systemically via lymphatics to lymph nodes, bone marrow, liver and spleen (9). Further corrosion releases metal ions which enter the bloodstream and become concentrated in the erythrocytes. Thus, metal ions may enter cells and remain in local tissues or they can be transported throughout the body, which can lead to cytotoxic, genotoxic and immunological effects, either locally or at distance from the implant (10).

Metal nanoparticles can pass through the cell plasma membrane mainly by diffusion or endocytosis (7). Diffusion can occur directly or through membrane channels, whereas endocytosis uses a receptor-mediated mechanism. The latter conveys 200nm or smaller metal nanoparticles, with a preference for 50 nm metal particles which are taken up faster and more extensively than smaller (≥ 14nm) and larger (≤ 500nm) particles (7, 11, 12). Another doorway for small particles is via pinocytosis, a less specific form of endocytosis. Larger fragments are taken up by phagocytic processes of specialized cells such as macrophages (13). Inside the cells, the particles are exposed to oxidative attacks

which are intended to destroy the foreign body, but result in the generation of metal ions and free radicals (mainly reactive oxygen and reactive nitrogen species). The cytotoxic effect is exerted by means of oxidative stress and chromosomal damage. Reactive oxygen species derived from Cr, Ni, Co and Ti may cause oxidative damage to the nucleus, proteins and lipids. This results in inhibition of DNA repair pathways, impaired nuclear signal transduction and defective gene expression (14). With most cytotoxic agents such as Ti, Co and V, apoptosis or necrosis occurs in some cells (15).

Many studies report elevated Cr and Co ion levels in blood and urine. Rates of wear can be assessed by evaluating ion levels in red blood cells, although serum gives a better estimate of the true systemic levels (16). Renal excretion of metal ions seems to balance their generation in patients with MoM hip arthroplasties (17), although levels of circulating Co and Cr ions remain several times above the normal levels. An approximately 5- to 10-fold increase from preoperative to postoperative values in blood Co levels has been shown in several series with different implants (18-21). Although elevated, these concentrations are well below the limits considered dangerous to health in workers exposed to industrial chemicals, and also lower than the levels found to cause cell toxicity *in vitro* (22).

### Systemic effects of metal ions

Most *in vitro* and *in vivo* studies that have been published in the literature are related to the effects induced by Cr and Co. Other known potential toxic ions released by orthopaedic implants are Titanium (Ti), Aluminum (Al), Vanadium (V) and Nickel (Ni). Co, Cr and possibly Ni and V are normal components of some enzymes of our body. They must be introduced with the diet, but become toxic at high dosage.

Co toxicity can affect many organs, and can cause various types of symptoms: neurological (tinnitus, vertigo, deafness, blindness, convulsions); cardiological (cardiomyopathy); haematological (polycythemia); and endocrine (hypothyroidism). Cr seems to be less cytotoxic but more genotoxic than Co (13, 23). It induces tubular necrosis and interstitial cell damage which can result in impaired renal functioning (24). Also potentially severe hepatic lesions have been described, with hepatocellular necrosis and possibly disseminated intravascular coagulation (25). As observed in experimental studies, Cr may compete with Fe in binding to apo-transferrin, causing anaemia. Chronic exposure to Cr has detrimental effects on male and female fertility as a result of decreased sperm production and impaired sperm and ova quality (26).

Al toxicity has been linked to neurological conditions such as memory loss, gait disturbance and involuntary movement, and the development of neuropathological conditions such as amyotrophic lateral sclerosis. Moreover, the accumulation of Al in the brain has been reported as a possible cause of Parkinson's disease, dialysis encephalopathy and Alzheimer's disease (27-29). Chronic Al exposure has been related to osteomalacia, pathological fractures, impaired bone remodelling, altered response to vitamin D and proximal myopathy (30).

In rats, intra-articular injected TiO<sub>2</sub> nanoparticles caused toxicological effects on the lungs with follicular lymphoid hyperplasia and inflammatory cells aggregated around the bronchia (31).

High concentrations of Al, Co and Ni may cause severe retinal degeneration in experimental animals (32).

Ionic Cr, Co, Ni, V, Al and Ti have mutagenic actions on cells in tissue culture. The genotoxic effects of the metal ions are thought to be mediated by either direct action, causing DNA breaks through attacks on free radicals, or by an indirect effect inhibiting the repair of DNA (33).

### Local effects of metal ions

Histological studies performed on peri-implant soft tissues taken at the moment of hardware retrieval, showed an inflammatory response all around the implant. In the presence of relatively large debris particles, the reaction is mainly due to macrophages. In the case of small nanoparticles, the inflammatory process seems to be more a cell-mediated hypersensitivity reaction (34). Patients with metal orthopaedic implants have not only elevated serum Co and Cr concentrations (as mentioned above) but also significantly elevated lymphocyte reactivity to Co and Ni (34). Lymphocyte reactivity is even greater in patients with MoM hip arthroplasties, supporting the hypothesis that lymphocyte metal-induced reactivity increases with increased metal exposure.

The pattern of inflammation in the peri-prosthetic tissue of loose MoM prostheses is significantly different from that of other implants, and is characterized by an unusual lymphocytic perivascular infiltration and plasma cells accumulation. Histological findings support a lymphocyte-dominated immunological response with diffuse and perivascular infiltrates of T and B lymphocytes and plasma cells, massive fibrin exudation, accumulation of macrophages, infiltrates of eosinophilic granulocytes and necrosis. There are usually only few metal particles (35-38). On the other hand, tissue samples obtained from hip arthroplasties with conventional implants show no pattern of lymphocytic infiltration and no plasma cells. The inflammation is predominantly histiocytic. In the presence of a cell-mediated reaction, a lymphocytic response to serum protein complexed with metal from implant alloy degradation products has been demonstrated (39).

In some cases the inflammatory reaction can be particularly aggressive and periprosthetic soft-tissue masses (pseudotumours, i.e. soft-tissue mass relating to the joint) can be found in patients with MoM hip resurfacing. These periprosthetic soft-tissue lesions have been described variously as metallosis, aseptic lymphocytic vasculitis-associated lesions (ALVAL), adverse reaction to metal debris (ARMD) and pseudotumours. The occurrence of such soft tissue reactions is rare, although the number of reports seems to be increasing (40-42). These reactions are locally destructive, requiring revision surgery in the majority of patients. Macroscopically there is a large amount of pericapsular metal debris in the soft tissues which are stained (metallosis) and embedded with dark metal debris. Incision of the capsule reveals a copious amount of black, tar-like joint fluid. Often there is a synovial-like biomembrane with the capacity to produce collagenase, interleukin 1, and tumour necrosis factor which may mediate the absorption of peri-implant bone. The inflammatory markers are usually normal, whereas the serum Co and Cr ion levels are significantly higher than usual (6-7 times more than in patients with the same implant but without pseudotumours) (43).

### Effects on osteoblasts

Although osteolysis is the main feature of peri-implant aseptic loosening, bone resorption may not be the only cause of bone loss. It is well known that normal bone turnover involves a balance between bone formation and bone resorption. The net loss of peri-implant bone may be the result of a reduction in bone formation, with or without a concomitant increase in bone resorption. The relationships between wear debris and bone resorption have been intensely studied, whereas much less is known about the effects of particulate debris on the growth and metabolism of osteoblastic cells. However, it seems relatively well established that metal ions can affect the function of osteoblasts and osteoblast-like cells (44-46).

Cytotoxicity has been demonstrated in osteoblast cultures exposed to metallic wear debris, although the metal ion concentrations within bone *in vivo* have not been established (47, 48).

Metal cytotoxicity, which may ultimately lead to cell death, can cause significant morphological changes, damage to proteins, and modified protein expression. Morphological changes have been observed after osteoblasts have been exposed to Co particles at concentrations of 100 µg/L or higher with the development of cytoplasmic vacuolations (44-46). Proteins from the extracellular matrix such as bone sialoprotein, osteocalcin, and osteopontin are important for calcification of the bone matrix and can be used as markers of osteoblastic activity. These proteins are synthesized by osteoblasts and released into the extracellular matrix. Millett et al. observed that the levels of osteocalcin in synovial fluid are lower in patients undergoing revision for aseptic loosening compared with those having primary hip arthroplasty (49). They hypothesised that the osteoblasts lining the joint space are less active, which is possibly due to an inhibitory effect of particulate wear debris. Other Authors demonstrated that Co and Cr inhibit the release of osteocalcin into the bone matrix *in vitro*, contributing to the delay in mineralization of bone tissue following exposure to metal (50-52). Another indirect sign of the dysregulation of the osteoblast-like cells induced by metals is the pronounced reduction of alkaline phosphatase activity observed after exposure to Co and Cr ions (53, 54). Also collagen type I synthesis is markedly reduced after exposure to Co and Cr particles or ions at concentrations of 10 µg/L or 100 µg/L (45, 55, 56). A decrease in protein, DNA, and RNA synthesis has been shown with Co and Cr ions (57). This is most significant with a cytotoxic metal, such as cobalt, which kills the osteoblastic cell and eliminates the source of the marker proteins.

Studies *in vitro* showed that osteoblasts exposed to Co and Cr ions undergo a time- and dose-dependent reduction in proliferation (54). Metal ions differentially affected osteoblast proliferation, viability, type-I collagen gene expression, and cytokine release. A ranking of the least to the most toxic metal ions (based on a 50% reduction in viability) reads as follows: Na < Cr < Mg < Mo < Al < Ta < Co < Ni < Fe < Cu < Mn < V. Metal-induced decreases in osteoblast proliferation are similar in ranking (46).

Beyond reduction in the number of cells, microscopic analysis has also demonstrated changes in cell shape and size. Co<sup>+2</sup> had a greater effect on these parameters than Cr<sup>+3</sup>. Cell counting showed a significant decrease in the number of osteoblasts, with Co<sup>+2</sup> again more toxic than Cr<sup>+3</sup>. Also the redox state of osteoblasts was altered, with oxidation and nitration of proteins and dysregulation of the expression of antioxidant enzymes (54).

Finally, in the presence of metal ions osteoblasts are able to release proinflammatory cytokines into the microenvironment, such as transforming growth factor beta 1 (TGF-β1), tumour necrosis factor alpha TNF-α, interleukin beta 1 (IL-β1) and, most commonly, IL-6 (45, 46). These cytokines can in turn, activate the differentiation of preosteoclasts into mature bone resorbing cells (58).

### Effects on osteoclasts

It is still not clear how metal ions act on osteoclasts, and the ion quantity required to cause an adverse effect, as the results of published studies are somewhat contradictory. Probably, the effects of metal ions vary according to the state of differentiation of the cells and to the concentration of metal ions.

Osteoclasts are highly specialized multinucleated cells that are responsible for lacunar bone resorption. Osteoclast precursors are mononuclear, bone-marrow-derived cells that are included in the monocyte fraction of blood cells. The classical osteoclast differentiation and activation pathway requires the presence of the osteoblastic macrophage-colony stimulating factor (M-CSF) and necessitates an interaction between the receptor activator of nuclear factor kappa B (RANK), which is expressed on osteoclast

precursors, and RANK ligand (RANKL), which is expressed by osteoblasts and several other cells.

It has recently been shown that some proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), IL-6 and IL-11 are able to induce osteoclast formation from bone marrow cells and circulating precursors through a RANKL-independent mechanism (58).

Another substance implicated in several bone conditions with localized or generalized pathological bone resorption is the TGF-β. It has been found in large amounts in synovial fluid in rheumatoid arthritis where marginal bone erosions are almost always observed. TGF-β serum levels are also elevated in case of osteolytic tumours with hypercalcaemia and in osteoporotic women. A RANKL-independent induction of human osteoclasts has been demonstrated also for TGF-β. Thus, it may play a role in these osteolytic conditions, which are associated with increased cytokine production (59).

Particle uptake by macrophages and metal ion effects on osteoblasts influence the production of M-CSF and RANKL as well as elicit the production of proinflammatory cytokines (IL-1, IL-6, IL-11, TNF-α), prostaglandins (PGE<sup>+2</sup>) and TGF-β. It is likely that this can have a significant impact on osteoclast activity (60, 61). Although both MCSF and RANKL have been identified as key players in osteoclast differentiation and activation, recent studies suggest these factors may also play a role in osteoclast survival. For example, RANKL has been demonstrated to be an essential factor in the maintenance of osteoclast viability *in vitro*. MacQuarrie et al. (2004) (62) observed that Ti and CoCr particles induced osteoclast apoptosis, whereas Co and Cr stimulated osteoclast differentiation. After the addition of anti-RANKL antibodies to the Co and Cr cultures, the number of cells significantly decreased. However, the Authors used metal particles close to the size of polyethylene debris, which is able to induce the macrophage response that is usually absent with nanoscale metal particles.

*In vitro* experiments have shown that Co ions induce the death of osteoclast precursors after 2 weeks. After 3 weeks, there was a decrease in the area of resorbed dentine, indicating a toxic effect of Co on pre-osteoclasts (63). Rousselle et al. investigated the effects of metal ions on mature osteoclasts isolated from the long bone of rabbits, and reported that although Co and Cr did not induce apoptosis of mature osteoclasts, coculture with Co ions decreased their size (64).

*In vivo* data suggest that the concentrations of Co and Cr ions reported in serum and hip synovial fluid of patients with MoM implants have an effect on human osteoclasts. These ions have a mild stimulatory effect on developing osteoclasts, but have an inhibitory effect on mature osteoclasts at higher concentrations (equivalent to the levels found in synovial fluid) (65). The reason for this difference might be explained by the substrate resorbing activity of the cells and the dose-related toxicity of metal ions. Metal ions such as Co<sup>+2</sup> which are present in serum, synovial fluid and peri-implant tissues, can also be incorporated into the mineral phase of bone development. Mature osteoclasts accumulate more intracellular metal ions through their resorbing phagocytic activity in comparison to immature osteoclasts, with a greater toxic effect (65).

Another study has shown that Co ions in solution or incorporated into calcium phosphate at clinically relevant concentrations, increase murine osteoclast differentiation and resorption activity *in vitro* (66). Authors observed a maximal 75% increase in osteoclast numbers and a 2.3- to 2.7-fold increase in mineral resorption from the tissue culture wells, at concentrations similar to those found in serum and in peri-implant tissues *in vivo*. This direct effect of Co<sup>+2</sup> on osteoclasts appears to act independently of the particulate phagocytosis/inflammation-mediated pathways, thus enhancing osteolysis and, possibly, aseptic implant loosening.

### Effects on bone resorption (osteolysis)

The effects of metal particles on bone cells and bone resorption is a crucial issue for orthopaedic implant durability. In orthopaedic implants, the most frequent manifestation of local osteolysis is reported with hip arthroplasties. The knee seems to be less vulnerable, but it is unclear why. Probably, the different mechanical loading, with consequent different mechanisms of wear, and a more effective barrier to debris migration at bone-implant interface, can account for this disparity.

It is well known that normal bone maintenance relies on the balance of bone formation and resorption which implies coordinated activity of osteoblasts and osteoclasts. Thus, either a reduction of osteoblastic bone formation or an increase in osteoclastic bone resorption can lead to a net bone loss (i.e. osteolysis). Osteolysis around an implant is the main concern for the orthopaedic surgeon and it is seen either as diffuse cortical thinning (Figure 1) or as a focal cyst-like lesion (Figure 2). The phenomenon was initially attributed to a reaction to bone cement (polymethyl methacrylate). However, later observations that osteolysis can be found also in association with well-fixed or loose uncemented implants, disproved this hypothesis.

According to some Authors, periprosthetic osteolysis is a cellular inflammatory reaction to wear debris (67). As previously said, there are numerous secretory products generated by the cells around implants that can negatively affect bone turnover, such as TNF- $\alpha$ , TGF- $\beta$  and pro-inflammatory cytokines (i.e. IL-1 and IL-6). Some of these, such as IL-10, can even modulate the process. Other factors involved with bone resorption are obviously the enzymes responsible for catabolism of the organic constituents of bone tissue, such as stromelysin and collagenase matrix metalloproteinases. Prostaglandins, especially PGE<sup>+2</sup>, act as

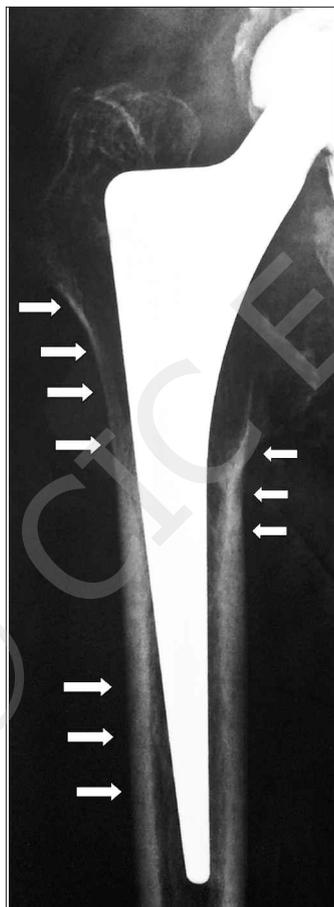


Figure 1 - Diffuse cortical thinning due to bone resorption around a hip stem (cortical thinning indicated by white arrows).



Figure 2 - A clearly-defined osteolytic area around the acetabular component of a hip prosthesis.

intercellular messengers in the osteolytic process induced by metal debris. PGE<sup>+2</sup> and other bone-resorbing factors such as collagenase, can be produced in large amounts also by the cells of the membrane at bone-implant interface in patients with a loose implant. Moreover, recent research shows that several mediators involved in stimulation/inhibition of osteoclast differentiation and maturation, such as RANKL and osteoprotegerin can play a key role in the triggering and progression of bone loss (68).

A higher rate of hypersensitivity reactions to cobalt skin testing has been observed in patients with peri-implant osteolysis compared to controls without osteolysis, indicating a delayed-type hypersensitivity reaction (69). The histological and immunohistochemical examination showed a perivascular accumulation of T lymphocytes and elevated levels of bone-resorbing cytokines (i.e. IL-1 and TNF- $\alpha$ ) produced by infiltrating lymphocytes and activated macrophages. Even though a causal relationship could not be established from the study, these findings suggest that early osteolysis is associated with abnormalities consistent with delayed-type hypersensitivity to metal. Granchi et al. observed that the normal implant lifespan of a total hip replacement, which averages 120 months, is reduced to 78 months in patients testing positive and/or with a history of allergic contact dermatitis caused by metals (70). Moreover, a significant increase (6.5%) of metal sensitization one year after the implant has been reported (71).

Although allergy can play a significant role, the question remains

largely unanswered as to why only some patients with an orthopaedic implant experience early osteolysis and occasionally, early implant loosening, whereas the majority of patients with the same implant show no radiological sign of peri-implant bone resorption and have an excellent and lasting clinical outcome. As previously said, metal particle release is a feature common to all patients who have an orthopaedic metal implant. The likelihood of osteolysis has been correlated with the amount of wear particles (72); the generation of wear particles depends on many factors including the properties of the implant, surgical accuracy and patient characteristics (73). Engh et al. estimated that wear and patient predisposition to osteolysis may together account for 53% of the variance in the total area of osteolysis (74). Recently, the concept of "individual susceptibility" to periprosthetic osteolysis has been introduced (75). This concept postulates that the local tissue homeostatic mechanisms more effectively regulate the inflammatory/osteolytic response in patients with no/ slight peri-implant osteolysis than those with severe osteolysis. The homeostatic mechanism acts through a variety of cytokines, chemokines, hormones and specific cell populations, including macrophages, dendritic and stem cells, which attempt to maintain tissue architecture, to balance adverse reactions and minimize inflammation. Seen from this point of view, osteolysis is a sort of failure of local tissue homeostatic mechanisms.

Although the complete pathway is far from being understood, it seems clear that osteolysis is the result of a complex host response to chronic exposure to implant debris. It is a multi-factorial process, dependent on implant design, material composition, surgical technique and, probably the most important, patient factors.

## Conclusions

Research into the biocompatibility of orthopaedic materials is becoming ever more important as the use of implants steadily increases, the expectations of implant longevity and performance grow, and as new implants are developed and marketed. The elevated metal body content found in the body fluids and remote organs of patients with metal implants is a matter of fact, but its clinical significance needs further elucidation. The effects of metal particles on bone cells and bone resorption is a crucial issue for orthopaedic implant durability but, again, available data are still incomplete. However it seems clear that osteolysis is a multi-factorial process, dependent on implant design, material composition, patient factors and surgical technique. In order to reduce peri-implant osteolysis and to lengthen the lifespan of orthopaedic implants, considerably more research will be required to understand the specific chemical forms and distribution of metal degradation products, and their effects on human cells and tissues.

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