

Metal allergy and second-generation metal-on-metal arthroplasties

Philippa J. Cousen and David J. Gawkrödger

Department of Dermatology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

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Summary

There are concerns about the induction of metal allergy with second-generation metal-on-metal prostheses, and the role that this may play in the development of complications such as 'pseudotumours' or failure of the implant. In this review, we attempt to set out the current knowledge on this subject. From a review of the literature, it is apparent that the first-generation metal-on-metal replacement hips did cause metal sensitization, and that joint failure was associated with this, although it is still not clear which one led to the other. Highly engineered second-generation metal-on-metal arthroplasties used in joint resurfacings are now increasingly employed. Several studies have recently shown an association between metal sensitization and peri-implant hypersensitivity reactions and implant loosening and failure, although the overall risk appears to be low. The pragmatic approach adopted by most contact dermatologists for patients known to be allergic to nickel, cobalt or chromium and who require joint replacement is to recommend prostheses made of titanium-based alloys. Patch testing continues to be a useful tool as laboratory investigations for metal hypersensitivity continue to emerge. The development of guidelines on the management of patients receiving metal-on-metal arthroplasties suspected of being metal-allergic is desirable.

Key words: metal allergy; nickel; prosthesis failure; pseudotumour; second-generation arthroplasty.

Second-generation metal-on-metal arthroplasties are increasingly used, especially in younger patients, but questions about metal sensitivity and its role in pseudotumour formation and implant failure have arisen. The development of the new type of metal-on-metal prosthesis over the last decade resulted from the acknowledgement of the ability of plastic-wear particles from metal-on-plastic prostheses to produce a foreign body reaction in the tissues surrounding the joint (with the potential consequence of aseptic loosening of the prosthesis) coupled with improvements in bioengineering (1). These second-generation metal-on-metal prostheses involve less invasive surgery, are better engineered, with a narrower joint space, and are associated with lower rates of wear debris.

All metals in contact with biological systems corrode, releasing ions that have the ability to form complexes with native proteins. These organo-metallic complexes are considered to be candidate antigens in human clinical situations. Skin hypersensitivity, usually delayed but potentially immediate, resulting from contact with metal, corrosion products or metallic salts is common, affecting up to 10% of the population (2). The most common metal sensitizers of clinical relevance are nickel, cobalt, and chromium. Metals used in orthopaedic implants are shown in Table 1. Hypersensitivity responses to titanium and vanadium have infrequently been reported (3).

EU regulatory interventions have been successful in some countries in decreasing the prevalence of nickel contact sensitization and allergic contact dermatitis (4). However, the rise in the proportion of the population in western countries that is elderly has led to an increase in the use of implanted metallic devices. Every year, 500 000 people in the United States and 300 000 in Europe receive an orthopaedic joint

Correspondence: Professor David J. Gawkrödger, Department of Dermatology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK. Tel: +44 114 271 2203; Fax: +44 114 271 3763. E-mail: david.gawkrödger@sth.nhs.uk

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Table 1. Metals and alloys commonly used in orthopaedics (1)

Vitallium alloy: cobalt 70%, chromium 25–30% and molybdenum 5–7%, trace nickel
Cobalt–chromium–tungsten–nickel alloy
Cobalt–chromium–molybdenum–nickel alloy
Austenitic stainless steel: nickel 8.5–14%, chromium 17–20%, molybdenum 2–3%, with manganese and >1% carbon, nitrogen, silicon, sulfur, phosphorus, and niobium
Titanium
Titanium with aluminium (6%) or with vanadium (4%)

replacement made of cobalt–chromium, stainless steel or titanium–aluminium–vanadium alloys (5).

Objectives, Materials, and Methods

Our objectives in this review were to set out the current knowledge on this subject. The method employed was to undertake a literature review using PubMed and other sources of references.

First-generation metal-on-metal hip prostheses and metal sensitization

In the 1960s and early 1970s, the early prostheses used for total hip arthroplasty were metal-on-metal, usually cobalt–chromium alloys, and several designs emerged, including ring metal-on-metal press fit prostheses. They were associated with several different complications (Table 2). Several case series using patch testing showed an increased frequency of metal sensitivity. In a series of 50 patients who had received total joint replacements, 38% were found to be metal-sensitive on patch testing (6). Other authors concurred, finding 9 of 32 (28%) patients who had received a metal-to-metal hip prosthesis to be metal-allergic; in comparison, the same authors observed the rate in patients receiving a metal-to-plastic prosthesis to be no higher (2.6%) than in a control group (7).

Several of these investigators suggested an association between metal sensitivity and loosening of metal-on-metal prostheses (features of which are shown in Table 3). In the group of 32 patients who received metal-on-metal hip prostheses, the two patients who developed prosthetic loosening were both sensitive to chromium (7). The prevalence of metal sensitivity in unexplained loosening

Table 2. Complications of hip replacement (1)

Short term	Dislocation Sciatic nerve damage Infection
Longer term	Mechanical failure Pseudotumour formation Metal allergies

Table 3. Features of hip prosthetic loosening (1)

Pain on walking
Rotation of the leg
Radiolucency around the prosthesis on X-ray
Biopsy of peri-implant tissue can show a foreign body reaction to polyethylene or metal-wear products

was 73.7% in patients with metal-on-metal prostheses, as compared with 14.8% in those with non-loosened prostheses (6). In another group of 35 patients with failed metal-on-metal prostheses, 16 were metal-sensitive on patch testing, 13 to cobalt, 4 to nickel, and 2 to chromium (8). Two patients of 15 with a failed metal-on-metal prosthesis were found to be metal-allergic, in comparison with 0 of 6 patients with a stable metal-on-metal prosthesis (9). Patch testing with cobalt, chromium and nickel in 14 patients with various types of aseptically loose cobalt–chromium alloy implants showed 9 with allergic reactions (10).

However, there has not been universal agreement on this association. Brown et al. tested the hypersensitivity hypothesis by reviewing all of their patients with sterile, loose metal-on-metal hip replacements (11). Twenty patients were patch tested with cobalt, chromium, and nickel, and all had negative results. Biopsy from surrounding tissues in 17 patients who had revision surgery showed no histological findings of delayed hypersensitivity (11).

Despite this, there is no doubt that concerns about metal allergy, along with design-related mechanical failure resulting from short stems, high frictional torque, equatorial bearing, and poor surface finishing, along with the early success of the Charnley metal-on-plastic prosthesis, all led to the gradual abandonment of the metal-on-metal bearings in the 1970s (12).

Metal-on-plastic hip replacement

As the use of metal-on-plastic prostheses became more widespread, the development of metal hypersensitivity in patients receiving these hips was investigated. Four of 66 patients (6%) patch tested before and 6–12 months after hip replacement with a metal-to-plastic Stanmore hip prosthesis developed a positive patch test reaction to a metal (13). Others found sensitization to be more common: in one series, 16 of 85 patients (18%) were sensitized to a metal as shown on patch testing, but in none of these cases did loosening of the prosthesis occur (14). In a prospective study, there was no evidence of the induction of metal hypersensitivity after metal-on-plastic total hip replacement (15).

Considerable experience with these implants suggests that skin reactions and joint loosening are uncommon in patients known preoperatively to be nickel-allergic who receive a hip replacement and that, unlike in the original metal-on-metal hips, metal allergy is not a common accompaniment or cause of prosthesis failure (1).

Periprosthetic bone resorption and aseptic loosening, however, are major problems leading to failure of metal-on-plastic prostheses. Bone loss can also compromise results after revision surgery. Periprosthetic osteolysis is thought to be largely caused by an inflammatory response to wear debris released from the bearing surface of the polyethylene components (12). Positive patch test results with acrylates and cement appear to be infrequent in patients with joint replacement arthroplasties (6, 8, 10, 15, 16). No differences in the frequency of positive patch test reactions to cement components between patients with stable or loosened total knee arthroplasty and controls with no implants were reported by Granchi et al. (16).

Second-generation metal-on-metal joint replacement and metal allergy

New second-generation metal-on-metal hip replacements were introduced in the 1980s with the aim of eliminating polyethylene wear and the resulting complications of osteolysis and aseptic loosening (17). Recent clinical studies on the early outcomes of contemporary total hip arthroplasties with metal-on-metal bearings have shown mostly favourable results without osteolysis (18). The use, and therefore the associated complications, of these second-generation metal-on-metal hip prostheses vary between different countries; up to the time of writing, their use seems to have been especially prevalent in the United States. The term 'hip resurfacing' is often used to describe the retention and shaping of the femoral head to accept a metallic surface covering that fits snugly into a metallic cup.

In a large case-control study, there was no increase in the risk of surgical revision in patients with metal allergies, and, in comparison with controls, the risk of metal allergy was not elevated in those who had undergone surgery (19). However, in a retrospective series of 165 patients (169 hips) who had undergone primary cementless total hip replacement with a contemporary metal-on-metal hip design, patch tests for metal allergy were performed on 9 subjects with an osteolytic lesion localized to the greater trochanter and on 9 randomly selected controls without osteolytic change (20). The patients with early osteolysis had a significantly higher rate of patch test positivity for cobalt (8 of 9 patients) than controls (2 of 9 patients) (20).

Further support for the concept that metal-on-metal joints can cause sensitization comes from a series of 200 patients who received metal-on-metal hip replacements, in which there were 5 cases of joint loosening with prosthetic failure (21). Of these, 3 were metal-allergic on patch testing (as compared with 2 from a group of 18 randomly selected controls) (21). Other authors found a higher rate of metal allergy in patients undergoing revision surgery for failed hip prosthesis, at 9 of 40 (23%) (22).

In one series, revision surgery was required because of aseptic loosening or technical failure in 14 of 217 (6.5%) patients who had received metal-on-metal total hip arthroplasties, at a mean time of 77 months after operation (18). Histological examination of the retrieved periprosthetic tissues showed metallosis and extensive lymphocytic and plasma cell infiltration around the metal debris (18). The authors suggested an association between hypersensitivity to metal debris and periprosthetic osteolysis and aseptic loosening in hips with a metal-on-metal articulation (18).

The development of 'pseudotumours' adjacent to the joint is a major problem with the second-generation metal-on-metal arthroplasties (23). Histological features compatible with a type IV hypersensitivity reaction were found in 6 of 10 patients who had periarticular masses following resurfacing arthroplasty (24). Further histopathological studies of periprosthetic tissues have shown inflammatory changes supporting the hypothesis of a relationship between the wear products of the metal articulation and a hypersensitivity reaction (25). Mahendra et al. showed a spectrum of necrotic and inflammatory changes in response to the deposition of cobalt-chromium wear particles in the periprosthetic tissue of 52 revised metal-on-metal arthroplasties (26). In a consecutive series of 125 patients who received a hip replacement followed up for 3–9 years, 3 required revision surgery: histological analysis in these cases showed a perivascular lymphocytic infiltrate of the pseudocapsule (27). Others examining the periprosthetic tissues of patients who had had osteolysis resulting in loss of biological fixation of a metal-on-metal hip arthroplasty found extensive necrosis in the hip capsule and perivascular lymphocytic infiltration that consisted of T cells rather than B cells, suggesting a hypersensitivity reaction (28). The term 'acute lymphocytic vascular-associated lesions' has been applied to these changes, which seem to be more common in women under the age of 40 years (29, 30). Tissue dendritic cells could act as antigen-presenting cells inducing delayed-type allergy. The outcome of revision surgery in patients who have had pseudotumours is often poor (23). Another study showed a significant interleukin (IL)-17 response to

nickel in nickel-allergic subjects with arthroplasty-linked complications, but not in nickel-allergic patients with symptom-free arthroplasties (31). The authors concluded that a predominant IL-17-type response to nickel may characterize a subgroup of nickel-allergic patients who may be prone to the development of lymphocytic peri-implant hyperreactivity (31).

Recently, it has been shown that osteoclast precursors can grow and differentiate towards mature osteoclasts on metallic titanium and aluminum, and that mature cells can directly corrode the metal surface and take up metal ions. The investigators suggested that this may induce the formation of osteolytic lesions in the periprosthetic bone, contributing to the loosening of the implant (32). This concept would also fit with the notion of metal allergy as a secondary phenomenon.

The insertion of a metal-on-metal joint results in an increase in the blood levels of the metals of which the alloys are composed; levels of cobalt and chromium are elevated at 3 months postsurgery, and remain high 12 months later (33). Some authors believe that high blood levels of metals in patients with failing joints indicate mechanical dysfunction that requires revision surgery (34). Metal hypersensitivity has also been reported as a cause of persistent pain in the replaced joint (35).

In a study of 22 patients undergoing metal device implantation, preoperative patch testing in those with a history of allergy to metals was felt to be helpful in guiding the choice of device (36). The preoperative patch test identified 5 patients who were allergic to a component of the proposed device, allowing selection of a more appropriate prosthesis (36).

Problems with other joint prostheses

The knee joint is the next most commonly replaced joint after the hip. In 50 patients who received a metal hinge arthroplasty of the knee, positive patch test reactions to metal constituents were found in 16 (32%), but this finding did not correlate with loosening of the prosthesis (37). More recently, in a prospective study of 94 subjects undergoing total knee arthroplasty, positive patch test reactions to metals were significantly more common in patients with a loosened prosthesis (56, 59%) than in stable patients (45, 48%) or controls with no implant (20%) (16). Implant failure was four times more likely in patients who had clinical symptoms of metal hypersensitivity before receiving a knee implant, suggesting that preoperative screening might be useful (16). In fact, this has been attempted in some manner when, prior to total knee arthroplasty, 92 patients underwent a modified lymphocyte stimulation test with nickel, chromium,

cobalt, and iron (38). There was a significant association between the preoperative presence of a positive modified lymphocyte stimulation test for chromium and the development of implant-related eczema ($p < 0.05$), but the authors did not comment on the long-term viability of the prosthesis (38). Metal ion concentrations in the patient's plasma have been shown to increase after total knee arthroplasty; however, the consequences of this are not clear at present. Clinical trials have been proposed to examine the effects of new zirconium coatings and plasma metal ion concentration (39).

With regard to trauma-related orthopaedic surgery, authors have reported a low frequency of sensitivity to nickel, cobalt and chromium in patients who have undergone internal fixation of a fracture or and osteotomy with a fixed metal implant (40).

Cutaneous reactions to orthopaedic implants

Cutaneous allergic reactions to orthopaedic implants are rare but well described, and usually take the form of an eczema. Localized or occasionally generalized eczemas are usually associated with static implants such as those used for tibial fractures or with screws, but they can occur with joint prostheses (41). Erythematous, urticarial and even vasculitic eruptions are also recognized (42). Following removal of the implant, clearance of the eruption is well recorded (42). An eczema can occur after knee replacements, and has been specifically described on the lateral part of the operated knee (43, 44).

In a 2-year prospective study that included 19 patients who developed a rash related to an orthopaedic implant, it was concluded that the likelihood of the eruption being allergic in nature was greater if the implant was static, if there was a prior history of metal reactions, if the eruption developed near the implant, and if the rash was an eczema, had developed late, and was persistent (45).

Cases of recurrent aseptic localized cellulitis resulting from metal hypersensitivity were reported in the 1990s in patients following hip replacement. Subsequent debate has arisen as to whether these erysipelas-like eruptions are, in fact, cases of authentic infectious cellulitis (46).

In vivo and *in vitro* tests for metal hypersensitivity

Historically, testing for delayed-type hypersensitivity has been performed *in vivo* by skin testing, with either an epicutaneous patch test or an intradermal test, and *in vitro* with a lymphocyte transformation test or a leukocyte migration inhibition test. Dermatologists accept the patch test as showing systemic delayed-type hypersensitivity to an allergen, but, among orthopaedic surgeons, there is a

reluctance to accept the applicability of skin testing to the immune responses to implants. Cutaneous exposure to an allergen may be viewed as a different form of exposure to the closed environment of an orthopaedic metal implant, where there are months to years of constant exposure. In epicutaneous exposure, for example in the patch test situation but actually pertaining to many forms of skin contact, metals ions are taken up by Langerhans cells as the antigen-presenting cells, whereas in the joint, tissue macrophages and dendritic cells fulfil this function (47). Langerhans cells have an antigen-presenting capability that is much greater than that of blood macrophages (48). With regard to the total hip replacement outcome, patch testing was not able to discriminate between stable and failed implants in a consecutive series of 223 patients. However, sensitivity to bone cement and a positive medical history of hypersensitivity had a negative influence on the survival of the total hip replacement (49).

The difficulty in interpreting the clinical relevance of positive patch test reactions prior to surgery remains. Recent guidance from Thyssen et al. recommends that clinicians refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic or has a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider. Their recommendations for the clinical work-up of a patient suspected of having an allergic reaction to a metal implant includes patch testing and possibly *in vitro* testing with the lymphocyte transformation test (50).

The lymphocyte transformation test involves measuring the proliferative response of lymphocytes following activation by an allergen *in vitro*. The incorporation of a radioactive thymidine marker into cellular DNA upon division allows quantification of a proliferation response when it is added to lymphocytes along with the specific antigen (47, 48). Some authors suggest that the lymphocyte transformation test in implant-related metal sensitivity is equal to or better than patch testing for assessment of implant-related allergy (47). Other authors have shown a close correlation between the lymphocyte transformation test result and the clinical patch test result in patients with nickel allergy (48). A recent prospective study by Frigerio et al. used both patch testing and the lymphocyte transformation test to assess patients preoperatively and then at 1 year post-implantation. Preoperative history-taking alone appeared to be insufficient for identifying patients with metal sensitivity. One year post-implantation (72 patients), 5 patients who had initially tested negative for a metal allergy became positive for at least one or more metal constituents of the prosthesis on at least one or the other test, suggesting prosthesis-induced sensitization (51).

The lymphocyte proliferation response has been used to investigate the possible role of the delayed-type hypersensitivity (type IV) reaction to nickel, chromium and cobalt in the causation of locally destructive soft tissue pseudotumours seen in patients following metal-on-metal hip resurfacing arthroplasty (52). It was shown that lymphocyte reactivity to cobalt, chromium and nickel was not significantly different in patients with pseudotumours than in those without pseudotumours, suggesting that systemic type IV hypersensitivity reactions to these metals as measured by the lymphocyte transformation test was not the dominant biological reaction involved in the development of these pseudotumours (52).

However, more recently, both T cell and B cell activation in response to implant metals has been demonstrated *in vitro* by the use of lymphocyte reactivity (53). These authors also evaluated lymphocyte reactivity to metal ions in subjects with and without total hip replacements, using proliferation assays and cytokine analysis. They found that, on exposure to metals, the lymphocytes of individuals with hip arthroplasties showed a proliferative response and an increased production of interferon- γ ; this indicates that a Th1-type (versus Th2-type) type response is probably associated with metal-induced reactivity. The involvement of an elevated and specific lymphocyte response suggests an adaptive (macrophage-recruiting) immune response to metallic implant debris rather than an innate (non-specific) immune response (54).

Another investigation, the leukocyte migration inhibition test, involves the measurement of mixed-population leukocyte migration activity. Leukocytes in culture actively migrate in a random fashion, but can be attracted preferentially to chemoattractants such as those released by staphylococci and other bacteria. When in the presence of a sensitizing antigen, they migrate more slowly, losing the ability to recognize chemo-attractants (47). Migration testing alone may be an inadequate detector of delayed-type hypersensitivity, but a combined approach using a battery of three *in vitro* assays to measure several components of lymphocyte activation improves the diagnosis of delayed-type hypersensitivity responses as compared with single assays (47). The suggested assays include: (1) lymphocyte proliferation, that is, a lymphocyte stimulation test; (2) enzyme-linked immunosorbent assays for migration inhibitory factor; and (3) lymphocyte migration inhibition (3).

Discussion

Most metallic orthopaedic implants perform well, with excellent short-term and long-term results, but for a significant number (up to 10%) there is an unsatisfactory

outcome (23). Hypersensitivity to a metal component of the implanted material is one potential adverse response. It is difficult to determine the frequency of an allergic response to a metal component of an implant; one estimate puts it at less than 1%, but it may be higher (3).

Loosening of first-generation metal-on-metal total hip prostheses in association with hypersensitivities to cobalt, nickel and chromium has been shown in several studies. Nonetheless, it is still unclear whether the devices failed because of metal hypersensitivity or whether the patients became metal-hypersensitive as a result of implant failure. Prospective studies have been suggested to evaluate the association between metal sensitization, prosthesis failure, and metal release (4).

Several authors have suggested that metal hypersensitivity could be a mechanism for pseudotumour formation, aseptic loosening and periprosthetic osteolysis after second-generation metal-on-metal total hip arthroplasties. Pseudotumour formation, seen in at least 1 in 1000 cases, is the most concerning late effect (23). Metallic-wear products seem to be involved in the formation of pseudotumours, possibly through the development of allergy, although consideration should be given to the possibility of a non-allergen-specific pathological reaction to the presence of metallic ions in some cases. The evidence linking osteolysis and aseptic loosening with metal hypersensitivity is circumstantial. Although it is reasonably well accepted that metal orthopaedic implants can cause delayed-type hypersensitivity to metals, the relationship between this and implant failure resulting from aseptic loosening still has to be fully explained. A cause-and-effect mechanism has not been established for the modern prostheses as it was for the first-generation ones (4, 55).

There is a growing consensus that metal particles are more proinflammatory than polymers *in vivo*. New mechanisms of implant debris-induced inflammatory reactions continue to be discovered, such as the 'danger signalling' inflammasome pathway (56). These provide new targets for pharmaceutical intervention and improved implant performance. It is possible that an adaptive immune response to the metal through the local release of cytokines such as interferon- γ or IL-2 plays a role in the pathogenesis of impaired implant performance (57). Previously, it was believed that metal release led to occlusion of blood

vessels of the periprosthetic bone, osteonecrosis, fatigue fracture, and subsequent loosening (10).

What are the current alternatives when a patient is shown to be metal-allergic? A retrospective study of 99 patients (110 hips) receiving total hip arthroplasties with cemented titanium stems at an average 9.5 years of follow-up showed a revision rate of 4% (58). This suggests that good long-term results can be achieved with cemented titanium stem implants, and that titanium implants can be used in patients with hypersensitivity to chromium, cobalt, and nickel (58).

Metal hypersensitivity is currently an important area in orthopaedics, because of its potential role in the formation of pseudotumours and in other mechanisms of prosthetic joint failure. Not enough is known about the propensity of the second-generation metal-on-metal arthroplasties to induce metal allergy, and what the effects of any induced allergy might be in terms of the development of complications of various types. Currently available testing methods cannot predict which patients will develop hypersensitivity reactions following insertion of metallic implants. Preoperative 'predictive' patch testing prior to implant at is not recommended at present, unless the patient has had a history of allergic reactions to metallic implants, in which case it may be helpful (48).

Thyssen et al. have set out a 'pragmatic approach' to the problem. This might be regarded as a basis for clearly needed guidelines to inform orthopaedic surgeons and dermatologists of the best way to proceed when metal allergy is suspected in patients receiving second-generation metal-on-metal joint replacements. The approach of most contact dermatologists in the situation of a patient shown on patch testing to be allergic to nickel, cobalt or chromium is to recommend the use of titanium-based alloys, as recommended by Thomas et al., who reported on behalf of the German Implant Allergy Working Party, although this may not be necessary in all cases (57). Although the question of whether metal allergy leads to joint failure remains unanswered, it is hoped that these second-generation metal-on-metal hip joints will continue to have long survival rates, particularly as surgery is being undertaken on an increasingly younger population.

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