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## **Metal Sensitivity in Patients with Orthopaedic Implants**

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## CURRENT CONCEPTS REVIEW

# METAL SENSITIVITY IN PATIENTS WITH ORTHOPAEDIC IMPLANTS

BY NADIM HALLAB, PHD, KATHARINE MERRITT, PHD, AND JOSHUA J. JACOBS, MD

- ▶ All metals in contact with biological systems undergo corrosion. This electrochemical process leads to the formation of metal ions, which may activate the immune system by forming complexes with endogenous proteins.
- ▶ Implant degradation products have been shown to be associated with dermatitis, urticaria, and vasculitis. If cutaneous signs of an allergic response appear after implantation of a metal device, metal sensitivity should be considered. Currently, there is no generally accepted test for the clinical determination of metal hypersensitivity to implanted devices.
- ▶ The prevalence of dermal sensitivity in patients with a joint replacement device, particularly those with a failed implant, is substantially higher than that in the general population.
- ▶ Until the roles of delayed hypersensitivity and humoral immune responses to metallic orthopaedic implants are more clearly defined, the risk to patients may be considered minimal.
- ▶ It is currently unclear whether metal sensitivity is a contributing factor to implant failure.

Implant-related metal sensitivity has been well documented in case and group studies; however, overall it remains a relatively unpredictable and poorly understood phenomenon in the context of orthopaedic implant materials<sup>1-3</sup>. Dermal hypersensitivity to metal is common, affecting about 10% to 15% of the population<sup>1,2,4,5</sup>. Dermal contact with and ingestion of metals have been reported to cause immune reactions, which most typically manifest as hives, eczema, redness, and itching<sup>1,6,7</sup>. Historically, the ability of implant materials to demonstrate appropriate host and material responses has resulted in the elimination of candidate materials based on observation of adverse host responses. However, some adverse responses are difficult to characterize in preclinical and clinical settings because of their infrequent or subtle nature. *In vivo* metal hypersensitivity or hypersensitivity-like reactivity to metallic biomaterials is one such response. Although little is known about the short and long-term pharmacodynamics and bioavailability of circulating metal degradation products *in vivo*<sup>5,8-10</sup>, there have been many reports of sensitivity responses temporally associated with implantation of metal components. Degradation products of metallic biomaterials include particulate wear debris, colloidal organometallic complexes (specifically or non-specifically bound), free metallic ions, inorganic metal salts or oxides, and precipitated organometallic storage forms.

All metals in contact with biological systems corrode<sup>11,12</sup>, and the released ions, while not sensitizers on their own, can activate the immune system by forming complexes with native proteins<sup>5,13,14</sup>. These metal-protein complexes are considered to

be candidate antigens (or, more loosely termed, allergens) for eliciting hypersensitivity responses. Nonbiodegradable polymeric biomaterials used for load-bearing in total joint arthroplasty are not easily chemically degraded *in vivo* and have not been intensely investigated or implicated in case or group studies as sources of hypersensitivity-type immune responses. This is presumably due to the relatively large size of the degradation products associated with the mechanical wear of polymers *in vivo*; these products may be large enough to prevent the formation of polymer-protein haptenic complexes with human antibodies. The biological response in this situation is a response to particles. However, immunogenic reactions associated with polymethylmethacrylate have been reported, albeit less frequently<sup>15</sup>, and may be due to a still-present unreacted monomer that serves in a hapten-like manner.

Metals known as sensitizers (haptenic moieties in antigens) are beryllium<sup>16</sup>, nickel<sup>14,6,7,16</sup>, cobalt<sup>16</sup>, and chromium<sup>16</sup>; in addition, occasional responses to tantalum<sup>17</sup>, titanium<sup>18,19</sup>, and vanadium<sup>17</sup> have been reported. Nickel is the most common metal sensitizer in humans, followed by cobalt and chromium<sup>14,6,7</sup>. The prevalence of metal sensitivity among the general population is approximately 10% to 15% (Fig. 1), with nickel sensitivity having the highest prevalence (approximately 14%)<sup>1</sup>. Cross-reactivity between nickel and cobalt is most common<sup>15</sup>. The amounts of these metals found in medical-grade alloys are shown in Table I.

Although the specifics associated with metal-protein binding and the biological mechanisms by which these com-

TABLE I Weight Percentages of Metals within the Three Most Common Orthopaedic Alloys

Implant Alloy	Nickel	Cobalt	Chromium	Titanium	Molybdenum	Aluminum	Vanadium
Stainless steel (ASTM F138)	13-15.5	—	17-19	—	2-4	—	—
Cobalt alloy (ASTM F75)	1	62-67	27-30	—	5-7	—	—
Titanium alloy (ASTM F136)	—	—	—	89-91	—	5.5-6.5	3.5-4.5

plexes become immunogenic remain relatively uncharacterized, much has been learned over the past thirty years. The following review attempts to help clarify (1) what is currently known about implant-related metal sensitivity, (2) what methods are used to test for metal sensitivity, and (3) the conclusions of case-specific and general metal-sensitivity studies regarding implant-related metal sensitivity.

### Metal Sensitivity

Metal hypersensitivity might be merely a clinical curiosity except for known overaggressive immune responses to haptenic antigens leading to putative clinical complications. Hypersensitivity can be either an immediate (within minutes) humoral response (initiated by an antibody or the formation of antibody-antigen complexes of type-I, II, and III reactions) or a delayed (within hours to days) cell-mediated response<sup>20,21</sup>. Implant-related hypersensitivity reactions are generally the latter type of response, in particular type-IV delayed-type hypersensitivity (DTH).

Cell-mediated delayed-type hypersensitivity is characterized by antigen activation of sensitized T<sub>DTH</sub> lymphocytes releasing various cytokines that result in the recruitment and activation of macrophages. T<sub>DTH</sub> lymphocytes are subset populations of T helper (T<sub>H</sub>) lymphocytes purported to be of the CD4+ T<sub>H-1</sub> subtype (and, in rare instances, of the CD8+ cytotoxic T-cell [T<sub>C</sub>] subtype). This T<sub>H-1</sub> subpopulation of T-cells is characterized by its cytokine release profile—for example, interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and interleukin-2 (IL-2). T<sub>H-1</sub> cells are generally associated with responses to intracellular pathogens and autoimmune diseases. Although T<sub>DTH</sub> cells mediate a delayed-type hypersensitivity reaction, only 5% of the participating cells are antigen-specific T<sub>DTH</sub> cells within a fully developed delayed-type hypersensitivity response. The majority of delayed-type hypersensitivity participating cells are macrophages.

The effector phase of a delayed-type hypersensitivity response is initiated by contact of sensitized T-cells with an antigen. In this phase, T-cells, which are antigen-activated, are characterized as T<sub>DTH</sub> cells and, in conjunction with activated antigen presenting cells (APCs), can secrete a variety of cytokines that recruit and activate macrophages, monocytes, neutrophils, and other inflammatory cells. These released cytokines include IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which promote production of granulocytes; monocyte chemotactic activating factor (MCAF), which promotes chemotaxis of monocytes toward areas of delayed-type hypersensitivity activation; IFN- $\gamma$  and TNF- $\beta$ , which produce a number of effects on local endothelial cells facilitating infiltration; and migration inhibitory factor (MIF),

which inhibits the migration of macrophages away from the site of a delayed-type hypersensitivity reaction. Therefore activation, infiltration, and eventual migration inhibition of macrophages is the final phase of a delayed-type hypersensitivity response. Activated macrophages, because of their increased ability to present class-II major histocompatibility complexes (MHCs) and IL-1, can trigger the activation of more T<sub>DTH</sub> cells, which in turn activate more macrophages, which activate more T<sub>DTH</sub> cells, and so on. This delayed-type hypersensitivity self-perpetuation response can create extensive tissue damage.

The specific T-cell subpopulations, the cellular mechanism of recognition and activation, and the antigenic metal-protein determinants elicited by these metals remain incompletely characterized. The subsets of participating lymphocytes of nickel-sensitive individuals were found to be primarily CD4+ and CD45RO+ cells, whereas CD8+ and CD8+CD11b+ lymphocytes were shown to be underrepresented<sup>22</sup>. Sensitive T-cells have been shown to recognize metals such as nickel in the context of major histocompatibility complex class-II molecules<sup>23,24</sup>. The Langerhans cells of the dermis are well characterized as the primary antigen presenting cells associated with dermal hypersensitivity. The dominant antigen presenting cell (if any) responsible for mediating an implant-related hypersensitivity response remains unknown. Candidate antigen presenting cells in the periprosthetic region include macrophages, endothelial cells, lymphocytes, Langerhans cells, dendritic cells, and, to a lesser extent, parenchymal tissue cells. While there is general consensus implicating the T-cell receptor in metal-induced activation, there are conflicting reports regarding which region or receptor specificity is responsible for dominating metal reactivity<sup>25,26</sup>. Some investigators have reported no preferential receptor selection<sup>22</sup>, while others have shown the CDR3B region of the VB17+ T-cell receptor to be critical in the sense that, without this region, metal reactivity is abrogated<sup>25,26</sup>. Metals have also been shown to act as facilitating agents in the cross-linking of receptors (for example, VB17 of CDR1 T-cell receptor) to create superantigen-like enhancement of T-cell receptor-protein contact<sup>25,26</sup>, whereby metallo-proteins or metal-peptide complexes that would not otherwise be antigenic are able to provoke a response. Furthermore, other investigators have shown that, entirely independent of a metal-altered endogenous protein antigen, metal has been reported to cross-link thiols of cell-surface proteins of murine thymocytes (that is, CD3, CD4, and CD45), which have been reported to result in the activation of a tyrosine kinase (p56lck), involved with the activation of T-cells through the T-cell receptor<sup>27-30</sup>. However, despite reports of non-hapten-related mechanisms of metal-induced lymphocyte activation, clonal

lymphocyte specificity associated with type-IV delayed-type hypersensitivity remains the dominant mechanism associated with implant-related hypersensitivity responses<sup>27-29</sup>.

### Testing for Metal Sensitivity

Historically, testing for delayed-type hypersensitivity has been conducted *in vivo* by skin testing (that is, so-called patch testing or intradermal testing) and *in vitro* by lymphocyte transformation testing (LTT) and leukocyte migration inhibition testing (termed LIF or MIF testing). While there are general patch-testing protocols and commercial kits for a variety of commonly antigenic substances<sup>20,31</sup> (for example, True-Test; Glaxo Dermatology, Research Triangle Park, North Carolina), there is continuing concern about the applicability of skin testing to the study of immune responses to implants; in particular, there is a lack of knowledge about, and availability of, appropriate metal challenge agents<sup>13,14,32-34</sup>. Unlike periprosthetic exposure, patch testing involves incorporating an antigen (for example, 1% aqueous nickel sulfate) in a carrier, such as petrolatum, and exposing this to dermal tissue by means of an affixed bandage. After exposure for approximately forty-eight to ninety-six hours, reactions are graded on a scale of 1 (mild or absent response) to 4 (severe red rash with small and possibly encrusted weeping blisters). This is quite different from the weeks to months of constant exposure prior to typical reports of eczemic reactions to orthopaedic implants<sup>2,35-39</sup>. Additionally, the haptenic potential of metals on open-testing dermal contact (in which dermal Langerhans cells are the primary hypersensitivity effector cells) is likely quite different from that in a closed periprosthetic *in vivo* environment<sup>21,40</sup>. Other concerns are that the diagnostic utility of patch testing possibly could be affected by immunological tolerance (that is, suppression of dermal response to implants)<sup>31,41</sup> or by impaired host immune response<sup>12,43</sup> and that the testing possibly could induce hypersensitivity in a previously insensitive patient<sup>44</sup>. Moreover, even if patch testing were a biologically reliable means of assessing metal sensitivity, no suitable standardized battery of tests of relevant metals currently exists.

*In vitro* proliferation testing (also known as lymphocyte transformation testing, or LTT) involves measuring the proliferative response of lymphocytes following activation. A radioactive marker is added to lymphocytes along with the desired challenge agent. The incorporation of radioactive [<sup>3</sup>H]-thymidine marker into cellular DNA upon division facilitates the quantification of a proliferation response through the measurement of incorporated radioactivity after a set time-period. On the sixth day, [<sup>3</sup>H]-thymidine uptake is measured with use of liquid scintillation. The proliferation factor, or stimulation index, is calculated with use of measured radiation counts per minute (cpm): proliferation factor = (mean cpm with treatment)/(mean cpm without treatment).

Although the use of proliferation testing in the assessment of metal sensitivity is less popular than patch testing, it has been well established as a method for testing metal sensitivity in a variety of clinical settings<sup>45-50</sup>. The use of lymphocyte transformation testing for implant-related metal sensitivity has

been limited, and therefore few conclusions can be drawn<sup>51-53</sup>. These investigations indicate that metal sensitivity can be more readily detected by lymphocyte transformation testing than by dermal patch testing<sup>51,52,54</sup>. Such reports seem to indicate that, compared with dermal patch testing, lymphocyte transformation testing may be equally or better suited for the testing of implant-related sensitivity<sup>45-53</sup>.

*In vitro* leukocyte migration inhibition testing involves the measurement of mixed-population leukocyte migration activity. Leukocytes in culture actively migrate in a random fashion, but they can be attracted preferentially to chemoattractants, such as those released by *Staphylococcus* and other bacteria. However, in the presence of a sensitizing antigen, they migrate more slowly, losing the ability to recognize chemoattractants, and are said to be migration-inhibited. Contemporary migration-testing techniques quantify the migration of lymphocyte populations *in vitro* through, under, or along media such as agarose layers, agarose droplets, capillary tube walls, membrane filters, and collagen gels. There are four predominant methodologies for measurement of *in vitro* leukocyte migration<sup>55</sup>:

1. Capillary tube<sup>56-58</sup>. Capillary tube segments filled with isolated leukocytes are placed in a cell-culture chamber and incubated in the presence or absence of an antigen or antigens. Leukocytes migrate from the capillary tube, spreading out in a fan-like manner. Various techniques are used to measure the extent and area of the fan.

2. Membrane migration or Boyden chamber<sup>59</sup>. A two-cell-culture chamber (separated by a membrane), through which leukocytes can pass only by active migration toward an antigen, is used to determine cell-migration ability.

3. Leukocyte migration with agarose technique (LMAT)<sup>60,61</sup>. Suspensions of leukocytes are placed in wells in an agarose gel on the bottom of a culture dish and incubated in the presence or absence of antigen. Leukocyte migration between the agarose layer and the dish results in a visually identifiable and measurable circular area.

4. Collagen gel<sup>62,63</sup>. Collagen is cast into a tube or layered onto a Petri dish and overlaid with leukocytes incubated in the presence or absence of antigen. Migration is measured either by direct histological observation of cells within the gel matrix or by scintigraphic determinations with use of radio-labeled cells.

Over the long term, migration testing alone (as well as any single assay) may be an inadequate detector of delayed-type hypersensitivity<sup>64</sup>. For instance, six months after human subjects were revaccinated with BCG (bacille Calmette and Guérin) tuberculin, leukocyte migration inhibition testing failed to show lymphocyte migration inhibition upon exposure to antigen, whereas lymphocyte proliferation assays conducted simultaneously exhibited antigen-specific hypersensitivity-related proliferation<sup>64</sup>. The aforementioned methods of migration testing may lack the sensitivity for detecting a delayed-type hypersensitivity response at certain times over the course of a hypersensitivity reaction, or the typical antigens used may be inappropriate for this type of testing. Thus, investigations in which only migration inhibition testing is

used as a determinant of metal sensitivity may underestimate the actual number of individuals with metal sensitivity.

While the utility of *in vitro* delayed-type hypersensitivity assays in various clinical settings has been demonstrated<sup>59,64-70</sup>, few investigators have applied *in vitro* methods (leukocyte migration inhibition testing) to assess biocompatibility of implanted devices<sup>54,71-73</sup>. There have been no major advancements in migration inhibition assays since they were first used to investigate delayed-type hypersensitivity reactions to metallic orthopaedic implants by Brown et al.<sup>71</sup>. *In vitro* delayed-type hypersensitivity testing remains a labor-intensive and clinically unpopular means of assessing metal hypersensitivity. Therefore, continuing improvements in lymphocyte transformation testing, migration inhibition, and cytokine enzyme-linked immunosorbent assay (ELISA) methods, alone or in combination with other immunologic assays, will likely enhance future assessment of patients with suspected biomaterial-induced delayed-type hypersensitivity responses. Many of these *in vitro* tests for delayed-type hypersensitivity can detect humoral (antibody) responses under appropriate conditions. Efforts to detect humoral responses and to correlate the results with clinical conditions are needed.

#### Case Studies of Implant-Related Metal Sensitivity

Implant degradation products as moieties in haptenic complexes, or as antichemotactic agents, have been shown in case studies to be temporally associated with specific responses such as severe dermatitis, urticaria, vasculitis<sup>35-37,39,74,75</sup>, and/or nonspecific immune suppression<sup>42,43,76-78</sup>.

The first apparent correlation of eczematous dermatitis with metallic orthopaedic implants was reported in 1966 by Foussereau and Laugier<sup>79</sup>, who noted that nickel was associated with hypersensitivity responses. Over the past twenty years, a growing number of case reports have linked immunogenic reactions with adverse performance of metallic cardiovascular<sup>74,80,81</sup>, orthopaedic<sup>2,25-39</sup>, plastic surgical<sup>82</sup>, and dental<sup>83-89</sup> implants. In some instances, clinically apparent immunological symptoms have led to device removal<sup>35-37,39,74,75</sup>. In these cases, reactions such as severe dermatitis<sup>19,38,39,74,81,90</sup>, urticaria (intensely sensitive and itching red round wheals on the skin)<sup>75,80</sup>, and/or vasculitis (patch inflammation of the walls of small blood vessels) have been linked with the relatively more general phenomena of metallosis (metallic staining of the surrounding tissue), excessive periprosthetic fibrosis, and muscular necrosis<sup>36,91,92</sup>.

In one of the earliest case studies implicating an orthopaedic implant as a source of metal sensitivity<sup>35</sup>, a twenty-year-old woman was seen with extensive eczematous dermatitis on the chest and back five months after stainless-steel screws had been implanted to treat a chronic patellar dislocation. Treatment with topical corticosteroids abrogated the condition for one year, after which it worsened, with increased generalized dermatitis. Additional application of topical corticosteroids yielded poor results, and "out of sheer desperation" the stainless-steel screws were removed. The day after screw removal, the eczema subsided, and it completely disappeared within seventy-two hours. "The orthopedist still doubted that the steel screws

could be the cause of her dermatitis and applied a stainless steel screw to the skin of her back. In a period of four hours, generalized pruritus and erythema developed."<sup>35</sup> Patch testing elicited reactions to nickel, nickel sulfate, and the steel screw. As described earlier, a hypersensitivity response to a metallic implant is purportedly not to the implant itself but to the dissolution or corrosion products. Testing with a new device or material or even with the removed devices presents problems. There may be false-positive results due to mechanical irritation or false-negative results due to a lack of readily available corrosion products.

In another example, a fifty-year-old woman had persistent abdominal pain and urticaria following a cholecystectomy. While plasma exchange, but not corticosteroids or antihistamines, provided temporary relief, only removal of all of the tantalum metal clips that had been used during the cholecystectomy resulted in permanent resolution of the abdominal pain and urticaria. The tantalum clips showed visible signs of corrosion, indicating one likely mechanism by which the sensitivity reactions occurred. These cases are not uncommon<sup>2,36-39,82</sup>. The temporal and physical evidence provided in this and other such case reports leaves little doubt that the phenomenon of sensitization to orthopaedic implants does occur in some patients<sup>2,5,8,37-39,75,81,90,93</sup>. It is these cases of severe metal sensitivity that raise the greatest concern.

Generally there are more case reports of hypersensitivity reactions to stainless-steel and cobalt-alloy implants than there are of such reactions to titanium-alloy components<sup>2,5,8,36-39,75,81,82,90,93</sup>. One such case report implicated cobalt hypersensitivity in the poor performance of cobalt-alloy plates and screws used in the fixation of a fracture of the left radius and ulna of a forty-five-year-old woman<sup>36</sup>. The patient had presented with periprosthetic fibrosis, patchy muscular necrosis, and chronic inflammatory changes peripherally seven years after implantation. After removal of all metal implants, the swelling disappeared, and eventually the patient became symptom-free. However, there remained a hypersensitivity to cobalt, as demonstrated by patch testing<sup>36</sup>.

Titanium-alloy implants have also been associated with instances of metal sensitivity. In a report on five individuals who underwent revision of a failed titanium total hip replacement<sup>92</sup>, none showed positive results on patch tests for titanium salt solutions. However, two did show a reaction to an ointment containing titanium. This difference may be critical in the establishment of relevant metal-implant-related patch-testing protocols, which currently do not exist. Tissues obtained from the joint capsules of all five patients had evidence of metallosis—that is, dark-gray tissue-staining filled with debris that was found to be 100% titanium on energy-dispersive x-ray analysis. Tissue analysis revealed the presence of macrophages, fewer T-lymphocytes, and an absence of both B-lymphocytes and plasma cells, characteristics of a type-IV delayed-type hypersensitivity reaction<sup>82</sup>. These results raise the possibility that metal sensitivity may occur in patients with implants made of metals (for example, titanium) thought to be more biocompatible than alloys containing nickel, cobalt, and chromium.

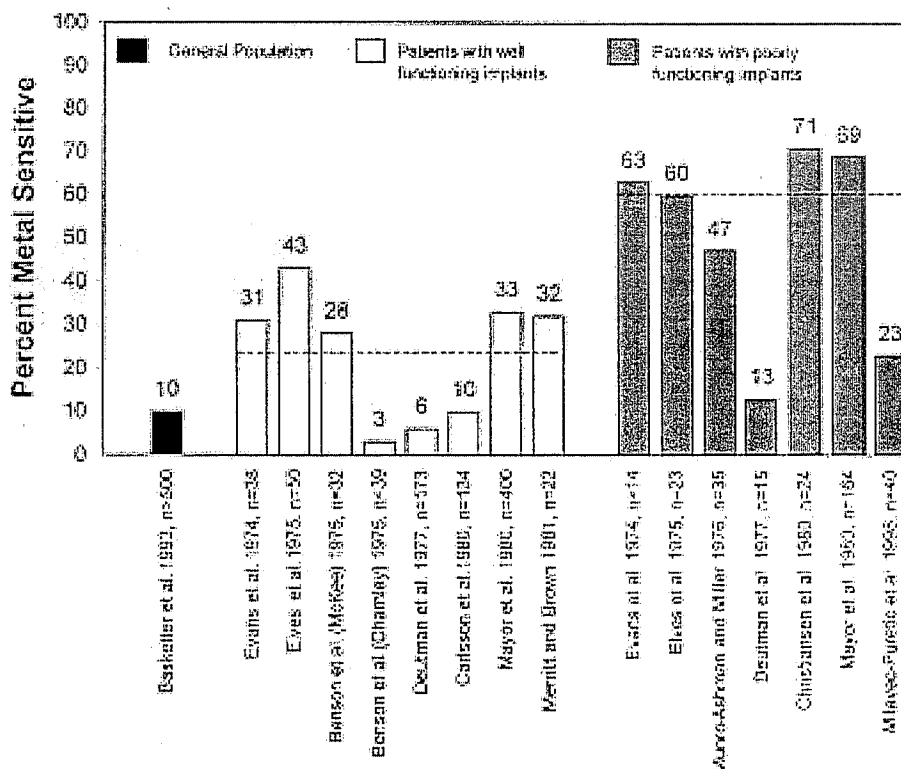
### Cohort Studies of Implant-Related Metal Sensitivity

Case studies such as those previously mentioned prompted a number of patient cohort studies in the late 1970s and 1980s investigating the possible association between metal sensitivity and implant failure<sup>1,41,73,93-100</sup>. These investigations generally indicated an association between the presence of a metal implant and metal sensitivity<sup>1,41,73,93-100</sup>. Data regarding the prevalence of metal sensitivity in these different investigations are presented in Figure 1. Unfortunately, these studies included heterogeneous patient populations and testing methodologies and consequently led to a disparate variety of conclusions. However, all of the patient populations included in Figure 1 were tested for allergies to one or a combination of metals, including nickel, cobalt, and/or chromium, after they received an implant. The prevalence of metal sensitivity among patients with a well-functioning implant is approximately 25%, roughly twice that of the general population. This approximation was derived with use of a weighted average based on the numbers of subjects in each study<sup>41,73,93-97</sup>. The average prevalence of metal sensitivity among patients with a failed or poorly functioning implant (as judged by a variety of criteria) was approximately 60% in the seven investigations shown in Figure 1<sup>93,95-100</sup>. Overall, the prevalence of metal sensitivity in patients with a failed or failing implant is approximately six times that of the general population and approximately two to three times that of all patients with a metal implant. However, this association does not prove a causal effect—that is, it is not known whether these

patients are sensitive because the device failed, whether the device failed because the patient had a preexisting metal sensitivity, or whether alternate dominating mechanisms (for example, genetic autoimmunity) were responsible for both.

A similar sensitivity to polymeric materials among patients with a well-functioning implant has not been demonstrated, to our knowledge. However, the prevalences of polymeric sensitivity in patients with a failing implant have been reported<sup>15,101</sup>. In one study, patch testing and mononuclear cell subset analysis demonstrated polymethylmethacrylate lymphocyte hypersensitivity in 50% of twenty-six patients with a loose total hip prosthesis<sup>15</sup>. However, in an earlier study of 112 patients with a well-functioning implant, patch testing revealed no hypersensitivity reactions to polymethylmethacrylate<sup>94</sup>. On the other hand, Granchi et al.<sup>52</sup>, in a study of mononuclear subsets within the peripheral blood of sixteen patients with a loose cobalt-alloy hip prosthesis, demonstrated decreased populations of CD4 and CD8 lymphocytes in all patients. This finding suggests that these activated lymphocytes may be recruited to the periprosthetic area (away from the peripheral circulation) or, alternatively, that implant debris may possess generalized lymphotoxicity (that is, immunosuppressive properties)<sup>52</sup>. Investigations of immune responses induced by metal from implant degradation can be categorized as having one of three central hypotheses: (1) metal degradation products are immunogenic<sup>27,28,102-105</sup>, (2) metal degradation products are immunosuppressive<sup>106-108</sup>, or (3) metal degradation products are

Fig. 1



Averaged percentages of metal sensitivity (for nickel, cobalt, or chromium) among the general population and among patients with well and poorly functioning implants, based on a number of published reports.

immunoneutral (that is, nonbioreactive)<sup>109,110</sup>. While all three hypotheses have been supported *in vitro*, the degree to which each applies to reactions in patients with implants remains controversial.

It is important to note that the association of metal release from implants with an adverse immunologic response remains conjectural, as cause and effect have not been established in symptomatic patients. As suggested above, it is unclear whether metal hypersensitivity causes implant failure or vice versa<sup>93</sup>. It is likely that some combination of these phenomena occurs whereby implant-loosening promotes immunogenic reactions, which in turn act to potentiate the loosening cascade. Therefore, the identification of implant-referable hypersensitivity processes depends upon the ability to perform multiple tests on individual patients before implantation; during the service of the device; and, in the case of an adverse outcome, before and after removal of the device. Such intensive studies have not been performed to date, in large part because standardized, effective testing methodologies have not been established.

Specific types of implants with a greater propensity to release metal *in vivo* may be more prone to induce metal sensitivity. Failures of total hip prostheses with metal-on-metal bearing surfaces have been associated with a greater prevalence of metal sensitivity than have those of similar designs with metal-on-ultra-high molecular weight polyethylene bearing surfaces<sup>119</sup>. In one of the earliest investigations of this phenomenon, Evans et al., in 1974, studied the cases of thirty-eight patients with a metal-on-metal implant<sup>97</sup>. Two years postoperatively, fourteen (37%) of the implants were loose and twenty-four (63%) were well-fixed. Nine of the fourteen patients with a loose implant were found to be sensitive to metal on dermal patch testing, whereas none of the twenty-four patients with a well-fixed implant showed evidence of metal sensitivity.

In contrast, other studies have indicated that, after total joint replacement with metallic components, some patients show an induction of metal tolerance—that is, a previously detected metal sensitivity abates after implantation of a metal-containing prosthesis. Rooker and Wilkinson<sup>31</sup> reported that, of fifty-four patients given patch tests both preoperatively and postoperatively, six tested positive for metal sensitivity preoperatively and, of these six, five had lost their sensitivity upon retesting at three to nineteen months postoperatively. None of the remaining forty-nine patients available for postoperative retesting showed indications of metal sensitivity. Carlsson and Moller<sup>111</sup> observed a similar phenomenon: three of eighteen patients were found to have lost their metal sensitivity on postoperative retesting. However, those authors admitted that this “may be attributable to false positive test reactions at the preoperative test,” acknowledging the inherently high degree of uncertainty associated with dermal patch testing, especially in the context of implant-related metal sensitivity.

An additional factor obscuring a clear connection between metal sensitivity and implant failure is the lack of any reported association between the prevalence of metal sensitivity and the duration for which the implant was *in situ*, infection, the reason for removal, or pain<sup>5</sup>. The prevalences of painful ar-

ticularities were reportedly the same among metal-sensitive and non-metal-sensitive patients undergoing revision<sup>5</sup>. Infection and a longer time *in situ* are associated with an increase in implant corrosion products, which should theoretically lead to an increased prevalence of metal sensitivity<sup>5</sup>. This lack of causal evidence implicating cell-mediated immune responses has prompted some to conclude that “implantation of cemented metal-to-plastic joint prosthesis is safe, even in the case of a pre-existing metal allergy, from both an orthopaedic and a dermatologic point of view”<sup>111</sup> and that even when a patient is known to be allergic to nickel, alloys such as stainless steel (that is, F138 with 13% to 15.5% weight nickel) can be used without the need for substituting alternate, non-nickel-containing alloys (for example, titanium)<sup>4</sup>. However, this is not universally accepted, and the majority of investigators have concluded that metal sensitivity can be a contributing factor in implant failure<sup>5,18,31,36,38,41,95,97,112</sup>.

### Overview

It is unclear whether hypersensitivity responses to metallic biomaterials affect implant performance in other than a few highly predisposed people<sup>5,20,113</sup>. It is clear that some patients have excessive eczematous immune reactions directly associated with implanted metallic materials<sup>2,35-39</sup>. Metal sensitivity may exist as an extreme complication in only a few highly susceptible patients (that is, less than 1% of joint-replacement recipients), or it may be a more common subtle contributor to implant failure. In addition to inducing direct immunogenic responses, metal degradation products may mediate indirect immunologic effects as a result of immune cell toxicity. It is likely that cases involving implant-related metal sensitivity have been underreported because of the difficulty of diagnosis. Mechanisms by which *in vivo* metal sensitivity occurs have not been well characterized. Thus, the degree to which a known condition of metal hypersensitivity may elicit an overaggressive immune response remains unpredictable<sup>20,113</sup>. Continuing improvements in immunologic testing methods will likely improve future assessment of patients susceptible to hypersensitivity responses. Until additional prospective, longitudinal evaluations are conducted to more clearly define the role of delayed-type and humoral immunity hypersensitivity reactions in patients with metallic orthopaedic implants, the risk to patients may be considered minimal<sup>15,31</sup>. However, in the event of temporally related cutaneous signs of allergic response to implant placement, metal sensitivity should be considered. Patients presenting with signs of an allergic reaction should be evaluated for sensitivity. Removal of a device that has served its function should be considered, since removal may alleviate the symptoms. Patients who have had an allergic reaction to a metallic device or to jewelry are more likely to have a reaction to an implanted device than are those with no such history. At this time, there is no evidence that there is an increased risk of a reaction to an implanted device in patients who have skin patch sensitivity but no history of reaction to metallic materials. The importance of this line of investigation is growing, as the use of metallic implants and the expectations of implant durability and performance are increasing<sup>114,115</sup>. ■

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