

Hypersensitivity Associated with Metallic Biomaterials

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1. Introduction

Biocompatibility can be defined as the ability of a biomaterial to demonstrate host and material response appropriate to its intended application (1). The determination of biocompatibility has been dominated historically by the characterization of candidate materials, based on the observation of adverse host responses. However, some adverse responses are subtler in clinical settings, and continue to foster debate and investigation. One of these responses is “metal allergy,” or hypersensitivity to metallic biomaterials.

All metals in contact with biological systems corrode (1,2) and the released ions, although not immune sensitizers on their own, can activate the immune system, by forming complexes with native proteins (3–5). These metal–protein complexes are considered to be candidate antigens (Ags) (or allergens) in human clinical applications. Polymers and oxide-based ceramics, such as alumina and zirconia, are not easily chemically degraded in vivo, and have not been intensely investigated as sources of allergic-type immune responses. Presumably, the relatively large ceramic and polymeric wear debris particles do not lead to the formation of polymer–protein or ceramic–protein haptenic complexes capable of eliciting human antibodies (Abs).

Metal hypersensitivity is a well-established phenomenon (6–8) and dermal hypersensitivity to metal is common, affecting about 10–15% of

the population (5–7,9). Dermal contact and ingestion of metals have been reported to cause reactions, which most typically manifest as hives, eczema, redness, and itching (6,9–11). Although little is known about the short- and long-term pharmacodynamics and bioavailability of circulating metal degradation products in vivo (2,5,12–14), there have been many reports of immunologic responses temporally associated with implantation of metal components. Individual case reports link hypersensitivity reactions with adverse performance of metallic cardiovascular (15–17), orthopedic (7,18–22), and plastic surgical (23), and dental (24–30) implants.

Metals known as sensitizers (haptenic moieties in Ags) include beryllium (31), nickel (Ni) (9–11,31), cobalt (Co), and chromium (Cr) (31). Occasional responses have been reported to tantalum (32), titanium (33,34), and vanadium (V) (32). Ni is the most common metal sensitizer in humans, followed by Co and Cr (6,9–11). Cross-sensitivity reactions between metals are also common, with Ni and Co the most frequently cross-reactive (6). The amounts of these metals found in medical grade alloys are shown in Table 1.

2. Types of Immune Responses

Metal hypersensitivity might be merely a clinical curiosity, except for known overaggressive immune responses to haptenic Ags leading to putative clinical complications. Hypersensitivity

Table 1
Weight Percent of Different Metals Within Three Common Alloys

Alloy	% Ni	% Co	% Cr	% Ti	% Mo	% Al	% V
Stainless Steel (ASTM F138)	13–15.5	—	17–19	—	2–4	—	—
Co Alloy (ASTM F75)	1 max	Balance	27–30	—	5–7	—	—
Ti Alloy (ASTM F136)	—	—	—	Balance	—	5.5–6.5	3.5–4.5

Mo, molybdenum; Al, aluminum.

can be either an immediate (within minutes) humoral response (initiated by antibody or formation of Ab–Ag complexes of types I, II, and III reactions), or a delayed (hours to days) cell-mediated (type IV) response (35,36).

Type I (immunoglobulin E [IgE]-mediated) humoral response is typified by the binding of soluble allergens (Ags) to B-lymphocytes, which then transform to IgE-secreting plasma cells and memory cells. (The term “allergen” specifically refers to nonparasitic Ags that elicit a type I response, although it is commonly used for Ags of types II, III, and IV, as well.) IgE binding to crystallizable fragment (Fc) receptors on basophils and mast cells occurs, sensitizing them. Upon re-exposure to the sensitizing allergen, degranulation of basophils or mast cells occurs, releasing pharmacologic agents, which cause vasodilation, increased vascular permeability, and smooth muscle contraction. Typical manifestations include systemic anaphylaxis, localized anaphylaxis, hay fever, asthma, hives, and eczema. Typical allergens include plant pollens (rye grass, ragweed, timothy grass, birch trees), drugs (penicillin, sulfonides, local anesthetics, salicylates), foods (nuts, seafood, eggs, peas, beans), insect venoms (bee, wasp, ant), mold spores, and animal hair. The typical initiation time of a type I response is 2–30 min (35,36).

Type II (Ab-mediated) hypersensitivity is characterized by activation of the complement system or cytotoxic T-cells, which eliminate cells that display Ag. Host Abs, reacting with foreign Ags, produce pores in the membrane of foreign cells, or serve as targets for guiding phagocytic cells. Typical Ags include transfused blood proteins, maternal IgG Abs that can cross the placenta and destroy fetal red blood cells (RBCs), and, less often, certain antibiotics (e.g., penicillin, cephalosporin, and streptomycin), which form hapten car-

rier complexes on RBCs, inducing hemolytic anemia. The typical initiation time of a type II response is 5–8 h (35,36).

Type III (immune complex-mediated) involves large amounts of circulating Abs specific to an invading Ag. These form locally high concentrations of Ab–Ag complexes, resulting in local mast cell degranulation (increasing vascular permeability) and chemotactically active neutrophils. This “arthus” reaction produces local accumulation of fluids (edema) and RBCs (erythema). Mild reaction is marked by redness and swelling; severe reactions are marked by tissue necrosis. Severe tissue damage is caused by neutrophilic release of lytic enzymes, in an attempt to phagocytize the immune complexes. Typical Ags include insect venoms, bacterial spores, fungi, dried fecal proteins, and, most commonly, antitoxins (e.g., antitetanus or antidiphtheria serum). The typical initiation time of a type III response is between 2 and 8 h (35,36).

Type IV delayed-type hypersensitivity (DTH) is immune-cell mediated. It is this type of response with which hypersensitivity reactions associated with orthopedic implants (metal sensitivity or metal allergy) are generally associated. Ag-sensitized T-DTH lymphocytes release various cytokines, which result in the accumulation and activation of macrophages. Only 5% of the participating cells are Ag-specific T-DTH cells, within a fully developed DTH response. The majority of DTH participating cells are macrophages. There are basically three phases of a DTH response. The first is characterized by at least a 1–2-wk exposure to the offending Ag. During this phase, there is induced proliferation of specific T-cells, induced by Ag. The second, effector, phase is initiated by contact of sensitized T-cells with Ag. In this phase, T-cells, which are Ag-activated, are termed T-DTH cells, and secrete a variety of cytokines

that recruit and activate macrophages, monocytes, neutrophils, and other inflammatory cells. These released cytokines include: interleukin-3 and granulocyte-macrophage colony-stimulating factor, which promote hematopoiesis of granulocytes; monocyte chemotactic-activating factor, which promotes chemotaxis of monocytes toward areas of DTH activation; interferon- γ and tumor necrosis factor- β , 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 DTH reaction. Activation, infiltration, and eventual migration inhibition of macrophages is the final phase of the DTH response. Activated macrophages, because of their increased ability to present class II major histocompatibility complex and interleukin-1, can trigger the activation of more T-DTH cells, which in turn activates more macrophages, which activate more T-DTH cells, and so on. This DTH self-perpetuating response can create extensive tissue damage.

Despite the usefulness of such a classification scheme, it is difficult to categorize an allergic response as purely one type or another because of a large number of secondary effects that cross classification boundaries. However, the primary hypersensitivity reactions associated with the use of metals as biomaterials is the establishment of type IV DTH. This is mediated by degradation products as moieties in haptenic complexes, leading to specific responses, such as severe dermatitis, urticaria, and/or vasculitis (15,18,20–22, 37–42).

In addition to direct immune system responses, leading to unforeseen symptomatology, metal degradation products may also be associated with other responses, such as metabolic alterations (40,43–46), alterations in host–parasite interactions (32,38–42), formation of lymphocyte toxins (42), and initiation and/or promotion of chemical carcinogenesis (47,48).

3. Testing for Delayed Hypersensitivity

Testing for DTH has historically been conducted in vivo, by skin testing (i.e., patch testing or intradermal testing), and in vitro, by leukocyte

migration-inhibition testing (termed leukocyte inhibitory factor [LIF] or MIF testing). Although in vivo testing protocols and commercial kits do exist (35,49) (e.g., True Test, Glaxo Dermatology, Research Triangle Park, NC), there is continuing concern about the applicability of skin testing to the study of immune responses to implants. Specifically, there is a lack of knowledge about, and availability of, appropriate challenge agents (50–52). Patch testing involves incorporating an Ag (e.g., 1% aqueous Ni sulfate) in a carrier, such as petrolatum, and exposing this to dermal tissue by means of an affixed bandage. After exposure of approx 48–96 h (the maximal time for a DTH response), reactions are graded on a scale of 1 (mild or absent response) to 4 (severe rash with small, possibly encrusted, weeping blisters). These testing conditions are different from the weeks to months of constant exposure that occur in orthopedic implant eczematous reactions (7,18–22). Additionally, the hapenic potential of metals, in the case of dermal contact (in which dermal Langerhans cells are the primary hypersensitivity effector cells), is probably different from the periprosthetic in vivo environment (36,53). In addition, the diagnostic utility of patch testing may be affected by possible immunological tolerance (i.e., suppression of dermal response to implants) (49,54), impaired host immune response (41,42), or the possible induction of hypersensitivity in a previously insensitive patient (55). Moreover, even if patch testing was a reliable means of testing, no suitable standardized testing battery of relevant metals currently exists.

In vitro leukocyte migration-inhibition testing involves the exposure of leukocytes obtained from peripheral blood to a possible Ag, and the subsequent measurement of leukocyte migration activity. Leukocytes in culture actively migrate in a random fashion, but can be attracted preferentially to chemoattractants, such as those released by *Staphylococcus*, *Streptococcus*, and other bacteria. Lymphocytes in the presence of a specific Ag, for which they possess an appropriate Ab, migrate more slowly, losing the ability to recognize chemoattractants, and are said to be migration-inhibited.

Testing for metal allergy has also been conducted using in vitro leukocyte migration-inhibition testing (termed LIF or MIF testing). In vitro

blood testing for delayed hypersensitivity was first used in 1928 by Rich and Lewis (56), who showed that there was tuberculin-induced migration inhibition of white blood cells. In the mid-1960s, George and Vaughan (57,58) introduced a leukocyte-filled capillary tube technique, in which Ag-induced cell migration (or inhibition thereof) could be detected as a fan of cells exiting the tube long the bottom of a cell culture chamber. A few years later, Carpenter et al. (59) improved this technique by placing lymph-, spleen-, and lung-derived cells in holes cut in an agar gel covering the bottom of a Petri dish. Radial migration, or the lack thereof (migration inhibition), away from the holes, was used as a measure of leukocyte activation. Others (58,60) have also successfully used this technique to investigate Ag-induced leukocyte migration-inhibition behavior.

4. Incidence of Hypersensitivity Responses Among Patients with Metal Implants

The incidence of metal sensitivity among the general population is approx 10–15%, with Ni sensitivity the highest ($\approx 14\%$), as is shown in Fig. 1. However, with patch testing, crossreactivity of Ni, Co and Cr is commonly observed, with crossreactivity between Ni and Co the most common (5,6). Interest in the possible correlation between metal sensitivity and implant failure prompted a number of investigations in the late 1970s and early 1980s (7,49,54,55,61–69).

The incidence of metal sensitivity among patients with well-functioning implants is roughly twice that of the general population, $\approx 25\%$, Fig. 1 (49,54,62,64,65,68,70–72). The average incidence of metal sensitivity among patients with a failed implant, using the five investigations shown in Fig. 2, is $\approx 50\%$ (62,64,70–72). This is approx 5 \times the incidence of metal sensitivity found in the general population, and 2 \times that of patients with metal implants. These findings are the basis for the consideration of metal sensitivity as a potentially important factor in implant failure.

However, the association of metal release from implants with adverse immunologic response has remained conjectural, because cause and effect have not been established in symptomatic

patients. In other words, it is unclear whether metal hypersensitivity causes implant failure or vice versa (71). It may also be that there is an interaction between these phenomena, in which implant loosening increases metal release, thereby stimulating sensitivity reactions, which in turn contribute to the loosening process. Metal hypersensitivity can be expected to occur in any population of patients; therefore, the identification of implant-induced hypersensitivity depends on the ability to perform tests on individual patients before implantation, during device service, and, in the case of an adverse outcome, before and after device removal.

5. Investigations of Implant-related Metal Sensitivity

The first apparent correlation of eczematous dermatitis (skin rash with redness and weeping blisters) with metallic orthopedic implants was observed in 1966 by Fousseureau and Laugier (73). In the following years, there were a number of case reports linking metal sensitivity (in particular, Ni) to eczematous reactions of patients with implants (18,22,54,71,74). In many cases, when the metallic implant was removed, the skin reactions abated.

In one of the earliest case studies implicating an orthopedic implant as the cause of metal allergy (18), a 20-yr-old woman received stainless steel screws to treat a chronic patellar dislocation. After 5 mo she presented with an extensive eruption of eczematous dermatitis on her chest and back. After treatment with topical corticosteroids, her condition abated for 1 yr, after which it recurred as a generalized dermatitis. An additional course of topical corticosteroid application yielded poor results, and, “out of sheer desperation,” the stainless steel screws were removed. The day after screw removal, her eczema subsided, with complete disappearance within 72 hr. “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” (18). Upon patch testing, she showed reactions to Ni, Ni sulfate, and the stainless steel screw. The findings in this case are not unique (7,19–23). The temporal and physical evidence

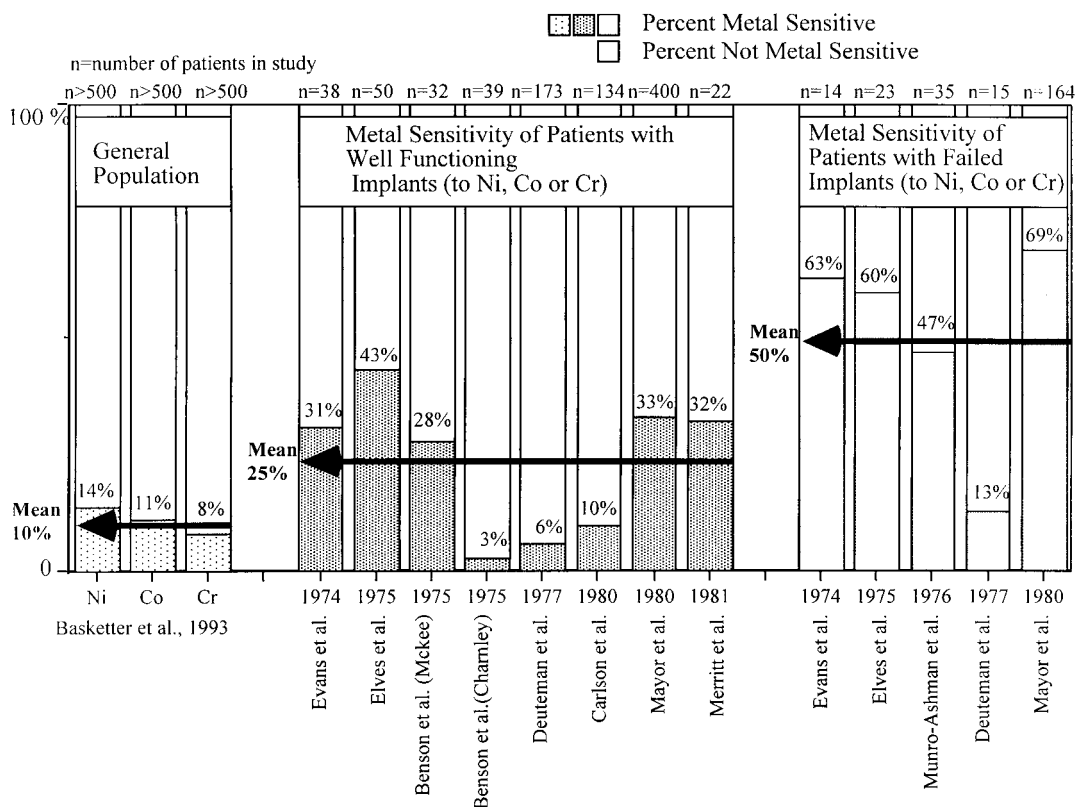


Fig. 1. Compilation of investigations showing the averaged percentages of metal sensitivity for Ni, Co and Cr, among the general population, among patients with a well-functioning implant, and among patient populations with failed implants. Means of each group are indicated by arrow. All patients were tested by means by a patch or LIF test (6,54,62,64,65,68,70–72).

provided in this and other such case reports leaves little doubt that the phenomenon of sensitization to orthopedic implants does occur in some patients (5,7,12,17,19–21,37,71,75).

Growing numbers of case reports link immune reactions with poor performance of metallic cardiovascular (15–17), orthopedic (7,18–22), and plastic surgical (23), and dental (24–30) implants. In some instances, symptoms attributable to an immunologic reaction have led directly to device removal (15,18,20–22,37). In these cases, severe dermatitis (inflammation of the skin) (15,17,19,20,34,75), urticaria (intensely sensitive and itching red round wheels on the skin) (16,37), and/or vasculitis (patch inflammation of the walls of small blood vessels) have been linked to the relatively more general phenomena of metallosis (metallic staining of the surrounding tissue),

excessive periprosthetic fibrosis, and muscular necrosis (22,76,77).

In a recent report on five individuals who underwent revision of failed Ti-alloy total hip replacements (23), none showed positive patch test results to Ti salt solutions. However, two did show a reaction to a Ti-containing ointment. Tissues obtained from the joint capsules of all five showed evidence of dark gray tissue staining and metallic debris, which were found to be 100% Ti by X-ray dispersion analysis. Histological analysis revealed the presence of macrophages, fewer T-lymphocytes, and an absence of B-lymphocytes and plasma cells, as would be seen in a type-IV, DTH reaction (23). These results raise the possibility that metal sensitivity may occur in patients with implants made of metals (e.g., Ti) thought to be less allergenic than Ni, Co and Cr.

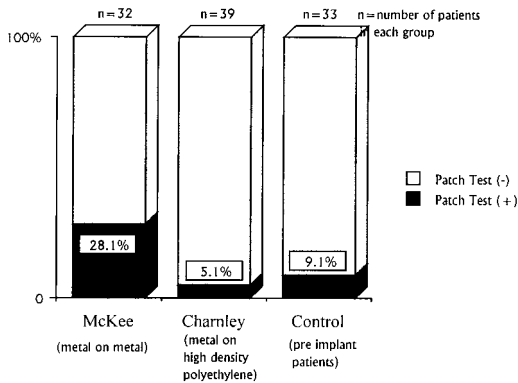


Fig. 2. This graph shows a comparison of metal sensitivity among patients with metal-on-metal-bearing surfaces, compared with metal-on-UHMWPE bearing surface (54).

Specific types of implants, with 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 were associated with greater prevalence of metal allergy than similar designs with metal-on-ultra-high-mol-wt-polyethylene (UHMWPE) bearing surfaces (54,72). Evans et al. reported that, of 38 patients having a metal-on-metal implant, with a minimum of 2-yr follow-up, 14 (37%) were loose and 24 (63%) were well-fixed. Among these 14 patients with loose implants, nine were metal-sensitive; none of the 24 patients with well-fixed implants showed evidence of metal sensitivity by patch test. Another investigation showed a greater incidence (25%) of metal sensitivity associated with metal-on-metal-bearing surfaces than with metal-on UHMWPE-bearing surfaces (Fig. 2) (54).

On the other hand, several published reports have indicated that, after total joint replacement with metallic components, some patients show an induction of metal tolerance (i.e., previously diagnosed metal sensitivity can abate after implantation of a metallic prosthesis). Rooker and Wilkinson (49) reported that, of 67 patients undergoing patch testing both pre- and postoperatively, six tested positive for metal sensitivity preoperatively, and five of these six lost their sensitivity upon retesting at 3–19 mo postoperatively (49). None of the remaining 49 patients available for PO retesting showed indications of metal sensitiv-

ity. In another investigation, Carlsson and Moller (78) observed a similar phenomenon, in which three patients lost their metal allergy at PO retesting, but admitted that this “may be attributable to false positive test reactions at the preoperative test,” acknowledging an inherent high degree of error and uncertainty, using dermal patch allergy testing. An additional confounding factor is the lack of any reported correlation between prevalence of metal sensitivity and implant residence time, infection, reason for removal, or pain (5). Painful articulation was reportedly the same among metal-sensitive patients as in nonsensitive patients undergoing revision (5).

This lack of causal evidence linking cell-mediated immune responses to implant failure 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 orthopedic and a dermatologic point of view” (78). Even in the case of a known Ni-allergic patient, alloys such as stainless steel (i.e., F138 and 12–14% weight Ni) can be used without the need for substituting alternate non-Ni-containing alloys (i.e., Ti) (9). However, this is not a consensus. Many investigators have concluded that metal sensitivity can be a contributing factor to implant failure (5,19,22,33,49,54,62,63,72).

6. Conclusions

It is unclear whether hypersensitivity responses to metallic biomaterials affect implant performance in other than a few highly predisposed individuals (5,35,79). It is clear that some patients experience intense eczematous immune reactions, directly associated with implanted metallic materials (7,18–22). Metal sensitivity may exist only as an unusual complication in a few highly susceptible patients (i.e., estimated to be less than 1% of joint replacement recipients) (5) or it may occur more commonly, and may be one of a number of contributing factors that lead to implant failure (e.g., pain, loosening, osteolysis, or recurrent dislocation). It is likely that cases involving implant-related metal sensitivity have been underreported, because alternate causes were attributed to failure of the implant. The mechanism by which metal sensitivity occurs has not been well characterized. Thus, the degree to which a known condition of

metal hypersensitivity can elicit a clinically important immune response remains unpredictable (35,79). Continuing improvements in immunologic testing methods will probably enhance future assessment of patients susceptible to hypersensitivity responses. Although further investigations are needed to more clearly define the role of DTH reactions in the failure of metallic orthopedic implants, at present, the risk to patients appears to be limited (5,49).

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