Chapter 12
Hypersensitivity to Implant Debris

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Abstract Total Joint Replacements (TJR) have been extremely successful over the past 50 years, restoring mobility and function to millions of people each year. However, over time these implants need replacing for a number of reasons, such as infection or increasing immune reactivity to implant debris. All implant metals degrade *in vivo*, and the released products biologically interact locally and systemically. Local and/or systemic immune reactivity to implant debris may become excessive, specifically to one or more of the materials (metals) used in the implant alloys. When this excessive reactivity to implant debris involves the adaptive immune system where lymphocytes respond to specific stimuli it can be characterized as a sensitivity or hypersensitivity response. Dermal hypersensitivity reactions to metals (such as Nickel) are common and affect approximately 10–15% of the population in USA and Europe. In its extreme form, metal sensitivity exists as a relatively rare complication in only a few highly susceptible patients with joint replacements (i.e., less than 1% of joint replacement recipients).

However, the role of implant-related metal sensitivity in implant performance is likely underreported due to the scarcity of diagnostic testing. The person-dependent mechanism(s) by which metal sensitivity occurs in some people and not others has not been completely explored with current hypersensitivity testing techniques. This issue is becoming increasing popular due to recent failures of metal-on-metal hips and increasing numbers of joint replacement procedures, worldwide. Better materials and availability of appropriate immunologic testing (e.g., LTT) will likely enhance future assessment of patients susceptible to hypersensitivity responses.

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1 Introduction

It is surprising to learn that almost all of the >1,000,000 total joint replacements/year that are performed in the USA are expected to eventually fail if their recipients live long enough. This eventual failure is due to implant debris-induced inflammatory reactions [1]. This is particularly horrible for millions of elderly people who may need a revision of their current implants in their last decades of life where the incidence of death caused by major surgery can be as high as 13% (vs. <1% in patients <75 years of age) [2]. Implant loosening due to debris-induced aseptic osteolysis accounts for over 75% of all total joint arthroplasty (TJA) implant revisions and is the predominant factor limiting the longevity of current total joint arthroplasties; the other reasons include infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and surgical error (3%) [3].

Excessive biologic reactivity to implant debris can be defined as any toxicologic or immunologic reactivity to implant debris that causes, or is in the process of causing, implant failure prematurely, where "prematurely" is generally considered less than 5–7 years. Particle-induced osteolysis, or "particle disease," generally refers to the slow process of peri-implant osteolysis, where implant loosening and inflammation are due to implant particulate debris interacting with innate immune system cells (i.e., tissue macrophages termed histiocytes) where modest inflammation persists for many years. This innate inflammatory response is typically associated with the eventual failure of metal-on-polymer THAs. Excessive reactivity to implant debris, or hypersensitivity to implant debris, is slightly different and typically involves the adaptive immune system where conditioned lymphocytes respond to specific stimuli. The degree to which excessive innate response factors into this hypersensitivity immune response is not known. Implant hypersensitivity has been predominantly characterized as specific, and of the delayed type hypersensitivity (DTH) response, and has been more associated with metal-on-metal bearing implants.

Implant surfaces are not known to cause hypersensitivity. Implant debris is the known cause of immune responses to implants. This distinction is important, because when debris is minimized, the chances of hypersensitivity decrease. But what is hypersensitivity to implants? In its broadest definition hypersensitivity to implants is any aseptic (nonbacterial) material-driven excessive immune response that causes peri-implant pathology, such as decreased bone homeostasis or massive local inflammation of T-cells or B-cells or macrophages. When an implant fails prematurely (<7 years) due to an exuberant immune response to a normal (and typically very tolerable) amount of implant debris, that is what can be categorized as "metal-allergy," "implant-allergy," "implant sensitivity," or "hypersensitivity." These terms have been used interchangeably in scientific studies. Implant-related metal sensitivity has been well reported in case and group studies; however, there is still much we do not know about this phenomenon [4–6]. All implant metals corrode and/or wear *in vivo* [7, 8], and the released products (particles and ion) interact with plasma proteins, and then with local and systemic cells including those

of the immune system. Materials such as polymers that are less chemically promiscuous (less able to alter proteins at the molecular level) are also less likely to activate the immune system and have not been as widely implicated in causing an implant allergic response. Dermal hypersensitivity reactions to metals have been reported to cause immune reactions, which most typically manifest as skin hives, eczema, redness, and itching, affecting approximately 10–15% of the US and Europe's population [4, 5, 9–12]. Implant materials have been optimized over time to eliminate materials that demonstrate adverse host responses. Some subtle adverse responses, such as *in vivo* metal hypersensitivity or hypersensitivity-like reactivity to metallic biomaterials, are difficult to characterize before and after surgery. Hypersensitivity is caused by the debris of metallic biomaterials that include particulate wear debris, colloidal organometallic complexes (specifically or nonspecifically bound), free metallic ions, inorganic metal salts/oxides, and precipitated organometallic storage forms (basically, particles and ions).

All metals begin to degrade via corrosion when in contact with their biological environment [7, 13]. The released metal ions can activate the immune system by forming complexes with native proteins [12, 14–16]. These metal–protein complexes are what elicit hypersensitivity responses. Plastic (polymeric) biomaterials used in orthopedics are not easily chemically degraded *in vivo* and have not been intensely investigated or found to be involved in case or group studies as sources of hypersensitivity-type immune responses. This is in part due to the relatively large degradation products (>50 nm) associated with polymeric debris *in vivo*, which do not readily form polymer–protein haptenic complexes with human antibodies. However, there have been reports of immunogenic reactions associated with polymethylmethacrylate (PMMA) [17], but these may be due to an unreacted PMMA monomer which is highly toxic and can elicit an immune response at very low levels.

Metals that are well known to cause hypersensitivity reactions are beryllium [18], nickel [9–11, 18], cobalt [18], and chromium [18] and to a lesser degree tantalum [19], titanium [20, 21], and vanadium [19]. The incidence of metal sensitivity among the general US population is approximately 10–15% (Fig. 12.1), where nickel hypersensitivity is the most prevalent (approximately 14%) [4], followed by cobalt and chromium [4, 12]. The amounts of these metals found in medical grade alloys are presented in Table 12.1.

2 Metal Sensitivity

Hypersensitivity can take one of two central forms (1) an immediate (within minutes) humoral response (initiated by antibody–antigen complexes of types I, II, and III reactions), or (2) a delayed (hours to days) cell-mediated response [22, 23]. Implant-related hypersensitivity reactions are generally associated with delayed-type responses and have been categorized as type IV DTH.

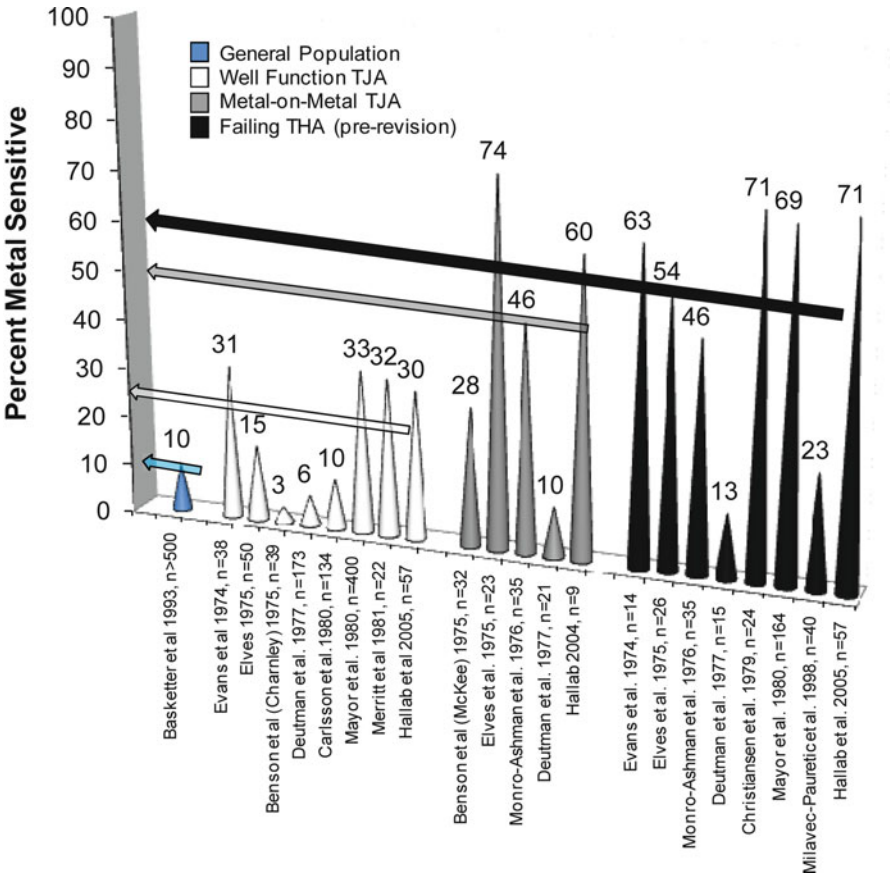

Fig. 12.1 A compilation of averaged incidence percentages of metal sensitivity (nickel, cobalt, or chromium) among different groups: (1) the general population, (2) patients after receiving a metal-containing TJA, (3) patients with metal-on-metal bearing arthroplasty, and (4) patient populations with significant osteolysis or due to be revised. Note: Studies by Hallab et al. used Lymphocyte Transformation Testing to measure hypersensitivity, all other used dermal patch testing (picture courtesy of Orthopedic Analysis Inc)

Cell-mediated DTH is an adaptive immune response and is characterized by antigen activation of sensitized T-helper lymphocytes releasing various cytokines, which result in the recruitment and activation of macrophages. These T_{H-1} cells are characterized by the cytokines they release, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-2 (IL-2). T_{H-1} cells are generally associated with responses to intracellular pathogens and autoimmune diseases. Metal-activated T-cells in conjunction with activated antigen presenting cells (APCs) can secrete a variety of cytokines that recruit and activate other innate immune cells, i.e., macrophages, monocytes, and neutrophils. These cytokines include IFN-γ and TNF-β which produce a number of effects on local endothelial

Table 12.1 Approximate weight percent of different metals within popular orthopedic alloys

Alloy	Ni	N	Co	Cr	Ti	Mo	Al	Fe	Mn	Cu	W	C	Si	V
Stainless Steel														
(ASTM F138)	10–15.5	<0.5	[a]	17–19	[a]	2–4	[a]	61–68	[a]	<0.5	<2.0	<0.06	<1.0	[a]
CoCrMo Alloys														
(ASTM F75)	<2.0	[a]	61–66	27–30	[a]	4.5–7.0	[a]	<1.5	<1.0	[a]	[a]	<0.35	<1.0	[a]
(ASTM F90)	9–11	[a]	46–51	19–20	[a]	[a]	[a]	<3.0	<2.5	[a]	14–16	<0.15	<1.0	[a]
(ASTM F562)	33–37	[a]	35	19–21	<1	9.0–11	[a]	<1	<0.15	[a]	[a]	[a]	<0.15	[a]
Ti Alloys														
CP-Ti (ASTM F67)	[a]	[a]	[a]	[a]	99	[a]	[a]	0.2–0.5	[a]	[a]	[a]	<0.1	[a]	[a]
Ti-6Al-4V (ASTM F136)	[a]	[a]	[a]	[a]	89–91	[a]	5.5–6.5	[a]	[a]	[a]	[a]	<0.08	[a]	3.5–4.5
45TiNi	55	[a]	[a]	[a]	45	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Zr Alloy														
(95% Zr, 5% Nb)	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]

[a]Indicates less than 0.05%

Note: Alloy compositions are standardized by the American Society for Testing and Materials (ASTM vol. 13.01)

cells facilitating infiltration and release of migration inhibitory factor (MIF), which inhibits the migration of macrophages away from the site of a DTH reaction. Therefore, in the final phases of a DTH response there is infiltration, activation, and eventual migration inhibition of innate immune cells such as macrophages, controlled by adaptive immune cells (T-cells). These locally attracted and activated macrophages have the increased ability to phagocytose, process, and present metal–protein complexes in class II MHC complexes and IL-1, which trigger the activation of more T cells, which in turn activates more macrophages, which activate more T-cells, in a vicious cycle. This DTH self-perpetuation response can create extensive tissue damage. Current research efforts to use immunosuppressive therapy in people to temporarily stop this cycle are currently underway by us and others.

There is much about implant debris sensitivity that remains incompletely understood, including all the reactive lymphocyte subpopulations and the cellular mechanisms of recognition and activation, as well as specific antigenic metal-protein determinants. The Langerhans cells are well characterized as the primary antigen presenting cells (APCs) associated with skin hypersensitivity. While APCs in the periprosthetic region include macrophages, endothelial cells, lymphocytes, Langerhans cells, dendritic cells and, to lesser extent, parenchymal tissue cells, tissue macrophages (histiocytes) are presumed to be the primary peri-implant APCs. The T-cell receptor (TCR) has been widely acknowledged as involved in metal-induced activation [24–26]. Metals have also been shown to act as both typical antigen (such as tetanus toxin), but have also been shown to cause nontypical activation of T-cells by cross-linking receptors (e.g., VB17 of CDR1 T-cell receptor) to create what is called "superantigen"-like enhancement of T-cell receptor–protein contact [24, 27]. Despite reports of nontypical DTH-like metal-induced lymphocyte activation, the traditional DTH response (where there is one clonally specific group of lymphocytes specific to a single lock-and-key type T-cell receptor mechanism of activation) remains the dominant mechanism associated with implant-related hypersensitivity responses [28–30].

3 Testing for Metal Sensitivity

Testing for metal allergy can be accomplished by skin testing (i.e., so-called patch testing or intradermal testing) or by lymphocyte transformation testing (LTT). There are commercial kits that contain some of the metals in orthopedic implants [22, 31] (e.g., TrueTest™, Glaxo Dermatology, Research Triangle Park, NC). However, there is concern about the applicability of skin testing to diagnose immune responses around implants [14–16, 32, 33]. Patch testing involves antigens (e.g., 1% aqueous nickel sulfate) in a carrier, such as petrolatum, that are placed on dermal tissue for approximately 48–96 h after which reactions are graded on a scale of 1 (mild or absent response) to 4 (severe red rash that can contain small encrusted weeping blisters). One problem with this is that the immunogenic potential of

metals on the dermis is likely quite different from the closed periprosthetic *in vivo* environment. On the skin dermal Langerhans cells are the primary hypersensitivity effector cells and around implants macrophages are the primary antigen presenting cells, which are not nearly as efficient as Langerhans dendritic cells [23, 34]. Other general concerns associated with patch testing include the possible induction of hypersensitivity in a previously insensitive patient [35].

In vitro metal allergy testing, called lymphocyte proliferation testing (also known as LTT), involves measuring the proliferative response of lymphocytes after they are activated by an antigen. A radioactive marker is used to precisely measure the amount of cell division over a set time period by measuring the amount of radioactive [H^3]-thymidine that is incorporated into the cellular DNA upon cell division after 4–6 days of exposure to antigen. [^{3}H]-thymidine uptake is measured using liquid scintillation, and the amount of immune response (proliferation factor or stimulation index) is calculated using measured radiation counts per minute (cpm):

$$\text{Proliferation factor} = (\text{cpm with treatment})/(\text{cpm without treatment}).$$

The use of proliferation testing to measure metal allergy and in the assessment of general drug sensitivity has been well established as a method of testing in a variety of clinical settings [36–40]. There is a growing use of LTT testing for implant-related metal sensitivity that has been shown to have diagnostic efficacy particularly in the area of metal-on-metal implants, which have led to higher rates of metal sensitivity responses [41–43]. Several investigations indicate that metal allergy can be more easily detected by LTT than by dermal patch testing [41, 44, 45]. Thus, given the growing number of studies utilizing the highly quantitative nature of LTT testing in orthopedics it is likely better suited for the testing of implant-related sensitivity than dermal patch testing [36–41, 46, 47].

4 Case Studies in Metal Implant-Related Metal Sensitivity

There have been many reports over the past 30 years of implants that have elicited an allergy or sensitivity type responses. In these reports implant degradation products have been shown to be temporally linked with specific responses such as severe dermatitis, urticaria, vasculitis [48–53], and/or nonspecific immune suppression [54–58].

One of the first correlations of eczema reaction to metallic orthopedic implants was made in 1966 by Foussereau and Lauggier [59], where a nickel-containing implant was associated with hypersensitivity reactions. There have been growing numbers of case reports over the past 40 years that link immune responses with adverse performance of metallic cardiovascular [48, 60, 61], orthopedic [5, 49, 50, 52, 53, 62], plastic surgical [63], and dental [64–70] implants. In some cases immunological reactions have necessitated device removal, which then results in

stopping the immune reactions [48–53]. Some of these severe skin reactions [48, 51, 53, 60–62, 71, 72] have been associated with the relatively more general phenomena of metallosis (dark metallic staining of tissue due to excessive implant debris), excessive periprosthetic fibrosis, and muscular necrosis [50, 73, 74].

In one of the earliest case studies implicating an orthopedic implant as a source of metal sensitivity [49], a 20-year-old woman was examined for extensive rashes on her chest and back, 5 months after she had stainless steel screws put in to treat chronic patellar dislocation. Topical steroids helped her condition for 1 year. Then, it worsened with further generalized dermal rashes. "Out of sheer desperation," [49] the stainless steel screws were removed, and in less than 72 h her eczema completely disappeared. "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 4 h, generalized puritus and erythema developed" [49]. Metal allergy patch testing showed reactions to nickel, nickel sulfate, and the steel screw. This satisfies Koch's postulate as a causative agent, that when the suspected cause is removed the symptoms abate, and when it is returned the symptoms also return, thus metal allergy associated with implant was solidified nearly 40 years ago as a real phenomenon.

In another example, a 50-year-old woman suffered from persistent abdominal pain and urticaria postoperatively following a cholecystectomy using tantalum metal clips that could only get symptom relief after a plasma exchange, but not with corticosteroids or antihistamines. After removal, the tantalum clips showed visible signs of corrosion, indicating that it was likely the corrosion debris that she was reactive to [5, 50, 52, 53, 63]. There are a number of case studies that show similar temporal and physical evidence of immune reactivity to orthopedic implants [12]. It is these cases of severe metal sensitivity that present the greatest problems.

There are more cases of stainless steel and cobalt alloy implant-induced immune responses than there are to titanium alloy components [5, 12, 51–53, 61, 62, 71, 75, 76]. A case report of cobalt hypersensitivity implicated in the poor performance of cobalt alloy plates and screws used in the fracture fixation of 45-year-old woman's left radius and ulna[43] indicated the induction of periprosthetic fibrosis, patchy muscular necrosis, and chronic inflammatory changes peripherally, 7 years after implantation. However, after the implant was removed and the symptoms (swelling) disappeared, the patient remained reactive to cobalt, as indicated by patch testing [50].

5 Cohort Studies of Implant-Related Metal Sensitivity

Cohort studies generally indicate a correlation between the presence of a metal implant and metal sensitivity [5, 31, 35, 77–85]. When these studies are compared (Fig. 12.1), the incidence of metal sensitivity among patients with well-functioning implants is approximately 25%, roughly twice as high as that of the general population [31, 35, 76, 77, 79, 80, 84, 86, 87]. The average prevalence of metal

sensitivity among patients with a failed or poorly functioning implant (as judged by a variety of criteria) is approximately 60% [35, 76, 80, 86, 87], where the prevalence of metal sensitivity in people with failed or failing implants is approximately 6 times that of the general population, and approximately 2–3 times that of all patients with well-functioning implants. It is unknown to what extent this association is reflective of a causal link between immunogenicity to implant debris and poor implant outcome.

Cohort studies showing sensitivity to polymeric materials among patients with well-functioning implants have not been well established, although it has been reported [17, 88], where a 50% incidence of PMMA hypersensitivity of patients ($n = 26$ subjects) was associated with loose total hip prostheses using patch testing and mononuclear cell subset analysis [17]. Other studies have refuted this, where people with well-functioning implants showed no hypersensitivity reactions to PMMA, as determined by patch testing ($n = 112$ subjects) [89].

Generally, investigations of immune responses to implant debris suggest one of three possible outcomes hypotheses (1) metal degradation products are immunogenic [26, 28, 29, 90–92], (2) metal degradation products are immunosuppressive [93–95], or (3) metal degradation products are immunoneutral (i.e., non-bioreactive) [96, 97]. While all three possibilities have been shown to occur, the type of reaction that will occur in any one individual is dependent on the individual, the environment, and the type of implant.

Specific types of implants that release more metallic debris *in vivo* are more likely to induce metal sensitivity. Total hip prostheses with metal-on-metal bearing surfaces have been associated with metal sensitivity to a greater extent than similar designs with metal-on-ultrahigh molecular weight polyethylene bearing surfaces [77, 86]. New generations of metal-on-metal total hip replacement have advantages like larger head sizes that decrease the rates of dislocation after surgery, but have greater reports of failures attributable to excessive inflammatory reactions to metal debris characterized as hypersensitivity-like responses. Some reports show that 76–100% of the people with these metal-on-metal implants which have aseptic implant failures requiring revision also have evidence of histological inflammation accompanied by extensive lymphocyte infiltrates. This is characteristic of delayed-type hypersensitivity responses that are characterized by infiltrations of lymphocytes not normally seen in the peri-implant tissue [98, 99]. These reports have shown that in people with metal-on-metal bearing implant with aseptic loosening, all those being revised have been shown to have extensive lymphocytic infiltrates around the metal debris, indicative of unwanted adaptive immune system reactivity. The rates of sensitivity of these people with well-performing metal-on-metal implants are shown in Fig. 12.1 and are nearly twice that of people with well-performing implants.

However, whether metal sensitivity is causal or not may be beside the point once sensitivity has been established as a negative feedback to implant performance. It is very likely that metal-stimulated lymphocytes participate in the pathogenesis of aseptic osteolysis given that activated lymphocytes release powerful cytokines such as IL-2, IFN-γ, and RANKL (receptor-activated NF-KB ligand), which can directly and indirectly affect bone resorption and turnover by promoting

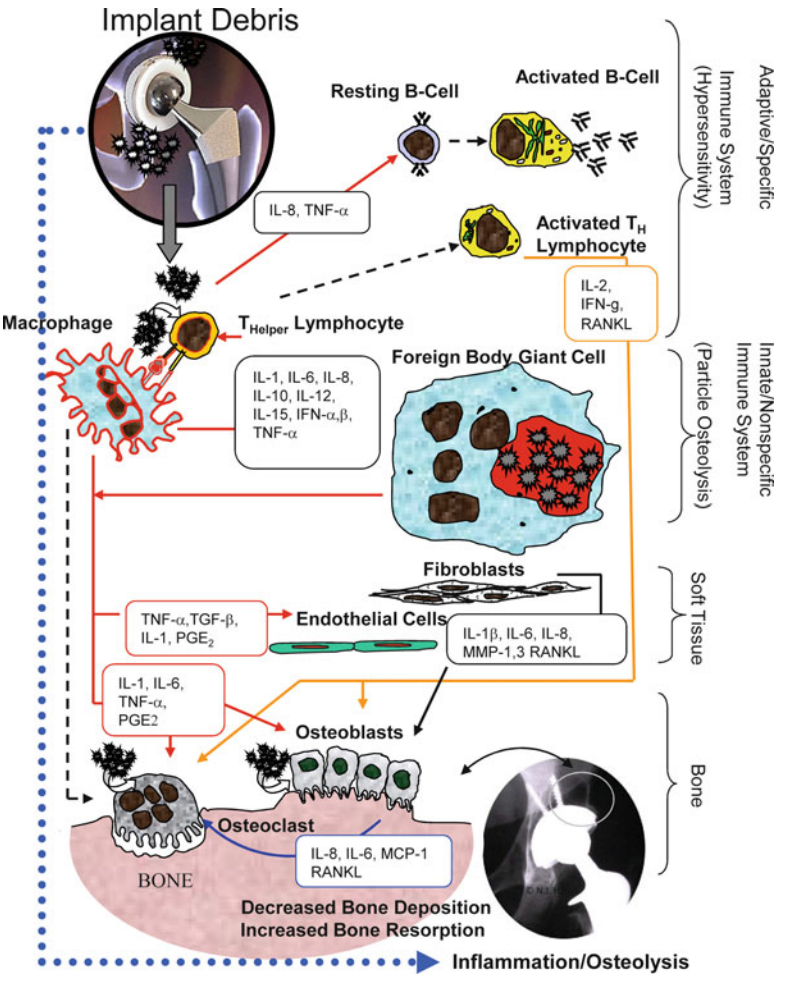

Fig. 12.2 The biologic reactivity of implant debris causes local immune responses primarily mediated by macrophages, which produce reactive oxygen intermediates and pro-inflammatory cytokines that affect a host of local cell types and induce a widening zone of soft-tissue damage and inflammation (picture courtesy of BioEngineering Solutions Inc) [100]

osteoclast activity (bone resorption) and inhibiting osteoblast activity (bone deposition) in a disruptive set of events that result in vicious cycle of inflammation and bone erosion, Fig. 12.2 [101].

Thus, it seems that, although metal-on-metal implants produce less overall debris than metal-on-polymer articulations do, the rates of revision/failure of metal-on-metal THAs may ultimately prove to be as high as metal-on-polymer bearings, and that these failures may be entirely due to exuberant biological responses to implant debris, be they toxic or hypersensitivity-like immune

responses. It is likely that, if metal sensitivity could be effectively screened out preoperatively, revision rates of metal-on-metal THAs would drop.

6 Conclusions

It is unclear whether hypersensitivity responses to metallic biomaterials affect implant performance in other than a few highly predisposed or implant-debris sensitized people [12, 22, 102]. It is clear that some patients experience excessive immune reactions directly associated with implanted metallic materials [5, 49, 50, 52, 53, 62]. Metal sensitivity exists as an extreme complication in only a few highly susceptible patients (i.e., less than 1% of joint replacement recipients), and a more common subtle contributor to implant failure. In addition to direct immunogenic responses, metal degradation products may mediate indirect immunologic effects due to cell toxicity, where immune reactions are secondary to this person-dependent toxicity responses. It is likely that implant-related metal sensitivity is underreported due to the scarcity of diagnostic testing. The person-dependent mechanisms by which *in vivo* metal sensitivity occurs in some people and not is others have not been identified, making it difficult to know whether a known condition of metal hypersensitivity will elicit an overaggressive immune response [22, 102]. Increasing popularity of immunologic testing will likely enhance future assessment of patients susceptible to hypersensitivity responses. In the event of temporally related signs of allergic response to implant placement, metal sensitivity should be considered, after infection has been ruled out. To appropriately weigh optimum treatment of patients presenting with signs of an allergic reactions, evaluation for sensitivity should be conducted. Removal of the device that has served its function should be considered, since removal may alleviate the symptoms that may produce other immune-related disorders. Patients who have allergic reactions to cheap jewelry are more likely to have reactions to orthopedic implants. It is important to note that there is increasing awareness of the phenomenon of metal hypersensitivity and many surgeons now take this into account when planning which implant is optimal for each patient. The importance of further study, diagnostic testing, and treatment for sensitivity to implant debris is paramount, as almost 1 in 2 people will eventually require an orthopedic implant, and revision surgery over the age of 75 can result in $>13\%$ mortality [2, 103].

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Biography

Dr. Nadim James Hallab was born in Baton Rouge, LA, USA, received his BS and MS in Mechanical Engineering at Texas A&M University, and his PhD in Biomedical Engineering at Tulane University in 1996. He was a postdoctoral fellow at Rush University Medical Center in the Orthopedic Department for 2 years, studying implant corrosion, metal-protein binding, and the biologic effects of soluble metallic implant debris. He is currently an Associate Professor in Orthopedic Surgery at Rush University Medical Center where he has been a researcher for the past 13 years, investigating implant debris generation and the biologic reactivity to implant debris. He is an adjunct faculty member in the Department of Cell Biology/Anatomy, Department of Immunology at Rush, and the Dept. of Biomedical Engineering at University of Illinois at Chicago. He is also currently the CEO of an implant debris analysis company (BioEngineering Solutions Inc.) and a metal allergy testing company (Orthopedic Analysis Inc.), which have been in business since 2004. He has over 65 peer reviewed publications and 15 book chapters in the field of implant degradation and immunologic reactivity to implant debris. Current awards include the 2002 Kappa Delta Award (Team Member) and the 2009 Harris Award for excellence in Orthopedic Research for the discovery that danger signaling mechanisms (inflammasome pathways) are associated with inflammation and hypersensitivity reactions to soluble and particulate implant debris. While occasionally still conducting corrosion and biomechanical testing research, the bulk of his current research involves innate and adaptive immunologic reactivity to implant debris.