Biologic Effects of Implant Debris

Nadim J. Hallab, Ph.D., and Joshua J. Jacobs, M.D.

Abstract

Biologic response to orthopedic implants debris is central to clinical performance. Eventual implant loosening due to aseptic osteolysis has been attributed to local inflammatory responses to wear and corrosion products that are produced by articulating implant interfaces. The response to implant debris is dominated by local immune activation, e.g. macrophages. Immune reactivity has been shown to depend on the number of particles produced or the dose (i.e., the concentration of phagocytosable particles per tissue volume, which can be characterized by knowing the size distribution and amount of debris). Elongated particles (fibers) are generally more pro-inflammatory than round particles, and there is a growing consensus that metals particles are more proinflammatory than polymers in vivo. Generally, to produce an in vitro inflammatory response, particles need to be less than 10 μm, i.e. phagocytosable. However, both soluble and particulate debris derived from Co-Cr-Mo alloy implants can induce monocyte/macrophage activation and secretion of pro-inflammatory cytokines such as IL-1β, TNFα, IL-6 and IL-8 via up-regulation of transcription factor NFκB, and activation of inflammasome danger signaling in human macrophages. Not only does activation of local (and systemic) inflammation result in decreased osteoblast function but osteoclast activity increases. Some people are more predisposed to implant debris induced inflammation and metal “allergy” testing services are becoming available. New pathways of implant debris-induced inflammatory reactions continue to be discovered, such as the “danger signaling” inflammasome pathway, which provides new targets for pharmaceutical intervention and improved implant performance.

Host response to orthopaedic implants debris is central to clinical performance. Implant loosening due to aseptic osteolysis accounts for over 75% of total joint arthroplasty (TJA) implant failure and is the predominant factor limiting the longevity of current TJAs. Other reasons for failure include infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and surgical error (3%). Recently, debris-induced immune reactivity, aseptic inflammation, and subsequent early failure have been reported to be as high as 4% to 5% at 6 to 7 years after surgery in current generation metal-on-metal TJA. This phenomenon has been attributed to local inflammatory responses to wear and corrosion products that are produced by articulating implant interfaces. Kerboull and colleagues found a 15% revision rate at 20 years, which was singularly correlated and predicted by a wear rate of greater than 0.1 mm per year of UHMWPE (ultra-high molecular weight polyethylene) acetabular liners. To date, wear remains the only positive correlate with aseptic osteolysis and implant loosening.

The degradation products of any orthopaedic implant include only two basic types of debris: particles and soluble (or ionic) debris. Particulate wear debris (of metals, ceramics, or polymers) range in size from nanometers to millimeters, while so called “metal ions” exist in soluble forms bound to serum protein (specifically or nonspecifically). The response to implant debris is dominated by local immune activation, e.g., macrophages. However, the effects of systemically elevated amounts of metallic and polyethylene wear particles, for example, in the liver, spleen, and other tissues of patients with failed reconstructions, have not been characterized...
been associated with remote toxicological or carcinogenic pathology to date.

**Particulate Debris Generation**

The relative amounts of debris produced by different kinds of articulating bearings are critical to any discussion of resultant biologic effects. Hard-on-hard material couples (i.e., metal-on-metal or ceramic-on-ceramic) generally produce smaller debris than do hard-on-soft material couples. Polymeric particles produced from implants generally fall into the range from 0.23 to 1 µm. Past investigations, primarily of UHMWPE wear debris in peri-implant tissues, have shown that 70% to 90% of recovered particulates were submicron (on a percentage of total number basis), with the mean size approximately 0.5 µm. Metal and ceramic particles (approximately 0.05 µm diameter) are generally an order of magnitude smaller than polymer particles. This translates to a theoretical increase in the yearly production of metal-on-metal particles of one to three orders of magnitude over that produced by metal-on-polymer articulating surfaces, such as polyethylene. Traditional particle-sizing techniques, such as scanning electron microscopy (SEM) or transmission electron microscopy (TEM), both number-based counting methods, have indicated that the majority of the wear (mass loss) from an implant is comprised of particles in the nanometer to submicron range. This understanding largely stems from the relatively low numbers of particles (e.g., 100s to 1000s) used in traditional number-based analysis techniques, such as SEM. New methodologies, such as low-angle laser light scattering (LALLS), essentially counts millions to billions of particles as they flow in front of a laser beam, which facilitates both a number and a volume understanding of particle distributions.

**Particulate Debris Reactivity Characterization**

It has been reported that the ingestion of small particles by cells occurs by endocytosis or pinocytosis for nanometer-sized particles (less than 150 nm). Larger particles (more than 150 nm to 10 µm) can be phagocytosed by a range of cell types, including osteoblasts, fibroblasts, endothelial cells, and macrophages. Macrophages are dedicated to phagocytosing debris and presenting antigens for T-cell recognition. Once ingested by macrophages and other peri-implant cells, a host of biologic reactions can occur, such as activation of T cells through antigen presentation, release of proinflammatory mediators, cytotoxicity, DNA damage, and oxidative stress. Macrophages are generally responsible for mediating debris-induced inflammation, leading to device loosening. Surprisingly, there are few guidelines on what type of debris is most bioreactive and only little agreement on which types of particles are most bioreactive. That said, there are a few general particle characteristics on which local inflammation has been shown to depend: 1. particle load (particle size and total volume), 2. aspect ratio, and 3. chemical reactivity.

**Greater Particle Load: Size and Volume Increase Inflammation**

Local inflammatory response generally is proportional to the particle load or concentration of phagocytosable particles per tissue volume. Particle load (dose) is dependent on both the average particle size and the amount (volume) of debris. This phenomena has been well established, with the first investigations over 30 years ago involving asbestos fibers. There is no research to suggest that particles should remain below a certain “guideline” aspect ratio.

**Elongated Particles (Fibers) Are More Proliferative Than Round Particles**

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**More Chemically Reactive Particles Are More Proliferative**

Generally, there is a growing consensus arising from investigations that have shown that metal particles are more proinflammatory or toxic, or both, when compared to polymers. Others have concluded that polymers are more proinflammatory than metals. This opinion is not unanimous. Others have concluded that polymers are more proinflammatory than metals.

**Controversial Particle Characteristics**

Does particle size matter? There seems to be a growing consensus that to produce an in vitro inflammatory response, particles need to be less than 10 µm, that is to say, within a phagocytosable range. Purportedly, particles with a mean size of 0.24 to 7.2 µm are generally the most proinflam-

### Table 1: Approximate Concentrations of Metal in Human Body Fluids and in Human Tissue with and Without Total Joint Replacements

<table>
<thead>
<tr>
<th>Human Body Fluids (x10⁻³ mM or x10 ppb)</th>
<th>Ti</th>
<th>Al</th>
<th>V</th>
<th>Co</th>
<th>Cr</th>
<th>Mo</th>
<th>Ni</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Normal</td>
<td>0.06</td>
<td>0.08</td>
<td>&lt; 0.02</td>
<td>0.003</td>
<td>0.001</td>
<td>*</td>
<td>0.007</td>
</tr>
<tr>
<td>TJA</td>
<td>0.09</td>
<td>0.09</td>
<td>0.03</td>
<td>0.007</td>
<td>0.006</td>
<td>*</td>
<td>&lt; 0.16</td>
</tr>
<tr>
<td>Synovial Fluid Normal</td>
<td>0.27</td>
<td>4.0</td>
<td>0.10</td>
<td>0.085</td>
<td>0.058</td>
<td>0.219</td>
<td>0.086</td>
</tr>
<tr>
<td>TJA</td>
<td>11.5</td>
<td>24</td>
<td>1.2</td>
<td>10</td>
<td>7.4</td>
<td>0.604</td>
<td>0.55</td>
</tr>
<tr>
<td>Whole Blood Normal</td>
<td>0.35</td>
<td>0.48</td>
<td>0.12</td>
<td>0.002</td>
<td>0.058</td>
<td>0.009</td>
<td>0.078</td>
</tr>
<tr>
<td>TJA</td>
<td>1.4</td>
<td>8.1</td>
<td>0.45</td>
<td>0.33</td>
<td>2.1</td>
<td>0.104</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Normal: Subjects without any metallic prosthesis (not including dental). TJA: Subjects with total joint arthroplasty. Data Not Available (*). Ti (titanium), Al (Aluminum), V (vanadium), Co (cobalt), Cr (chromium), Mo (molybdenum), Ni (nickel).
Implant debris can elicit inflammation, osteolysis, hypersensitivity, and neuropathy. Concerns about implant debris becoming carcinogenic and toxic, or either, persist.

**Inflammation**

Both soluble and particulate debris derived from Co-Cr-Mo alloy implants can induce monocyte-macrophage activation and secretion of proinflammatory IL-1β, TNF-α, IL-6, and IL-8, as well as up-regulate transcription factor NFκB and downstream proinflammatory cytokines. However, it remains unknown exactly how implant debris initiates these proinflammatory immune responses. While the NFκB pathway induction of TNF-α and IL-6 cytokines can occur via a variety of proinflammatory receptors and pathways, only recently has the potent proinflammatory cytokine IL-1β been shown to be produced by inflammasome danger-signaling in human macrophages. Inflammation activation of macrophages to secrete TNF-α, IL-1β, IL-6, and PGE2 stimulate differentiation of osteoclast precursors into mature osteoclasts and increase peri-prosthetic bone resorption, which is not replaced by new bone (Fig. 1). Not only does this activation of local (and systemic) inflammation result in a decreased osteoblast deposition and increased osteoclast digestion of bone, wear-debris particles have been shown to affect and compromise mesenchymal stem-cell differentiation into functional osteoblasts. Particles can inhibit collagen synthesis by mature osteoblasts and induce apoptosis of osteoblasts.

**Metal Ions (Soluble Debris)**

There is continuing concern regarding the release of soluble metal ions [aluminum (Al), chromium (Cr), vanadium (V), cobalt (Co), and titanium (Ti), among others], which bind to proteins, remain in solution, and disperse into the surrounding tissues, bloodstream, and remote organs. Normal human serum levels of prominent implant metals are within the following ranges: 1 to 10 ng/ml Al, 0.15 ng/ml Cr, less than 0.01 ng/ml V, 0.1 to 0.2 ng/ml Co, and less than 4.1 ng/ml Ti. Following TJA, levels of circulating metal have been shown to increase (Table 1). Patients with Ti-base alloy implants have demonstrated elevated titanium, aluminum, and vanadium levels in joint pseudocapsules (with up to 200 ppm of Ti, six orders of magnitude greater than that of controls, 880 ppb of Al, and 250 ppb of V). Spleen aluminum levels and liver titanium concentrations can also be markedly elevated in patients with failed titanium-alloy implants.

Cobalt, chromium, vanadium, and possibly nickel are essential trace metals in that they are required for normal homeostasis. In excessive amounts, however, cobalt has been reported to lead to polycythemia, hypothyroidism, cardiomyopathy, and carcinogenesis; chromium can lead to nephropathy, hypersensitivity, and carcinogenesis; nickel can lead to eczematous dermatitis, hypersensitivity, and carcinogenesis; and vanadium can lead to cardiac and renal dysfunction, and has been associated with hypertension and manic-depressive psychosis. Despite the potential toxicologic possibilities, the association of metal release from orthopaedic implants with any metabolic, bacteriologic, immunologic, or carcinogenic toxicity remains speculative.

**Debris Bioreactivity**

Implant debris can elicit inflammation, osteolysis, hypersensitivity, and neuropathy. Concerns about implant debris becoming carcinogenic and toxic, or either, persist.

**Hypersensitivity: Metal Allergy**

All metals corrode in vivo and the released ions can activate the immune system by forming complexes with native proteins. Nonbiodegradable polymeric biomaterials [including PMMA (polymethylmethacrylate) bone cement] have not been intensely investigated or implicated in case or group studies as sources of hypersensitivity type immune responses. Metals known as sensitizers include beryllium, nickel, cobalt, and chromium, while occasional responses have been reported to tantalum, titanium, and vanadium. Nickel is the most common metal sensitizer in humans (approximately 14% of people show dermal reactivity to Ni), followed by cobalt and chromium. The specific T-cell subpopulations, the cellular mechanism of recognition and activation, and the antigenic metal-protein determinants created by these metals, remain incompletely characterized.

**Testing for Metal Sensitivity**

Current testing for metal sensitivity involves proliferation testing (LTT, lymphocyte transformation testing) and patch testing. While general patch testing protocols and commercial kits (e.g., TrueTest™, Glaxo Dermatology, Research Triangle Park, North Carolina) do exist for a variety of commonly antigenic substances, there is continuing concern about the applicability of skin testing for the study of immune responses to implants regarding the questionable equivalence of dermal Langerhans cells to peri-implant antigen presenting cells or the possible induction of hypersensitivity in a previously insensitive patient, or both.

The use of proliferation testing has been well established as a method for testing hypersensitivity in a variety of clinical settings. Some investigations indicate that metal sensitivity can be more readily detected by LTT than by dermal patch testing. Such reports seem to indicate LTT testing may be equally or better suited for the testing of implant-related sensitivity than dermal patch testing. In vitro proliferation testing of metals (LTT) involves measuring the proliferative response of lymphocytes obtained from peripheral blood
by routine blood draw and 7-day incubation of PBMCs (peripheral blood mononuclear cells) with different metals. Proliferation testing has been well established as a method for testing metal sensitivity in a variety of clinical settings.32

Lymphocyte Transformation Testing Methods
Research-based testing services are available for physicians concerned about patients with a history of metal sensitivity or with aseptic TJA inflammation of unknown etiology; Orthopedic analysis, Inc., at Rush University is one such facility. In this testing, lymphocytes isolated from a blood draw are cultured for 1 week in the presence of metals [0.01 and 0.1 mM Al, Co, Cr, Mo (molybdenum), Ni, V, and Zr (zirconium)] and measured for a response. This assay facilitates a dose response quantification of metal-induced hypersensitivity responses in terms of gen-

Figure 1 Debris-induced inflammation is primarily mediated by macrophages, where macrophages ingest debris which results in the release of proinflammatory cytokines that affect local cell types and induce a widening zone of soft-tissue damage and inflammation (Courtesy of BioEngineering Solutions, Inc., Oak Park, Illinois).
eralized lymphocyte reactivity (i.e., proliferation). Issues of sensitivity and specificity remain unresolved, as well as how implant performance is related to positive reactivity results. Metal-specific reactivity is gauged by comparing non-treated to treated lymphocytes from the same individual and categorized using the following general criteria: two- to four-fold response equals mild reactivity, five- to eight-fold equals moderate reactivity, and greater than eight equals high reactivity.

Case Studies in Metal Implant-Related Metal Sensitivity

Over the past 25 years, growing numbers of case reports have linked immunogenic reactions with the adverse performance of metallic cardiovascular, orthopaedic, plastic, surgical, and dental implants, many of which have required device removal. Hypersensitivity symptoms include severe dermatitis, urticaria (intensely sensitive and itching red, round wheels on the skin), and vasculitis (patch inflammation of the walls of small blood vessels), or any alone. These symptoms have been linked with the relatively more general phenomena of metallosis (metallic staining of the surrounding tissue), excessive periprosthetic fibrosis, and muscular necrosis. Generally, there are more case reports of hypersensitivity reactions associated with stainless steel and cobalt alloy implants than with titanium alloy components.

Cohort Studies of Implant-Related Metal Sensitivity

Data (from select investigations) regarding the prevalence of metal sensitivity are compiled in Figure 2. The average prevalence of metal sensitivity among patients with a failed or poorly functioning implant (as judged by a variety of criteria) using the n = 7 investigations (Fig. 2) is approximately 60%. Overall, the prevalence of metal sensitivity in patients with failed or failing implants is approximately six-times that of the general population and approximately two- to three-times that of all patients with metal implants. Failures of total hip prostheses with metal-on-metal bearing surfaces have been associated with greater prevalence of metal sensitivity than similar designs with metal-on-UHMWPE bearing surfaces.33,34 The majority of investigators have concluded that metal sensitivity can be a contributing factor to implant failure. The importance of this line of investigation is increasing as the use of metal-on-metal arthroplasty implants grow and as expectations of implant durability and performance increase.

Debris-Induced Carcinogenicity

The carcinogenic potential of the metallic elements used in TJA remains an area of concern, but to date remains speculative. The carcinogenic potential of orthopaedic implant materials has been established in animal studies. High doses of serum cobalt, chromium, or nickel content associated with metal internal fixation implants have been shown to produce small increases in rat, dog, and cat sarcomas, including lymphomas, osteosarcomas, and fibrosarcomas. Recent epidemiologic studies have found no significant increase in leukemia or lymphoma in humans. However, these studies have yet to be conducted on people with metal-on-metal prostheses. The association of metal release from orthopaedic implants with carcinogenesis
remains conjectural, since causality has not been definitely established in human subjects.

**Debris-Induced Toxicity**

Clinically, any toxic effects of metal released from implants, either locally or systemically, have not been established. In vitro, investigations of implant alloys using selected metals and selected cell lines generally agree (rather predictably) that high concentrations of metals can negatively impact cellular function. Clinically nontolerable levels of metal have not been established for implants, and the degree to which soluble metals are able to contribute to clinical pathology is not well understood. However, metal-induced toxic effects should not be confused with the well-established proinflammatory effects of metal particles.

**Conclusions**

Released implant debris induces inflammation and osteolysis and limits implant performance. Yet it remains unknown which patients are more predisposed to implant debris-induced inflammation and why they are more reactive. While parameters such as total surface area and particle size do matter, the most important determinant of inflammation is particle load (assuming particles are under 10 µm and able to be phagocytosed by cells). However, it is important to note that not all particles are not equally bioreactive. The few general guidelines associated with particle bioreactivity are:

1. Greater numbers of particles are more proinflammatory. The inflammatory response is proportional to the particle load (the concentration of phagocytosable particles per tissue volume, which is characterized by both the size distributions and the total mass).  
2. Elongated particles (fibers) are generally more proinflammatory than round particles. This phenomena has been well established, with the first such investigations over 30 years ago involving asbestos fibers.  
3. More chemically reactive particles are more proinflammatory. There is a growing consensus of investigations that have shown metal particles are more proinflammatory when compared to polymers in vivo. Implant debris activates macrophages to secrete TNF-α, IL-1β, IL-6, and PGE2, which stimulates differentiation of osteoclast precursors into mature osteoclasts and increases peri-prosthetic bone resorption, which is not replaced by new bone.

With the growing number of people receiving metal-on-metal implants and the issue of metal sensitivity growing, research-based testing services are available for physicians concerned about patients with a history of metal sensitivity or with aseptic TJA inflammation of unknown etiology. Given that modern total joint replacement implant designs have been in use for more than half a century, concerns about neuropathy, toxicity, and carcinogenicity have been largely mitigated, yet remain incompletely addressed. New pathways by which sterile challenge agents such as implant debris lead to inflammatory reactions continue to be discovered, such as the “danger signaling” and the inflammasome pathway. Consequently, new therapies and testing are continually being developed to mitigate the subtle, low-grade local inflammation that leads to eventual poor implant performance.

**Disclosure Statement**

Nadim J. Hallab, Ph.D., is the principle of Orthopedic Analysis Inc., a metal allergy testing company, and thus has a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment and stock ownership.

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