Supplement

The Inflammatory Effects of Breast Implant Particulate Shedding: Comparison With Orthopedic Implants

Nadim James Hallab, PhD; Lauryn Samelko, PhD; and Dennis Hammond, MD

Aesthetic Surgery Journal
2019, Vol 39(S1) S36–S48

DOI: 10.1093/asj/sjy335
www.aestheticsurgeryjournal.com
OXFORD UNIVERSITY PRESS

Abstract

Currently, there is a dearth of information regarding the degree of particle shedding from breast implants (BIs) and what are the general biological consequences of BI debris. Thus, it is unclear to what degree BI debris compromises the long-term biological performance of BIs. For orthopedic implants, it is well established that the severity of biological reactivity to implant debris governs long-term clinical performance. Orthopedic implant particulate debris is generally in the range of 0.01 to 100 μm in diameter. Implant debris-induced bioreactivity/inflammation is mostly a peri-implant phenomenon caused by local innate immune cells (eg, macrophages) that produce proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, interleukin-6, and prostaglandin 2 (PGE2). In orthopedics, there have been few systemic concerns associated with polymeric implant debris (like silicone) other than documented dissemination to remote organs (eg, liver, spleen, etc.) with no known associated pathogenicity. This is not true of metal implant debris where normal (well-functioning) implants can induce systemic reactions such as delayed type hypersensitivity. Diagnostic analysis of orthopedic tissues has focused on innate (macrophage mediated) and adaptive (lymphocyte-mediated hypersensitivity) immune responses. Orthopedic implant debris-associated lymphocyte cancers have not been reported in over 40 years of orthopedic literature. Adaptive immune responses such as hypersensitivity reactions to orthopedic implant debris have been dominated by certain implant types that produce specific kinds of debris (eg, metal-on-metal total joint prostheses). Orthopedic hypersensitivity responses and atypical BI bioreactivity such as BI-associated anaplastic large cell lymphoma share cross-over markers for diagnosis. Differentiating normal innate immune reactivity to particles from anaplastic large cell lymphoma reactions from delayed type hypersensitivity reactions to BI-associated implant debris remains unclear but vital to patients and surgeons.

Editorial Decision date: December 19, 2018.

It is well established that implant debris causes local inflammation, limiting the long-term performance of over 1 million orthopedic total joint arthroplasties implanted each year in the United States.[1,2] What is less known is the extent and untoward effects of breast implant (BI) debris. Orthopedic implant debris primarily induces local innate immune responses (ie, monocytes/macrophages activate nuclear factor kappa B [NFκB] and secretion of interleukin [IL]-1β, tumor necrosis factor [TNF]α, IL-6, and IL-8[3-8]), resulting in localized inflammation.[3,9] Over the long term, orthopedic implant debris causes inflammation that eventually results in bone loss and loss of orthopedic implant fixation.[10] This phenomenon of bone loss is called aseptic osteolysis and results in pain and premature loosening of orthopedic implants.[11-13] This review will focus on what is known in orthopedics and what may apply to the sequala of BI debris bioreactivity in terms of biomaterial degradation, dissemination of debris, and consequent local/systemic effects.

Dr Hallab is a Professor and Dr Samelko is an Instructor and Fellow, Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL. Dr Hammond is a plastic surgeon in private practice in Grand Rapids, MI.

Corresponding Author:
Dr Nadim James Hallab, PhD, Department of Orthopedic Surgery, Rush University Medical Center, 1735 W Harrison MC107, Chicago, IL 60612, USA.
E-mail: nhallab@rush.edu

Orthopedic Particulate Debris

Different types of joint arthroplasty implants produce different kinds and amounts of implant debris, with different sizes and shapes dependent on the type of implant and material. For instance, hard-on-hard articulating joint replacement materials such as metal-on-metal hip replacements generally produce smaller sized (nanometer to submicron) round debris, whereas traditional metal-on-polymer bearings produce larger (approximately micron sized) debris that is more elongated in shape (Figure 1). Histological analysis of peri-implant tissues have identified different types and sizes of particles.[14-20] Implant debris generated from joint replacements with metal-on-poly bearings are comprised of polymer particles that generally fall into the range from 0.23 to 1 μm, with little metallic debris.[21-23] Debate continues regarding exactly what size particle produces the greatest inflammatory response.[24-27] Purportedly, particles with a mean size of 0.2 μm to 10 μm are generally the most proinflammatory. However, within this range there is no consensus as to which specific size(s) and/or dose of particles (particles/cell or particles/tissue volume) are maximally inflammatory[26,28-30] in vivo, because there is a plethora of variables, including composition of material, dose of particles, shape of the materials, etc. Shape of particulate debris is also important. Elongated (fibers) particles are more proinflammatory than round particles,[31,32] a fact well established over 30 years ago with studies of asbestos fibers.[33] However, at what aspect ratio (aspect ratio: length to width) in the transition from round particles to fibers elevated inflammation is generally initiated remains unknown. Thus, to date, there is no "guideline" aspect ratio for implant debris particles to remain below. The composition of implant particulate is also important because more chemically reactive particles are more proinflammatory. Metal particles are more proinflammatory compared with other materials such as polymers and ceramics.[34-37]

Although there is a dearth of information regarding the release of implant debris from current generation BIs, some reports have shown both the release and biological response of silicone particulate from BIs.[38-43] This establishes the fact that debris can come from BIs, interact locally, and is associated with some degree of immune response such as granulomas.[38-43] Additionally, some study of BI surfaces has shown BI particles < 100 μm in diameter on the surface of textured BIs.[44] Recent evidence of similar tissue embedded silicone particles were found released from a BI, where histology was performed due to suspicion of so-called BI-associated alloplastic large cell lymphoma (BIA-ALCL) and consequent pathological confirmation (Figure 2). Co-localization of implant debris and immune reactions to that implant debris is difficult histologically to identify due to statistical 2-dimensional sampling of large 3-dimensional tissue volumes. The histology shown in Figure 2 demonstrates lymphocyte accumulation in the presence of a large BI debris particle. This pathology is also consistent with histology observed around BIs where implant-related adaptive immune responses such as delayed type hypersensitivity (DTH) have been suspected or implicated.[45-51] In a case study of capsule biopsies, Dargan et al reported a similar atypical lymphoid reaction to a removed textured BI demonstrating large lymphoid cell reactions consistent with delayed hypersensitivity reaction; patch testing to samples of the implant were positive.[48]

Systemic Particle Distribution

Particles from orthopedic implants have been found systemically beyond the local environment of the implant periprosthetic tissue and are primarily in the submicron size range. Numerous cases exist of metallic, ceramic, or polymeric wear debris from hip and knee prostheses in regional and pelvic lymph nodes along with the findings of gross dark staining by metallic debris, fibrosis (buildup of fibrous tissue), lymph node necrosis, and histiocytosis (abnormal function of tissue macrophages). Metallic wear particles have been detected in the para-aortic lymph nodes in up to 70% of patients with total joint replacement components. Thus, lymphatic transport is likely a major route for dissemination of debris where particles migrate via perivascular lymph channels as free or phagocytosed particles within macrophages. Within lymph nodes, disseminated particles are mostly submicron in size. However, some metallic particles as large as 50 μm and polyethylene particles as large as 30 μm have also been found. These particles can further travel to the liver and spleen where they are found within macrophages or, and in some cases, in nodules of inflammatory tissue granulomas throughout the organs. The size of metallic particles are nearly an order of magnitude less in the liver and spleen than those in lymph nodes, indicating that some additional filtration occurs before the particles end up in those organs. This is not overly concerning because the cells of liver, spleen, and lymph nodes normally accumulate small amounts of a variety of foreign materials without apparent clinical significance. However, accumulation of excess particles can induce nodules of inflammatory tissue (granulomas) or granulomatous lesions in the liver and spleen (Figure 3). The level of reaction to particles in the liver, spleen, and lymph nodes is likely modulated, as it is in other tissues, by: (1) the number of particles (dose); (2) their rate of accumulation; (3) the duration that they are present; and (4) the biological reactivity of cells to these particles (size and materials composition).

It is well established that when ruptured, BI silicone debris will be disseminated systemically and cause local and systemic pathologies, such as granulomas.[52-54] This

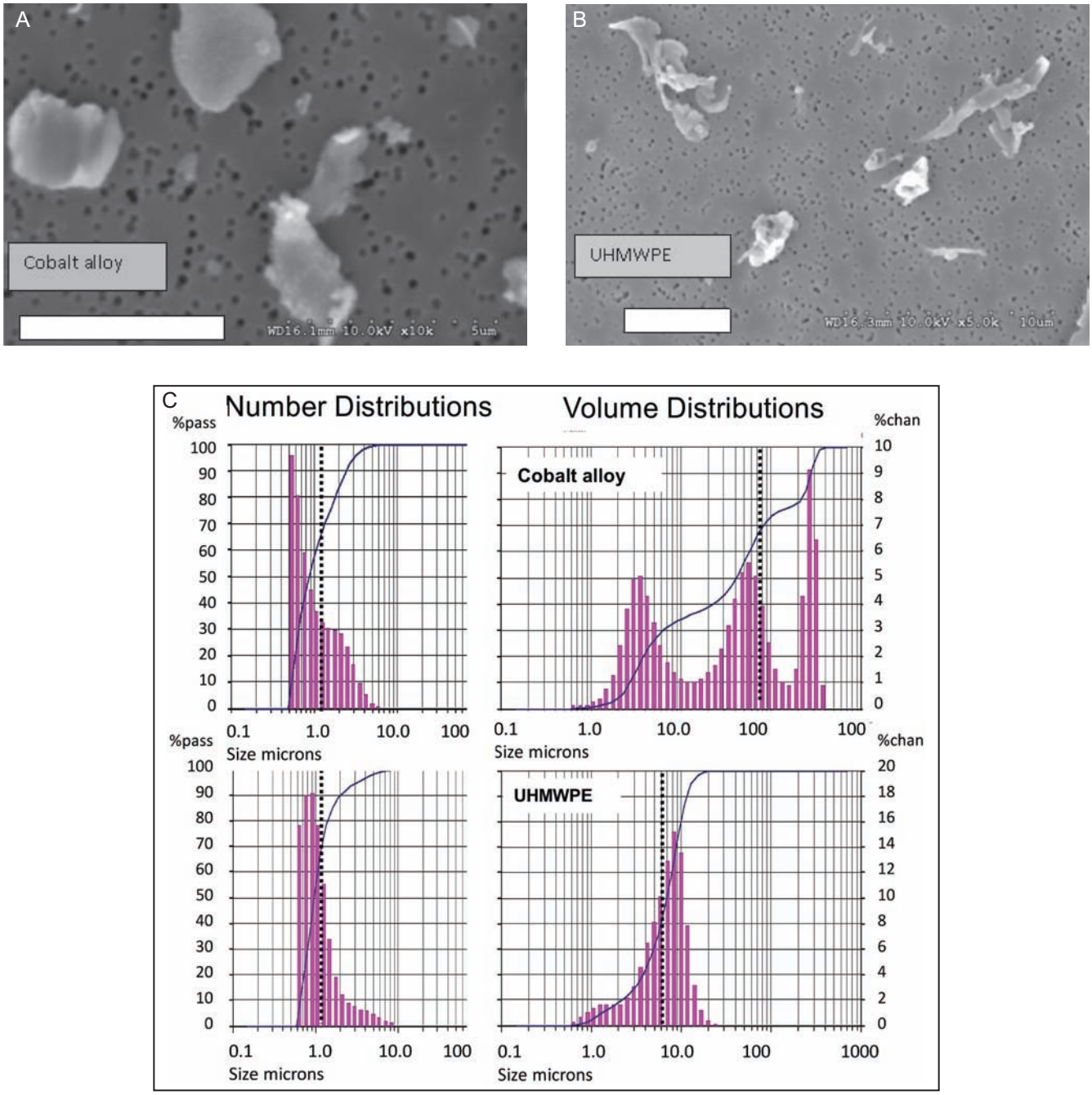

Figure 1. Implant debris from metal (A) cobalt alloy (B) polymeric (ultra-high molecular weight polyethylene [UHMWPE]) debris. Note: Bar = 5 µm. Characterization of implant debris employing laser light scattering enables us to count millions of particles as they flow by in front of a laser facilitating both (C) number-based and volume-based distributions. Here, a low angle laser light scattering (LALLS) analysis demonstrates that similar size distributions based on the percentage of total number of particles in each size range (number-based) can have very different distributions when expressed as particle size percentage of total volume. Note: The x-axis is particle diameter and the y-axis is the percentage of total number of particles in each size range or the percentage of total mass in each size range (courtesy of and with permission from BioEngineering Solutions, Inc.).

was evidenced dramatically in case reports such as one of systemically developed granulomas with histologically identified silicone debris and secondary morbidities such as vision loss. This pathology was caused by a ruptured BI combined with cosmetic silicone injections, which disseminated to remote locations such as the patient's

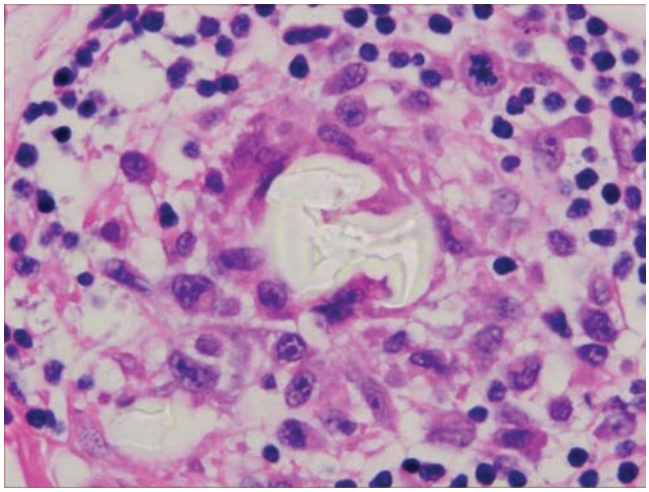

Figure 2. A histological section of peri-breast implant tissue demonstrates the presence of a large breast implant particle (> 20-µm diameter) shed and encapsulated by macrophages and surrounded by lymphocytes from a case of suspected breast implant-associated anaplastic large cell lymphoma (courtesy of and with permission from Dr. Roberto Miranda, MD Anderson Cancer Center).

arms. However, upon removal of the implant and debridement and immunosuppressive treatment, there was dramatic granuloma regression.[53] Other systemic pathologies, such as late-onset systemic sclerosis, have been reported associated with BI rupture.[54] However, it is important to note that there is little to no evidence of systemic BI debris dissemination or pathology associated with nonruptured BIs.

Local Inflammatory Effects of Implant Debris

Produced implant debris are relatively sterile, inert, and generally do not "look" like a pathogen in a molecularly recognizable pattern yet cause an immune response through mechanisms such as the inflammasome danger signaling pathway (Figure 4).[55] Similar to pathogen-associated molecular patterns, nonpathogenic-derived stimuli were found to activate immune cells via the inflammasome pathway, activated by danger associated molecular patterns.[56] Nonbiologically derived danger signals include cell damaging stimuli such as UV light, particulate adjuvants present in modern vaccines,[57,58] and, as it turns out, implant debris.[59] When implant particles activate the inflammasome pathway, cells release IL-1β, IL-18, IL-33, and other proinflammatory cytokines. This happens as follows:

Implant debris → phagocytosis via macrophages → lysosome damage → reactive oxygen species → inflammasome activation (NALP3/ASC) → caspase-1 → secretion of IL-1β and other IL-1-family cytokines (Figure 4)

Once "ingested" by immune cells, particles (or danger associated molecular patterns, such as asbestos and implant debris, etc.) induce some degree of lysosomal destabilization. Lysosomal destabilization leads to the release/rupture of lysosome contents that include the protease and acid-rich extreme environment inside lysosomes used to break down ingested particles/bacteria, etc. This inflammasome activation then activates Caspase-1, which converts cytokines such as pro-IL-1β and pro-IL-18 (and others) into their active mature form.

BI-like silicone particles have been found to induce similar local innate inflammation with signature inflammatory cytokines such as IL-1β and TNF-α in animal models. However, the resulting inflammatory responses were significantly less than metal implant particles employing the same animal models.[8,60] In orthopedics, the single case study of a silicone-based spinal implant resulted in histopathologic results consistent with a foreign-body reaction (ie, a silicone granulomatous reaction).[61] The author points out this case of biological reaction to spinal cord stimulator cover particle shedding is consistent with other cases of foreign-body reactions to silicone particles, including BI particles.[62-64] Differences in innate immune cell behavior such as resident tissue macrophages (histiocytes) between the breast and other areas such as the hip or knee can be influenced by their environment and thus may be more (or less) likely to induce inflammatory responses to particle challenge. However, very little is known of these site-specific differences, and it remains an active area of immunological research. Additionally, other factors such as the use of acellular dermal matrix will undoubtedly influence the inflammatory environment where reports demonstrate the ability of acellular dermal matrix (ADM) to decrease inflammation.[65] However, with this type of treatment or material, the possibility of hypersensitivity responses remains present.

Hypersensitivity

Over the past 40 years, many reports have documented adaptive immune responses (metal allergy- or hypersensitivity-type responses) to orthopedic implant debris. This specific adaptive immune response is characterized by antigen activation of sensitized T-helper lymphocytes releasing various cytokines, which results in the further recruitment of lymphocytes and activation of macrophages. These metal-activated T cells, along with participating antigen-presenting cells, secrete a variety of cytokines that activate other innate immune cells in an autocrine and paracrine manner. These cytokines and chemokines include IL-17, IFN-γ, TNF-α, and migration inhibitory factor. Case and group reports of orthopedic implant hypersensitivity relate the release of implant debris to specific responses such as severe dermatitis, urticaria,

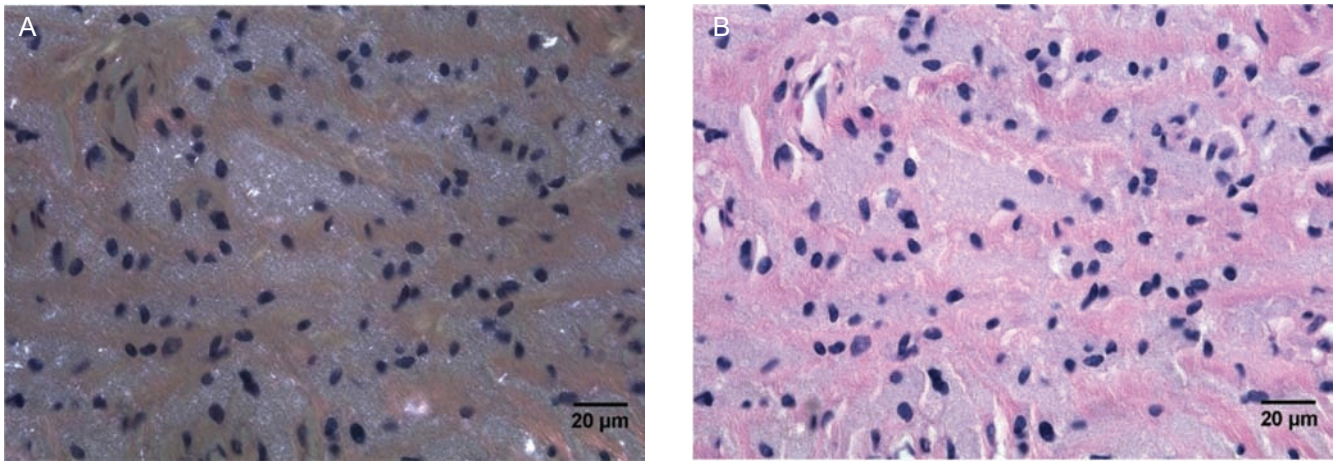

Figure 3. Polymeric particles in macrophages can be readily detected under polarized light. (A) Transmitted light and (B) polarized light micrographs show fine particulate polyethylene in a sheet of macrophages in the hip joint capsule from a well-functioning total hip replacement with a Cobalt-Chromium-Molybdenum (CoCrMo) stem with CoCrMo head and cross-linked polyethylene acetabular liner in service for 19 years (original magnification 600 × courtesy of and with permission from Deborah Hall and Robert Urban, Department of Orthopedic Surgery, Rush University Medical Center).

vasculitis,[66-71] and/or nonspecific immune suppression.[72-76] BI-related hypersensitivity responses have not been as widely identified and have largely been relegated to case reports.[45-51] However, these case reports have pointed to the possibility of this phenomenon happening on a wider scale and associated with the so-called red breast syndrome, where corticosteroid or similar antiinflammatory medications have been forwarded as treatment options.[46]

Incidence of Hypersensitivity Responses Among Orthopedic Patients with Metal Implants

For orthopedic implants, many group studies have established a solid correlation between implant related DTH responses and implant performance. The incidence of metal sensitivity among people with well-functioning implants is about twice as high as that of the general population, approximately 25% vs 10% (Figure 5). Moreover, the incidence of metal sensitivity among people with a "failing" implant (in need of revision surgery) or with a well-performing metal-on-metal articulating implant is approximately 50–60% (Figure 5). Cohort studies over the past 30+ years have indicated a strong correlation between metal implants and metal sensitivity,[35] clearly indicating that metal exposure and metal sensitivity can be a contributing factor to implant failure (Figure 5).[77-79] Studies involving allergy and hypersensitivity responses to BIs have been conducted.[45-51,80-82] However, the degree to which innate or adaptive immune responses are present in BI patient populations remains unknown.

Testing for Metal Sensitivity

Given the relatively small amount of implant debris from nonarticulating, nonloaded BIs (vs total joint arthroplasty), the concern regarding this type of debris is focused on a very select subset of people who are predisposed to exuberant immune responses to implant debris. There are methods for diagnosing implant debris-specific immune reactivity, such as metal lymphocyte transformation testing for metal orthopedic implant debris. Past case studies of BI-related hypersensitivity responses have been limited to patch testing.[45-51] There are only 2 accepted testing methods for diagnosing implant-related DTH responses: skin testing (ie, so-called patch testing) and cell culture blood testing (called metal lymphocyte transformation testing). Well-established patch testing commercial kits exist for some implant materials but not for BI materials such silicone or polyurethane.[77,83] Although studies have shown an association with BIA allergy-type responses (IgE presence and mast cells) and BIA-ALCL in certain types of BIs,[82] currently there is no way to test specific types of BI surfaces of similar composition (eg, silicone). There is continuing concern about sensitizing patients utilizing commercial or improvised patch testing, given that administrating high concentrations of challenge agents (silicone or metal salt solutions) in petroleum jelly on the skin for 48 hours can be used to sensitize animals in DTH model studies.[84-86] In vitro metal allergy testing, called lymphocyte proliferation testing (also known as lymphocyte transformation test [LTT]), involves measuring the proliferative response of lymphocytes after they are activated by an antigen. Several investigations indicate that metal allergy can be more readily detected by LTT than by dermal patch testing.[87-89] Thus, given the growing number of studies employing 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.[89-96] Commercially available LTT testing has not been established for silicone or polyurethane implant materials to date, and current

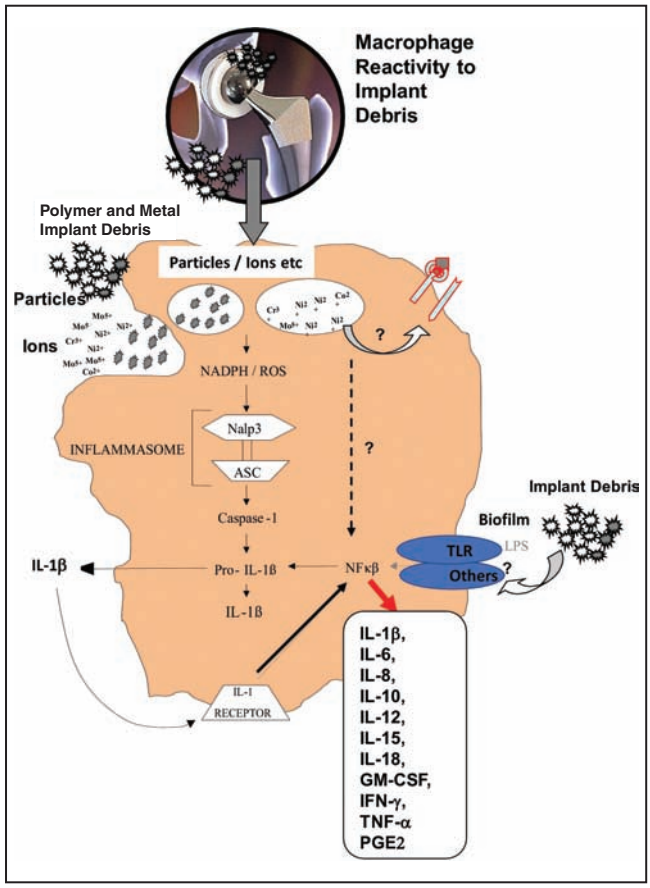

Figure 4. Numerous cytokines from peri-implant cells reacting to implant debris can negatively affect bone turnover. Interleukin (IL)-1, interleukin-6, and tumor necrosis factor (TNF)-α are some of the most potent cytokines responsible for increasing bone loss and enhancing proinflammatory responses (picture courtesy of and with permission from BioEngineering Solutions Inc). Metal-induced inflammasome activation occurs when soluble and/or particulate implant debris activates the Nalp3 inflammasome when chemicals inside intracellular compartments used to digest foreign material (such as phagosomal NADPH-induced reactive oxygen species and/or Cathepsin B) leak out of these compartments in an event called phagosomal destabilization. The inflammasome complex, Nalp3-ASC, then induces the activation of caspase-1, which in turn allows mature interleukin-1β to be secreted. Interleukin-1β is a very potent proinflammatory cytokine that exerts an autocrine and paracrine effect that induces a broader, more potent inflammatory response (eg, activation of NFκB proinflammatory responses) (courtesy of and with permission from BioEngineering Solutions, Inc.). Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; NADPH, nicotinamide adenine dinucleotide phosphate; PGE2, prostaglandin 2; ROS, reactive oxygen species; TLR, toll like receptor.

efforts are underway to develop this testing for BI materials (Orthopedic Analysis LLC, Chicago IL).

In orthopedics, histological evidence of hypersensitivity has been termed aseptic lymphocytic vasculitis-associated lesions (ALVAL), which has been coined to describe the histopathology that is observed for activated lymphocyte accumulations around implants. The use of "vasculitis" in this term may not be accurate, because there is little vessel inflammation and histology demonstrates blood vessel thickening associated with lymphocyte tissue trafficking, activation, and perivascular lymphocyte accumulation.[97,98] There is noteworthy similarity between orthopedic implant ALVAL (histological evidence of hypersensitivity) reactions and that of ALCL reactions around BIs (Figures 3 and 6). Histological analysis of ALVAL lymphocyte accumulations demonstrates activated proliferative T cells (and to some extent B cells) that are CD3+ and CD4+ and show KI-67 antigen marker of lymphocyte proliferation[99-101] in vivo and have shown activation markers such as CD25+ and CD69+ reactivity when challenged in vitro by implant debris.[102] This is particularly relevant to ALCL associated with BIs, because similar lymphocyte histology and activation markers CD30+ (KI-1) have been shown histologically in peri-BI tissues.[39] Complicating differential diagnosis and delineation of these responses are reports of CD30+ histology in hypersensitivity-like responses.[103-108] Conversely, case, group, and epidemiologic studies of failing or failed orthopedic implants have not been associated with lymphocyte-associated cancers. This is true despite intense surveillance of orthopedic implants that have failed due to metal debris and have been associated with proliferating lymphocyte accumulations (ie, metal-on-metal bearing total hip implants).[99-101] Thus, histological and diagnostic analysis of orthopedic tissues has focused on lymphocyte-mediated adaptive (hypersensitivity) immune responses to investigate the presence and activation of lymphocytes in the peri-implant space. Conversely, immunohistochemical markers for lymphocyte-associated cancers have not been reported in over 40 years of orthopedic literature (eg, CD30 as a marker of lymphocyte-associated malignancy around BIs has not been investigated with orthopedic implant-associated ALVAL). Complicating the issue further is that activation markers such as CD30 used to diagnose ALCL are expected with activated lymphocytes to implant debris. In the case of metal implant debris, CD30+ would likely be indicative of DTH adaptive immune responses and not malignancy, as has been reported in the context of BIs as well.[81]

There have been case reports of malignancies associated with BIs and orthopedic implants.[109-111] However, there have been far more case reports of similar malignancies arising in similar site-specific locations such as the hip without the presence of a orthopedic implant.[112-116] Thus, without epidemiologic or group incidence data, it is important to note that association does not mean correlation. Additionally, even in the case of correlation, it does not mean causal. Thus, association between disease state and implant in case reports is far from evidence of causality, which is particularly pertinent because the mechanism

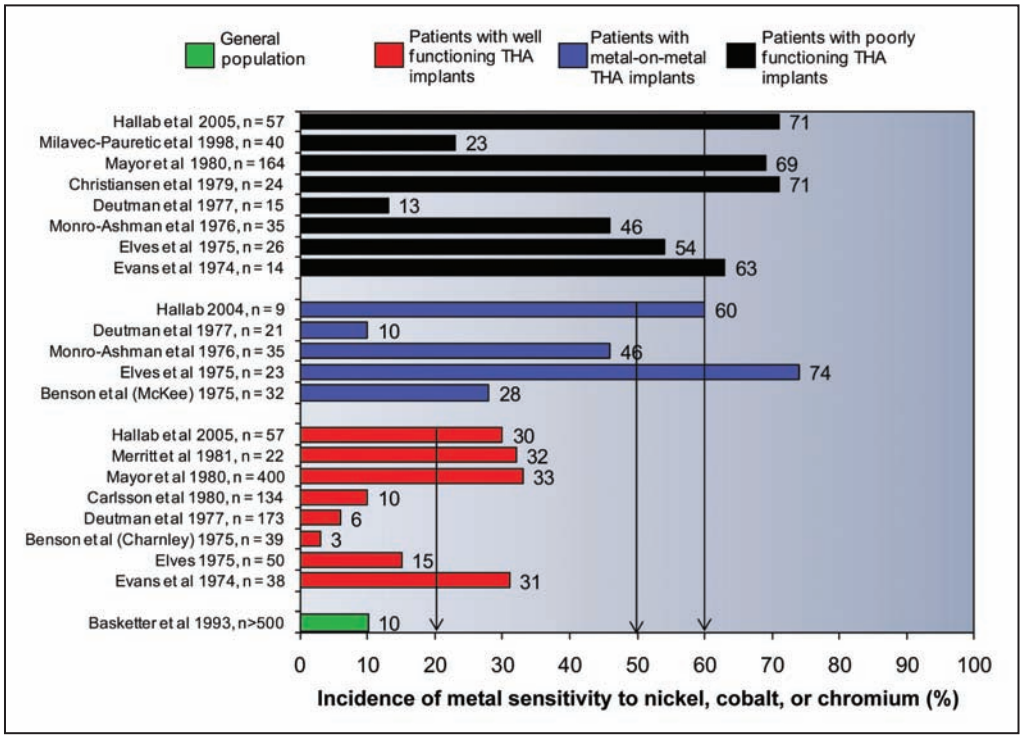

Figure 5. A compilation of investigations showing the averaged percentage of metal sensitivity among the general population, people with well-functioning implants, people with metal-on-metal implants, and people with failing implants (prior to getting them revised). Metal incidence rates include a positive response to allergy testing for nickel, cobalt, and/or chromium. All patients were tested by means of a patch or metal-lymphocyte transformation test (courtesy of and with permission from Orthopedic Analysis LLC). Abbreviation: THA, total hip arthroplasty.

by which BI debris would induce malignancy (either directly or indirectly) is unknown and has not been reproduced in vitro or in vivo in animal models. There is no known theory or precedent why silicone or polyurethane particles would be genotoxic and capable of directly inducing malignancy. Indirect mechanisms of BI debris-induced genotoxicity theoretically include (1) providing a colonization site for an existing systemic disease; (2) providing an immunosuppressive environment that decreases immunosurveillance of malignancy; and (3) providing a proinflammatory (lymphocyte-specific) environment that over time leads to unregulated proliferation and could result in BIA-ALCL. This latter scenario would presuppose that a significant portion of BI patients develop lymphocyte reactivity to their BI and that a small subset would progress to unregulated lymphocyte malignancy (ie, BIA-ALCL). This latter theory has been proposed by others and supported in case studies.[117]

Differences in the reasons for initial implant placement between BIs and orthopedic implants may lead to different approaches to histopathological analysis and differentially biased conclusions. For orthopedic implants such as total hip arthroplasties, it is rare that a total hip arthroplasty (THA) (compared with BI) would be used following local cancer treatment. Relative to orthopedic implants, the high incidence of BIs used for reconstruction following cancer-associated mastectomy may result in an inherent bias towards ALCL type histopathological analysis and away from other possible responses such as ALVAL-associated DTH responses typical for orthopedic implants. Several reports have shown no correlation between orthopedic implants and any increased incidence of cancer in human orthopedic patients.[118-120] Additionally, we have reported that peri-implant cells tested in vitro become toxic prior to significant DNA strand breaks when tested at increasing concentrations of metal ions found in implants.[121,122] Thus, oddly, to date there is no analogue of BIA-ALCL in orthopedic implants in general. However, site-specific immune reactivity has been well established and may be involved (peri-glandular vs non-peri-glandular tissue). Additionally, no reported studies have demonstrated an increased incidence of cancer (ie, ALCL analogues) in orthopedic implants identified as infected. Continued monitoring and robust and long-term epidemiological studies are required to fully understand any increased risk of genotoxicity from orthopedic and BI debris.[73,120,123,124] Despite continued multi-center studies of registry data analysis in

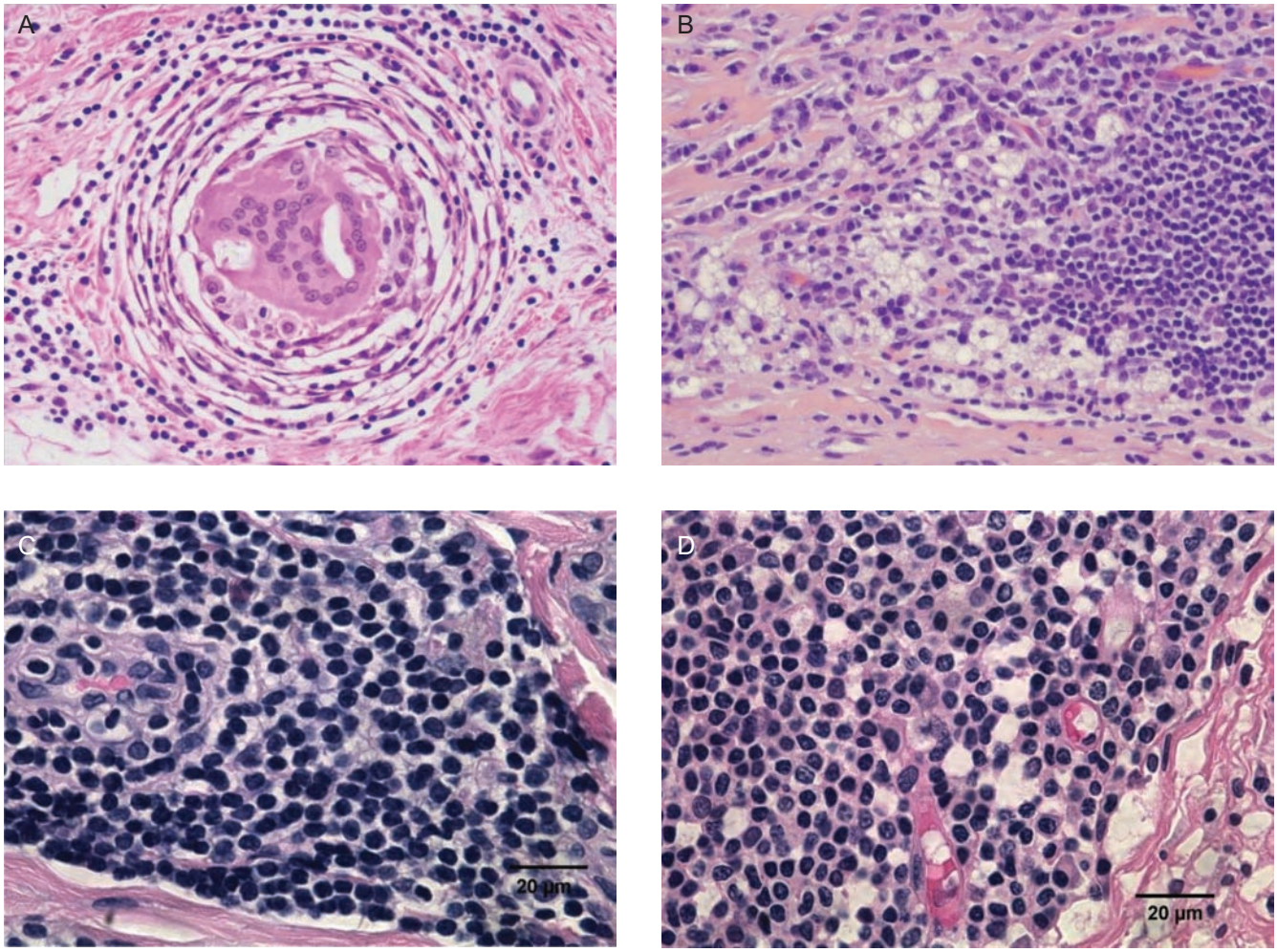

Figure 6. Histological sections from both (A,B) breast implant and (C,D) total hip arthroplasty peri-implant tissues demonstrating the similarity between breast implant-associated anaplastic large cell lymphoma and aseptic lymphocytic vasculitis-associated lesion-hypersensitivity responses in peri-implant tissues. (A,B) Images are from a suspected breast implant-associated anaplastic large cell lymphoma patient and demonstrate the ability of breast implant particulate to shed into peri-implant tissue. (A) Breast implant-associated foamy macrophages and lymphocytes indicative of implant debris evelopment and reactivity (courtesy of Dr Roberto Miranda, MD Anderson Cancer Center). (B) Semiorganized structure of lymphocytes surrounding well-enveloped breast implant debris and macrophage, consistent with both breast implant-associated anaplastic large cell lymphoma and delayed type hypersensitivity responses. (courtesy of Dr Roberto Miranda, MD Anderson Cancer Center). (C) Tissue from inner surface of the joint psuedocapsule shows an inflammatory response dominated by perivascular lymphocytic infiltrate indicative of aseptic lymphocytic vasculitis-associated lesions (original magnification 600 × courtesy of Deborah Hall and Robert Urban, Department of Orthopedic Surgery, Rush University Medical Center). (D) Tissue from inner surface of the joint psuedocapsule shows an inflammatory response dominated by perivascular lymphocytic infiltrate indicative of aseptic lymphocytic vasculitis-associated lesions with foamy macrophages and lymphocytes indicative of implant debris envelopment and reactivity (original magnification 600 × courtesy of and with permission from Deborah Hall and Robert Urban in the Dept Orthopedic Surgery, Rush University Medical Center).

Europe and Australia, no biofilm-related malignancy risk in orthopedic patients has been reported.

CONCLUSIONS

All implants will produce implant debris over time to some degree. This debris typically emanates from the bearing surfaces of the joint replacement and eventually leads to granulomas that cause subtle inflammation. This is dramatically different for BI and orthopedic total joint implants, where loading, articulation multi-component micromotion, and corrosion likely produce orders of magnitude more implant debris in a distinctly different environment from that of a breast capsule. For total joint replacements, debris-induced inflammation grows over

time and requires implant revision. Thus, it is even more surprising that inflammation-induced BIA-ALCL-like responses have not been reported for orthopedic implants in other than a few case reports over the past 40 years,[125] indicating the critical role the local environment may play in this disease and how anatomically site specific this may be. The take-home message for BIs is 2-fold: (1) increased implant debris will result in increased pathogenic inflammation over time. Conversely, less particulate debris will result in less inflammation and improved performance. And (2), a subset of patients susceptible or predisposed to BIA-ALCL or hypersensitivity-type adaptive immune responses will be more vulnerable to implant debris than the general population, and utilizing implants that minimize this response may be paramount in these patients. Many questions regarding BI debris remain unanswered. For example, to what degree do lessons learned from orthopedics translate to BI debris, given that orthopedic implant debris involves highly loaded implants with articulating surfaces generating a relatively large amount of debris that is sequestered (largely) locally? On the other hand, although mild, BIs undergo far more loading cycles per year than orthopedic implants (eg, 8.4 million for BI [breaths per year] vs 1 million steps for an active total hip patient). And to what degree do BI capsules mimic those of a pseudosynovial compartment, and how does "easy" access of BI debris' proximity to breast tissue, muscle, and fat affect subsequent reactivity? Studies are necessary to determine the size, shape, and amount of prototypical BI debris in peri-implant tissues with different types of surfaces and materials (eg, textured vs nontextured) utilizing tissue digestion and particle isolation techniques previously employed.[126] This is required to determine if this debris can induce significant inflammation. What are the biological ramifications of different types of BI debris in different people? Additional study is needed to assess the range of biological responses to BI debris in both well- and poorly functioning implant populations, including ALCL groups, to determine the extent of hypersensitivity and other person-dependent inflammatory responses. These investigations will need to determine the extent to which BI debris effects macrophages, that is, what concentration of clinically relevant BI debris demonstrates proinflammatory effects both in vitro and in vivo in cell and animal models for both innate (eg, macrophage) and adaptive (eg, lymphocyte/T cell) mediated inflammation. There is continuing need for clinical studies to define the role of person-specific responses to both orthopedic and BI debris, including effects of preexisting health conditions and pathologies, hypersensitivity responses, and genetic susceptibility to particle-induced inflammation.

Disclosures

Dr Hallab has received travel funds from Establishment Labs and is principal at BioEngineering Solutions, Inc. Dr Hammond serves as a consultant for Mentor Corporation, Establishment Labs, and the Musculotransplant Foundation. Dr Samelko declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding

This supplement is sponsored by Allergan plc (Dublin, Ireland), Aesthetic Surgery Education & Research Foundation (ASERF) (Garden Grove, CA), Establishment Labs (Alajuela, Costa Rica), Mentor Worldwide, LLC (Irvine, CA), Polytech Health & Aesthetics GmbH (Dieburg, Germany), and Sientra, Inc. (Santa Barbara, CA).

REFERENCES

1. Charnley J. The reaction of bone to self-curing acrylic cement. A long-term histological study in man. *J Bone Joint Surg Br*. 1970;52(2):340-353.
2. Charnley J. *Low Friction Arthroplasty of the Hip, Theory and Practice*. Berlin: Springer-Verlag; 1979.
3. Kaufman AM, Alabre CI, Rubash HE, Shanbhag AS. Human macrophage response to UHMWPE, TiAlV, CoCr, and alumina particles: analysis of multiple cytokines using protein arrays. *J Biomed Mater Res A*. 2008;84(2):464-474.
4. Sethi RK, Neavyn MJ, Rubash HE, Shanbhag AS. Macrophage response to cross-linked and conventional UHMWPE. *Biomaterials*. 2003;24(15):2561-2573.
5. Trindade MC, Lind M, Nakashima Y, et al. Interleukin-10 inhibits polymethylmethacrylate particle induced interleukin-6 and tumor necrosis factor-alpha release by human monocyte/macrophages in vitro. *Biomaterials*. 2001;22(15):2067-2073.
6. Catelas I, Petit A, Zukor DJ, Antoniou J, Huk OL. TNF-alpha secretion and macrophage mortality induced by cobalt and chromium ions in vitro-qualitative analysis of apoptosis. *Biomaterials*. 2003;24(3):383-391.
7. Catelas I, Petit A, Marchand R, Zukor DJ, Yahia L, Huk OL. Cytotoxicity and macrophage cytokine release induced by ceramic and polyethylene particles in vitro. *J Bone Joint Surg Br*. 1999;81(3):516-521.
8. Hallab NJ, Cunningham BW, Jacobs JJ. Spinal implant debris-induced osteolysis. *Spine (Phila Pa 1976)*. 2003;28(20):S125-S138.
9. Lewis JB, Randol TM, Lockwood PE, Wataha JC. Effect of subtoxic concentrations of metal ions on NFkappaB activation in THP-1 human monocytes. *J Biomed Mater Res A*. 2003;64(2):217-224.
10. Willert HG, Semlitsch M. Reactions of the articular capsule to wear products of artificial joint prostheses. *J Biomed Mater Res*. 1977;11(2):157-164.
11. Arora A, Song Y, Chun L, et al. The role of the TH1 and TH2 immune responses in loosening and osteolysis of cemented total hip replacements. *J Biomed Mater Res A*. 2003;64(4):693-697.
12. Jacobs JJ, Roebuck KA, Archibeck M, Hallab NJ, Glant TT. Osteolysis: basic science. *Clin Orthop Relat Res*. 2001:71-77.
13. Archibeck MJ, Jacobs JJ, Roebuck KA, Glant TT. The basic science of periprosthetic osteolysis. *Instr Course Lect*. 2001;50:185-195.

14. Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am*. 1998;80(2):268-282.
15. Urban RM, Hall DJ, Sapienza CI, et al. A comparative study of interface tissues in cemented vs. cementless total knee replacement tibial components retrieved at autopsy. *Trans SFB*. 1998;21.
16. Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am*. 2000;82(4):457-476.
17. Punt IM, Cleutjens JP, de Bruin T, et al. Periprosthetic tissue reactions observed at revision of total intervertebral disc arthroplasty. *Biomaterials*. 2009;30(11):2079-2084.
18. Choma TJ, Miranda J, Siskey R, Baxter R, Steinbeck MJ, Kurtz SM. Retrieval analysis of a ProDisc-L total disc replacement. *J Spinal Disord Tech*. 2009;22(4):290-296.
19. Punt IM, Visser VM, van Rhijn LW, et al. Complications and reoperations of the SB Charité lumbar disc prosthesis: experience in 75 patients. *Eur Spine J*. 2008;17(1):36-43.
20. van Ooij A, Kurtz SM, Stessels F, Noten H, van Rhijn L. Polyethylene wear debris and long-term clinical failure of the Charité disc prosthesis: a study of 4 patients. *Spine (Phila Pa 1976)*. 2007;32(2):223-229.
21. Jacobs JJ, Shanbhag A, Glant TT, Black J, Galante JO. Wear debris in total joint replacements. *J Am Acad Orthop Surg*. 1994;2(4):212-220.
22. Campbell P, Ma S, Yeom B, McKellop H, Schmalzried TP, Amstutz HC. Isolation of predominantly submicron-sized UHMWPE wear particles from periprosthetic tissues. *J Biomed Mater Res*. 1995;29(1):127-131.
23. Maloney WJ, Smith RL, Castro F, Schurman DJ. Fibroblast response to metallic debris in vitro. Enzyme induction cell proliferation, and toxicity. *J Bone Joint Surg Am*. 1993;75(6):835-844.
24. Green TR, Fisher J, Matthews JB, Stone MH, Ingham E. Effect of size and dose on bone resorption activity of macrophages by in vitro clinically relevant ultra high molecular weight polyethylene particles. *J Biomed Mater Res*. 2000;53(5):490-497.
25. Green TR, Fisher J, Stone M, Wroblewski BM, Ingham E. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. *Biomaterials*. 1998;19(24):2297-2302.
26. Matthews JB, Besong AA, Green TR, et al. Evaluation of the response of primary human peripheral blood mononuclear phagocytes to challenge with in vitro generated clinically relevant UHMWPE particles of known size and dose. *J Biomed Mater Res*. 2000;52(2):296-307.
27. Matthews JB, Green TR, Stone MH, Wroblewski BM, Fisher J, Ingham E. Comparison of the response of primary murine peritoneal macrophages and the U937 human histiocytic cell line to challenge with in vitro generated clinically relevant UHMWPE particles. *Biomed Mater Eng*. 2000;10(3-4):229-240.
28. Ingram J, Matthews JB, Tipper J, Stone M, Fisher J, Ingham E. Comparison of the biological activity of grade GUR 1120 and GUR 415HP UHMWPE wear debris. *Biomed Mater Eng*. 2002;12(2):177-188.
29. Rader CP, Sterner T, Jakob F, Schütze N, Eulert J. Cytokine response of human macrophage-like cells after contact with polyethylene and pure titanium particles. *J Arthroplasty*. 1999;14(7):840-848.
30. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Human monocyte response to particulate biomaterials generated in vivo and in vitro. *J Orthop Res*. 1995;13(5):792-801.
31. Laquerriere P, Grandjean-Laquerriere A, Jallot E, Balossier G, Frayssinet P, Guenounou M. Importance of hydroxyapatite particles characteristics on cytokines production by human monocytes in vitro. *Biomaterials*. 2003;24(16):2739-2747.
32. Sieving A, Wu B, Mayton L, Nasser S, Wooley PH. Morphological characteristics of total joint arthroplasty-derived ultra-high molecular weight polyethylene (UHMWPE) wear debris that provoke inflammation in a murine model of inflammation. *J Biomed Mater Res A*. 2003;64(3):457-464.
33. Bruch J. Response of cell cultures to asbestos fibers. *Environ Health Perspect*. 1974;9:253-254.
34. Ramachandran R, Goodman SB, Smith RL. The effects of titanium and polymethylmethacrylate particles on osteoblast phenotypic stability. *J Biomed Mater Res A*. 2006;77(3):512-517.
35. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am*. 2001;83-A(3):428-436.
36. Hallab NJ, Anderson S, Caicedo M, Brasher A, Mikecz K, Jacobs JJ. Effects of soluble metals on human peri-implant cells. *J Biomed Mater Res A*. 2005;74(1):124-140.
37. Caicedo M, Reddy A, Samee I, Jacobs JJ, Hallab N. Cobalt Ions and Co-Cr-Mo alloy particles induce human monocyte co-stimulatory molecules CD-86, ICAM-1 and the cytokine IL-8: implications for innate activation of adaptive immune responses. *6th Combined Meeting of the Orthopaedic Research Societies*. 2007;6:535.
38. Webb LH, Aime VL, Do A, Mossman K, Mahabir RC. Textured breast implants: a closer look at the surface debris under the microscope. *Plast Surg (Oakv)*. 2017;25(3):179-183.
39. Clemens MW, Nava MB, Rocco N, Miranda RN. Understanding rare adverse sequelae of breast implants: anaplastic large-cell lymphoma, late seromas, and double capsules. *Gland Surg*. 2017;6(2):169-184.
40. Katzin WE, Feng LJ, Abbuhl M, Klein MA. Phenotype of lymphocytes associated with the inflammatory reaction to silicone gel breast implants. *Clin Diagn Lab Immunol*. 1996;3(2):156-161.
41. Katzin WE, Centeno JA, Feng LJ, Kiley M, Mullick FG. Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation. *Am J Surg Pathol*. 2005;29(4):506-511.
42. Story SK, Schowalter MK, Geskin LJ. Breast implant-associated ALCL: a unique entity in the spectrum of CD30+ lymphoproliferative disorders. *Oncologist*. 2013;18(3):301-307.

43. de Faria Castro Fleury E, Gianini AC, Ayres V, Ramalho LC, Seleti RO, Roveda D Jr. Breast magnetic resonance imaging: tips for the diagnosis of silicone-induced granuloma of a breast implant capsule (SIGBIC). *Insights Imaging*. 2017;8(4):439-446.
44. Webb LH, Aime VL, Do A, Mossman K, Mahabir RC. Textured breast implants: a closer look at the surface debris under the microscope. *Plast Surg (Oakv)*. 2017;25(3):179-183.
45. Labadie JG, Korta DZ, Barton N, Mesinkovska NA. Cutaneous hypersensitivity-like reactions associated with breast implants: a review. *Dermatol Surg*. 2018;44(3):323-329.
46. Ganske I, Hoyler M, Fox SE, Morris DJ, Lin SJ, Slavin SA. Delayed hypersensitivity reaction to acellular dermal matrix in breast reconstruction: the red breast syndrome? *Ann Plast Surg*. 2014;73(Suppl 2):S139-S143.
47. Maharaj S. An atypical immune-inflammatory disorder secondary to breast implant exposure. *J Long Term Eff Med Implants*. 2012;22(1):33-48.
48. Dargan D, McGoldrick C, Khan K. Type IV hypersensitivity to a textured silicone breast implant. *J Plast Reconstr Aesthet Surg*. 2012;65(7):969-972.
49. Audino SA, Maharaj SV. Prosthetic mammoplasty sensitivity syndrome: a case for causation. *J Long Term Eff Med Implants*. 2011;21(3):241-250.
50. Cantisani C, De Gado F, Grieco T, Faina P, Calvieri S, Scuderi N. Patch test reactions and breast implants. *J Plast Reconstr Aesthet Surg*. 2008;61(12):1540-1541.
51. Marcusson JA, Bjarnason B. Unusual skin reaction to silicone content in breast implants. *Acta Derm Venereol*. 1999;79(2):136-138.
52. Samreen N, Glazebrook KN, Bhatt A, et al. Imaging findings of mammary and systemic silicone deposition secondary to breast implants. *Br J Radiol*. 2018;91(1089):20180098.
53. Chen TA, Mercado CL, Topping KL, Erickson BP, Cockerham KP, Kossler AL. Disseminated silicone granulomatosis in the face and orbit. *Am J Ophthalmol Case Rep*. 2018;10:32-34.
54. Meijs J, de Vries-Bouwstra JK, Cohen Tervaert JW, Hoogenberg K. A case of late-onset systemic sclerosis with ruptured silicone breast implants. *Neth J Med*. 2018;76(5):243-248.
55. Caicedo MS, Pennekamp PH, McAllister K, Jacobs JJ, Hallab NJ. Soluble ions more than particulate cobalt-alloy implant debris induce monocyte costimulatory molecule expression and release of proinflammatory cytokines critical to metal-induced lymphocyte reactivity. *J Biomed Mater Res A*. 2010;93(4):1312-1321.
56. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440(7081):237-241.
57. Dostert C, Pétrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science*. 2008;320(5876):674-677.
58. Hornung V, Bauernfeind F, Halle A, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol*. 2008;9(8):847-856.
59. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: a novel mechanism for implant debris reactivity. *J Orthop Res*. 2009;27(7):847-854.
60. Cunningham BW, Hallab NJ, Hu N, McAfee PC. Epidural application of spinal instrumentation particulate wear debris: a comprehensive evaluation of neurotoxicity using an in vivo animal model. *J Neurosurg Spine*. 2013;19(3):336-350.
61. Dimar JR 2nd, Endriga DT, Carreon LY. Osteolysis and cervical cord compression secondary to silicone granuloma formation around a dorsal spinal cord stimulator: a case report. *J Neurol Surg Rep*. 2016;77(2):e67-e72.
62. Lopiccolo MC, Workman BJ, Chaffins ML, Kerr HA. Silicone granulomas after soft-tissue augmentation of the buttocks: a case report and review of management. *Dermatol Surg*. 2011;37(5):720-725.
63. Joyce TJ. Re: Grading of radiographic osteolytic changes after silastic metacarpophalangeal arthroplasty and a prospective trial of osteolysis following use of Swanson and Sutter prostheses. *J Hand Surg Eur Vol*. 2007;32(2):236-237; author reply 237.
64. Bassetto F, Scarpa C, Caccialanza E, Montesco MC, Magnani P. Histological features of periprosthetic mammary capsules: silicone vs. polyurethane. *Aesthetic Plast Surg*. 2010;34(4):481-485.
65. Leong M, Basu CB, Hicks MJ. Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction. *Aesthet Surg J*. 2015;35(1):40-47.
66. Merle C, Vigan M, Devred D, Girardin P, Adessi B, Laurent R. Generalized eczema from vitallium osteosynthesis material. *Contact Dermatitis*. 1992;27(4):257-258.
67. King L Jr, Fransway A, Adkins RB. Chronic urticaria due to surgical clips. *N Engl J Med*. 1993;329(21):1583-1584.
68. Barranco VP, Soloman H. Eczematous dermatitis from nickel. *JAMA*. 1972;220(9):1244.
69. Thomas RH, Rademaker M, Goddard NJ, Munro DD. Severe eczema of the hands due to an orthopaedic plate made of Vitallium. *Br Med J (Clin Res Ed)*. 1987;294:106-107.
70. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: clinical recognition and management. *Ann Thorac Surg*. 1994;57(4):1017-1018.
71. Halpin DS. An unusual reaction in muscle in association with Vitallium plate: a report of possible metal hypersensitivity. *J Bone Joint Surg Br*. 1975;57(4):451-453.
72. Bravo I, Carvalho GS, Barbosa MA, de Sousa M. Differential effects of eight metal ions on lymphocyte differentiation antigens in vitro. *J Biomed Mater Res*. 1990;24(8):1059-1068.
73. Gillespie WJ, Frampton CM, Henderson RJ, Ryan PM. The incidence of cancer following total hip replacement. *J Bone Joint Surg Br*. 1988;70(4):539-542.
74. Merritt K, Brown SA. *Biological Effects of Corrosion Products from Metal*. Philadelphia: American Society for Testing and Materials; 1985.

75. Poss R, Thornhill TS, Ewald FC, Thomas WH, Batte NJ, Sledge CB. Factors influencing the incidence and outcome of infection following total joint arthoplasty. *Clin Orthop*. 1984;182:117-126.
76. Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT. Prosthetic metals interfere with the functions of human osteoblast cells in vitro. *Clin Orthop*. 1997;(339):216-226.
77. Rooker GD, Wilkinson JD. Metal sensitivity in patients undergoing hip replacement. A prospective study. *J Bone Joint Surg Br*. 1980;62-B(4):502-505.
78. Rostoker G, Robin J, Binet O, et al. Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. *J Bone Joint Surg Am*. 1987;69(9):1408-1412.
79. Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin Orthop Rel Res*. 1996;326:71-79.
80. Kadin ME, Morgan J, Xu H, et al. IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. *Hum Pathol*. 2018;78:54-62.
81. Kadin ME, Morgan J, Xu H, Glicksman CA. CD30 + T cells in late seroma may not be diagnostic of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J*. 2017;37(7):771-775.
82. Kadin ME, Epstein AL, Adams W, et al. Evidence that some breast implant associated anaplastic large cell lymphomas arise in the context of allergic inflammation. *Blood*. 2017;130:4030.
83. Hensten-Pettersen A. Allergy and hypersensitivity. In: Morrey BF, ed. *Biological, Material, and Mechanical Considerations of Joint Replacements*. New York: Raven Press; 1993:353-360.
84. Merritt K, Brown SA. Tissue reaction and metal sensitivity. An animal study. *Acta Orthop Scand*. 1980;51(3): 403-411.
85. Kuby J. *Immunology*. 2nd ed. New York: W.H. Freeman and Company; 1991.
86. Korenblat PE. *Contact Dermatitis*. 2nd ed. Philidelphia: W.B. Saunders Company; 1992.
87. Granchi D, Verri E, Ciapetti G, et al. Effects of chromium extract on cytokine release by mononuclear cells. *Biomaterials*. 1998;19(1-3):283-291.
88. Granchi D, Ciapetti G, Savarino L, Cavedagna D, Donati ME, Pizzoferrato A. Assessment of metal extract toxicity on human lymphocytes cultured in vitro. *J Biomed Mater Res*. 1996;31(2):183-191.
89. Carando S, Cannas M, Rossi P, Portigliatti-Barbos M. The lymphocytic transformation test (L.T.T.) in the evaluation of intolerance in prosthetic implants. *Ital J Orthop Traumatol*. 1985;11(4):475-481.
90. Veien NK, Svejgaard E, Menné T. In vitro lymphocyte transformation to nickel: a study of nickel-sensitive patients before and after epicutaneous and oral challenge with nickel. *Acta Derm Venereol*. 1979;59(5):447-451.
91. Svejgaard E, Morling N, Svejgaard A, Veien NK. Lymphocyte transformation induced by nickel sulphate: an in vitro study of subjects with and without a positive nickel patch test. *Acta Derm Venereol*. 1978;58(3):245-250.
92. Veien NK, Svejgaard E. Lymphocyte transformation in patients with cobalt dermatitis. *Br J Dermatol*. 1978;99(2):191-196.
93. Secher L, Svejgaard E, Hansen GS. T and B lymphocytes in contact and atopic dermatitis. *Br J Dermatol*. 1977;97(5):537-541.
94. Everness KM, Gawkrodger DJ, Botham PA, Hunter JA. The discrimination between nickel-sensitive and non-nickel-sensitive subjects by an in vitro lymphocyte transformation test. *Br J Dermatol*. 1990;122(3):293-298.
95. Granchi D, Savarino L, Ciapetti G, et al. Immunological changes in patients with primary osteoarthritis of the hip after total joint replacement. *J Bone Joint Surg Br*. 2003;85(5):758-764.
96. Granchi D, Ciapetti G, Stea S, et al. Evaluation of several immunological parameters in patients with aseptic loosening of hip arthroplasty. *Chir Organi Mov*. 1995;80(4):399-408.
97. Campbell P, Ebramzadeh E, Nelson S, Takamura K, De Smet K, Amstutz HC. Histological features of pseudotumor-like tissues from metal-on-metal hips. *Clin Orthop Relat Res*. 2010;468(9):2321-2327.
98. Campbell P, Ebramzadeh E, Nelson S, Takamura K, De Smet K, Amstutz HC. Histological features of pseudotumor-like tissues from metal-on-metal hips. *Clin Orthop Relat Res*. 2010;468(9):2321-2327.
99. Thomas P, Braathen LR, Dörig M, et al. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy*. 2009;64(8):1157-1165.
100. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am*. 2005;87(1):28-36.
101. Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am*. 2005;87(1):18-27.
102. Hallab NJ, Anderson S, Stafford T, Jacobs JJ. T-cell vs B-cell metal-hypersensitivity responses in patients with arthroplasty. *Trans 50th Orthopaedic Research Society*. 2004;50:1490.
103. Gochoco A, Jones E, Soutendijk C, Alpdogan O, Shi W, Sahu J. Amlodipine-induced hypersensitivity reaction mimicking CD30(+) mycosis fungoides. *JAAD Case Rep*. 2016;2(4):320-322.
104. Stephan F, Haber R, Kechichian E, Kamar F. Lamotrigine-induced hypersensitivity syndrome with histologic features of CD30 + lymphoma. *Indian J Dermatol*. 2016;61(2):235.
105. Yasukochi Y, Takenaka K, Yurino A, et al. Atopic dermatitis with CD30-positive anaplastic large cell lymphoma. *Eur J Dermatol*. 2014;24(1):132-133.
106. Magro CM, Olson LC, Nguyen GH, de Feraudy SM. CD30 positive lymphomatoid angiocentric drug reactions: characterization of a series of 20 cases. *Am J Dermatopathol*. 2017;39(7):508-517.

107. Weingertner N, Mitcov M, Chenard MP, Cribier B. Intralymphatic CD30 + T-cell proliferation during DRESS: a mimic of intravascular lymphoma. *J Cutan Pathol*. 2016;43(11):1036-1040.
108. Zychowska M, Woźniak Z, Maj J. Primary cutaneous CD30 + lymphoproliferative disorders in a patient with severe atopic dermatitis: is there a causative link? *Acta Derm Venereol*. 2018;98(1):123-125.
109. Palraj B, Paturi A, Stone RG, et al. Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature. *J Foot Ankle Surg*. 2010;49(6):561-564.
110. Yoon HJ, Choe JY, Jeon YK. Mucosal CD30-positive T-cell lymphoproliferative disorder arising in the oral cavity following dental implants: report of the first case. *Int J Surg Pathol*. 2015;23(8):656-661.
111. Kellogg BC, Hiro ME, Payne WG. Implant-associated anaplastic large cell lymphoma: beyond breast prostheses. *Ann Plast Surg*. 2014;73(4):461-464.
112. Zekry KM, Yamamoto N, Hayashi K, Takeuchi A, Tsuchiya H. Primary lymphoma of the pelvis: a case report. *J Orthop Case Rep*. 2017;7(6):6-9.
113. Wienerroither V, Sauerschnig M, Beham-Schmid C, et al. Operative R0 resection of diffuse large B-cell lymphoma of the pelvis: a case report. *J Med Case Rep*. 2018;12(1):293.
114. Tarazi M, English CL, Guest K, Balasubramaniam D. Myofibroblastic infiltration of the bowel: a case report and literature review. *Int J Surg Case Rep*. 2018;51:248-251.
115. Nguyen KA, Su C, Bai HX, et al. Disease site as a determinant of survival outcome in patients with systemic anaplastic lymphoma kinase positive anaplastic large cell lymphoma with extranodal involvement: an analysis of 1306 cases from the US National Cancer Database. *Br J Haematol*. 2018;181(2):196-204.
116. Zekry KM, Yamamoto N, Hayashi K, Takeuchi A, Tsuchiya H. Primary lymphoma of the pelvis: a case report. *J Orthop Case Rep*. 2017;7(6):6-9.
117. Kadin ME, Epstein AL, Adams W, et al. Evidence that some breast implant associated anaplastic large cell lymphomas arise in the context of allergic inflammation. *Blood*. 2017;130:4030.
118. Smith AJ, Dieppe P, Porter M, Blom AW; National Joint Registry of England and Wales. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. *BMJ*. 2012;344:e2383.
119. Tharani R, Dorey FJ, Schmalzried TP. The risk of cancer following total hip or knee arthroplasty. *J Bone Joint Surg Am*. 2001;83-A(5):774-780.
120. Nyrén O, McLaughlin JK, Gridley G, et al. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J Natl Cancer Inst*. 1995;87(1):28-33.
121. Caicedo M, Jacobs JJ, Reddy A, Hallab NJ. Analysis of metal ion-induced DNA damage, apoptosis, and necrosis in human (Jurkat) T-cells demonstrates Ni2 + and V3 + are more toxic than other metals: Al3 + , Be2 + , Co2 + , Cr3 + , Cu2 + , Fe3 + , Mo5 + , Nb5 + , Zr2 + . *J Biomed Mater Res A*. 2008;86(4):905-913.
122. Hallab NJ, Vermes C, Messina C, Roebuck KA, Glant TT, Jacobs JJ. Concentration- and composition-dependent effects of metal ions on human MG-63 osteoblasts. *J Biomed Mater Res*. 2002;60(3):420-433.
123. Mathiesen EB, Ahlbom A, Bermann G, Lindgren JU. Total hip replacement and cancer. A cohort study. *J Bone Joint Surg Br*. 1995;77(3):345-350.
124. Visuri T, Koskenvuo M. Cancer risk after Mckee-Farrar total hip replacement. *Orthopedics*. 1991;14(2):137-142.
125. Tuck M, Lim J, Lucar J, Benator D. Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation. *BMJ Case Rep*. 2016;2016. pii: bcr2016217317. doi: 10.1136/bcr-2016–217317.
126. Hallab NJ, Jacobs JJ. Biologic effects of implant debris. *Bull NYU Hosp Jt Dis*. 2009;67(2):182-188.