Implant Material Bio-compatibility, Sensitivity, and Allergic Reactions

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Abstract

Generally biocompatibility to implant-debris governs long-term clinical performance. The following chapter covers: the kinds of implant-debris and the biologic responses to implant-debris. Implants produce debris from wear and corrosion that take the form of particles and ions. Particulate debris generally ranges from 0.01 to 100 s um. Wear rates of articulating bearing such as total hip arthroplasties generally range from 0.1 to 50mm^3/yr. Metal-on-metal total joint replacement components are well known to produce increases in circulating metal in people (>ten-fold that of people without implant, i.e., 2-5parts per billion-Cobalt and 1-3 ppb-Chromiun). Debris bioreactivity is both local and systemic. Local inflammation is primarily mediated by local immune cells called macrophages, which produce pro-inflammatory mediators/cytokines TNFα, IL-1β, IL-6, and PGE2. Although there are many concerns associated with systemic reactivity to implant-debris, to date well-established systemic reactivity has been limited to developed hypersensitivity/allergy reactions. Elevated amounts of in the remote organs such as the liver, spleen of patients with TJA and high levels of circulating metal have not (yet) been associated with remote toxicological or carcinogenic pathologies. Not all implant debris is similarly biocompatible/

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nonbiocompatible. Additionally, the amount of debris-induced-inflammation depends on both the person and amount/kind/size of implant debris. The inflammation and bone loss associated with debris necessitates continued surveillance by physicians to monitor patients/implants over time using traditional physical exams, x-rays, and when appropriate new biological assays such as the testing of metal content and individual biological response such as hypersensitivity metal-LTT assays.

Keywords

Orthopedic implant · Implant-debris · Biologic responses · Particles · Ions · Inflammation · Macrophages · Innate immune resposne · Adaptive immune response · Cytokines · Hypersensitivity · Allergy · Metal-LTT assays

Abbreviations

Al	Aluminum
ALVAL	Aseptic lymphocyte vasculitis associated lesion
Co	Cobalt
Cr	Chromium
$Cr(PO_4)4H_2O$	Chromium orthophosphate
DAMP	Danger associated molecular patterns
DTH	Delayed type hypersensitivity adaptive (lymphocyte mediated) immune response that occurs over days to weeks to years (vs. that of an immediate response).
Hypersensitivity	Adaptive immune responses typically local inflammation mediated by T-cells or B-cells where antigen presenting cells such as macrophages act as gate keepers.
IL-1b	Interleukin 1 almost exclusively produced by inflammasome reaction, such as occurs in a macrophage response to implant debris particles
IL-6	Interleukin 6
IL-18	Interleukin 18
IL-33	Interleukin 33
Inflammasome	Key molecular components of a pro-inflammatory pathway that reacts to danger signals (not pathogens) that are produced when cells are damaged, typically composed of multiprotein oligomers consisting of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3).
LALLS	Low angle laser light scattering
metal-LTT	Metal-lymphocyte transformation test (proliferation assay) used as a human diagnostic test for delayed type hypersensitivity responses to implant metals
NALP3/ASC	Inflammasome complex of proteins
PAMP	Pathogen associated molecular pattern
PGE_2	Prostaglandin E2
PMMA	Polymethylmethacrylate
ppb	Parts per billion (ng/mL or ug/L)
PTFE	Teflon (polytetraflouroethylene)
RANKL	Receptor activator of nuclear factor Kappa Beta ligand
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
THA	Total hip arthroplasty
Ti	Titanium
TJA	Total joint arthroplasty
TJR	Total joint replacement

TNF-a	Tumor necrosis factor – alpha
UHMWPE	Ultra high molecular weight polyethylene
V	Vanadium

Introduction

Implant debris and not the implant itself causes slow progressive local inflammation that limits the long term performance of over one million total joint arthroplasties implanted each year in the USA (Charnley 1979, 1970). The direct costs of this slow progressive Adverse Reactivity to Implant Debris (ARID) is approximately $20 billion in the USA per year and is expected to double over the next 10 years (Kurtz et al. 2007a, b, 2009). One of the most important human costs of this bio-implant failure is the increased incidence of death during revision orthopedic surgery which is as high as 13% in people older >75–80 years of age while it is <1% in patients <70 years of age. Biocompatibility mediated implant failures also have elevated complication rates associated with re-operation, with a >20% chance of post-operative dislocation (vs <1% in patients <75 years of age) (Radcliffe et al. 1999). Some designs of orthopedic implants release more bioreactive debris (i.e., metal particles and ions) that result in extraordinarily high failure rates, with levels of failure reported as high as 5% at 6 years post-op, such as some past metal-on-metal total hip arthroplasties designs as well as some types of highly modular implants (i.e., several components that press fit together) (Cooper et al. 2013; Jacobs and Hallab 2006; Korovessis et al. 2006; Milosev et al. 2006). The mechanism of implant debris induced inflammation is best known as an activator of local innate immune responses, i.e., monocytes/macrophages activate NFκβ and secretion of potent inflammatory cytokines such as IL-1β, TNFα, IL-6, and IL-8 (Catelas et al. 1999, 2003; Hallab et al. 2003a; Kaufman et al. 2008; Sethi et al. 2003; Trindade et al. 2001) resulting in localized inflammation (Kaufman et al. 2008; Lewis et al. 2003).

Over the long term all accumulating implant debris and the subsequent slow progressive inflammation results in bone loss and loss of implant fixation (Willert and Semlitsch 1977), termed "aseptic osteolysis," and results in pain and premature loosening of orthopedic implants (Archibeck et al. 2001; Arora et al. 2003a; Jacobs et al. 2001). Clinically, aseptic osteolysis (noninfection related bone loss) generally only refers to measureable bone loss as determined on an x-ray (Fig. 1). It is the particulate and soluble degradation products of orthopedic biomaterials (generated by wear and corrosion) that mediate these Adverse Reactivity to Implant Debris (ARID) effects. Debris may be present as particulate material (i.e., as small colloidal nanometer size complexes or larger >0.3um particles), or soluble products such as free metallic ions which can then react with their proteinaceous and cellular environment. Implant particulate debris can have large specific surface areas by virtue of their small size and large number and thus have a large format for interaction with the surroundings. This chapter will focus on orthopedic implant degradation product bio-compatibility, and ensuing local and systemic consequences of this debris including local inflammatory tissue reactivity and sensitivity and allergic reactions, respectively.

Implant Debris Types: Particles and Ions

All orthopedic implants produce debris of two basic types: particles or soluble debris (e.g., metal ions). The biologic consequences of particles and soluble debris blurs as the size of particles decreases into the nanometer range and become "effectively soluble." Particulate debris (metal, ceramic, or polymers) is generally in the range of 40 nm to 1 mm in size, while so-called common forms of "soluble debris" is currently limited to metal and are quickly bound to serum proteins upon release (such as albumin).

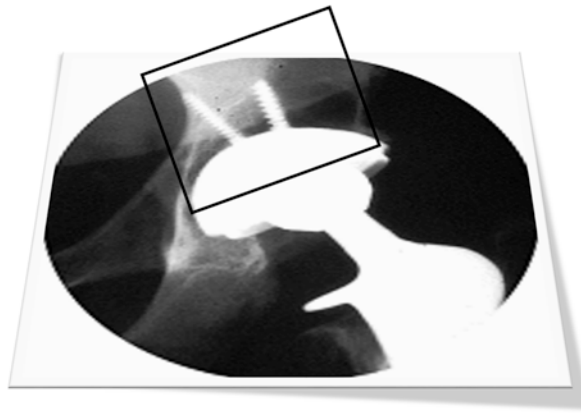

Fig. 1 Peri-implant aseptic osteolysis above the acetabular cup of a metal-on-polymer bearing total hip replacement. Inset shows a granuloma surrounding acetabular fixation screw, which is a common site for bone resorption due to the ease with which particles can migrate and cause inflammatory soft tissue and osteolysis. (Courtesy of Bio-Engineering Solutions Inc.)

Particulate Debris

Different types of orthopedic implants produce different types and amounts of wear debris, with different sizes and shapes of that are generally implant design and material specific. For example, total joint implants with "hard-on-hard" articulating surfaces such as metal-on-metal total hips arthroplasty implants generally produce smaller sized fairly round (submicron), debris. More common metal-on-polymer or ceramic-on-polymer THA bearings produce larger (micron sized) polymeric debris (Fig. 2) that fall into the range of 0.2um to 1um, with little metallic debris. Other sources of metal debris include corrosion and wear at metal-to-metal connections between modular components (Campbell et al. 1995; Jacobs et al. 1994a; Maloney et al. 1993). Highly cross-linked ultrahigh molecular weight polyethylene (X-UMWPE) used in current models of hip replacements provides less war than previous generations of UHMWPE; however, the particle produces are generally smaller (e.g., 0.1microns in size) compared to 0.8–2um of previous generations of UHMWPE (Catelas et al. 2004; Scott et al. 2005). Articulating surfaces comprised of metal and ceramic bearings produce particles that can be an order of magnitude smaller than polymeric particles (at approximately $<$0.05um in diameter, i.e., in the nanometer range).

Histological analysis of peri-implant tissues has identified different types and sizes of particles (Choma et al. 2009; Jacobs et al. 1998a; Punt et al. 2008, 2009; Urban et al. 1998, 2000; van Ooij et al. 2007). However, the sizes of debris in tissues vary dramatically from that identified using simulators and analysis of synovial fluids and tissues. Metal corrosion based stainless steel debris has been found as closely packed, plate-like particle aggregates mostly at steel screw-plate junctions containing particles of chromium compound ranging in size from 0.5 to 5.0 microns (Urban et al. 1996). Similarly large, cobalt alloy corrosion debris has been shown in tissues to be made of a chromium-phosphate ($Cr(PO_4)4H_2O$) hydrate rich material termed "orthophosphate" and ranges in size from $<$1um to $>$500 micrometers (Urban et al. 1996, 1997).

Particle Characterization: Differently than basic histological analysis, more specific means of characterizing implant debris particles include Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) techniques. Both of these characterize particles by counting and sizing particles on a number of high, medium, and low power microscopy fields. These techniques are employed for digested tissues and simulator fluids and synovial fluid analysis, after the particulate debris has been isolated and dried on a membrane/mounting media. Because the particles

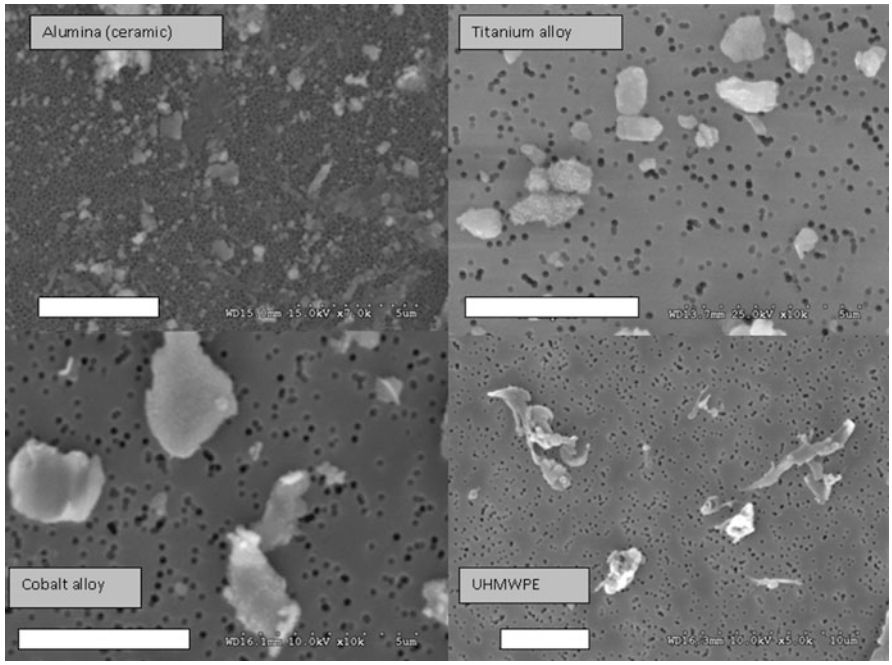

Fig. 2 Implant debris from metal (Cobalt alloy and Titanium) and ceramic (alumina) debris are more rounded in comparison to polymeric (UHMWPE) debris which is more elongated in shape. Note: Bar = 5um. (Courtesy of BioEngineering Solutions Inc.)

observed in the high power fields are over represented when scaled up to the total, these methods have inappropriately biased our understanding that the majority of the wear (mass loss) from an implant is comprised of particles in the nanometer to submicron range. That is while most of the particles identified on a counting (number-based) analysis are in the small ranges (<1um), they do not typically make up the size of debris that is responsible for the majority of the mass loss, i.e., while billions of small particles only add up to 0.01 mg of implant debris it only takes 100's to 1000's of larger particles to equal >10 mg of implant debris. This biased understanding stems from the limited number of particles in tissues and the relatively low numbers of particles (e.g., 100's–1000's) that are counted using image based analysis techniques such as SEM. Other types of analytical techniques, such as low angle laser light scattering (LALLS), have the ability to sample millions to billions of particles, as they pass in front of a laser detection system where the one-in-a-million large particle can be detected and thus provide a more accurate distribution of the total debris.

The ability to comprehensively characterize implant debris is critical to the assessment of consequent biological responses and weigh the effects of new designs and bearing surfaces to older implants. The bias of SEM techniques those of all "number-based" analysis where two very similar number based distributions can look very different when analyzed on a "volume-based" perspective (Fig. 3). Thus for an accurate and comprehensive evaluation of implant debris particulate, both a number and volume based analysis/distribution are required.

Metal Ions (Soluble Debris)

There is continuing clinical concern regarding metal released from orthopedic implant is the form of particles and ions. These ions immediately bind to serum proteins and disseminate into surrounding tissues, bloodstream, and remote organs. Normal

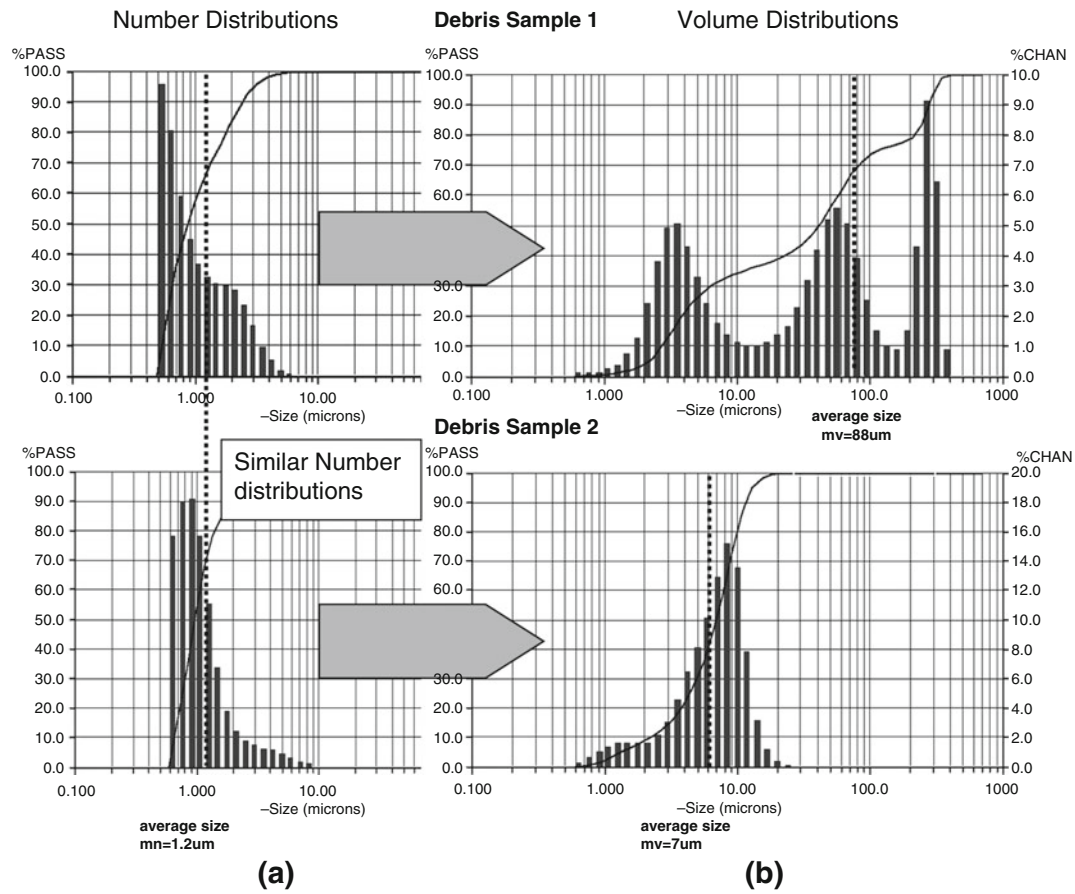

Fig. 3 LALLS analyses of two implant debris samples using a (**a**) volume and (**b**) number distributions demonstrate that similar number distributions and estimates of particle size can result from two very different sizes particles when analyzed using a volume distribution, which shows the size of the particle as a percent of the total volume. Note: The x-axis is particle diameter and the y-axis is (**a**) percentage of total number of particles in each size range and (**b**) the percentage of total mass in each size range. (Courtesy of BioEngineering Solutions Inc)

metal serum levels are generally <1part per billion, ppb (ng/mL): 1–10 ng/ml Al, 0.15 ng/ml Cr, <0.01 ng/ml V, 0.1–0.2 ng/ml Co, and <4.1 ng/ml Ti. Implants do release enough metal to increase these levels systemically following total joint arthroplasty (Table 1). Particles of metal that are released contribute to this increased metal because of the large surface areas available for corrosion (i.e., electrochemical dissolution) (Jacobs et al. 1998a; Urban et al. 1996, 1997, 1998, 2000).

Metal Ion Release: Metal ions released from orthopedic implants have been of concern for over 40 years. Increased levels of systemic circulating Co and Cr are detected following even successful total joint replacements with Co-alloy based components. The same is true of other metal alloy orthopedic implants, e.g., increased serum Ti and Cr concentrations can be found in some individuals with well-functioning Ti and/or Cr containing THR components (Table 1) (Dorr et al. 1990; Jacobs et al. 1994b, 1998a; Michel et al. 1984; Stulberg et al. 1994). Other metals associated with the surgery itself have also been reported where increases in Ni have been noted immediately following surgery, likely related to the use of stainless steel surgical instruments.

Although several factors affect systemic metal ion levels in TJA patients, the most important

Table 1 Approximate concentrations of metal in human body fluids and in human tissue with and without total joint replacements. (Dorr et al. 1990; Jacobs et al. 1994b, 1998a; Michel et al. 1991; Stulberg et al. 1994)

Body fluids (ng/mL or ppb)		Ti	Al	V	Co	Cr	Mo	Ni
Serum	Normal	0.06	0.08	<0.02	0.003	0.001	*	0.007
	TJA	0.09	0.09	0.03	0.007	0.006	*	<0.16
Urine	Normal	<0.04	0.24	0.01	*	0.001	*	*
	TJA	0.07	0.24	<0.01	*	0.009	*	*
Synovial fluid	Normal	0.27	4.0	0.10	0.085	0.058	0.219	0.086
	TJA	11.5	24	1.2	10	7.4	0.604	0.55
Joint capsule	Normal	15.0	35	2.4	0.42	2.6	0.177	69
	TJA-F	399	47	29	14	64	4.65	100
Whole blood	Normal	0.35	0.48	0.12	0.002	0.058	0.009	0.078
	TJA	1.4	8.1	0.45	0.33	2.1	0.104	0.50
Body tissues (µg/g)								
Skeletal muscle	Normal	*	*	*	<12	<12	*	*
	TJA	*	*	*	160	570	*	*
Liver	Normal	100	890	14	120	<14	*	*
	TJA	560	680	22	15,200	1130	*	*
Lung	Normal	710	9830	26	*	*	*	*
	TJA	980	8740	23	*	*	*	*
Spleen	Normal	70	800	<9	30	10	*	*
	TJA	1280	1070	12	1600	180	*	*
Psuedocapsule	Normal	<65	120	<9	50	150	*	*
	TJA	39,400	460	121	5490	3820	*	*
Kidney	Normal	*	*	*	30	<40	*	*
	TJA	*	*	*	60	<40	*	*
Lymphatic	Normal	*	*	*	10	690	*	*
Tissue	TJA	*	*	*	390	690	*	*
Heart	Normal	*	*	*	30	30	*	*
	TJA	*	*	*	280	90	*	*

Normal: Subjects without any metallic prosthesis (not including dental)
TJA: Subjects with total joint arthroplasty
* = Data Not Available

factor is elevated metal implant degradation (wear and/or corrosion). Systemic titanium ion levels up to a hundred times higher than normal have been reported in cases of failed metal-backed patellar components where mechanical implant failures caused high wear such as a wearing through of the polymer liner in a THA and the more wear resistant Co alloy head bores into the titanium alloy acetablular cup. Surprisingly in these cases of excessive Ti-alloy wear and metal release, there was no reported increases in still serum or urine Al, serum or urine V levels, or which are other minor percentages of titanium alloy cups (6% Al and 4% V). Fretting corrosion, of modular implant components has been associated with elevations in serum Co and urine Cr (Jacobs et al. 1998a, b, 1999b). Despite significant increases in Co and Cr concentrations found in the heart, liver, kidney, spleen, and lymphatic tissue from orthopedic implant degradation (Table 1), the majority of metal debris remains local around and in the pseudocapsule that forms around a total joint implant and act much like a joint capsule (Jacobs et al. 1994).

Local Tissue Effects of Wear and Corrosion

The key determining factor of long-term implant performance is implant debris that can trigger a local inflammatory response that causes osteolysis and aseptic implant loosening. Bone homeostasis is dependent upon the intricate balance of bone formation and bone resorption powers which comprises the corresponding function of osteoblasts (bone building cells) vs. osteoclasts (bone resorbing cells) and osteocytes (bone mechanotransduction and signaling network cells). If implant debris induced inflammation causes disruption in bone homeostasis by mitigating osteoblastic bone formation and/or augmenting osteoclastic bone resorption, this will result in a net bone loss (i.e., osteolysis). This osteolysis near the bone-implant interface is the principal pathology associated with the localized effects of TJR degradation. This bone loss happens as a diffuse thinning of the cortical or as focal cyst-like lesions. The first materials to be associated with osteolytic lesions due to massive production amounts of implant debris were particulate polymethylmethacrylate (PMMA) bone cement and old acetabular cups made of PTFE (Teflon). This was based on histological studies showing implant debris associated with macrophages, giant cells, and a vascular granulation tissue. It is now well established that osteolysis in both well-fixed and loose uncemented implants results from the generation of particle debris from any material (Jacobs et al. 2001; Vermes et al. 2001a).

It was first described by Goldring et al. (1983) that the bone-implant interface in patients with loose total hip replacements is comparable to synovial-like membrane and bone resorbing factors such as PGE_2 and collagenase are produced by cells within the membrane. Total hip arthroplasty is more frequently associated with particle induced osteolysis than total knee arthroplasty, and this remains unclear why this is the case. However, it has been postulated that various biomechanical factors such as implant/bone mechanical loading environments, differential mechanisms of hip and knee wear, and differences in interfacial barriers to migration account for this apparent disparity.

All implant debris leads to subtle progressive inflammation that can ultimately result in implant failure. As to exactly how this occurs still remains somewhat contentious, however, increasing evidence continues to indicate that danger signaling by the innate immune system mediates implant debris induced inflammation, which is how the immune system in general detects and reacts to nonpathogen derived biologic stimuli (Caicedo et al. 2008, 2013a; Dostert et al. 2008; Hornung et al. 2008; Naganuma et al. 2016). It has been established over the past 40 years that implant debris induced inflammation is primarily driven by macrophage reactivity to sterile implant debris that results in up-regulation and activation of pro-inflammatory transcription factors (e.g., NFκB) that produce, amplify, and result in the secretion of inflammatory cytokines like IL-1β, TNFα, IL-6, and IL-8 (Jacobs et al. 2001) (Fig. 4). Prostaglandins (e.g., PGE_2) are also involved and mediate implant debris induced inflammation and osteolysis. IL-10 and IL-1Ra are key anti-inflammatory cytokines that act to lessen this inflammatory state induced by implant debris, but it remains less understood the degree which these anti-inflammatory cytokines can decrease the pathology of particle induced osteolysis. Additional factors involved with osteolysis include matrix metalloproteinases collagenase and stromelysin, which are enzymes that mediate the catabolism of the organic component of bone. Also, activated bone and immune cells can generate bone mediators known to play a role in stimulation of osteoclast differentiation and maturation, such as RANKL (also referred to as osteoclast differentiation factor).

Implant debris is sterile and relatively inert and does not have the prototypical molecular characteristics of a pathogen. Therefore, how does implant debris elicit an immune inflammatory response? More specific, how can extra- and intra-cellular mechanisms detect and react to sterile nonbiological material such as implant debris? For the past half century, this question had remained largely unknown. However, new discoveries and advancements in immunology have implicated the NLRP3 inflammasome danger signaling pathway to play a pivotal role in the detection and response to sterile nonbiological stimuli (Fig. 5) (Caicedo et al. 2010).

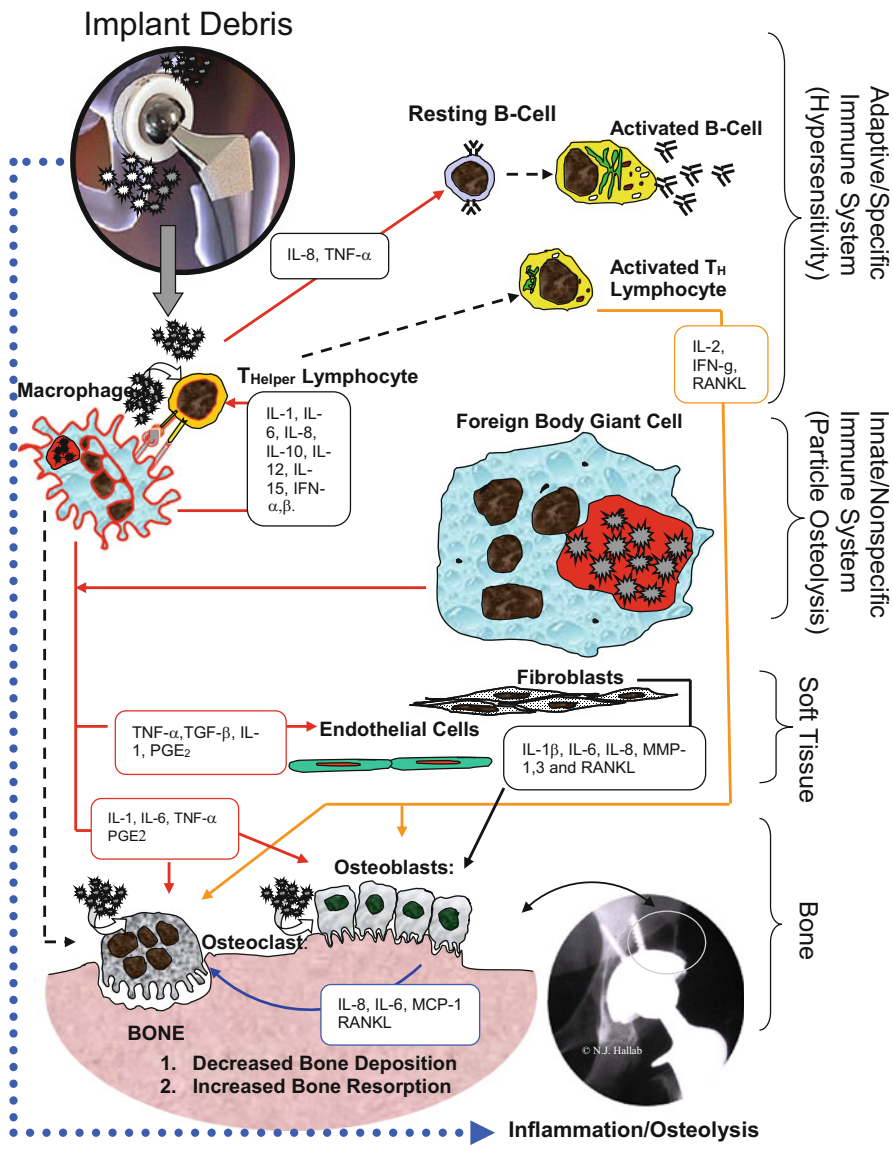

Fig. 4 Numerous cytokines from peri-implant cells reacting to implant debris can negatively affect bone turnover. IL-1, IL-6, and TNF-α are some of the most potent cytokines responsible for increasing bone loss and enhancing pro-inflammatory responses. (Picture courtesy of Bio-Engineering Solutions Inc)

The discovery of the inflammasome danger signaling pathway was pivotal since it was the first biological mechanism to explain how immune cells transduce sterile, nonpathogen derived stimuli (e.g., cell stress and necrosis) into an inflammatory response (Mariathasan et al. 2004; Mariathasan and Monack 2007). Additional nonbiological derived danger signals (e.g., DAMPs) that activate the inflammasome include cell damaging stimuli such as UV light, particulate adjuvants present in modern vaccines (Dostert et al. 2008; Hornung et al. 2008) and, as it turns out, orthopedic implant debris (Caicedo et al. 2008).

When particles activate the inflammasome pathway, immune cells subsequently release

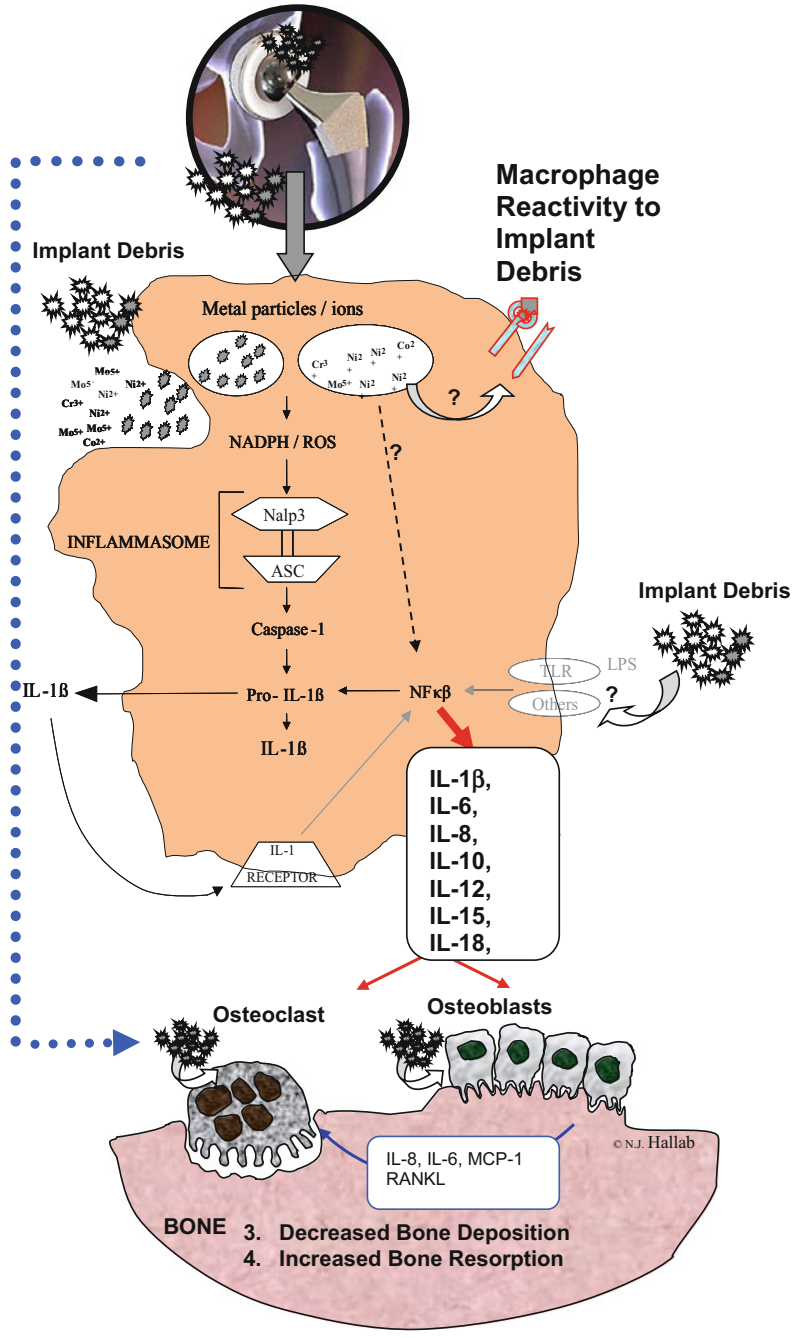

Fig. 5 Metal-induced inflammasome activation occurs when soluble and/or particulate implant debris activate the Nalp3 inflammasome when chemicals inside intracellular compartments used to digest foreign material (such as phagosomal NADPH induced reactive oxygen species and/or Cathepsin B) leaks out of 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 IL-1β to be secreted. IL-1β is a very potent pro-inflammatory cytokine that exerts an autocrine and paracrine effect inducing a broader more potent inflammatory response (e.g., activation of NFκβ pro-inflammatory responses). (Courtesy of BioEngineering Solutions Inc)

pro-inflammatory cytokines such as IL-1β, IL-18, IL-33, and a multitude of more. The sequence of events is as follows:

> Implant Debris → Phagocytosis → Lysosomal damage and rupture of protease enzymes (e.g. Cathepsin-B) → ROS (reactive oxygen species) production → Inflammasome (NALP3/ASC) activation → Caspase-1 → Secretion of mature IL-1β (and other IL-1-family dependent cytokines) (Fig. 20).

More specifically, upon ingestion (phagocytosis) of sterile particles by immune cells (or other DAMPs such as asbestos and implant

debris) will cause a degree of lysosomal destabilization. Consequently, lysosomal destabilization will result in the rupture and release of protease enzymes and of the acid rich extreme microenvironment within a lysosome into the cell cytosol, which are used within the lysosome compartment to breakdown ingested DAMPs (e.g., implant debris) and PAMPs. This lysosomal destabilization leads to an increase in NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) and an associated increase in reactive oxygen species (ROS). Subsequently, the release of ROS species leads to the activation of the intracellular multiprotein "inflammasome" complex that is composed of NALP3 (NACHT-, LRR-, and pyrin domain-containing protein 3) in association with ASC (apoptosis-associated speck-like protein containing a CARD domain) (Mariathasan and Monack 2007; Petrilli et al. 2007). Activation of the inflammasome will result in Caspase-1 activation, which then converts cytokines such as pro-IL-1β and pro-IL-18 (and others) into their active mature form. In summary, this illustrates the general numerous steps involved in the activation of the inflammasome danger signaling pathway and the numerous new potential biological points of pharmacologically blocking this response to prevent or mitigate particle induced inflammatory responses and osteolysis.

Systemic Effects of Wear and Corrosion

To some extent, implant surfaces and the implant debris generated are continually releasing chemically active metal ions into the surrounding peri-implant tissues. The released metal ions will bind to serum proteins and may reside in local tissues and also be transported via the bloodstream and the lymphatics to remote organs. This is of concern since it is known the potential toxicity effects of these elements used in modern orthopedic implant alloys: titanium, aluminum, vanadium, cobalt, chromium, and nickel. Metal toxicity can happen by changing: (i) cell/tissue metabolism, (ii) host/parasite interactions, (iii) immunologic interactions, and (iv) by inducing chemical carcinogenesis (Beyersmann 1994; Britton 1996; Goering and Klaasen 1995; Hartwig 1998; Luckey and Venugopal 1979).

Essential trace metals include cobalt and chromium and are necessary for the homeostatic function of various enzyme reactions. However, these elements in excessive quantities can become highly toxic. Accordingly, excessive cobalt can result in heart problems (cardiomyopathy), increased red blood cells (polycythemia), decreased thyroid functions (hypothyroidism), and carcinogenesis, while excessive chromium has been associated to nephropathy, hypersensitivity, and carcinogenesis. Also, metals such as nickel can result in skin rashes (eczematous dermatitis), hypersensitivity reactions, and cancer, and excessive vanadium exposure has been associated to heart and kidney dysfunction, and hypertension and depressive psychosis. Aluminum toxicity can lead to renal failure and blood anemia, bone softening (osteomalacia), and neurological problems. It is important to note, however, that these metal toxicities are generally due to excessively elevated levels of the soluble forms of these elements and most likely do not pertain to the levels of metals released from implant degradation.

Currently, any associated metal toxicity related to metal release from orthopedic implant is conjectural since it has yet to be established the cause and effect of this specific association. It is very difficult, however, to discern any metal toxicity effects related to an implant given the types of health concerns typically associated with the elderly, as well as those expected to occur in any orthopedic patient population (Jacobs et al. 1999a).

Systemic Particle Distribution: It is not well understood as to what determines the amount of implant debris accumulation in remote organs. When the magnitude of particulate debris produced by an implant is augmented, there is a corresponding increase in both the local and systemic burden of implant debris. Mostly, systemic implant debris (located beyond the peri-implant tissue microenvironment) is in the submicron size range. Numerous cases have located 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). Moreover, up to 70% of patients with total joint replacement components had metallic wear particles detected in their para-aortic lymph nodes. The consequences of this occurrence are not clear; however, prototypical immune inflammatory responses in lymph nodes to metallic and polymeric debris involve similar responses seen locally, which include activation of macrophages and associated production of cytokines.

Therefore, lymphatic transport is likely the main course for debris dissemination where particles are transported by perivascular channels as independent particles or as phagocytosed particles within macrophages. Disseminated particles within lymph nodes are primarily submicron in size; however, some metallic particles as large as 50 micrometers and polyethylene particles as large as 30 micrometers have also been detected. Additionally, these particles have been located within macrophages in the liver and spleen and in some instances, in nodules of inflammatory tissue granulomas throughout the organs. Typically, metallic particle size is nearly an order of magnitude less in the liver and spleen, than that in lymph nodes, suggesting there is an additional filtration point that occurs prior to particles culminating in those organs. This is not overly concerning since it is a common function of the cells of the liver, spleen, and lymph nodes to accumulate small quantities of a variety of foreign materials without evident clinical significance. However, nodules of inflammatory tissue (granulomas) or granulomatoid lesions in the liver and spleen can be induced by the accumulation of excessive particle debris. The degree of reaction to particles in the liver, spleen, and lymph nodes is probably modulated, as it is in other tissues by: (1) the dose of particles, (2) their rate of accumulation, (3) the period that they are present, and (4) the biologic reactivity of cells to these particles (size and materials composition). It is not unexpected that metallic particles in the liver or spleen are more common in patients with previously failed implants compared to patients with a primary well-functioning TJR.

It would be expected that in diseases which obstruct the continual lymph flow through lymph nodes, such as a metastatic tumor, or those that disrupt the general flow of circulation, such as chronic heart disease or diabetes, would result in reduced particle migration to remote organs, whereas other pathologies, like acute or chronic-active inflammation, likely augment particle migration (Jacobs et al. 1999a, 2001; Vermes et al. 2001b) via the recruitment of more immune cells to transport the debris away.

Hypersensitivity. In general terms, hypersensitivity responses to metal implants can be defined as an adaptive immune response that is mediated by T cells and typically causes a local inflammatory response around the implant. It is imperative to clarify that "hypersensitivity responses" have a wide range of intensity that can span from mild to severe and need not be on the severe end to be termed "hypersensitivity." Early implant failure (<7 years) that is caused by an exacerbated immune response to otherwise tolerable amounts of implant debris is likely caused and orchestrated by an adaptive immune response. This response is also often termed "metal-allergy," "implant-allergy," or "implant sensitivity." While soluble metals (i.e., metal ions) released from metal prostheses do not act as sensitizers alone, they are able to combine with self-proteins and form metal-protein complexes (haptens) that have the ability to activate the immune system. On the other hand, polymeric wear debris has not been implicated in allergic type immune responses due to its inability to properly degrade in vivo (Hallab et al. 2000a, b, 2001a, b). The most common metals regarded as sensitizers/allergens (metal haptens) include, but are not limited to beryllium, chromium, cobalt, nickel, tantalum, titanium, and vanadium. Nickel, cobalt, and chromium are the most common metal allergens reported in humans and nickel still constitutes 10–16% of medical grade stainless steel (Table 2). In general, the literature exhibits more case reports of hypersensitivity reactions associated with nickel-containing stainless steel and cobalt-alloy implants compared to Titanium-alloy devices (Burt et al. 1998; Cramers and Lucht 1977; Elves et al. 1975; Gordon et al.

Table 2 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	*	17–19	*	2–4	*	61–68	*	<0.5	<2.0	<0.06	<1.0	*
CoCrMo alloys (ASTM F75)	<2.0	*	61–66	27–30	*	4.5–7.0	*	<1.5	<1.0	*	*	<0.35	<1.0	*
(ASTM F90)	9–11	*	46–51	19–20	*	*	*	<3.0	<2.5	*	14–16	<0.15	<1.0	*
Ti alloys														
CPTi (ASTM F67)	*	*	*	*	99	*	*	0.2–0.5	*	*	*	<0.1	*	*
Ti-6Al-4 V (ASTM F136)	*	*	*	*	89–91	*	5.5–6.5	*	*	*	*	<0.08	*	3.5–4.5
45TiNi	55	*	*	*	45	*	*	*	*	*	*	*	*	*
Zr alloy (97.5% Zr, 2.5% Nb)	*	*	*	*	*	*	*	*	*	*	*	*	*	*

Note: Alloy compositions are standardized by the American Society for Testing and Materials (ASTM vol. 13.01)
* Indicates less than 0.05%

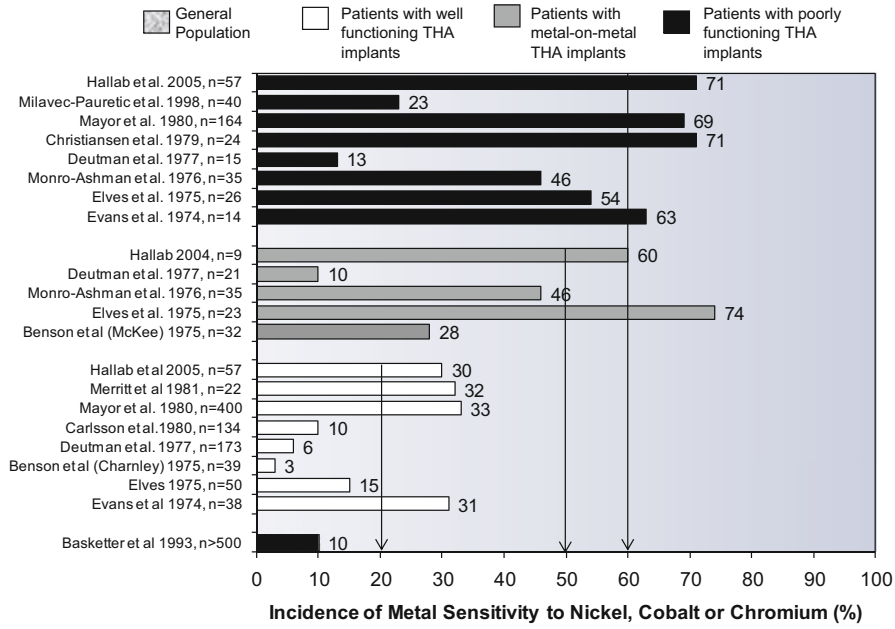

Fig. 6 A compilation of investigations showing the averaged percentage of metal sensitivity among the general population, people with well-functioning implants, people with metal-on-metal implants and people with failing implants (prior to getting them revised). Metal incidence rates include a positive response to allergy testing for nickel, cobalt, and/or chromium. All subjects were tested by means of a patch or metal-LTT (lymphocyte transformation test). (Courtesy of Orthopedic Analysis LLC)

1994; King et al. 1993; Merle et al. 1992; Rostoker et al. 1987; Thomas et al. 1987).

Incidence of Hypersensitivity Responses Among Patients with Metal Implants: People with well-function implants exhibit an incidence of hypersensitivity reactions (25%) twice as high as that of the general population (10%) (Fig. 6). Interestingly, the incidence of metal related hypersensitivity in people with poorly functioning metal prostheses (revision surgery candidates) or well-functioning metal-on-metal hip prostheses is 50–60% (Fig. 6). This higher incidence of metal hypersensitivity in cohorts of patients with metal prostheses has led to speculation that immune reactivity to metal implant components may play a role in implant loosening. Group studies performed over the last three decades have demonstrated a correlation between metal implants and metal sensitization (Hallab et al. 2001a), clearly concluding that metal sensitization can be an important causative factor to implant failure (Merritt and Rodrigo 1996; Rooker and Wilkinson 1980; Rostoker et al. 1987).

Therefore, metal sensitivity testing (metal-LTT) may be beneficial for people with a history of metal allergy before receiving a metal prosthesis. The significance of this line of research cannot be understated, as the use, durability, and performance expectations of metallic spinal implants continue to increase (Black 1996; Jacobs and Goodman 1996).

Metal Sensitivity Mechanism

Generally, metal sensitivity responses can be classified as: 1-Humoral immediate responses that can develop within minutes and are initiated by antibody-antigen complexes (Type I, II, III) and 2-cell-mediated delayed type hypersensitivity responses type IV, which may develop within hours to days (Hensten-Pettersen 1993; Kuby 1991). Immune responses to metal implant degradation products are almost exclusively classified as being delayed type hypersensitivity responses (DTH). This specific type of DTH response has

been predominantly classified as a Th1 type of response, where helper T cells are characterized by the release of a unique signature set of cytokines that include interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-2 (IL-2). While this specific subset of cells are intended to detect and eradicate intracellular pathogens, they can also potentially induce autoimmune disorders (i.e., Rheumatoid arthritis, Lups, etc.) when mistakenly activated (Arora et al. 2003b; Hallab et al. 2008).

In this manner, activated and primed antigen presenting cells in combination with metal-activated T helper lymphocytes secrete a variety of pro-inflammatory cytokines that effect the recruitment and activation of innate immune cells (i.e., monocytes, macrophages, neutrophils) (Hallab et al. 2013). Some of these cytokines include, but are not limited to IFN-γ and TNF-β, which in turn induce pro-inflammatory physiological changes on local cells (i.e., endothelial cells) to aid the inflammatory response. The main characteristics of a DTH immune response are recruitment, recognition/activation, and migration inhibition of local immune cells (e.g., macrophages, T lymphocytes). Additionally, the release of potent pro-inflammatory cytokines like IL-1β from activated antigen presenting cells effect further recruitment and activation of T cells, which in turn activate additional macrophages exacerbating the immune response. Therefore, in certain types of DTH responses, including those associated with autoimmune diseases, there is a lack of self-regulation (off-switch) that can result in the perpetuation of the inflammatory response resulting in extensive tissue damage. Immunosuppression has been proposed as a strategy to mitigate the effects of the vicious pro-inflammatory cycle of DTH responses in these individuals in order to aid anti-inflammatory immune mechanisms to operate (Looney et al. 2006; Schwarz et al. 2000).

Testing for Metal Sensitivity

At present, there are two modalities accepted for human diagnostic testing for metal sensitivity: 1-patch testing (dermal testing) and 2-blood testing in vitro using a lymphocyte proliferation test (metal-LTT).

Dermal Skin Testing: Commercially available patch testing kits and protocols for the evaluation of metal induced hypersensitivity reactions have been used for over 40 years for purposes of orthopedic implants (Hensten-Pettersen 1993; Rooker and Wilkinson 1980). While patch testing can be a helpful tool in diagnosing dermal sensitivity to several metals, there are important limitations that must be considered when using this modality to assess DTH responses to orthopedic implant degradation products. (1) Primarily, performing patch testing pre-operatively has the potential to pre-sensitize the patient to one or more implant metals (Merritt and Brown 1980). The process of skin patch testing involves mixing metal ion/salts with an organic vehicle (i.e., petroleum Jelly) and the application of this mixture in direct contact with skin for 48 h. The extent to which dermal patch testing induces metal sensitization in humans is not known, but has been well established as a method to induce metal sensitization in animal models (Bonefeld et al. 2015; Vennegaard et al. 2014); therefore, it can potentially be a hazard for the purposes of diagnosing metal DTH responses in future orthopedic implant patients and a significant concern given how routinely this procedure is performed (Granchi et al. 2012). (2) An additional limitation of patch testing is the simulation of immunological potential of metal haptens in a nonsterile dermal environment compared to a significantly different sterile environment found in the peri-implant tissue (Korenblat 1992; Kuby 1991). For example, Langerhans cells – specialized antigen presenting cells of the skin – possess Birbeck granules which are unique antigen-processing/endosomal-processing organelles not found in macrophages/histiocytes in the peri-implant tissue (Mc et al. 2002; Valladeau et al. 2001). (3) Patch testing results are scored subjectively by a healthcare professional (i.e., Allergist) using a 0 to 3+ system, where results may not be easily compared between providers. (4) Immunological responses to patch testing challenge may be severely diminished due to the nature of the site of challenge and inherent

tolerance to environmental factors (i.e., metals) (Benson et al. 1975; Poss et al. 1984; Rooker and Wilkinson 1980; Wang et al. 1997a). The environment of immune challenge during patch testing can be highly variable and is non-standardized as they are usually placed directly on the back of patients (hairless area) for 2 to 3 days and it can be inconsistent from patient to patient. It may also be uncomfortable and the environment under which the test is performed (i.e., cleanliness) cannot controlled or standardized. (5) Lastly, there are no standardized, well-established metal salt concentrations available for patch testing or the availability of all orthopedic implant metals in commercially available patch testing kits (e.g., aluminum, molybdenum, vanadium, and zirconium) (Table 2).

Lymphocyte Transformation Testing (LTT): Also termed lymphocyte proliferation test measures the division/proliferation of peripheral blood T lymphocytes in vitro after exposure to specific antigens during a period of 6 days. Lymphocytes are isolated from a patient's blood sample (simple blood draw) by density gradient separation of mononuclear cells. The proliferation of these lymphocytes is measured 4–6 days (DTH response) after initial antigen exposure using a radiolabeling technique. Radioactive [H^3]-thymidine is incorporated into the DNA of dividing (proliferating) cells and allows for the quantification of actual cell division in response to several metal challenge agents (i.e., Al + 3, Co + 2, Cr + 3, Mo + 5, Ni + 2, V + 3, and Zr + 4) at different concentrations ranging from 0.001 to 0.1 mM. This specific modality of detection of cell proliferation has the ability to detect the specific subset of cells undergoing cell division in response to the antigen challenge. The final amount of proliferation is measured as a Stimulation Index (SI).

> Proliferation Index or Stimulation Index (SI) = (proliferation with treatment, cpms)/(proliferation of equal amount of starting cells of the same individual without treatment, cpms).

Lymphocyte transformation testing (LTT) has gradually become a more widely used and accepted test modality for the diagnosis of orthopedic implant-related metal sensitivity as well as in cohort and basic science studies of metal-induced DTH responses (Everness et al. 1990; Secher et al. 1977; Svejgaard et al. 1976, 1978; Veien and Svejgaard 1978; Veien et al. 1979). LTT testing is performed by isolating mononuclear cells from a patient's peripheral blood sample (i.e., T-cells, B-cells and other lymphocyte populations) and directly exposing them to metal challenge in order to simulate the local peri-implant environment (not possible with dermal patch testing) (Hallab et al. 1998b, 2000, 2000a, b, 2001b, 2013, 2003b). An advantage of LTT testing is that is highly quantitative and not dependent on subjective assessment of results (vs. patch testing) (Thomas et al. 2009). The stimulation Index (SI) is quantified from multiwell replicates of each challenge agent at each concentration tested that allows for the calculation of an average and standard deviation for each antigen tested. This enables assessment of a dose dependent response where a metal sensitive individual may exhibit lymphocyte proliferation at a lower or higher dose of metal challenge (Fig. 2). LTT has also shown to have a greater sensitivity to detect lymphocyte metal sensitization (>80%) compared to patch testing (Carando et al. 1985; Cederbrant et al. 1997; Federmann et al. 1994; Nyfeler and Pichler 1997; Primeau and Adkinson 2001; Torgersen et al. 1993). A recent study performed by Carossino et al. (2016; Innocenti et al. 2014) where patch testing, LTT, and cytokine analysis were performed concluded that "The lymphocyte transformation is the most suitable method for testing systemic allergies." This testing modality is gaining momentum and is increasingly becoming more relevant to the orthopedic community given the growing numbers of TJA performed each year (Kurtz et al. 2009).

Furthermore, other prospective and longitudinal studies as the one discussed in the next section regarding metal-on-metal devices substantiate the concept that LTT or Patch Testing are necessary in a clinical setting, especially for patients receiving specific types of devices that may be more prone to induce metal sensitization. There are also further case and group studies supporting the clinical utility and routine use of metal sensitivity testing for total joint replacement (TJR) patients that have

a history of metal allergy and/or for patients with aseptic/idiopathic implant related pain (Campbell et al. 2010; Hallab et al. 2013; Kwon et al. 2010, 2011; Thomas et al. 2009; Willert et al. 2005; Willert and Semlitsch 1977). Interestingly, while instability and infection are the primary causes of early implant failure, recent reports have put forward algorithms that include metal-induced DTH testing as a possible indication for patients with post-operative pain (Fig. 3) (Park et al. 2016). This specific algorithm suggests that metal-LTT and dermal testing should be performed as a last resort after imaging techniques (MRI, CT) and other infection indications have been ruled out.

Studies of Implant Related Metal Sensitivity Using Diagnostic Testing

Several studies performed over the past four decades have associated metal allergy or metal sensitivity with adverse implant immune responses, where the quantity of implant degradation products has been temporarily linked to symptoms such as severe dermatitis, urticaria, vasculitis (Abdallah et al. 1994; Barranco and Solloman 1972; Halpin 1975; King et al. 1993; Merle et al. 1992; Thomas et al. 1987), and/or nonspecific immune suppression (Bravo et al. 1990; Gillespie et al. 1988; Merritt and Brown 1985; Poss et al. 1984; Wang et al. 1997b). Some case studies have demonstrated cessation of metal sensitivity symptoms after removal of the implant and the reappearance of symptoms once a comparable implant was re-introduced. This agrees with Koch's postulate, an important test for causality in medicine, and demonstrates metal-induced sensitivity responses as causal for early implant failure (Barranco and Solloman 1972). Nevertheless, the majority of the evidence demonstrating the significant clinical utility of metal sensitivity testing can be credited to several retrospective cohort studies that have shown a strong correlation between metal exposure, metal sensitivity, and the performance of metal implants (Benson et al. 1975; Brown et al. 1977; Carlsson et al. 1980; Cramers and Lucht 1977; Deutman et al. 1977; Fischer et al. 1984; Kubba et al. 1981; Mayor et al. 1980; Merritt 1984; Merritt and Brown 1981; Pinkston and Finch 1979; Rooker and Wilkinson 1980). As mentioned previously, these studies demonstrate that people with well performing implants and people with painful/failing implants exhibit rates of metal hypersensitivity two fold or six fold higher compared to the general population, respectively (Caicedo et al. 2013b). It is also clear, based on current and past cohort studies, that specific types of metal implants known to release higher concentrations of ions and/or particles are more likely to induce metal sensitization (Hallab et al. 2013; Kwon et al. 2011).

While metal on metal total hip arthroplasties (MoM THA) provide the advantage of lower implant wear compared to metal-on-polymer (MoP) implants, they are known to release higher concentration of metal ions and particles and thus have a higher incidence of failure attributable to excessive inflammatory responses. Previous studies have shown hypersensitivity-like responses, including histological inflammatory evidence accompanied by severe lymphocyte infiltrates, in as high as 76–100% of patients with poorly performing MoM devices (Korovessis et al. 2006; Milosev et al. 2006). In a prospective study using a cohort of MoM patients, it was shown that in vivo metal sensitivity responses may develop even in well performing (asymptomatic) MoM implants (Hallab et al. 2013) where a significant increase in the rate of diagnosed metal sensitivity increased from 5% preoperatively to 56% within the first 4 years postoperatively (Hallab et al. 2013). In this study increases in serum levels of Co and Cr occurred at early stage, at 3 months postoperatively. However, lymphocyte sensitivity responses only became more evident at 1–4 years post-op. This delay in detection of metal sensitivity responses postoperatively suggests that metal sensitization may develop over-time as exposure to metal ion levels increase. The rates found, while still high compared to conventional implants (25%), are lower than 81% in failing MoM implants previously reported for painful/symptomatic MOM patients by Thomas et al. (2009).

Pain levels have also been shown to correlate with metal sensitivity (Metal-LTT with SI >2) where patients with highly painful implants were

significantly higher compared to patients with nonpainful implants (Caicedo et al. 2013b). Furthermore, TJA patients that reported low implant pain levels also exhibited a relatively lower incidence of metal sensitization further supporting a correlation between aseptic implant pain levels and metal sensitivity. Additionally, not only do TJA female patients referred for metal sensitivity testing exhibit a higher average pain level compared to males, but also show a higher incidence and severity of metal sensitization (Caicedo et al. 2017). This supports the utility of metal DTH testing in patients with aseptic implant-related pain, especially for female orthopedic patients.

Conclusions

Implant degradation and debris is unavoidable and results in activation of the immune system resulting in local inflammation that over time causes more bone loss then homeostatic mechanisms can keep up with, and the result is implant loosening, via aseptic osteolysis. This reactivity may activate the adaptive immune systems and result in allergic type responses involving T-cells. Both innate (macrophage) and adaptive (T lymphocyte) immune system reactivity can act to limit the lifetime of current total joint replacement implants. Advances at the molecular and cellular level continue to increase our understanding of immune reactivity based bone loss. There are a new treatment and diagnostic options available for patients and surgeons ranging from diagnosing preexisting or developed conditions of metal allergy (metal-LTT), general management of inflammation (e.g., NSAIDS) to selective blocking of cellular mediators (e.g., anti-IL-6, anti-TNFα, IL-1β-receptor antagonist). These options should be part of the modern arsenal used to help fight the problem of adverse reactivity to implant debris, i.e., induced inflammatory bone loss. There is increasing need for using patient specific diagnosis and treatment to mitigate the role of metal hypersensitivity and genetic susceptibility to implant debris-induced inflammation.

References

Abdallah HI, Balsara RK, O'Riordan AC (1994) Pacemaker contact sensitivity: clinical recognition and management. Ann Thorac Surg 57:1017–1018

Archibeck MJ, Jacobs JJ, Roebuck KA, Glant TT (2001) The basic science of periprosthetic osteolysis. Instr Course Lect 50:185–195

Arora A, Song Y, Chun L, Huie P, Trindade M, Smith RL, Goodman S (2003a) The role of the TH1 and TH2 immune responses in loosening and osteolysis of cemented total hip replacements. J Biomed Mater Res A 64(4):693–697

Arora A, Song Y, Chun L, Huie P, Trindade M, Smith RL, Goodman S (2003b) The role of the TH1 and TH2 immune responses in loosening and osteolysis of cemented total hip replacements. J Biomed Mater Res 64A(4):693–697

Barranco VP, Solloman H (1972) Eczematous dermatitis from nickel. JAMA 220(9):1244

Benson MK, Goodwin PG, Brostoff J (1975) Metal sensitivity in patients with joint replacement arthroplasties. Br Med J 4:374–375

Beyersmann D (1994) Interactions in metal carcinogenicity. Toxicol Lett 72(1–3):333–338

Black J (1996) Prosthetic Materials. VCH Publishers, Inc., New York

Bonefeld CM, Nielsen MM, Vennegaard MT, Johansen JD, Geisler C, Thyssen JP (2015) Nickel acts as an adjuvant during cobalt sensitization. Exp Dermatol 24(3):229–231

Bravo I, Carvalho GS, Barbosa MA, de Sousa M (1990) Differential effects of eight metal ions on lymphocyte differentiation antigens in vitro. J Biomed Mater Res 24(8):1059–1068

Britton RS (1996) Metal-induced Hepatoxicity. Semin Liver Dis 16(1):3–12

Brown GC, Lockshin MD, Salvati EA, Bullough PG (1977) Sensitivity to metal as a possible cause of sterile loosening after cobalt-chromium total hip-replacement arthroplasty. J Bone Joint Surg Am 59-A(2):164–168

Burt CF, Garvin KL, Otterberg ET, Jardon OM (1998) A femoral component inserted without cement in total hip arthroplasty. A study of the tri-lock component with an average ten-year duration of follow-up. J Bone Joint Surg Am 80(7):952–960

Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ (2008) 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 27(7):847–854

Caicedo MS, Pennekamp PH, McAllister K, Jacobs JJ, Hallab NJ (2010) Soluble ions more than particulate cobalt-alloy implant debris induce monocyte costimulatory molecule expression and release of pro-inflammatory cytokines critical to metal-induced lymphocyte reactivity. J Biomed Mater Res A 93(4): 1312–1321

Caicedo MS, Samelko L, McAllister K, Jacobs JJ, Hallab NJ (2013a) Increasing both CoCrMo-alloy particle size and surface irregularity induces increased macrophage inflammasome activation in vitro potentially through lysosomal destabilization mechanisms. J Orthop Res 31(10):1633–1642

Caicedo MS, Samelko L, Hallab NJ (2013b) Lymphocyte reactivity to nickel correlates with reported high-pain levels in patients with Total joint arthroplasties: implications for pain-related hypersensitivity responses, Metal-on-metal total hip replacement devices. ASTM STP STP 1560:1–17

Caicedo MS, Solver E, Coleman L, Jacobs JJ, Hallab NJ (2017) Females with unexplained joint pain following total joint arthroplasty exhibit a higher rate and severity of hypersensitivity to implant metals compared with males: implications of sex-based bioreactivity differences. J Bone Joint Surg Am 99(8):621–628

Campbell P, Ma S, Yeom B, McKellop H, Schmalzried TP, Amstutz HC (1995) Isolation of predominantly submicron-sized UHMWPE wear particles from periprosthetic tissues. J Biomed Mater Res 29(1): 127–131

Campbell P, Ebramzadeh E, Nelson S, Takamura K, De SK, Amstutz HC (2010) Histological features of pseudotumor-like tissues from metal-on-metal hips. Clin Orthop Relat Res 468(9):2321–2327

Carando S, Cannas M, Rossi P, Portigliatti-Barbos M (1985) The lymphocytic transformation test (L.T.T.) in the evaluation of intolerance in prosthetic implants. Ital J Orthop Traumatol 11(4):475–481

Carlsson AS, Macnusson B, Moller H (1980) Metal sensitivity in patients with metal-to-plastic total hip arthroplasties. Acta Orthop Scand 51:57–62

Carossino AM, Carulli C, Ciuffi S, Carossino R, Zappoli Thyrion GD, Zonefrati R, Innocenti M, Brandi ML (2016) Hypersensitivity reactions to metal implants: laboratory options. BMC Musculoskelet Disord 17(1):486

Catelas I, Petit A, Marchand R, Zukor DJ, Yahia L, Huk OL (1999) Cytotoxicity and macrophage cytokine release induced by ceramic and polyethylene particles in vitro. J Bone Joint Surg Br 81(3):516–521

Catelas I, Petit A, Zukor DJ, Antoniou J, Huk OL (2003) TNF-alpha secretion and macrophage mortality induced by cobalt and chromium ions in vitro-qualitative analysis of apoptosis. Biomaterials 24(3): 383–391

Catelas I, Medley JB, Campbell PA, Huk OL, Bobyn JD (2004) Comparison of in vitro with in vivo characteristics of wear particles from metal-metal hip implants. J Biomed Mater Res B Appl Biomater 70(2):167–178

Cederbrant K, Hultman P, Marcusson JA, Tibbling L (1997) In vitro lymphocyte proliferation as compared to patch test using gold, palladium and nickel. Int Arch Allergy Immunol 112(3):212–217

Charnley J (1970) The reaction of bone to self-curing acrylic cement. A long-term histological study in man. J Bone Joint Surg Br 52(2):340–353

Charnley J (1979) Low friction arthroplasty of the hip, theory and practice. Springer, Berlin

Choma TJ, Miranda J, Siskey R, Baxter R, Steinbeck MJ, Kurtz SM (2009) Retrieval analysis of a ProDisc-L total disc replacement. J Spinal Disord Tech 22(4): 290–296

Cooper HJ, Urban RM, Wixson RL, Meneghini RM, Jacobs JJ (2013) Adverse local tissue reaction arising from corrosion at the femoral neck-body junction in a dual-taper stem with a cobalt-chromium modular neck. J Bone Joint Surg Am 95(10):865–872

Cramers M, Lucht U (1977) Metal sensitivity in patients treated for tibial fractures with plates of stainless steel. Acta Orthop Scand 48:245–249

Deutman R, Mulder TH, Brian R, Nater JP (1977) Metal sensitivity before and after total hip arthroplasty. J Bone Joint Surg Am 59-A:862–865

Dorr LD, Bloebaum R, Emmanual J, Meldrum R (1990) Histologic, biochemical and ion analysis of tissue and fluids retrieved during total hip arthroplasty. Clin Orthop Relat Res 261:82–95

Dostert C, Petrilli V, Van BR, Steele C, Mossman BT, Tschopp J (2008) Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 320(5876):674–677

Elves MW, Wilson JN, Scales JT, Kemp HB (1975) Incidence of metal sensitivity in patients with total joint replacements. Br Med J 4:376–378

Everness KM, Gawkrodger DJ, Botham PA, Hunter JA (1990) The discrimination between nickel-sensitive and non-nickel-sensitive subjects by an in vitro lymphocyte transformation test. Br J Dermatol 122(3): 293–298

Federmann M, Morell B, Graetz G, Wyss M, Elsner P, von Thiessen R, Wuthrich B, Grob D (1994) Hypersensitivity to molybdenum as a possible trigger of ANA-negative systemic lupus erythematosus. Ann Rheum Dis 53(6):403–405

Fischer T, Rystedt I, Safwenberg J, Egle I (1984) HLA -A, -B, -C and -DR antigens in individuals with sensitivity to cobalt. Acta Derm Venereol (Stockh) 64:121–124

Gillespie WJ, Frampton CM, Henderson RJ, Ryan PM (1988) The incidence of cancer following total hip replacement. J Bone Joint Surg Br 70(4):539–542

Goering PL, Klaasen CD (1995) Hepatoxicity of metals. Academic, New York

Goldring SR, Schiller AL, Roelke M, Rourke CM, O'Neill DA, Harris WH (1983) The synovial-like membrane at the bone-cement interface in loose total hip replacements and its proposed role in bone lysis. J Bone Joint Surg 65A:575–584

Gordon PM, White MI, Scotland TR (1994) Generalized sensitivity from an implanted orthopaedic antibiotic minichain containing nickel. Contact Dermatitis 30:181–182

Granchi D, Cenni E, Giunti A, Baldini N (2012) Metal hypersensitivity testing in patients undergoing joint replacement: a systematic review. J Bone Joint Surg Br 94(8):1126–1134

Hallab NJ, Jacobs JJ, Skipor AK, Black J, Glant T, Mikecz K (1998b) In vitro testing of metal induced luekocyte activation. Trans Soc Biomater 21:76

Hallab NJ, Jacobs JJ, Skipor A, Black J, Mikecz K, Galante JO (2000) Systemic metal-protein binding associated with total joint replacement arthroplasty. J Biomed Mater Res 49(3):353–361

Hallab NJ, Jacobs JJ, Skipor A, Black J, Mikecz K, Galante JO (2000a) Systemic metal-protein binding associated with total joint replacement arthroplasty. J Biomed Mater Res 49(3):353–361

Hallab NJ, Mikecz K, Jacobs JJ (2000b) A triple assay technique for the evaluation of metal-induced, delayed-type hypersensitivity responses in patients with or receiving total joint arthroplasty. J Biomed Mater Res 53(5):480–489

Hallab N, Merritt K, Jacobs JJ (2001a) Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 83-A(3):428–436

Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ (2001b) Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. J Biomed Mater Res 56(3):427–436

Hallab NJ, Cunningham BW, Jacobs JJ (2003a) Spinal implant debris-induced Osteolysis. Spine 28(20): S125–S138

Hallab NJ, Skipor A, Jacobs JJ (2003b) Interfacial kinetics of titanium- and cobalt-based implant alloys in human serum: metal release and biofilm formation. J Biomed Mater Res 65A(3):311–318

Hallab NJ, Caicedo M, Finnegan A, Jacobs JJ (2008) Th1 type lymphocyte reactivity to metals in patients with total hip arthroplasty. J Orthop Surg 3:6

Hallab NJ, Caicedo M, McAllister K, Skipor A, Amstutz H, Jacobs JJ (2013) Asymptomatic prospective and retrospective cohorts with metal-on-metal hip arthroplasty indicate acquired lymphocyte reactivity varies with metal ion levels on a group basis. J Orthop Res 31(2):173–182

Hallab NJ, Caicedo M, McAllister K, Skipor A, Amstutz H, Jacobs JJ (2013) Asymptomatic prospective and retrospective cohorts with metal-on-metal hip arthroplasty indicate acquired lymphocyte reactivity varies with metal ion levels on a group basis. J Orthop Res 31(2):173–182

Halpin DS (1975) An unusual reaction in muscle in association with a vitallium plate: a report of possible metal hypersensitivity. J Bone Joint Surg 57-B (4):451–453

Hartwig A (1998) Carcinogenicity of metal compounds: possible role of DNA repair inhibition. Toxicol Lett 102–103:235–239

Hensten-Pettersen A (1993) Allergy and hypersensitivity. In: Morrey BF (ed) Biological, material, and mechanical considerations of joint replacements. Raven Press, New York, pp 353–360

Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, Fitzgerald KA, Latz E (2008) Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 9(8):847–856

Innocenti M, Carulli C, Matassi F, Carossino AM, Brandi ML, Civinini R (2014) Total knee arthroplasty in patients with hypersensitivity to metals. Int Orthop 38(2):329–333

Jacobs JJ, Goodman SL (1996) What in vitro, in vivo and combined approaches can be used to investigate the biologic effects of particles? In: Wright TM, Goodman SB (eds) Implant Wear: the future of total joint replacement. American Academy of Orthopedic Surgeons, Rosemont, pp 41–44

Jacobs JJ, Hallab NJ (2006) Loosening and osteolysis associated with metal-on-metal bearings: a local effect of metal hypersensitivity? J Bone Joint Surg Am 88(6):1171–1172

Jacobs JJ, Gilbert JL, Urban RM (1994) Corrosion of metallic implants. In: Stauffer RN (ed) Advances in Orthopaedic surgery, vol 2. Mosby, St. Louis, pp 279–319

Jacobs JJ, Shanbhag A, Glant TT, Black J, Galante JO (1994a) Wear debris in total joint replacements. J Am Acad Orthop Surg 2(4):212–220

Jacobs JJ, Skipor AK, Urban RM, Black J, Manion LM, Starr A, Talbert LF, Galante JO (1994b) Systemic distribution of metal degradation products from titanium alloy total hip replacements: an autopsy study. Trans Orthop Res Soc New Orleans:838

Jacobs JJ, Gilbert JL, Urban RM (1998a) Corrosion of metal orthopaedic implants. J Bone Joint Surg Am 80 (2):268–282

Jacobs JJ, Skipor AK, Patterson LM, Hallab NJ, Paprosky WG, Black J, Galante JO (1998b) Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am 80(10):1447–1458

Jacobs J, Goodman S, Sumner DR, Hallab N (1999a) Biologic response to orthopedic implants. In: Orthopedic basic science. American Academy of Orthopedic Surgeons, Chicago, pp 402–426

Jacobs JJ, Silverton C, Hallab NJ, Skipor AK, Patterson L, Black J, Galante JO (1999b) Metal release and excretion from cementless titanium alloy total knee replacements. Clin Orthop 358:173–180

Jacobs JJ, Roebuck KA, Archibeck M, Hallab NJ, Glant TT (2001) Osteolysis: basic science. Clin Orthop Relat Res 393:71–77

Kaufman AM, Alabre CI, Rubash HE, Shanbhag AS (2008) Human macrophage response to UHMWPE, TiAlV, CoCr, and alumina particles: analysis of multiple cytokines using protein arrays. J Biomed Mater Res A 84(2):464–474

King J, Fransway A, Adkins RB (1993) Chronic urticaria due to surgical clips. N Engl J Med 329(21):1583–1584

Korenblat PE (1992) Contact dermatitis, 2nd edn. W.B. Saunders Company, Philidelphia

Korovessis P, Petsinis G, Repanti M, Repantis T (2006) Metallosis after contemporary metal-on-metal total hip

arthroplasty. Five to nine-year follow-up. J Bone Joint Surg Am 88(6):1183–1191

Kubba R, Taylor JS, Marks KE (1981) Cutaneous complications of orthopedic implants. A two-year prospective study. Arch Dermatol 117:554–560

Kuby J (1991) Immunology, 2nd edn. W.H. Freeman and Company, New York

Kurtz S, Ong K, Lau E, Mowat F, Halpern M (2007a) Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 89(4):780–785

Kurtz SM, Ong KL, Schmier J, Mowat F, Saleh K, Dybvik E, Karrholm J, Garellick G, Havelin LI, Furnes O, Malchau H, Lau E (2007b) Future clinical and economic impact of revision total hip and knee arthroplasty. J Bone Joint Surg Am 89(Suppl 3): 144–151

Kurtz SM, Ong KL, Schmier J, Zhao K, Mowat F, Lau E (2009) Primary and revision arthroplasty surgery caseloads in the United States from 1990 to 2004. J Arthroplasty 24(2):195–203

Kwon YM, Thomas P, Summer B, Pandit H, Taylor A, Beard D, Murray DW, Gill HS (2010) Lymphocyte proliferation responses in patients with pseudotumors following metal-on-metal hip resurfacing arthroplasty. J Orthop Res 28(4):444–450

Kwon YM, Ostlere SJ, Lardy-Smith P, Athanasou NA, Gill HS, Murray DW (2011) "Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. J Arthroplasty 26(4):511–518

Lewis JB, Randol TM, Lockwood PE, Wataha JC (2003) Effect of subtoxic concentrations of metal ions on NFkappaB activation in THP-1 human monocytes. J Biomed Mater Res A 64(2):217–224

Looney RJ, Schwarz EM, Boyd A, O'Keefe RJ (2006) Periprosthetic osteolysis: an immunologist's update. Curr Opin Rheumatol 18(1):80–87

Luckey TD, Venugopal B (1979) Metal toxicity in mammals. Plenum, New York

Maloney WJ, Smith RL, Castro F, Schurman DJ (1993) Fibroblast response to metallic debris in vitro. Enzyme induction cell proliferation, and toxicity. J Bone Joint Surg Am 75(6):835–844

Mariathasan S, Monack DM (2007) Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. Nat Rev Immunol 7(1):31–40

Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, Roose-Girma M, Erickson S, Dixit VM (2004) Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature 430 (6996):213–218

Mayor MB, Merritt K, Brown SA (1980) Metal allergy and the surgical patient. Am J Surg 139:477–479

Mc DR, Ziylan U, Spehner D, Bausinger H, Lipsker D, Mommaas M, Cazenave JP, Raposo G, Goud B, de la Salle H, Salamero J, Hanau D (2002) Birbeck granules are subdomains of endosomal recycling compartment in human epidermal Langerhans cells, which form where Langerin accumulates. Mol Biol Cell 13(1): 317–335

Merle C, Vigan M, Devred D, Girardin P, Adessi B, Laurent R (1992) Generalized eczema from vitallium osteosynthesis material. Contact Dermatitis 27:257–258

Merritt K (1984) Role of medical materials, both in implant and surface applications, in immune response and in resistance to infection. Biomaterials 5:53–57

Merritt K, Brown S (1980) Tissue reaction and metal sensitivity. Acta Orthop Scand 51:403–4111

Merritt K, Brown S (1981) Metal sensitivity reactions to orthopedic implants. Int J Dermatol 20:89–94

Merritt K, Brown SA (1985) Biological effects of corrosion products from metal. American Society for Testing and Materials, Philadelphia

Merritt K, Rodrigo JJ (1996) Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. Clin Orthop Relat Res 326:71–79

Michel R, Hoffman J, Loer F, Zilkens J (1984) Trace element burdening of human tissue due to corrosion of hip-joint prostheses made of cobalt-chromium alloys. Arch Orthop Trama Surg 103:85–95

Michel R, Nolte M, Reich M, Loer F (1991) Systemic effects of implanted prostheses made of cobalt-chromium alloys. Arch Orthop Trauma Surg 110:61–74

Milosev I, Trebse R, Kovac S, Cor A, Pisot V (2006) Survivorship and retrieval analysis of Sikomet metal-on-metal total hip replacements at a mean of seven years. J Bone Joint Surg Am 88(6):1173–1182

Naganuma Y, Takakubo Y, Hirayama T, Tamaki Y, Pajarinen J, Sasaki K, Goodman SB, Takagi M (2016) Lipoteichoic acid modulates inflammatory response in macrophages after phagocytosis of titanium particles through Toll-like receptor 2 cascade and inflammasomes. J Biomed Mater Res A 104(2): 435–444

Nyfeler B, Pichler WJ (1997) The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. Clin Exp Allergy 27(2):175–181

Park CN, White PB, Meftah M, Ranawat AS, Ranawat CS (2016) Diagnostic algorithm for residual pain after total knee arthroplasty. Orthopedics 39(2):e246–e252

Petrilli V, Dostert C, Muruve DA, Tschopp J (2007) The inflammasome: a danger sensing complex triggering innate immunity. Curr Opin Immunol 19(6):615–622

Pinkston JA, Finch SC (1979) A method for the differentiation of T and B lymphocytes and monocytes migrating under agarose. Stain Technol 54(5):233–239

Poss R, Thornhill TS, Ewald FC, Thomas WH, Batte NJ, Sledge CB (1984) Factors influencing the incidence and outcome of infection following total joint arthoplasty. Clin Orthop 182:117–126

Primeau MN, Adkinson NF Jr (2001) Recent advances in the diagnosis of drug allergy. Curr Opin Allergy Clin Immunol 1(4):337–341

Punt IM, Visser VM, van Rhijn LW, Kurtz SM, Antonis J, Schurink GW, van Ooij A (2008) Complications and

reoperations of the SB Charite lumbar disc prosthesis: experience in 75 patients. Eur Spine J 17(1):36–43

Punt IM, Cleutjens JP, de Bruin T, Willems PC, Kurtz SM, van Rhijn LW, Schurink GW, van Ooij A (2009) Periprosthetic tissue reactions observed at revision of total intervertebral disc arthroplasty. Biomaterials 30 (11):2079–2084

Radcliffe GS, Tomichan MC, Andrews M, Stone MH (1999) Revision hip surgery in the elderly: is it worthwhile? J Arthroplasty 14(1):38–44

Rooker GD, Wilkinson JD (1980) Metal sensitivity in patients undergoing hip replacement. A prospective study. J Bone Joint Surg 62-B(4):502–505

Rostoker G, Robin J, Binet O, Blamutier J, Paupe J, Lessana-Liebowitch M, Bedouelle J, Sonneck JM, Garrel JB, Millet P (1987) Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. J Bone Joint Surg 69-A(9):1408–1412

Schwarz EM, Looney RJ, O'Keefe RJ (2000) Anti-TNF-alpha therapy as a clinical intervention for periprosthetic osteolysis. Arthritis Res 2(3):165–168

Scott M, Morrison M, Mishra SR, Jani S (2005) Particle analysis for the determination of UHMWPE wear. J Biomed Mater Res B Appl Biomater 73(2):325–337

Secher L, Svejgaard E, Hansen GS (1977) T and B lymphocytes in contact and atopic dermatitis. Br J Dermatol 97(5):537–541

Sethi RK, Neavyn MJ, Rubash HE, Shanbhag AS (2003) Macrophage response to cross-linked and conventional UHMWPE. Biomaterials 24(15):2561–2573

Stulberg BN, Merritt K, Bauer T (1994) Metallic wear debris in metal-backed patellar failure. J Biomed Mat Res Appl Biomater 5:9–16

Svejgaard E, Thomsen M, Morling N, Hein CA (1976) Lymphocyte transformation in vitro in dermatophytosis. Acta Pathol Microbiol Scand C 84C(6): 511–523

Svejgaard E, Morling N, Svejgaard A, Veien NK (1978) Lymphocyte transformation induced by nickel sulphate: an in vitro study of subjects with and without a positive nickel patch test. Acta Derm Venereol 58 (3):245–250

Thomas RH, Rademaker M, Goddard NJ, Munro DD (1987) Severe eczema of the hands due to an orthopaedic plate made of Vitallium. Br Med J 294:106–107

Thomas P, Braathen LR, Dorig M, Aubock J, Nestle F, Werfel T, Willert HG (2009) Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. Allergy 64(8):1157–1165

Torgersen S, Gilhuus-Moe OT, Gjerdet NR (1993) Immune response to nickel and some clinical observations after stainless steel miniplate osteosynthesis. Int J Oral Maxillofac Surg 22(4):246–250

Trindade MC, Lind M, Nakashima Y, Sun D, Goodman SB, Schurman DJ, Smith RL (2001) Interleukin-10 inhibits polymethylmethacrylate particle induced interleukin-6 and tumor necrosis factor-alpha release by human monocyte/macrophages in vitro. Biomaterials 22(15):2067–2073

Urban RM, Jacobs JJ, Sumner DR, Peters CL, Voss FR, Galante JO (1996) The bone-implant interface of femoral stems with non- circumferential porous coating: a study of specimens retrieved at autopsy. J Bone Joint Surg Am 78-A(7):1068–1081

Urban RM, Jacobs J, Gilbert JL, Rice SB, Jasty M, Bragdon CR, Galante GO (1997) Characterization of solid products of corrosion generated by modular-head femoral stems of different designs and materials. In: Marlowe DE, Parr JE, Mayor MB (eds) STP 1301 modularity of orthopedic implants. ASTM, Philadelphia, pp 33–44

Urban RM, Hall DJ, Sapienza CI, Jacobs JJ, Sumner DR, Rosenberg AG, Galante JO (1998) A comparative study of interface tissues in cemented vs. cementless total knee replacement tibial components retrieved at autopsy. Trans SFB 21:255

Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M (2000) Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. J Bone Joint Surg Am 82(4):457–476

Valladeau J, Caux C, Lebecque S, Saeland S (2001) Langerin: a new lectin specific for Langerhans cells induces the formation of Birbeck granules. Pathol Biol (Paris) 49(6):454–455

van Ooij A, Kurtz SM, Stessels F, Noten H, van Rhijn L (2007) Polyethylene wear debris and long-term clinical failure of the Charite disc prosthesis: a study of 4 patients. Spine 32(2):223–229

Veien NK, Svejgaard E (1978) Lymphocyte transformation in patients with cobalt dermatitis. Br J Dermatol 99(2): 191–196

Veien NK, Svejgaard E, Menne T (1979) In vitro lymphocyte transformation to nickel: a study of nickel-sensitive patients before and after epicutaneous and oral challenge with nickel. Acta Derm Venereol 59(5): 447–451

Vennegaard MT, Dyring-Andersen B, Skov L, Nielsen MM, Schmidt JD, Bzorek M, Poulsen SS, Thomsen AR, Woetmann A, Thyssen JP, Johansen JD, Odum N, Menne T, Geisler C, Bonefeld CM (2014) Epicutaneous exposure to nickel induces nickel allergy in mice via a MyD88-dependent and interleukin-1-dependent pathway. Contact Dermatitis 71(4):224–232

Vermes C, Chandrasekaran R, Jacobs JJ, Galante JO, Roebuck KA, Glant TT (2001a) The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. J Bone Joint Surg Am 83(2):201–211

Vermes C, Glant TT, Hallab NJ, Fritz EA, Roebuck KA, Jacobs JJ (2001b) The potential role of the osteoblast in the development of periprosthetic osteolysis: review of in vitro osteoblast responses to wear debris, corrosion products, and cytokines and growth factors. J Arthroplasty 16(8 Suppl 1):95–100

Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT (1997a) Prosthetic metals impair murine immune response and cytokine release in vivo and in vitro. J Orthop Res 15(5):688–699

Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT (1997b) Prosthetic metals interfere with the functions of human osteoblast cells in vitro. Clin Orthop 339:216–226

Willert HG, Semlitsch M (1977) Reactions of the articular capsule to wear products of artificial joint prostheses. J Biomed Mater Res 11:157–164

Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 87(1):28–36