Immunological response to metallic implants

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Mechanisms

Inflammation: Biologic effect of implant debris

Hypersensitivity: Metal-induced allergy

Testing

Methodology

*In vivo versus in vitro* (dermal patch testing)

Metals in human body fluids

LTT or LAT (proliferation or activation of T Ly)

Case report (LAT testing)

Clinical significance
**Inflammation:** Biologic effect of implant debris

Particulate wear debris (of metals, ceramics or polymers) range in size from nanometers to millimeters.

Polymeric particles produced from implants generally fall into the range from 0.23 to 1 µm.

Metal and ceramic particles are generally an order of magnitude smaller than polymer particles.

There are few guidelines on what type of debris is most bioreactive and only little agreement on which types of particles are most bioreactive.
General particle characteristics on which local inflammation has been shown to depend:

1. Particle load (particle size and total volume)

2. Aspect ratio

3. Chemical reactivity

1. Greater particle load: Size and volume increase inflammation

Inflammatory response generally is proportional to the particle load or concentration of phagocytosable particles per tissue volume, and is also dependent on the average particle size. To produce an in vitro inflammatory response, particles need to be more than 150 nm to 10 μm, that is to say, within a phagocytosable range.
2. Elongated particles (fibers) are more proinflammatory than round particles

This phenomena has been well established, with the first investigations over 30 years ago involving asbestos fibers. Bruch J. Response of cell cultures to asbestos fibers. Environ Health Perspect. 1974

3. More chemically reactive particles are more proinflammatory

There is a growing consensus that metal particles are more proinflammatory or toxic, or both, when compared to polymers. Ramachandran et al. The effects of titanium and polymethylmethacrylate particles on osteoblast phenotypic stability. J Biomed Mater Res A. 2006

This opinion is not unanimous. Others have concluded that polymers are more proinflammatory than metals. von Knoch et al. Migration of polyethylene wear debris in one type of uncemented femoral component with circumferential porous coating: an autopsy study of 5 femurs. J Arthroplasty. 2000
Debris-induced immune activation is primarily mediated by innate immunity = macrophages

"nonspecific immunity"

Debris-induced immune activation

Aseptic inflammation

Aseptic osteolysis

Implant failure

Debris-induced immune activation

Aseptic inflammation

Aseptic osteolysis

Implant failure

Hallab & Jacobs Bulletin of the NYU Hospital for Joint Diseases 2009
Nobel Prize in Medicine 2011

Bruce A. Beutler
Jules A. Hoffmann
Ralph M. Steinman

For their discoveries concerning the specific activation of innate immunity:
NLR = NOD like receptors (NALP3)
TLR = Toll like receptors

Ralph M. Steinman
For his discovery of the dendritic cell and its role in adaptive immunity.
Phagocytosing debris induce inflammasome danger-signaling (NALP3).

Potent proinflammatory cytokine IL-1β is produced.
1. **Decreased osteoblast function**
- Decreased osteoblast deposition (compromise mesenchymal stem-cell differentiation into functional osteoblasts)
- Inhibition of collagen synthesis
- Induction of apoptosis

2. **Osteoclast activity increases**
- Stimulate differentiation of osteoclast precursors into mature osteoclasts
- Increase bone resorption, which is not replaced by new bone

**NFκβ pathway induction of TNF-α, IL-1β, IL-6, and PGE2**
Hypersensitivity to “metal ions”: Metal-induced allergy

All metals corrode in vivo and the released ions can activate the immune system by forming complexes with native proteins (hapten concept).

Metals known as sensitizers include beryllium, nickel, cobalt, and chromium, while occasional responses have been reported to tantalum, titanium, and vanadium.

The specific T-cell subpopulations, the cellular mechanism of recognition and activation, and the antigenic metal-protein determinants created by these metals, remain incompletely characterized.

Type I: IgE-mediated hypersensitivity
Type II: IgG-mediated cytotoxicity
Type III: immune complex deposition
Type IV: T-cell–mediated hypersensitivity
Haptens are chemically reactive small molecules (mostly <1000 D) that bind covalently to a larger protein or peptide.

T-cell sensitization occurs when such hapten-carrier complexes are taken up by antigen-presenting cells (APCs) and then transported into the local draining lymphoid tissue, where they are processed and presented on major histocompatibility complexes (MHCs).
Testing

In vivo dermal patch testing

Allergens are applied epicutaneously to uninvolved skin for 48 h and the skin reaction is evaluated at the time of their removal and again 24 h later.

There is continuing concern about the applicability of skin testing for the study of immune responses to implants regarding the questionable equivalence of dermal Langerhans cells to peri-implant antigen presenting cells.

Similar dermal patch is not optimal for testing T-cell–mediated drug hypersensitivity.
# Metals in human body fluids

Approximate concentrations of metal in human body fluids and in human tissue with and without total joint replacements.

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

Normal: Subjects without any metallic prosthesis (not including dental). TJA: Subjects with total joint arthroplasty. Data Not Available (*). Ti (titanium), Al (Aluminum), V (vanadium), Co (cobalt), Cr (chromium), Mo (molybdenum), Ni (nickel).

- **Ti**
  - Serum: TJA 1.5x of normal
  - Synovial Fluid: TJA 43x of normal

- **Co or Cr**
  - Serum: TJA 2.3x or 6x of normal
  - Synovial Fluid: TJA 118x or 128x of normal
LTT or LAT = measurement of metal-reacting T cells
(Alternatively: cytokine production)

T cells play a key role in delayed-type hypersensitivity reactions. Their reactivity can be assessed by their proliferation or activation in response to the antigen.

LTT = lymphocyte transformation test

Generating antigen-reactive T-cell lines and T-cell clones from peripheral blood mononuclear cells (PBMC) cultures isolated from patients and stimulated with antigen (48h). Its require 3H-thymidine incorporation!

LTT-MELISA® (Memory Lymphocyte Immuno Stimulation Assay), an commercial lymphocyte transformation test (www.melisa.org)

Stimulation indices (SI) is calculated as counts per minutes (cpm) in culture medium (CM) with antigen divided by cpm in CM without antigen. A stimulation index of is a 2 cut-off value

SI < 2: is considered negative
SI ≥ 2 but <3: a possible sensitization
SI ≥ 3: positive sensitization

SI 2–3 “weakly positive”
SI 3–5 “positive”
SI > 5 “strongly positive”
LAT = lymphocyte activation test

Measurement of CD69 up regulation on antigen-reactive T-cells and T-cell clones from peripheral blood mononuclear cells (PBMC) cultures isolated from patients and stimulated with antigen. Its require FACS, it distinguish CD4+ and CD8+ T cells, highly quantitative.

Freshly isolated PBMC (2 \cdot 10^5) are cultured for 48h in U-bottomed tissue culture plates in the presence of indicated drug or metal concentrations, and PHA (positive control) or culture medium without antigen. CD69 expression on CD4+/CD8+ T cells is measured by flow cytometry with anti-human monoclonal antibodies (mAb) PE-CD69, PerCP-CD3, FITC-CD4, APC-CD8 and PE-IgG1 as isotype control (BD).
Clinical significance

Host response to orthopaedic implants debris is central to clinical performance.

Implant loosening due to aseptic osteolysis accounts for over 75% of total joint arthroplasty implant failure (infection only 7%) and is the predominant factor limiting the longevity of current TJAs.

Debris-induced immune reactivity, aseptic inflammation, and subsequent early failure have been reported to be as high as 4% to 5% at 6 to 7 years after surgery in current generation metal-on-metal TJA.


Milosev et al. *Survivorship and retrieval analysis of Sikomet metal-on-metal total hip replacements at a mean of seven years.* J Bone Joint Surg Am. 2006
Cohort Studies of Implant-Related Metal Sensitivity
(metal sensitivity for nickel, cobalt or chromium)

The prevalence of metal sensitivity in patients with failed implants is approximately six-times that of the general population and approximately two- to three-times that of all patients. Metal-on-metal have been associated with greater prevalence of metal sensitivity than similar designs with metal-on-UHMWPE.

Hallab Bulletin of the NYU Hospital for Joint Diseases 2009