Immunology Devices Panel of the Medical Devices Advisory Committee Meeting:
Biological Responses to Metal Implants and Dental Amalgams

November 13, 2019
Current Nonclinical Pre-Market Evaluation of Metal Implants*

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Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

*Correlates to Section 4 of review paper
November 2019: Immunology Devices Panel of the Medical Devices Advisory Committee Meeting
Section 4: What does CDRH Review?

- CDRH uses multiple types of assessments to understand whether materials used to manufacture medical devices can cause an adverse biological response.
- Corrosion and other physical or chemical processes can lead to the release of metal ions and small particles.
- Adverse tissue responses can occur at the site of the implant or in other places in the body.
Section 4: What does CDRH Review? (cont.)

- The assessments used to evaluate metal-related biological responses vary depending on the type of device, and where it is used in the body.
- For some device types, guidance documents describe the evaluations that are commonly used to screen for potential adverse tissue responses.
Recent Medical Device Guidance Documents

This list contains the most recent final medical device guidance documents. For a complete listing, please see the Guidance Documents homepage.

### Recent Final Guidance Documents

<table>
<thead>
<tr>
<th>Title</th>
<th>Issued Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular Catheters, Wires, and Delivery Systems with Lubricious Coatings - Labeling Considerations - Guidance for Industry and Food and Drug Administration Staff</td>
<td>10/10/19</td>
</tr>
<tr>
<td><strong>Coronary, Peripheral, and Neurovascular Guidewires - Performance Tests and Recommended Labeling - Guidance for Industry and Food and Drug Administration Staff</strong></td>
<td>10/10/19</td>
</tr>
<tr>
<td>Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act - Guidance for Industry and Food and Drug Administration Staff</td>
<td>09/27/19</td>
</tr>
</tbody>
</table>

# Section 4: What does CDRH Review? (cont.)

Assessments can include:

<table>
<thead>
<tr>
<th>Topic</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocompatibility</td>
<td>4.2</td>
</tr>
<tr>
<td>Corrosion and Ion Release</td>
<td>5.0*</td>
</tr>
<tr>
<td>Device-Specific Fatigue Testing</td>
<td>-</td>
</tr>
<tr>
<td>Animal Studies</td>
<td>4.2.2, 4.2.5</td>
</tr>
<tr>
<td>Clinical Studies</td>
<td>7.0*</td>
</tr>
</tbody>
</table>

*discussed by other FDA speakers
Section 4.2: Biocompatibility

- CDRH’s 2016 Biocompatibility Guidance (FDA 2016)
  https://www.fda.gov/media/85865/download
  - Defines biocompatibility as “the ability of a device material to perform with an appropriate host response in a specific situation”

Section 4.2: Biocompatibility (cont.)

• CDRH’s 2016 Biocompatibility Guidance (FDA 2016)
  https://www.fda.gov/media/85865/download
  – Describes biocompatibility endpoints to consider for devices with various types and duration* of tissue contact and lengths of contact
  – NOTE: Manufacturing and sterilization can impact both chemistry and surface characteristics

* < 24 hours, 24 hours to 30 days, or > 30 days
Section 4.2: Biocompatibility (cont.)

Biocompatibility Endpoints Related to Immune Response*

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Toxicity (Acute, Subchronic, Chronic)</td>
<td></td>
</tr>
</tbody>
</table>

*Other biocompatibility endpoints that also could be impacted by metals: cytotoxicity, irritation or intracutaneous reactivity, material-mediated pyrogenicity, genotoxicity, hemocompatibility (hemolysis, complement activation, thrombosis), carcinogenicity, reproductive or developmental toxicity, biodegradation (for absorbable materials), organ-specific toxicity
Section 4.2.1: Sensitization

• Common ISO 10993-10 methods:
  – Guinea Pig Maximization Test (GPMT): most sensitive
  – Guinea Pig Closed Patch (Buehler) Test: intact skin contacting devices, only
  – Mouse Local Lymph Node Assay (LLNA): lacks TLR-4, so will not work with nickel-based materials
Section 4.2.2: Implantation

• ISO 10993-6 methods focus on local responses to the implanted device:
  – Macroscopic and microscopic methods evaluate the local tissue response (e.g., fibrosis, necrosis and inflammation)
  – Not typically designed to assess device failures (e.g., coating delamination/particulate generation) resulting from mechanical loading
* Animal studies are also often used to assess local and systemic organ specific toxicities (e.g., neurotoxicity)
Section 4.2.5: Systemic Toxicity

• Common ISO 10993-11 biological test methods focus on systemic responses to chemicals released from the device in extracts

• Other approaches to assess systemic toxicity include:
  – Analytical chemistry testing and toxicological risk assessment
  – Leveraging data from large animal implantation studies of the device
Section 4.2.5.3: Biological Testing (Device)

• ISO 10993-11 methods focus on systemic responses to the implanted device:
  – Clinical chemistry, hematology, and histopathology are used to assess adverse tissue effects.
  – Not typically designed to assess device failures (e.g., coating delamination/particulate generation) resulting from mechanical loading.
Section 4.3: Immunotoxicity Guidance

- Considers need for testing for immunological effects:
  - Hypersensitivity (Type I and Type IV)
  - Chronic Inflammation
  - Immunosuppression
  - Immunostimulation
  - Autoimmunity
Section 4.3: Immunotoxicity Guidance (cont.)

• Includes examples of possible tests, but detailed methods are not provided

• Routine testing for induction of autoimmune disease in animal models is not generally recommended

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunotoxicity-testing-guidance
CORROSION AND METAL ION RELEASE*

Presented by: Dave Saylor, PhD
Office of Science and Engineering Labs FDA/CDRH
Immunology Devices Panel: Metal-Containing Implants
November 13-14, 2019

*Correlates to Section 5 of review paper
# Corrosion and metal ion release

<table>
<thead>
<tr>
<th>Device characteristics</th>
<th>Environment</th>
<th>Release mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Bio-chemical</td>
<td>Uniform</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Mechanical</td>
<td>Local</td>
</tr>
<tr>
<td>Design</td>
<td>Electrical</td>
<td>Galvanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fretting</td>
</tr>
</tbody>
</table>
In vitro test methods

• Local (pitting and crevice)
  – Quantify voltage needed to induce breakdown (hyper-physiological)
  – ASTM F2129 (recognized)

• Uniform
  – Direct measurement during immersion in physiologically relevant media
  – Metal ion release - ASTM F3306 (recognized)
  – Absorbable metals – ASTM F3268 (recognized)
  – No current guidance or standards for stimulation devices

• Galvanic
  – Measure acceleration of corrosion due to contacting dissimilar metals
  – ASTM F3044 (recognized)

• Fretting
  – Microscopically evaluate damage during and/or after mechanical testing
  – No general standard test method
  – Device specific standards and guidances (e.g. ASTM F1875 - recognized)
In vivo corrosion studies are extremely limited:

- Literature data only, but provides evidence of enhanced exposure
- While scarce, available data suggest at least qualitative consistency with in vitro test results

**In vivo** corrosion

**(Burian, 2006)**

**(Halwani, 2010)**

**Systemic**

**Local**

<table>
<thead>
<tr>
<th>Metallic levels (μg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium</td>
</tr>
<tr>
<td>Chromium</td>
</tr>
<tr>
<td>Cobalt</td>
</tr>
<tr>
<td>Nickel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1-NiTi/SS</th>
<th>2-NiTi</th>
<th>3-SS</th>
<th>6-3SS</th>
<th>7-Elgiloy-Ta</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Corrosion: What we know

For typical device alloys (Ti-alloys, CoCr-alloys, SS, NiTi):

• Ti and CoCr alloys will not “fail” local or uniform corrosion testing
• Fretting/wear can accelerate corrosion even in normally corrosion resistant materials
• Surface oxides that develop during processing can reduce corrosion resistance - optimally, these are removed during processing
• 3 <= pH <=8 does not have a large impact on ion release
• Galvanic interactions between these alloys tend to be small
• Limited data suggest in vitro test results roughly correspond to clinical observations

Cardiovascular
< 6 µg/L serum Ni
< 20 µg/L urine Ni
< 21 µg/g tissue Ni

Orthopedic
< 228 µg/L serum Co
< 300 µg/L urine Ni
< 750 µg/g tissue Cr
Corrosion: Gaps and Challenges

- Implications of *in vitro* results for patient exposure, and ultimately risk, are not yet established.
- Unclear if *in vitro* test conditions are appropriately conservative to represent implant environments.
- Though some alloys (e.g. Ti and CoCr) will not “fail” *in vitro* corrosion testing; but, metal release can occur *in vivo*.
- Recent clinical evidence suggests Platinum electrodes can corrode, but no standardized test methods exist and implications for risk are unknown.

Gap: *in vitro* to *in vivo* correlations
Biologic Responses to Orthopedic Implants: Innate and Adaptive Immune Responses to Implant Debris

• Nadim James Hallab, PhD
• Rush University Medical Center, Chicago IL
• Invited Speaker
Disclosures:

**BioEngineering Solutions Inc**: *Principal*
(Implant Testing, Particle Analysis and Production)

**Orthopedic Analysis LLC**: *Chief Scientific Officer and Lab Director*
(Metal Allergy Testing, LTT)

Have been an Ad hoc Consultant or received travel at some time over the past 20 years:

- Alphatec
- Applied Spine Tech
- Arthrex
- Establishment Labs
- Empirical Testing Corp
- Element
- FDA
- Medtronic
- Nuvasive
- Smith and Nephew
- Zimmer-Biomet
Introduction

1. General immune reactivity to implant debris
2. Innate (macrophage mediated) reactivity responses
3. Adaptive immunity reactivity responses
4. Implant Debris and Human Factors that may contribute to increased likelihood of an adverse response.
Reasons for long term implant failure

- Bone Fracture, 5-10%
- Infection, 2-10%
- Implant Fracture/Failure, 10%

Aseptic Osteolysis or Loosening, 75% (10-20 years)

References:

Two types of Implant Debris

1-Particles
2-Soluble ("ions")

Ions in serum
Reactivity =
Where do particulate implant debris go?

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.
What do long term failures due to aseptic osteolysis look like? …they are predominantly driven by slow compromising of the implant/bone interface… e.g. granuloma (over 10-20 years)

Macrophage Induced Granuloma

1. Decreased Bone Deposition
2. Increased Bone Resorption

Inflammation/Osteolysis

Adaptive/Specific Immune System (Hypersensitivity)

Innate/Nonspecific Immune System (Particle Osteolysis)

Soft Tissue Bone

Bone

Endothelial Cells

Fibroblasts

Osteoblasts:

- IL-1, IL-6, TNF-α, TGF-β, IL-1, PGE₂

Foreign Body Giant Cell

Osteoclasts:

- IL-8, IL-6, MCP-1
- IL-8, IL-6, RANKL

Inflammation/Osteolysis

IL-2, IFN-γ, RANK

IL-1, IL-6, IL-10, IL-12, IL-15, IFN-α, β, TNF-α, TGF-β, IL-1, PGE₂

Osteoclasts:

1. Decreased Bone Deposition
2. Increased Bone Resorption

RANKL

MMP-1, 3, 13

© N.J. Hallab
Innate Immune Responses to Implant Debris
Macrophages...the central player

without particles

with UHMWPE particles
This macrophage phagocytosis is central to innate immune reactions.
2. Innate immune response to Implant debris.

…nonspecific defense mechanisms that come into play immediately or within hours after exposure

EVERYONE HAS THIS RESPONSE

Macrophage-Mediated
- Non-specific
- Subtle
- Long term inflammation
- Mediated by inflammasome activation
- Causes cytokine and chemokine release
We found that the inflammasome pathway that mediates monocyte/macrophage reactivity and sensing of sterile (non biological) challenge, also applies to implant debris too!

And is among the more promising “checkpoint” targets for mitigating implant debris reactivity and for diagnosing individual-specific excessive innate immune reactivity to implant debris.
Other debris induced monocyte/macrophage reactivity can occur such as increases in co-stimulatory molecule expression that are important to the immune synapse between macrophages and lymphocytes (the nexus of the innate to adaptive immune system).

**Will Metal implant debris will induce variable monocyte up-regulation of surface co-stimulatory molecules and pro-inflammatory cytokine secretion that can result in autologous CD4+ T cell activation.**
Many contributing and other players in Innate Debris Inflammation

Toll-Like Receptor Signaling

Cytokine Signaling
A small subset of failures due to aseptic osteolysis occur earlier than 10 years and involve more than just an innate immune response.

- Hypersensitivity 1-5% (adaptive immune responses)
- Inflammation 70-74% to particles (Innate Immune responses)

References:

Inflammatory reaction to Implants particles
3. Inflammatory reaction to Implants particles

Innate

Adaptive Immune
Inflammatory reaction to Implants particles

Adaptive immune (Type IV hypersensitivity DTH)

NOT EVERYONE GETS THIS RESPONSE

T-cell Mediated
- Specific
- not-subtle
- delayed
- inflammation
- mediated by APCs
- causes cytokine and chemokine release

Adaptive Immune

T-Helper
• Skin – metal-DTH – Contact Dermatitis

Implant Debris-Hypersensitivity: Clinical Presentation

“Revision to a ceramic (Alumina) Shortly after the patient had a TKA with a conventional metal implant, she began to show signs of severe metal allergic hypersensitivity, including pain, a rash mimicking psoriatic arthritis and limited motion.

Sam Nasser, MD, Michael P. Mott, MD, of Warren and Paul H. Wooley, PhD,

What are symptoms of Excessive Peri-implant Hypersensitivity
Most common = aseptic pain and inflammation!
(Typically No eczema)
Metal-on-Metal Bearings and Hypersensitivity in Patients with Artificial Hip Joints. A Clinical and Histomorphological Study

Well Established Science (35 years, >500 studies, pubmed)

>100 Case studies of metal hypersensitivity to orthopedic implants (pubmed)

>50 Group studies of metal allergy/hypersensitivity to orthopedic implants (pubmed)

>100’s animal model studies where lymphocyte cell proliferation/reactivity to a specific metal challenge has been well induced and studied (pubmed)
PRESENTATION OF THE ANTIGEN

THE CYSTEINE CHAPEL
Mechanism by which Lymphocytes may become activated

Corrosion and Wear

Metal Particles + Metal Ions + Serum Proteins

Cell Activation

Lymphocyte

APC

Type IV Hypersensitivity is a mechanism NOT intensity of response (i.e. can be mild)
Only two commonly CLIA (CMS) approved Diagnostic Tests for DTH

1- Dermal Patch Testing
2- Lymphocyte Transformation Testing

(both have been used for >40 years)

Historically testing for metal hypersensitivity has been conducted using patch testing
For Ortho Patch Testing (unstandardized, unquantified)

Patch Test

Pro’s:
1. Availability
2. Well established (standard for cutaneous allergy)
3. Easy to perform

Con’s:
1. Potential to act as sensitizing agent – Induction of Sensitivity.
2. Clinical Applicability to Peri-Implant Regions (eg. APC)
3. Expensive (2 office visits to allergist + testing)
4. Confusion in current challenge agents (metal vs ceramic, e.g. titanium vs titanium oxide)
5. Dependent on a skin hygiene/condition during 48hrs
6. Highly Subjective Grading Scale (what is +1,+2,+3?)
7. Non-quantitative
2. Lymphocyte Transformation Testing
(LTT assay)
Indicator of Lymphocyte (hypersensitivity) responses to metals etc.

1) **BLOOD DRAW**
Isolate human PBMC from blood draw (4 tubes)

**FICOLL-PAQUE DENSITY BASED CELL SEPARATION**

2) **CULTURE WITH Metal Ions**
Culture hPBMCs for total of 6 D

3) **Measure cell proliferation to metal-proteins**

**STIMULATION INDEX** = \[
\frac{\text{Metal treated lymphocyte proliferation (cpm)}}{\text{Non-treated (control) Lymphocyte Proliferation}}
\]

= Relative Amount of Proliferation

The average for each treatment is normalized to that of the negative control (no treatment) producing a ratio, generally termed a proliferation factor, proliferation index, proliferation ratio or stimulation index, SI. The SI is used to compare lymphocyte reactivity to the different metals.
### Metal-LTT Analysis Report

**Panel 1**

<table>
<thead>
<tr>
<th>Control cpm</th>
<th>Positive control (PHA) cpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1083.3</td>
</tr>
<tr>
<td></td>
<td>24409.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metal</th>
<th>Mild (cpm)</th>
<th>Reactive (cpm)</th>
<th>Highly Reactive (cpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Cobalt</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Nickel</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Vanadium</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Zirconium</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
<tr>
<td>Iron</td>
<td>0.001 mM</td>
<td>0.01 mM</td>
<td>0.1 mM</td>
</tr>
</tbody>
</table>

**Lymphocyte Stimulation Index**

- Mildly Reactive: 2 to 4
- Reactive: 4 to 8
- Highly Reactive: above 8

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RUSH UNIVERSITY MEDICAL CENTER

2201 W. Campus Park Drive, Suite 211 Chicago, IL 60612

www.orthopedicanalysis.com

Phone: (312) 735-7121 Page: 1 of 2
Metal-LTT

Pro’s:
1. Quantitative/Not user dependent– clear results (replicate wells)
2. Facilitates threshold levels
3. Incorporates dose-dependence, allows testing of different concentrations (critical)
4. Objective numerical results (non-dependent on who administers).
5. Well established orthopedic clinical impact of challenge agents (ions and particles, no petroleum jelly/skin)
6. Well established in drug allergy and organ transplant testing
7. Able to detect general adaptive immune disfunction
8. Cost is less than that of two physician office visits for patch testing

Con’s:
1. 24 hrs to get blood to the lab at room temp
2. Availability (available in US mostly, growing)
Apparently, you are highly reactive to all metals!!
Over 40 studies of metal immune responses using LTT testing reported in pubmed over last 10 years.
Sensitivity and Specificity of metal-LTT testing to detect a condition of metal sensitivity is high but alone cannot predict implant performance!

LTT: 80% sensitivity, 85% specificity vs Patch Testing: 64% sensitivity, 85% specificity for drug, cotrimoxazole-related, allergy

Sensitivity (true positive rate… the higher it is the less false positives)

Specificity (true negative rate… the higher it is the less false negatives)


Metal exposure over time at relatively high levels initiates metal pathogenesis of sensitivity reactivity prior to symptoms.
Not surprisingly...battlefield injury metal exposure (average 10 yrs from injury) also initiates metal sensitivity reactivity in soldiers with retained metal fragments ...again showing over time “metal implants" can act as sensitizers.
Innate immune responses are also integral to a hypersensitivity-increased inflammatory bone loss response (when the inflammasome pathway is blocked so is DTH potentiated inflammatory bone loss).
Th-17 cell lymphocytes have been implicated in mediating metal hypersensitivity and are.

Again we are way past “does this exist” and into the picayune science of what kind of response to mitigate, so Th17 is the current answer and drugs like anti-IL-17 are being tested as potential therapies.
4. Factors that may contribute to increased likelihood of an adverse innate and/or adaptive immune response

a. **Implant debris factors**

b. Biological/human factors
   - gender,
   - implant site,
   - duration,
   - medical history,
1) Greater particle load/dose increases inflammation:

\[ \text{Dose} = F(\text{size and volume}) \]

Inflammation volume, which is characterized by both the size and proportional to the particle load (the concentration of phagocytosable particles per tissue volume).

<table>
<thead>
<tr>
<th>Implant</th>
<th>Wear Rate (mm(^3)/mc)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal-UHMWPE THA</td>
<td>78.3</td>
<td>Callaghan JJ, Rosenberg, AG and Rubinash H. The Adult Hip, Lippincott Williams &amp; Wilkins, Table 20-2, 2007</td>
</tr>
<tr>
<td>Metal-Metal THA</td>
<td>0.88</td>
<td>Catelas I et al, JBMR Applied, 2004; 70(2):167-178</td>
</tr>
<tr>
<td>Metal-UHMWPE TKA NexGen</td>
<td>47.3</td>
<td>Callaghan JJ, Rosenberg, AG and Rubinash H. The Adult Hip, Lippincott Williams &amp; Wilkins, Table 20-2, 2007</td>
</tr>
</tbody>
</table>
1-A  So why is the current paradigm smaller particles are worse..... The inflammatory response is proportional to the particle load (the concentration of phagocytosable particles per tissue volume, which is characterized by both the size and total volume… …but is that all?).

![Equal Mass](image)

<table>
<thead>
<tr>
<th>Implant</th>
<th>Average Particle Diameter (μm ECD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal-UHMWPE THA</td>
<td>0.66</td>
<td>Callaghan JJ, Rosenberg, AG and Rubash H. The Adult Hip. Lippincott Williams &amp; Wilkins, 14</td>
</tr>
<tr>
<td>Ceramic-UHMWPE THA</td>
<td>0.78</td>
<td>Minoda Y et al. Biomaterials. 2005, 29(30):6034-40</td>
</tr>
<tr>
<td>Metal-Metal THA</td>
<td>0.05</td>
<td>Cabelas I et al., JBMR Applied, 2004, 70(2):157-178</td>
</tr>
<tr>
<td>Metal-UHMWPE TKA (Vanguard RP; Biomet and)</td>
<td>1.5</td>
<td>Minoda Y et al. Knee Surgery, Sports Traumatology, Arthroscopy, 2017, 25(9):2887-2893</td>
</tr>
<tr>
<td>Metal-UHMWPE TKA (MHLXUHMWPE NexGen CR, Zimmer)</td>
<td>0.6</td>
<td>Iwakiri K et al. JBMR-B 2009 91B(2): 799-804</td>
</tr>
<tr>
<td>Metal-UHMWPE TKA (NexGen CR, Zimmer)</td>
<td>1.2</td>
<td>Iwakiri K et al. JBMR-B 2009 91B(2): 799-804</td>
</tr>
</tbody>
</table>
Cobalt alloy…“nanoparticles caused more mitochondrial damage (within 24 h), more DNA damage (within 24 h), albeit for equal volumes (or amount) of debris, smaller Cobalt alloy particles (higher dose) induced slightly more biologic responses.
For equal volumes (or amount) the smaller the UHMWPE particles are, the LESS the biologic effect

size UHMWPE wear particles (0.1–1.0 μm)...caused significantly elevated osteolytic cytokine release from PBMNCs."

Thus smaller implant debris is not always worse and size-effects are specific to the type of implant debris including shape....
2. **Elongated (fibers) particles are more pro-inflammatory than round particles.** This phenomena has been well established with the first such investigations over 30 years ago, involving asbestos fibers. However, it remains unknown at what point (aspect ratio: length/width) in the transition of round particles to fibers that elevated inflammation is generally initiated, and thus to date there is only a rough “guideline” of aspect ratio for implant debris particles to remain below 4.
3) More chemically reactive particles are generally more pro-inflammatory: There is a growing consensus of investigations that have shown metals particles are more proinflammatory when compared to most polymers.
INNATE IMMUNE MATERIAL DIFFERENCES:
Murine Models of implant debris induced osteolysis show some types of metal debris is more pro-inflammatory than some types of polymeric debris.
Each bar is a different study and/or cohort.

Group Studies: Incidence of Metal Sensitivity

Material Differences: Adaptive Immune
4. Factors that may contribute to increased likelihood of an innate and/or adaptive adverse response

a. Implant debris factors
b. Biological/human factors
   - Sex,
   - Age,
   - Duration,
   - Medical history,
This agrees with past studies that show:

1) Females exhibit higher rates of rheumatoid arthritis and osteoarthritis and

2) Increased risk of experiencing adverse local tissue reactions and aseptic loosening after metal-on-metal hip resurfacing arthroplasty


Sex differences

Metal implant debris particles caused more inflammatory bone loss in females vs males (but not UHMWPE particles).
Medical History Factors:

Some are obvious such as smoking and obesity which are both associated with >2x higher implant revision rates (and infection)

• Singh JA1,2,3, et al BMC Med. Current tobacco use is associated with higher rates of implant revision and deep infection after total hip or knee arthroplasty: a prospective cohort study. 2015 Nov 19;13:283
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

Marco S. Caicedo, PhD, Edward Solove, BS, Lavasha Coleman, BS, Joshua J. Jacobs, MD, and Nadim J. Hallab, PhD

Medical History:

Males that were found to be metal sensitive did not know this at higher rate than females (i.e. history).
Duration of Implant

Factors that may contribute to increased likelihood of an adverse response:

Metal sensitivity likely occurs most often at less than 5 years generally (may differ for some implants).

n = 1,038 male individuals
n = 1,575 female individuals
Researchers are focused on countering this cycle pharmacologically and diagnosing problems early.

Innate immune responses to implant debris mediate the majority of long-term problems/revisions…and to date there are no diagnostic tests to determine who is more reactive to this kind of response.
Biologic Responses to Orthopedic Implants: Innate and Adaptive Immune Responses to Implant Debris

Nadim James Hallab

Professor
Department of Orthopedic Surgery,
Rush University Medical Center, Chicago, IL
BIOMATERIALS
BIOCOMPATIBILITY*

Laura Santambrogio M.D. Ph.D.
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Invited Speaker

*Correlates to Section 6 of review paper
Financial Interest Disclosure
BIOMATERIALS HAVE TRANSFORMED REGENERATIVE MEDICINE
Stents

Before

After

Lenses

Valves

Replacement Prostheses

Dental Implants
Testing of Implanted Medical Devices

Lifetime:
- Durability
- Fatigue
- Wear

Performance:
- Bio-performance
- Clinical Outcome
Testing for Biocompatibility

In Vitro Cell cultures

In Vivo Animal Studies

- How a medical product is broken down chemically in the body
- The toxicity of the product and its breakdown components
- How quickly the product and byproduct(s) are excreted from the body
Lessons Learned on Biocompatibility

Santambrogio 2012
Implant Wear Particles

**Polyethylene (PE)**

*White to pale gray*
- Nanoparticulate < 1 µm, non-visible
- Microparticulate 1 to ≤10 µm, oil red O ++, POL ++
- Macroparticulate > 10 to 100 µm, oil red O ++, POL +++
- Supra-macroparticulate > 100 µm, POL +++

**Conventional**

*Greyish to intensely black*
- Nanoparticulate <1 µm, non-visible
- Microparticulate 1 to < 100 µm
- Macroparticulate > 100µm
  - Round 1 ≤ r ≤ 1.5
  - Oval/irregular 1.5 < r ≤ 2.5
  - Needle/rod-shaped r > 2.5

- Cobalt
- Chromium
- Molybdenum
- Nickel
- Niobium
- Tantalum
- Titanium

**Ceramic**

*Brownish/grey/greenish*
- Nanoparticulate < 1 µm, non-visible
- Microparticulate 1 to ≤10 µm
- Macroparticulate > 10 to 100 µm
- Supra-macroparticulate > 100 µm

- Aluminum oxide
- Niobium oxide
- Silicon Nitride
- Titanium nitride
- Yttrium oxide
- Zirconium oxide
- Hydroxyapatite (HA)

**Corrosion**

*Greenish/yellowish to layered black-red-yellowish*
- Cobalt: Solid precipitates: oxides, chlorides, phosphates
- Chromium: Round/globular nanoparticle aggregates < 5 µm
- Molybdenum: Irregular/small nanoparticle aggregates ≤ 10µm
- Titanium: Sheet-like particle aggregates >10 µm
- Vanadium: Iron/steel alloy (PBR +), < 1 µm to > 0.5 mm
- Others

**Metallic Particles**

**Polymethyl methacrylate orthopaedic cement (PMMA)**

- **Polymethyl methacrylate** (dissolved during tissue processing)
  - Barium sulphate
  - Zirconium dioxide

- **Radiographic contrast agents**
  - (Additive to PMMA)
Different size particles, polymers and ions are generated \textit{in vivo} by wear of the implants.
Large Debris (over 100 µm) Induce Frustrated Phagocytosis and Osteolysis

Journal of Immunology 2010
Tissue Macrophages Phagocytose wear debris in the low \( \mu m \) range.
Tissue Macrophages Phagocytose wear debris in the low \( \mu m \) range

Sharf et al. Nature Comms 2012
Wear Debris Induce Endosomal Damage

Total cells

Cytosol

Cathepsin B
Cathepsin S
Cyclophilin

Scharf Nature Comms 2011
Wear Debris Induce NLRP3 Inflammasome Activation

Scharf Nature Comms 2012
Wear Debris Include Alkane Polymers

Unmodified Alkane

Carboxyl

Hydroxyl Modified Alkane
Molecular Docking of Alkane Polymers to TLR1/2 heterodimers
Direct Binding of Alkane Polymers to TLR2

Pam$_3$CSK$_4$

hTLR2 pocket

hTLR1 channel

Direct Binding of Alkane Polymers to TLR2

PLOS 2008
Alkane Polymers Activate the TLR2 Signaling Pathway

PLOS 2008
UHMWPE polymers

DAMPs

TLR2/TLR4

NALP3

PYCARD

Caspase1

TXNIP

ROS

Endosome

Phagocytosis

Large wear particles (>20 µm)

Frustrated phagocytosis

Small wear particles (<20 µm)

NFκB

Nucleus

Pro-IL-1β
Pro-IL-18

IL-1β
IL-18

IL-6
TNF
IFN-γ

Cathepsins

NOX
Metals (Cr, Co, Ti alloy)
Phagocytosis of Co and Cr particles by Tissue Macrophages
Phagocytosis of Co and Cr particles by Tissue Macrophages Produces Metal Ions

Accumulation of Co and Cr in Periprosthetic Tissues

Generation of Corrosion products in Periprosthetic Tissues


2µm

500 nm
Metal-catalyzed Fenton Reaction produces Reactive Oxygen Species

Fe$^{3+}$ + O$_2$•$^-$ → Fe$^{2+}$ + O$_2$
Fe$^{2+}$ + H$_2$O$_2$ → Fe$^{3+}$ + OH$^-$ + •OH

O$_2$•$^-$ + H$_2$O$_2$ → OH$^-$ + •OH + O$_2$
Fe$^{3+}$

![Cell Lysate](image1.png)

![Supernatant](image2.png)

DCF (nM)

<table>
<thead>
<tr>
<th>Co$^{2+}$</th>
<th>Cr$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
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<tr>
<td>100</td>
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<td>1000</td>
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<tr>
<td>100</td>
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<tr>
<td>1000</td>
<td>1000</td>
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</tbody>
</table>

Increased Oxidative Stress and Tissue Necrosis

Displacement of Protein-bound Metals (Zn, Fe, Mg..)
Displacement of Protein-bound Metals (Zn, Fe, Mg..)

Aldolase

Immune Cell Infiltrate in Bone

Cell Death, Tissue necrosis

Modalities

**Apoptosis** (intrinsic caspase-dependent and independent, extrinsic by death or dependence receptors)

**Autophagy**

Entosis

**Necroptosis**

**Pyroptosis**

Mitotic Catastrophe

Toxicity vs Hypersensitivity
Hypersensitivity
Conclusions

- Phagocytosis Wear debris (Inflammasome and TLR Activation)
- Metal-catalyzed Oxidative Damage
- Formation of Corrosion Products and Tissue Necrosis
- Metal Displacement from Relevant Proteins
Testing
In Vitro Cell Cultures

- TLR/Iflammasome Activation
- Cytokine Production
- ROS Production
- Metal Ions
Testing

Long Term in Vivo Animal Studies

- Implant of Particulate Debris
- Devices Implant
Biomarkers

- Establishing Thresholds for Blood Metal Ions Concentrations
  - Increased in Blood Ions Overtime
    - Tissue Biopsy
      - Aldolase Catalase... Metal Ions
Clinical Responses to Metal Implants*

Stephen Weber, MD
Ben Fischer, PhD

Office of Product Evaluation and Quality
FDA/CDRH

*Correlates to Section 7 of review paper
Introduction

• Problems with metal implants have been known for decades, but...

• Recent issues with metal-on-metal hips and gynecological metal implants have heightened concerns

• A broad spectrum of clinically manifested responses (both local and systemic) are known to occur.
Terminology is Critical

• ARMD-adverse reaction to metal debris-systemic and local
• ALTR-adverse local tissue reaction-local
• ALVAL-Aseptic Lymphocytic vasculitis associated lesion-pathological diagnosis
• Metallosis-presence of metal particles in periprosthetic tissues
• “Allergy” or hypersensitivity
Metal Hypersensitivity

• Allergic contact dermatitis (ACD) is the main allergic clinical manifestation
• ARMD not synonymous with true allergy
• Little if any evidence of implant failure from true allergy
• Patch testing ineffective
Adverse Local Tissue Reactions (ALTR)–
various local manifestations of ARMD

- Pseudotumor
- Osteolysis
- Necrosis
- Metallosis
- ALVAL subset of ALTR
Systemic Adverse Reaction to Metal Debris (ARMD)

• Systemic manifestations of ARMD
  – Cardiac, neurological, and thyroid effects most common
  – Not always reversible with implant removal
  – Cancer risks not proven by registry studies

• Elevated metal ion levels poorly correlated with other ARMD

• Cobaltism- most commonly associated
  – Can sometimes lead to multi organ failures

• Other metals can be involved- nickel, chromium, titanium, etc.
Elevated Serum Metal Ion Levels

• Poor correlation with metal ion levels and ARMD
• Well-functioning implants can have elevated metal ion levels
Sex Issues in Metal Responses

• Exist in other areas of medicine for females
  – Hepatic, rheumatic, thyroid autoimmune more common in female patients
• Osteoarthritis, rheumatoid arthritis, dysplasia also more common
• Significantly higher rates of failure of MOM hips in females
• Higher susceptibility in women may influence failure of gynecologic metal implants?
Device areas- Orthopedic

- ARMD presents as differential of painful hip
- Not always MOM-trunnionosis
- Work-up with history, physical, metal ion levels (>7 ppb)
- Consider metal artifact reduction sequence magnetic resonance imaging (MARS MRI) or ultrasound
- Asymptomatic patients can be followed
- High risk groups consider revision to metal-on-poly hip
- Revision difficult
Device related- Dental

• Most relate to temporomandibular joint (TMJ) implants
  – Many failures
  – Multiple surgeries complicate evaluation
  – Failed TMJ implants can show ALVALS type pathology

• Endosseous dental implants also at risk
Interventional Device Area- Cardiovascular Devices

• Vascular stents
• Contact dermatitis to pacemakers
• Metal reaction related to subsequent thrombus?
• Systemic reactions also reported
  – Chest discomfort
  – Dyspnea
  – Fever
  – Pericarditis
Interventional Device Area-Neurologic and Gastroenterological Devices

- Primarily reactions to Ni mixed with other metals
- Case report of focal neurological syndrome four weeks after clips or coils
- Rare reports of hypersensitivity with gastroenterological devices
- Patch testing inconsistent
Interventional Device Area- Gynecological Devices: *Nitinol-based Hysteroscopic Sterilization and Copper Intrauterine Devices*

- **Short-term risks**
  - Mild to moderate pain
  - Cramping, bleeding, dizziness

- **Long-term risks**
  - Local ALTR’s?
    - Pelvic pain
    - Organ perforation
    - Migration of device
  - Systemic ARMD’s?
    - Hypersensitivity reactions
    - Joint or muscle pain
    - Excessive fatigue
    - Hair loss
    - Weight and mood changes
    - Persistent fever
Partial List of Symptoms Reported with Essure

<table>
<thead>
<tr>
<th>General</th>
<th>GU/GYN</th>
<th>Musculoskeletal</th>
<th>Derm</th>
<th>Neuro</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Pelvic Pain</td>
<td>Joint Pain</td>
<td>Alopecia</td>
<td>Headache</td>
<td>N/V</td>
</tr>
<tr>
<td>Weight Changes</td>
<td>Menstrual Irreg.</td>
<td>Low Back Pain</td>
<td>Rash</td>
<td>Migraine</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Mood Swings</td>
<td>Hot Flashes</td>
<td>Leg Pain</td>
<td>Hives</td>
<td>“Brain Fog”</td>
<td>Chest Pain</td>
</tr>
<tr>
<td>Irritability</td>
<td>Breast Change</td>
<td>Muscle Weakness</td>
<td>Raynauld’s</td>
<td>Depression</td>
<td>Palpitations</td>
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<tr>
<td>Sweating</td>
<td>Menopause</td>
<td></td>
<td></td>
<td>Memory Loss</td>
<td>Tooth Loss</td>
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<tr>
<td>Fever</td>
<td>Cysts</td>
<td></td>
<td></td>
<td>Vertigo</td>
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<tr>
<td>Insomnia</td>
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<td></td>
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<tr>
<td>Allergies</td>
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</tbody>
</table>

Disease Diagnoses

- Rheumatoid Arthritis
- Lupus
- Multiple Sclerosis
- Myasthenia Gravis
- Immune Thrombocytopenia
- Fibromyalgia
Challenges

• Terminology used is often inconsistent
• Current diagnostic studies are inadequate to identify either patients at risk for adverse biologic responses to metals preoperatively, or those who may have an adverse response to an existing implant
• Gender appears to be associated with significant differences in the biologic response to some implants
• The percentage of patients with well-functioning implants and abnormal diagnostic tests is unknown
Summary

• A more nuanced evaluation of the entire spectrum of device/biomaterial-specific Adverse Reaction to Metal Debris is needed
• Management of the asymptomatic patient if few risk factors should be limited to monitoring
• Management of symptomatic patients remains controversial
• Incorporating all clinical manifestations and pathogenetic mechanisms is needed to treat symptomatic patients
Clinical Biological Reactions to Orthopaedic Hip Implants

Young-Min Kwon MD, PhD

Associate Professor
Harvard Medical School
Department of Orthopaedic Surgery
Massachusetts General Hospital
Clinical Biological Reactions to Orthopaedic Hip Implants

- **Systemic**
  - Carcinogenesis
  - Teratogenecity
  - ‘Cobaltism’

- **Local**
  - Osteolysis
  - ‘Hypersensitivity’
  - Adverse Local Tissue Reactions (ALTR, Pseudotumours)
Clinical Biological Reactions to Orthopaedic Hip Implants

- What We Know
- What We Do Not Know
- What We Need to Know
Systemic Adverse Reactions

- Metal ions lead to the generation of free radicals
  - Induce DNA cross-links
- Chromosome translocations and aneuploidy
  - Lymphocytes at 6, 12 and 24 months post MoM THA (Briggs et al. BJJ 2015)
- Permanent modification of genetic material
  - First step in carcinogenesis
  - Concern
Carcinogenesis

- Carcinogenic potential of cobalt and chromium wear particles
- Currently available data on risk of cancer
- These studies limited by a small number of patients and short follow up period
Teratogenicity

- Concern for mutagenic or teratogenic effects
  - MoM performed in young patients, including females of child bearing age

- Cord blood levels of cobalt and chromium
  - 60% of the mean maternal blood levels in patients with MoM HR (Ziaee et al. JBJS B 2007)
    - Placenta may exert a modulatory effect

- Effects on foetus unknown
‘Cobaltism’

- **Series of Case Reports** describing temporal association of multiple-organ metal toxicity (*Gessner J* 2019; *Shapiro et al.* 2018; *Kakela et al.* *Acta Orthop* 2014)
- Neurologic, endocrine and cardiac toxicity
  - Case reports with ASR MoM THA
  - Cobalt serum level 35-112 ug/L
- **Currently, Limited to case reports**
- Further studies required
Systemic Cobalt Toxicity

• 72 yo Female
• CoC THA revised to MoP for ceramic liner fracture
• Constitutional Symptoms:
  – Fatigue
  – Taste alteration
  – Weakness
  – Vertigo
  – Weight loss
Systemic Cobalt Toxicity

- 72 yo Female
- CoC THA revised to MoP for ceramic liner fracture
- Recent Diagnosis
  - Hearing and Vision Loss
  - Hypothyroidism
  - Diabetes Mellitus
  - Cardiomyopathy
  - Neuropathy
Systemic Cobalt Toxicity

- 72 yo Female
- CoC THA revised to MoP for ceramic liner fracture
- **Cobalt 1,302 ug/L**
- **Chromium 63 ug/L**
Systemic Cobalt Toxicity

- 72 yo Female
- CoC THA revised to MoP for ceramic liner fracture
- Revised to CoC THA
- **Cobalt 1.9ug/L (1,302)**
- **Chromium 1.4 ug/L (63)**
- Clinical Improvement
  - DM, Thyroid function, Cardiac function
Local Abnormal Tissue Reactions

- **A.L.T.R:** Local
- **Pseudotumour:** Mass
- **A.R.M.D** (Adverse reaction to metal debris): Local or Systemic
- **A.L.V.A.L:** Histological Diagnosis
- **Metallosis:** Metal staining of tissues
- **Trunnionosis:** Taper corrosion
Adverse Local Tissue Reactions (ALTR)

- Initially Observed in Patients following MoM resurfacing & MoM THA
- Concerns in MoP THA
  - Fretting and Corrosion
  - Taper Modularity
    - Head-Neck
    - Neck-Stem
  - MACC
Why Does ALTR Occur?

- Implant factors
- Surgical factors
- Patient factors
Implant Factors
Minor Changes in Hip Implant Design can have Dramatic Influence on its Performance
MoM Cup Design: Coverage Arc

- Hip Implants with a reduced angle subtended by the acetabular component (Coverage Arc) provides less coverage

- MoM ASR (Steele JOA 2011, Underwood JBJS Br 2011, Griffin CORR 2010)
MoM Cup Design: Dome Geometry

- Increased thickness at the dome than at the rim
- Moves the COR of the femoral head out from the center of the acetabular component
- Increases edge loading risk
- ASR (*Steele JOA 2011*)
Dual Taper Modularity Materials

• Types of Neck and Stem materials include:
  • Ti Neck on Ti Stem (Ti/Ti)
  • Co-Cr Neck on Ti Stem (Co-Cr/Ti)
  • Co-Cr Neck on Co-Cr Stem (Co-Cr/Co-Cr)
• ALTR reported largely with
  • Co-Cr Neck on Ti Stem (Co-Cr/Ti) (*Kwon et al. JoA 2017*)
Modularity Type

Monolithic ‘Dual Taper’ Stem-Sleeve Mid-Stem
MoP Taper Hip Implant Factors

- Taper Material
  - Taper Metallurgy
  - Alloy Rigidity
- Taper Geometry
  - Angle
  - Contact Area
  - Surface Roughness
- Femoral Head Size
- Lever Arm
**Surgeon Factor: Taper Assembly**

- **Impact of Assembly on Deformation of Taper**
  - 8kN Optimal for CoCr head on Ti 12/14 tapers  
    *(HPanagiotidou et al. JOR 2017)*

- **Assembly Contamination**
  - 50% Reduction in load to failure with contaminated assembly vs. well cleaned assembly *(Jauch et al J Biomech 2011)*
Patient Factors
Patient Factors

• ? Activity Level (Loading conditions)
  – Increased BMI and high activity level may place significant torsional loads on implant

• ? Biological Reactivity/Systemic Susceptibility
  – Symptoms: Asymptomatic
  – Histology
  – Retrieval analysis
‘Asymptomatic’ Pseudotumours

• Some patients with bilateral MoM THA presented with symptom in one hip only
• However, pseudotumours found in both symptomatic and asymptomatic MoM hips
‘Asymptomatic’ Pseudotumours
“Asymptomatic” Pseudotumors After Metal-on-Metal Hip Resurfacing Arthroplasty
Prevalence and Metal Ion Study

Young-Min Kwon, DPhil(Oxon), FRCS(Orth), FRACS(Orth), *
Simon J. Ostlere, FRCR,† Peter McLardy-Smith, FRCS(Orth),†
Nicholas A. Athanasou, FRCPA, PhD,† Harinderjit S. Gill, DPhil(Oxon),† and
David W. Murray, MD, FRCS(Orth)†

• N=201 consecutive MoMHRA
• Asymptomatic
• ‘Screened’ using US/MRI
• 7% Prevalence
• Size ranges 2 × 1 × 2 cm to 8 × 7 × 8 cm
‘Asymptomatic’ Pseudotumours

- **Williams et al. JBJS Am 2011**
  - N=73 Asymptomatic ‘Screened’ using US
  - Prevalence 14% MoMHRA

- **Wynn-Jones et al. Acta Orthop 2011**
  - N=77 Asymptomatic ASR ‘Screened’ using MRI
  - Prevalence 31%

- **Bosker et al. Paper #303, AAOS 2012**
  - Prevalence 35% following CT screening
  - No difference in clinical outcome scores
Asymptomatic Pseudotumors in Patients with Taper Corrosion of a Dual-Taper Modular Femoral Stem

MARS-MRI and Metal Ion Study

Young-Min Kwon, MD, PhD, Sariah Khormaei, MD, PhD, Ming Han Lincoln Liow, MD, Tsung-Yuan Tsai, PhD, Andrew A. Freiberg, MD, and Harry E. Rubash, MD

Investigation performed at the Center for Metal-on-Metal Hip Replacement Evaluation and Treatment, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
MoM ‘Pseudotumour’ Histology

- Spectrum of histological features *(Campbell CORR 2010)*
  - ALVAL Scoring system
  - Synovial lining
  - Cell types;
  - Tissue organization
MoP Taper Corrosion ALTR

- Adverse Tissue Reactions (Pseudotumours)
  - Fretting and Corrosion
- Potential biological mechanisms
  - ? Hypersensitivity reaction (Type IV T cell)
  - ? Dose dependent necrosis
Original article

Metal Ion Levels Are Not Correlated With Histopathology of Adverse Local Tissue Reactions in Taper Corrosion of Total Hip Arthroplasty

Ming Han Lincoln Liow, MD\textsuperscript{a}, Kenneth L. Urish, MD\textsuperscript{a}, Frederic I. Preffer, PhD\textsuperscript{b}, Gunnlaugur P. Nielson, MD\textsuperscript{b}, Young-Min Kwon, MD, PhD\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a} Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
\textsuperscript{b} Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
Taper Corrosion ALTR Histology

- **Low to Moderate ALVAL Score**
  - Associated with the presence of wear debris (79%) and Necrosis
- **High ALVAL Score**
  - Wear debris in only 31%
- **No significant correlation**
  - ALVAL score and Metal ion levels
  - Importance of individual patient reactivity
## Wear Analysis of Retrieved THA Implants

<table>
<thead>
<tr>
<th></th>
<th>Pseudotumour Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of implants</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Gender (female: male)</td>
<td>16:2</td>
<td>10:8</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>56 (range 39 - 65)</td>
<td>56 (range 45 - 70)</td>
</tr>
<tr>
<td>Mean Time <em>in vivo</em> (years)</td>
<td>3.9 (range 1.1 – 6.6)</td>
<td>2.5 (range 1.0 – 5.8)</td>
</tr>
<tr>
<td>Mean Femoral component size (mm)</td>
<td>46 (range 42 - 52)</td>
<td>46 (range 42 - 52)</td>
</tr>
<tr>
<td>Mean Cup Abduction Angle (degrees)</td>
<td>48 (range 12-80)</td>
<td>49 (range 31-61)</td>
</tr>
<tr>
<td>Mean Cup Anteversion (degrees)</td>
<td>11 (-2-31)</td>
<td>3 (0-21)</td>
</tr>
</tbody>
</table>

*Glyn-Jones, Kwon et al. JBJS Am 2011*
Non-Contact Optical CMM

- Linear and volumetric wear
- Resolution of 20 nanometers
- Maps both Cup and Femoral components without stitching
‘Low’ Wear Pseudotumours

Glyn-Jones, Kwon et al. JBJS Am 2011
‘Low’ Wear Pseudotumours

- *Matthies et al. CORR 2012, Di Laura et al. JBJS A 2018*
  - Retrieval study of 105 MoM hips
  - No significant association between many pseudotumours and component wear rates
  - Suggesting important patient susceptibility factors
Revision Surgery for ALTR
Revision THA for ALTR

- Revision Surgery for ALTR Challenging
  - Bone and muscle necrosis
  - Need for thorough and safe debridement
  - Adequate component fixation and stability
Revision Surgery Outcome

- **High Rate Complications for ALTR Revision**
  - Reported in MoM THA and MoP
  - 14% - 25%

- **Re-Revision Rates**
  - High 10% - 19%
  - Outcome Limited
Results: Complication Rate

Complication Rates Following Revision of Failed Dual Taper THA

- No complications: 80%
- Dislocation: 20%
- Infection: 3%
- Neurovascular injury: 9%
- Dislocation: 2%
- Periprosthetic Fx: 1%
- Pseudotumor Recurrence: 4%
- Greater Trochanter Fx: 2%
- Component Losening: 0%
Results: Risk Factors

- Risk Factors Associated with Revision Complications
- MARS MRI
  - Abductor deficiency (p=0.05)
- Intra-Operative Tissue Damage (p=0.04)
  - Extensive tissue damage noted in all patients with dislocations or pseudotumour recurrence
Complications - Other

The Fate of Elevated Metal Ion Levels After Revision Surgery for Head-Neck Taper Corrosion in Patients With Metal-on-Polyethylene Total Hip Arthroplasty

Young-Min Kwon, MD, PhD *, John MacAuliffe, MEng, Yun Peng, PhD, Paul Arauz, PhD

Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA
Results: Metal Ion Decline

- **For Cobalt Ion Level**
  - 1% decline per day during the first 4 months,
  - Slowed to 0.4% per day over the subsequent 6 months

- **For Chromium Ion Level**
  - Rate of decline 0.4% decline per day over the first 4 months
  - Decline of Chromium levels slower than decay of Cobalt levels (p < 0.001)
How to Evaluate ALTR in THA
## D.Dx of Painful THA

<table>
<thead>
<tr>
<th>Extrinsic to the Hip</th>
<th>Intrinsic to the Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine disease:</td>
<td></td>
</tr>
<tr>
<td>Stenosis; Disc Herniation; Spondylolysis or Spondylolisthesis</td>
<td>Intracapsular/Implant-Related:</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>Infection</td>
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<tr>
<td>Hernia (Femoral, Inguinal)</td>
<td>Loosening</td>
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<tr>
<td>Peripheral Nerve Injury (e.g. Sciatic, Femoral, Meralgia Paresthetica)</td>
<td>Instability/Subluxation</td>
</tr>
<tr>
<td>Malignancy or Metastases</td>
<td>Periprosthetic fracture</td>
</tr>
<tr>
<td>Metabolic Bone Disease (e.g. Paget’s Disease, Osteomalacia)</td>
<td>Adverse soft tissue reaction</td>
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<tr>
<td>Complex Regional Pain Syndrome</td>
<td>Extracapsular:</td>
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<tr>
<td>Psychological Disorder</td>
<td>Trochanteric bursitis</td>
</tr>
<tr>
<td></td>
<td>Iliopsoas tendonitis</td>
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<tr>
<td></td>
<td>Rectus femoris tendonitis</td>
</tr>
</tbody>
</table>

Kwon, Jacobs *et al.* JoA 2012
Systematic Evaluation Algorithm

Helpful to clinicians to tailor risk-benefit ratio for individual patient

• THA Implant type (HR, Stemmed MoM, Taper, femoral head <36mm and ≥36mm, Recalled)
• Symptomatic vs. Asymptomatic
• Follow up
  – Frequency and duration

• Cross-Sectional Imaging
  – MRI vs. US
  – Indications

• Metal ions levels
  – Threshold
  – Indication for repeat testing

• Indications for revision surgery
Consensus Risk Stratifications

- **Concerted Initiative**
  - American Association of Hip and Knee Surgeons (AAHKS)
  - American Academy of Orthopaedic Surgeons (AAOS)
  - The Hip Society
- **Hip Arthroplasty Task Force**
Consensus Risk Stratifications

- Patient Factors
  - Symptoms, Clinical Examination
- THA Implant Factors
  - HR, Modular MoM, Recalled, Dual Taper
- Radiographs
- Infection Work Up (ESR, CRP, Hip Aspiration)
- Metal Ion Levels
- Cross-Sectional Imaging (*MARS MRI/US/CT*)
- Treatment Recommendations
Risk Stratification Algorithm for Management of Patients with Metal-on-Metal Hip Arthroplasty

Consensus Statement of the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and The Hip Society

Young-Min Kwon, MD, PhD, Adolph V. Lombardi, MD, FACS, Joshua J. Jacobs, MD, Thomas K. Fehring, MD, Courtland G. Lewis, MD, and Miguel E. Cabanela, MD

Risk Stratification Algorithm for Management of Patients with Dual Modular Taper Total Hip Arthroplasty: Consensus Statement of the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons and the Hip Society

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f Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL

Mod Risk
High Risk
Summary

• Systemic Adverse Biological Reactions to Orthopaedic Hip Implants
  – Concern
  – Current studies limited by a small number of patients and short follow up period
  – Further research required
Summary

• Local Adverse Biological Reaction
• Complex interplay of Implant, Patient and Surgical factors
• Spectrum of Clinical Presentations & Etiologies
  – Majority Symptomatic
  – ? Minority ‘Asymptomatic’
  – Majority with High-Wearing
    (Elevated Metal Ion Levels)
  – ? Minority with Low-Wearing
    (‘Low’ Metal Ion Levels)
Summary

• ALTR Histology Spectrum
  – No clear dose-response relationship between metal corrosion load (Metal Levels) and ALTR (ALVAL Scores)
  – ? Metal wear/taper corrosion alone may not explain histological reactions

• Further research needed
  – Role of individual patient reactivity
  – Further standardize histological evaluation
Summary

- Revision Surgery for ALTR
  - Metal ion levels declined to low levels
    - Cobalt and Chromium ion levels
    - 3 Months post-revision, metal ion levels declined by 80% of pre-revision level
    - Decline of Chromium levels slower than Cobalt levels
    - Variations among individual patients
Summary

- **Revision Surgery for ALTR**
  - High Complication Rate (25%)
  - Re-revision Rate (10%)
- **Complications correlated with extent of tissue necrosis**
  - Systematic evaluation warranted to optimize revision outcome
  - Early diagnosis will facilitate initiation of appropriate treatment
Summary

• Systematic Evaluation of THA Patients for ALTR
  – Low Threshold for Further Evaluation
    • Metal ion Levels
    • Cross-Sectional imaging
• Evidence-Based Evaluation Algorithms
  – Continue to evolve with updated evidence
    • Early recognition of ‘At-Risk’ patients to optimize revision outcome
• Further Research required to identify Multi-Factorial Etiology of ALTR
EVALUATING ADVERSE BIOLOGICAL RESPONSES TO METAL IMPLANTS*

Immunology Devices Panel of the Medical Devices Advisory Committee Meeting
November 13, 2019
Elizabeth Stafford Ph.D.
elizabeth.Stafford@fda.hhs.gov

*Correlates to Section 8 of review paper
Introduction

• **Current Toolbox:**
  • Metal ion testing
  • LTT (lymphocytic transformation test)
  • Skin-based Patch Testing
  • Tissue Samples (Histology)
  • Imaging:
    – X-rays, MRI, CT, Ultrasound

• **Analytical Challenges**

• **Adding to the Toolbox**
Measures of Acquired Responses

**Skin Patch Testing**
- **Pro:** Non-invasive
- **Con:**
  - Specialist evaluation
  - Analytical variability
  - No clear relationship between implant/test

**Lymphocyte Transformation Test**
- **Pro:** Non-invasive
- **Con:**
  - Technically challenging
  - Analytical variability
  - Test result and implant status not always clear

Sections 8.2.1 and 8.2.4
### Imaging Adverse Responses

#### Visualization

<table>
<thead>
<tr>
<th>Soft tissue</th>
<th>Bone</th>
<th>Radiation</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>🔄 Ultrasound</td>
<td>✗</td>
<td>✗</td>
<td>Deep tissues</td>
</tr>
<tr>
<td>🔄 X-Ray</td>
<td>✗</td>
<td>✓</td>
<td>Limited data</td>
</tr>
<tr>
<td>🔄 CT</td>
<td>✓</td>
<td>✓</td>
<td>Signal from metals</td>
</tr>
<tr>
<td>🔄 MRI</td>
<td>✓</td>
<td>✓</td>
<td>Requires special training, MARS</td>
</tr>
</tbody>
</table>

#### Pros:
- Non-invasive
- Serial images

#### Cons:
- May not be helpful for screening adverse reactions
- Requires specialized reader

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Sections 8.3.2

Robinson et al. doi: 10.3109/17453674.2014.964618
Measures of Acquired and/or Innate Response

**Histology**

- **Pros:**
  - Well established techniques
  - Cellular level visualization

- **Cons:**
  - Invasive
  - Requires special reader
  - Retrospective

**Metal Ion Testing**

- **Pros:**
  - Non-invasive

- **Cons:**
  - Technically challenging
  - High levels may not mean an adverse effect

Campbell et al. 2014. doi: 10.1007/s11999-010-1372-y

Sections 8.2.2 and 8.3.1
Analytical Challenges: Metal Ion Testing

Sample Quality

- Collection methods
  - Metal-containing needles
  - Interactions with collection tube
- Matrix effects
  - Whole blood recommended for Cr
  - Serum ≠ plasma ≠ whole blood
  - Anticoagulants may alter apparent values

Instrumentation Issues

- ICP-MS Interference
  - Spectral Shift:
    - Elements/Isotopes with same mass (isobaric)
    - Polyatomic with same mass
  - Matrix effect
    - Sample introduction
    - Sample pre-tx and dilution
- Limits of detection
  - Measure clinically relevant concentrations

Choice of instrumentation and careful analytical procedure critical to success
Analytical Challenges: Metal Ion Testing

• ICP-MS Precision -
  – Repeatability within individual labs can be good
    • Many CV < 5%
  – Imprecision is higher close to detection limits
  – Reproducibility between labs challenging
    • Small differences in laboratories’ protocols may lead to significant differences in test results
Are we measuring the right thing(s)?

Total Immune Response to Metal Implants
Challenges Present and Goals Future:

- Tests we have provide limited clinical information
- Current challenge:
  - Analytical and methodology limitations in clinical decision making
  - Understand biology to build good tests and tools
- Goal – Tests that:
  - Measure a relevant pathological process
  - Give analytically reproducible and robust answers
  - Provide clinically useful information
    - Predict response before implantation
    - Screen for implant failure (monitoring)
    - Evaluate problematic implants
Implant Reactivity:

Summary / Gap Analysis

November 13, 2019: Immunology Devices Panel of the Medical Devices Advisory Committee Meeting

Yelizaveta (Lisa) Torosyan, MD, PhD
DEVICE vs. PATIENT Factors in Implant-related Outcomes: Interindividual Variability of Host Responses Complicating Predictive Evaluation of Implant Performance

**Expected Reactivity**
- e.g., wound healing

**EXAGGERATED REACTIVITY**
- Proportionate Host Response to EXCESSIVE DEBRIS
- DISPROPORTIONATE HOST RESPONSE to Expected Debris

**Patient: High Susceptibility**

**Device: High Corrosion**

**PATIENT**
- Procedure

**Device**
Knowledge Uncertainty Increasing from Device- to Patient-related Characteristics: *Lack of Predictive Testing as the Main Gap*
Clinical Challenges in Implant Reactivity: Unclear Symptomatology Affecting Diagnostic and Therapeutic Management

Unclear Risk Assessment for Enhanced Susceptibility

Predominance of subclinical vs. clinical features

Various Genetic/Demographic Risk Modifiers

Unclear Treatment Choices

Uncertainty of Clinical Diagnoses and Nosological Entities
Terminological Challenges in Implant Reactivity: Correct Terms are Prerequisites for Correct Diagnostics and Safety Analysis

• (Hyper)sensitivity 🚫 “Allergy”:
  - Sensitivity as an exaggerated response to expected wear
  - Not limited to delayed (type IV) reaction
  - Non-adaptive immune responses (e.g., inflammasome sensing)

• ALTR (Adverse Local Tissue Reaction) 🚫
  ALVAL (Aseptic Lymphocyte-dominated Vasculitis-Associated Lesion):
  - More diverse histopathology of ALTRs includes innate (macrophage-dominated) responses
  - Unlike the ALVAL subset, ALTRs in general are not limited to histopathological definitions and may include clinical/radiographic manifestations

• ARMDs (Adverse Reaction to Metal Debris):
  - A spectrum of local and systemic reactions
  - *Systemic* manifestations may mimic known autoimmune/ inflammatory conditions
Recognition of Both Immunity Types for Encompassing the Full Spectrum of Implant Reactivity: the Balanced View of Adaptive and Innate Responses
FBR Conundrum in Implant Reactivity:
How to See the Inflammation Forest through the Trees of Host Responses

Foreign Body Reaction (FBR): Friend or Foe?

- Resolution of Acute Inflammation and Wound Healing
- Delayed Type IV Hypersensitivity
- Cell Death & Tissue Necrosis
- Local and systemic ARMDs
- Damage-associated Molecular Pattern (DAMP)

Chronic Inflammation & Post-Inflammatory Peri-implant Tissue Remodeling

- Reactive Oxygen Species (ROS) Generation
- Toll-like Receptor & Inflammasome Activation
- Frustrated Phagocytosis
- Cytokine Release
- 'Implant Allergy'
- Toxicity
- Danger Signaling
Inflammatory Underpinnings of Implant Reactivity:
Encompassing 2,000 Year-Old Terminology and 21st Century Pathogenetic Concepts

From main INFLAMMATORY SYMPTOMS defined by Celsus and Galen ...

...to INFLAMMASOME as a key regulator in anti- vs. pro-inflammatory responses and subsequent tissue changes
CLINICAL Implications of ‘Allergy’-to-Inflammation Transition: Pathogenetically Determined and More Accurate Diagnostic/Prognostic Testing
PRECLINICAL Implications of ‘Allergy’-to-Inflammation Transition: Pathogenetically Determined and More Precise Biocompatibility Testing

- Inflammogenicity:
  - Pro-inflammatory potential (cytokine release patterns)
  - Tissue remodeling potential (destruction or overgrowth)

Patient’s Host Responses

Material’s Phys / Chem Properties

Desired Implant Function

Guidance

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Lessons Learned

• Variability of individual susceptibility affecting predictability of patient’s response (e.g., debris ≠ ALTR)

• Prior pathogenetic understanding and terminology overemphasizing the role of adaptive immunity (e.g., “implant allergy”)

• Implant reactivity often remaining a diagnosis of exclusion:
  – Unclear nomenclature and diagnostic criteria
  – Clinical overlap with other immune and inflammatory diseases
  – Lack of diagnostic and therapeutic management

• Lack of (pre)clinical tests based on the current concepts in implant reactivity

Lessons to Apply

• Transition from “allergy” to overall reactivity:
  – Inflammation as a driver of excessive FBR and subsequent peri-implant tissue changes
  – Involvement of both immunities (adaptive & innate)
  – Predominance of innate responses in the clearance of implant debris

• Mimicry of systemic immune/inflammatory diseases as a source of:
  – Common regulatory cascades and signaling pathways
  – Common diagnostic/therapeutic targets

• Development of pathogenetically-determined testing:
  – The entire spectrum of possible ARMDs
  – Pre-implantation risk based on individual susceptibility
  – Post-implantation detection of (sub)clinical features
  – Preclinical (biocompatibility) tests assessing proinflammatory and tissue destructive potentials
**SUMMARY** on Implant Reactivity Lessons for Enhancing Real-World Implant Performance

**Lessons Learned**

- Variability of individual susceptibility affecting predictability of patient’s response (e.g., debris ALTR)
- Prior pathogenetic understanding and terminology overemphasizing the role of adaptive immunity (e.g., “implant allergy”)
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Panel Discussion:
*Turning Challenges into Opportunities*
Thank you!