Incidence of Lymphocyte Reactivity to Implant Metals in Nickel Reactive Patients with a Painful Total Joint Arthroplasty: Greater Understanding in Implant Selection.

Marco Caicedo1, Edward Solver1, Latasha Coleman1, Nadim Hallab2.
1Orthopedic Analysis, LLC, Chicago, IL, USA, 2Rush University Medical Center, Chicago, IL, USA.

Disclosures:
M. Caicedo: 3A; Orthopedic Analysis, LLC. E. Solver: 3A; Orthopedic Analysis, LLC. L. Coleman: 3A; Orthopedic Analysis, LLC. N. Hallab: 3A; Orthopedic Analysis, LLC.

Introduction: INTRODUCTION: It is well established that cell-mediated sensitivity responses to implant metals can trigger untoward inflammatory responses around the bone implant interface limiting the implant performance. Previous studies have reported an incidence of metal hypersensitivity in 10% of the general population, 20% of patients with well performing implants and in 60% of patients with failing implants1. While pre-op and post-op screening for metal sensitivity is increasingly being incorporated into orthopedic surgery and allergy practices, it remains unclear which specific metal or battery of metals are appropriate to test in order to obtain useful information to choose a suitable device for a metal sensitive patient. Nickel, the most common sensitizer, has been used as a general measure of metal allergy2; however, nickel allergy testing alone cannot aid the surgeon in choosing an alternate implant material to which the patient is not sensitive to. Do nickel sensitive patients respond to other implant metals or bone cement that can potentially alter a surgeon’s choice of implant material? We hypothesized that highly nickel sensitive patients with reported high pain levels in their total joint arthroplasty (TJA) will also show incidences of sensitivity to other alternate implant metals as determined by a metal-lymphocyte transformation test (metal-LTT). We tested this hypothesis by calculating the incidence of lymphocyte sensitization to soluble ions and particles of Co-alloy, Ti-alloy, Zirconium and bone cement in highly nickel sensitive people with a highly painful TJA (8-10 on a scale of 10).

Methods: MATERIALS AND METHODS: Subject Groups: Blinded de-identified data from 2081 TJA (knees and or hips) subjects tested for metal hypersensitivity using a metal-LTT was approved by IRB and reviewed. Subjects with TJAs and a history of metal allergy n=330 (i.e. Jewelry or metal) were plotted against their reported pain levels: No pain/no implant (controls) n=34, low pain (1-3 on a scale of 10) n=28, Moderate pain (4-7 on a scale of 10) n=147 and high pain (8-10 on a scale of 10) n=138. Incidences of sensitization to Cobalt Chromium Molybdenum ions, Co-alloy particles, Aluminum Vanadium ions, Ti-alloy particles, Zirconium and Bone cement particles were calculated in Highly nickel sensitive people (SI>8) with painful (8-10 out of 10) TJA (n=44). Metal-LTT (as performed by Orthopedic Analysis, LLC): Peripheral blood mononuclear cells (PBMCs) were collected from 30mL of peripheral blood by Ficoll gradient separation. PBMCs were cultured with Ni+2 at 0.1mM and 0.01mM. 3H Thymidine was added at day 5 of culture and 3H thymidine incorporation was analyzed using a beta scintillation counter at day 6. A stimulation Index(SI) of reactivity was calculated by dividing scintillation counts per minute of metal-treated cells over untreated controls. Statistical Analysis: Low, Moderate and high pain level groups were analyzed for statistical differences in SI to Nickel at 0.01 and 0.1 mM compared to the no pain/no implant control group. Non-parametric Mann Whitney test (two-tailed) was used to determine statistical significance at p<0.05.

Results: RESULTS: Nickel SI compared to reported pain levels in TJA subjects with a history of metal allergy: To calculate incidence of metal hypersensitivity between four groups of pain levels, SI in response to Nickel at 0.01 and 0.1 mM (Figure 1) were plotted against three groups of subjects defined as having no pain (n=34), low pain (n=28), moderate pain (n=147) or high pain (n=138) in their TJA. Each dot represents each subject tested. The low, moderate and high pain groups exhibited significantly higher average SI (10.4, 10.1 and 12.0 respectively) to nickel at 0.1mM compared to the low pain group (4.1).

Incidence of reactivity to alternate metals in highly nickel sensitive subjects: Highly Nickel reactive subjects with painful TJAs presented incidences of reactivity to other metal constituents of implant alloys (Figure 2). 16% of highly nickel sensitive patients were reactive (SI>4) to either Cobalt, Chromium or Molybdenum ions. 22% were reactive (SI >4) to Co-alloy particles. Also, 16 % were reactive (SI>4) to either Aluminum or Vanadium ions and 33% to Ti-alloy particles. The lowest incidence of reactivity was to Zirconium (a constituent of Oxinium) were only 4% (SI>4) exhibited reactivity. Finally 17% of highly nickel sensitive patients exhibited reactivity (SI >4) to bone cement particles.

Discussion: DISCUSSION: The higher average of metal-specific lymphocyte reactivity of individuals with low, moderate and high pain groups compared to the no pain group supports a correlation between metal sensitization and poor implant performance (not due to infection or mechanical problems). Interestingly, while nickel sensitivity has been used as a general measure of “metal allergy”, our results indicate that nickel sensitive patients with highly painful implants (potential revision patients) are also sensitized to other implant alloy metals and bone cement to different degrees. These results support our hypothesis that Nickel sensitive patients can also be sensitized to other implant alloy metals. This data has important implications in the correct
diagnosis of metal hypersensitivity pre-op and post-op. While a confirmation of nickel allergy may be helpful in avoiding metal-alloys containing nickel (i.e. Stainless steel, Nitenol, Cobalt-alloy), it does not rule out possible sensitivity to other “nickel-free” implant alloys or bone cement (i.e. Pure Titanium, Ti-alloy, Zirconium-alloy, etc.) that may be inappropriately chosen by the physician. These results indicate the importance of testing all implant materials in patients, not just nickel. It is noteworthy that Zirconium, elicited the least incidence of reactivity (4%) in nickel sensitized patients compared to Ti-alloy (33%).

**Significance:** SIGNIFICANCE: Our data shows that highly nickel sensitive patients with painful TJAs also exhibit different incidences of reactivity to other implant alloy metals that can be potentially implanted. Further investigation is being performed to more accurately determine a stronger/predictive correlation between TJA-associated pain levels and metal hypersensitivity responses in nickel and other more prevalent implant metals.

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**References:**

![Graphs](image-url) (Fig 1. Lymphocyte stimulation index to Nickel at 0.01 mM (left) and 0.1 mM (right) in people with a history of metal allergy based on pain levels.)
Fig 2. Incidence of hypersensitivity responses to other implant metals in patients with high TJA pain levels and high LTT “metal-allergy” scores to Nickel (SI > 8).