

# Metal Hypersensitivity to Implant Materials

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*Hypersensitivity to TMJ implant materials is an issue that we are frequently hearing from TMJ patients. Given this concern we contacted Marco Caicedo, Ph.D., Senior Scientists and COO at Orthopedic Analysis in Chicago, IL. Orthopedic Analysis is an independent diagnostics company dedicated to the quantitative analysis of immune responses to biomaterials (i.e metal allergy to implant materials). The TMJ Association thanks Dr. Caicedo for writing this state-of-the-art article.*

## What is a metal hypersensitivity?

Metal hypersensitivity (or metal sensitivity) can be defined as an immune reaction that is triggered by specific cells of the body's immune system in response to certain metals (like: nickel, cobalt, and chromium).<sup>[14]</sup> While metal hypersensitivity can be considered a type of allergy, it does not induce the immediate allergy symptoms that occur when exposed to seasonal or household allergens like pollen, animal dander, mold, etc. Metal hypersensitivities have a delayed onset from the time of exposure to the materials and are not caused by specific antibodies or histamine release that lead to the classical indications of a common allergy like itching, watery eyes, or sneezing.

Metal hypersensitivity requires a first-step sensitization stage where specific cells of the immune system (T lymphocytes) recognize, activate, proliferate and form immunological memory upon contact with sensitizing agents like metals.<sup>[2,4,14]</sup> Immunological memory occurs once the immune system is exposed for the first time to a new antigen (virus, fungus, or chemical). Once immunological memory has been formed, a secondary exposure to metal leads to all the classical inflammatory symptoms of delayed type hypersensitivity, which are described below as compared with an immediate type hypersensitivity which you would get from a food allergy or bee sting.

## What are the symptoms of a metal hypersensitivity?

The symptoms of a metal hypersensitivity can be best described in cases of skin allergic contact dermatitis due to metal exposure from jewelry, belts and other metal-containing accessories.<sup>[13]</sup> The most common symptoms reported are a rash around the contact area, but may also include blisters, vesicles (small, fluid-filled elevations of the skin), redness, itching and general inflammation around the area exposed to the contact allergen.<sup>[12]</sup> Generally, symptoms of a metal hypersensitivity do not appear until the second day after exposure and they may continue for several days before returning to a normal state.

Metal hypersensitivity symptoms caused by metal implant devices (e.g., Total Temporomandibular Joint, Total Hip and knee replacements) are more challenging to describe because the implant is inside the body, restricting access to visual examination. However, several studies of tissues surrounding the

implant in subjects with aseptically (not infected) failed prostheses indicate the presence of immune cells typically observed in a hypersensitivity response (such as lymphocytes and macrophages) interacting with implant debris products in the affected area.<sup>[3,7,8,16]</sup> Implant debris products are metal particles resulting from friction and wear, metal corrosion from the implant, and metal ions leached from the implant, as well as particles going through a corrosion process. General symptoms that have been reported by patients with non-infected failing metal prostheses are pain, swelling, loss of range and motion in the affected joint, effusions from the joint, inflammation and premature osteolysis (bone loss) around the metal device.<sup>[6,7,9]</sup> Effusions from an inflamed joint are the excess fluids from the joint caused by inflammation. Patients may have one or more symptoms that can occur at any time during the lifetime of the implant, depending on the degree of sensitization and exposure. Because all of these symptoms can also be caused by other problems not associated with metal hypersensitivity, it is important to consult with your doctor and conduct a thorough clinical history to confirm a diagnosis

### **What happens to my TMJ if I have a metal hypersensitivity?**

All implant materials undergo wear and corrosion when in the body, producing debris. Microscopic metal particles and soluble concentrations of metal ions leached from the implant surface are released over time in the surrounding implant tissue.<sup>[11]</sup> While exposure to minute concentrations of metal may not trigger an adverse response in the majority of cases, people with a known hypersensitivity to any of the components of their implant may respond differently. Immune cells in contact with a metal (e.g., nickel, cobalt, chromium) may activate, divide and recruit more immune cells, initiating an inflammatory response. The response can range from mild to severe depending on the degree of sensitization and on the amount of wear debris that is being generated.<sup>[2,14]</sup> This vicious cycle of inflammation can lead to detrimental effects around the bone-implant interface causing symptoms that can include myofascial pain, muscle spasms, headaches, earaches, tinnitus, vertigo, and facial swelling in TMD patients.<sup>[16]</sup>

Continuous exposure to metal sensitizing agents can create a chronic painful inflammatory state around the implant, which can also lead to a loss of bone maintenance mechanisms, potentially resulting in osteolysis (bone loss) and implant loosening.<sup>[8,16]</sup>

### **How can I find out if I have a metal hypersensitivity?**

There are two kinds of testing that have been historically used to diagnose hypersensitivity to metals: 1. The patch skin test and 2. The lymphocyte transformation test (LTT) using white blood cells. While the techniques for these two tests are very different, they both diagnose hypersensitivity type responses.

1. Patch testing in which a sample of the suspected allergy-causing material is applied to the skin is considered the gold standard to detect SKIN contact hypersensitivities to chemicals and metals. Patch testing has been used historically to diagnose metal hypersensitivity in patients with failing orthopedic devices (before LTT testing was developed.)<sup>[1]</sup> Patch testing is widely available

through allergy and immunology practices. There are definite concerns regarding the applicability of this testing for people with implants, however. The central concern is that patch testing has the potential to sensitize the patient to the very same metals they are testing for, so that the patch test itself can cause you to be more sensitive to the implant metals. Furthermore, the on-the-skin approach is a much different environment compared to the deep tissue around an implant. Patch testing can be costly as it may require two visits to the physician (one for application and one to read a subjective result) and it does not provide a wide range of clinically relevant orthopedic challenge agents (metals and bone cement materials) applicable for the purpose of diagnosing a metal hypersensitivity to a specific orthopedic device (i.e. TMJ).<sup>[15]</sup>

2. The lymphocyte transformation test (LTT) is a blood test that can detect if the patient has a metal hypersensitivity. The lymphocyte transformation test has been available for over 25 years and was first used as a test to detect drug hypersensitivity reactions. The LTT is now used for multiple applications that include, but are not limited to immune function testing, drug allergies and metal allergy.<sup>[5]</sup> The LTT requires drawing a blood sample at a physician's office or local laboratory with special tubes. Once the sample is submitted and processed at a laboratory with the expertise to perform the test, it provides results within 7 to 10 days. Advantages of the LTT include a non-subjective evaluation (it doesn't depend on a physician's visual judgment), and can be used to test numerous clinically relevant orthopedic metals and other materials tested at different concentrations with a simple blood draw.

### **What are the facts about metal hypersensitivity and implant performance?**

Several studies of metal hypersensitivity and its correlation to orthopedic implants have been performed in the past. It is a fact that 10-15 % of the general population have a hypersensitivity to one of the most common sensitizers (nickel, cobalt, chromium).<sup>[4,16]</sup> Studies also reveal that 20-25% of people with well-performing total joint replacements have a metal hypersensitivity and 60% of individuals with poorly performing implants have a metal hypersensitivity.<sup>[4,16]</sup> Recently, it has been well documented that devices with metal-on-metal articulations (compared to traditional metal on polyethylene) release more metal debris and consequently have induced a greater rate of failures that have been attributed to metal toxicity, hypersensitivity and other adverse tissue reactions.<sup>[10]</sup>

Clearly, metal hypersensitivity is correlated with poor implant performance and the utility of testing could be lifesaving by avoiding certain metals and risky revision surgeries for people with painful implants undergo. However, implant outcome or the current status of a prosthesis cannot be based solely on a metal hypersensitivity test. The patient's clinical history, results from other clinical tests performed and more importantly, the patient's current health status and quality of life must be considered by the doctor before making a conclusive diagnosis.

## Where can I get tested for Metal hypersensitivity and what will the results tell me?

**Patch testing:** Patch testing may be performed at most allergy and/or immunology practices by appointment.

**Lymphocyte Transformation tests:** While some Clinical laboratories around the country offer lymphocyte transformation tests on their testing menu, they may not offer specific metal concentrations or panels of metals that are relevant to a metal prosthesis.

*Orthopedic Analysis, LLC* is a CLIA certified laboratory based in Chicago that concentrates specifically in the diagnosis of immune responses to implant materials (i.e. metal hypersensitivity). Samples may be submitted from any State in the U.S through the mail in a kit provided by the company.  
[www.orthopedicanalysis.com](http://www.orthopedicanalysis.com)

## References

- [1] Atanaskova MN, Tellez A, Molina L, et al. The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. *Arch Dermatol* 2012; 148 687-93
- [2] Caicedo MS, Pennekamp PH, McAllister K, et al. Soluble ions more than particulate cobalt-alloy implant debris induce monocyte costimulatory molecule expression and release of proinflammatory cytokines critical to metal-induced lymphocyte reactivity. *J Biomed Mater Res A* 2010; 93 1312-21
- [3] Hallab N. Metal sensitivity in patients with orthopedic implants. *J Clin Rheumatol* 2001; 7 215-8
- [4] Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001; 83-A 428-36
- [5] Hallab NJ. Lymphocyte transformation testing for quantifying metal-implant-related hypersensitivity responses. *Dermatitis* 2004; 15 82-90
- [6] Hallab NJ, Anderson S, Stafford T, et al. Lymphocyte responses in patients with total hip arthroplasty. *J Orthop Res* 2005; 23 384-91
- [7] Hallab NJ, Jacobs JJ. Biologic effects of implant debris. *Bull NYU Hosp Jt Dis* 2009; 67 182-8
- [8] Jacobs JJ, Hallab NJ. Loosening and osteolysis associated with metal-on-metal bearings: A local effect of metal hypersensitivity? *J Bone Joint Surg Am* 2006; 88 1171-2
- [9] Jacobs JJ, Roebuck KA, Archibeck M, et al. Osteolysis: basic science. *Clin Orthop Relat Res* 2001; 71-7

- [10] Langton DJ, Jameson SS, Joyce TJ, et al. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *J Bone Joint Surg Br* 2010; 92 38-46
- [11] Mathew MT, Abbey S, Hallab NJ, et al. Influence of pH on the tribocorrosion behavior of CpTi in the oral environment: synergistic interactions of wear and corrosion. *J Biomed Mater Res B Appl Biomater* 2012; 100 1662-71
- [12] Seyfarth F, Schliemann S, Antonov D, Elsner P. Teaching interventions in contact dermatitis. *Dermatitis* 2011; 22 8-15
- [13] Thyssen JP, Hald M, Avnstorpe C, et al. Characteristics of nickel-allergic dermatitis patients seen in private dermatology clinics in Denmark: a questionnaire study. *Acta Derm Venereol* 2009; 89 384-8
- [14] Wang Y, Dai S. Structural basis of metal hypersensitivity. *Immunol Res* 2013; 55 83-90
- [15] Mihalko W, et al.. Skin Patch Testing and Associated Total Joint Outcomes. AAOS, Chicago, IL 2013
- [16] Wolford LM. Factors to consider in joint prosthesis systems. *Proc (Bayl Univ Med Cent )* 2006; 19 232-8