

# METAL SENSITIVITY TESTING AND ASSOCIATED TOTAL JOINT OUTCOMES

AAOS BIOMEDICAL ENGINEERING AND BIOLOGICAL IMPLANTS COMMITTEES  
WILLIAM M. MIHALKO, MD, PhD AND STUART B. GOODMAN, MD, PhD  
MICHAEL AMINI, MD, NADIM HALLAB, PhD

## INTRODUCTION

Cutaneous and excessive local reactions to metals utilized in orthopaedic implants have been documented for decades. In the last couple of decades there has been a rise in the incidence of cutaneous reactions to certain metals and materials in the general population. The association between cutaneous reactions and reaction to an implanted orthopaedic device has been less understood. There have been reports that have shown poor correlation to those who react to a skin test and those that react to an implanted material within a Total Joint Arthroplasty (TJA), while some reports have shown a subset of patients may convert their patch test after surgery is performed. This exhibit will review the available literature on this topic and the possible approaches orthopaedic surgeons may consider when a hypersensitivity comes into question.

## METHODS

A literature search on PubMed was conducted to review the literature pertaining to skin patch testing, LTT and outcomes in Total Joint Arthroplasty. The past few reports of the North American Skin Patch Testing Group were reviewed to show the general population trends in the past decade. Several reports have demonstrated a correlation between skin patch testing and painful, swollen, stiff TKA. There have also been several reports concerning negative pre-operative patch tests and subsequent positive post-operative patch tests to metal contained in a TJA.

## RESULTS

The North American Skin Patch testing group in 2009 reported the results of testing almost 5000 patients to represent a cross section of the population to a wide variety of materials. They found that nickel (Ni) was the most common reactant (21%) with other substances found in orthopaedic implants (cobalt 8% and chrome 8%) were on the rise. Symptoms that were associated with metal hypersensitivity included: pain, swelling, epicutaneous rash, patient dissatisfaction, and loss of function. Patch testing, however, involves the incorporation of a metallic material into an aqueous solution and then into petroleum jelly and applied by an adhesive tape to the skin for 24-96 hours, at which point it is removed and the reaction can be recorded from mild to severe (1-4). There is a significant subjectivity to the intermediate reaction grades in patch test reporting. Skin testing also involves a different exposure mechanism with Langerhans cells being the primary cell initiating hypersensitivity reaction compared to the periprosthetic environment where corrosion products and local macrophages and lymphocytes are involved in the reaction process. All of these differences will be compared and contrasted in the exhibit.

## DISCUSSION

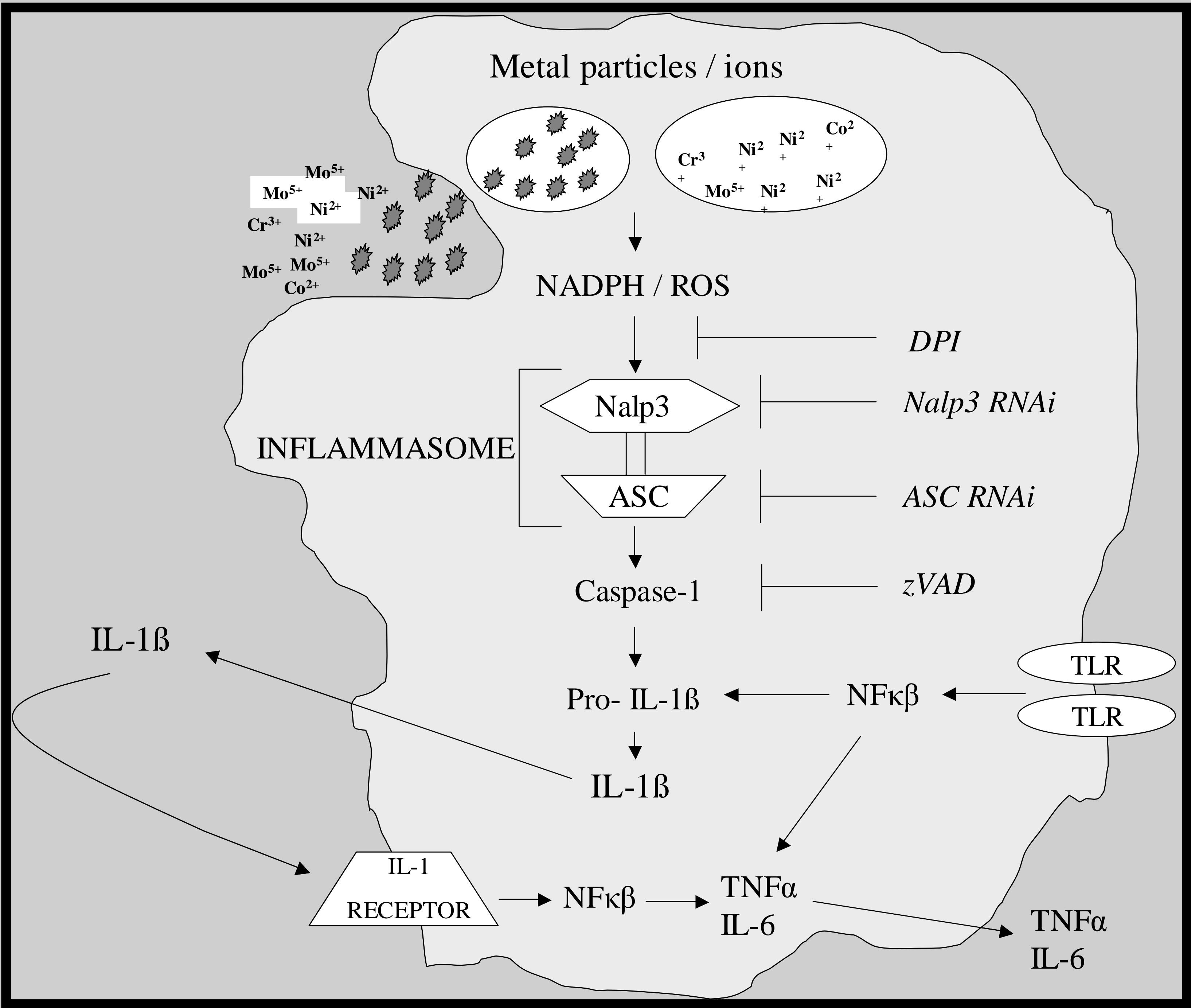
When extensive patient workup reveals aseptic inflammation, along with negative radiological findings in a patient with a painful TJA, the surgeon often times thinks about hypersensitivity to an implant material as the cause for concern. Patch testing can be performed and/or an in-vitro lymphocyte transformation test can be performed to aid in possibly diagnosing an allergy as a cause for the pain. Currently, this diagnosis is mainly one of exclusion and all other possible causes of pain after TJA need to be ruled out as well. This report will aid in serving as a source for all surgeons concerning the possible diagnosis of a hypersensitivity reaction for some TJA patients with poor outcomes.



# INTRODUCTION

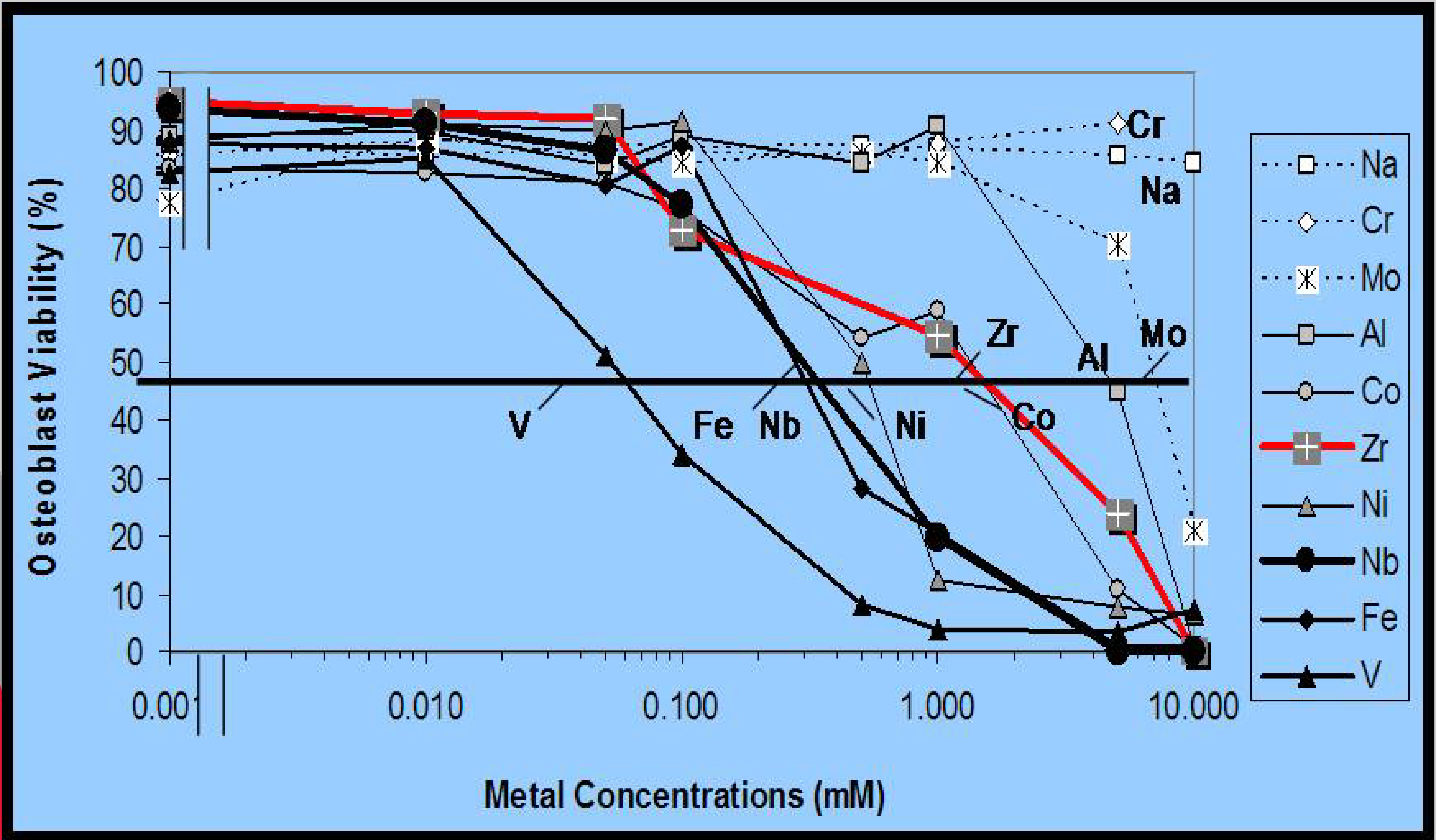
All patients react to the presence of metal and debris, which is produced by mechanical wear and by corrosion. Typically wear is responsible for the most debris about a THA/TKA and the debris can be particulate or ionic (soluble). There are two types of responses to debris from a TJA :

- 1. Innate (non-specific immunity)
  - Immediate maximal response, not antigen specific
  - No immunologic memory developed from exposure
  - Controlled by macrophage (osteolysis)
- 2. Adaptive (specific immunity)
  - Antigen dependent with a time line from exposure to maximum response
  - Results in immunologic memory controlled by lymphocytes (acute local tissue response)



## Soluble and Particulate Co-Cr-Mo Alloy Implant Metals Activate the Inflammasome Danger Signaling Pathway in Human Macrophages: A Novel Mechanism for Implant Debris Reactivity

Marco S. Caicedo,<sup>1,2</sup> Ronak Desai,<sup>2</sup> Kyrion McAllister,<sup>2</sup> Anand Reddy,<sup>2</sup> Joshua J. Jacobs,<sup>2</sup> Nadim J. Hallab<sup>1,2</sup>  
<sup>1</sup>Department of Immunology, Rush University Medical Center, Chicago, Illinois 60612, <sup>2</sup>Department of Orthopedic Surgery, Rush University Medical Center, Chicago, Illinois 60612  
Received 18 September 2008; accepted 7 November 2008  
Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jor.20826



	Less Toxic	More Toxic	Concentration
Lymph	Al, Cr, Fe, Mo, Nb, Ni, Zr	Co, Ni, V, (Nb)	1 mM
Fibroblasts	Al, Co, Cr, Fe, Mo, Nb, Ni, Zr	V, Co, (Fe)	5 mM
Osteoblasts	Al, Cr, Mo, Nb, Zr	Co, Ni, V, (Fe), (Nb)	1 mM

Table depicts the concentration of particles that are toxic to different types of cell about a TJA



# DIAGNOSING METAL SENSITIVITY

Symptoms ascribed to metal hypersensitivity include: **pain, swelling, cutaneous rash, patient dissatisfaction, loss of function.**

## Examination and Testing

As with any painful TKA, the clinician should perform a careful history and physical examination, including **blood tests (ESR, CRP, CBC and differentials)** along with the possibility of an arthrocentesis to rule out the presence of an infection.

Explore **other causes of chronic pain after TKA** including mid-flexion instability, complex regional pain syndrome, or somatization disorder.

**Consider metal hypersensitivity** only after these laboratory tests along **with negative radiological findings indicate no loosening, infection or other tissue abnormalities.**

**Patch testing** or an in vitro **lymphocyte transformation test (LTT)** can be performed.

LTT for metals

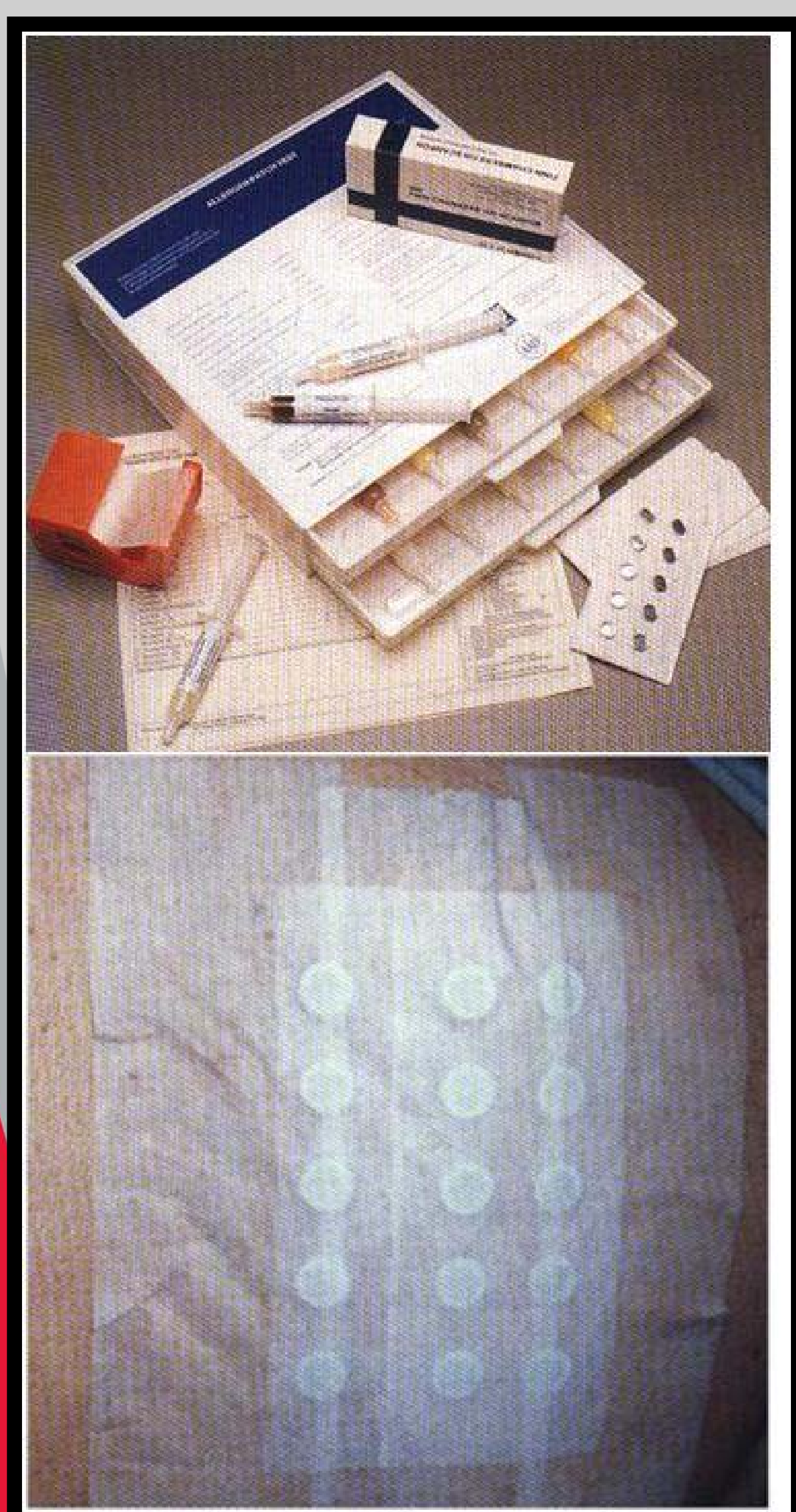
- ✓ Blood LTT test reimbursed by Medicare
- ✓ Has become relatively standardized with several laboratories in the US (i.e. all use 2-3 different dose concentrations, 0.001-0.1mM, for each implant metal tested)
- ✓ Limited number of laboratories that perform metal related LTT in the United States
- ✓ Typically costs between \$250 and \$500 (generally less than half of total cost of a patch test)

Cons of LTT and patch testing:

- ✓ Clinical cause for pain and the results of the patch testing or lymphocyte transformation test **cannot** be easily correlated
- ✓ Some evidence indicates the utility of LTT testing in specific situations (e.g. in metal on metal THA symptomatic patients (6))
- ✓ Lack of large scale prospective evidence implicating pre-existing metal allergy as a cause of implant failure in people knowingly implanted with components containing metal(s) they are reactive to. Conducting these studies are problematic given the number of retrospective studies showing elevated levels of metal sensitivity in cohorts of failing or failed implants. (7-11)

## Patch Testing

- ✓ Is not a test of reactivity of deep tissue
- ✓ Mechanism is mediated by Langerhans Cell
- ✓ Involves the soluble forms of metallic ions and not debris
- ✓ Testing is performed in a grid pattern with known locations of suspected allergens
- ✓ VERY subjective!
- ✓ Not standardized
- ✓ Not quantified



It is important to note that there are problems associated with skin patch testing that are considerations for the patient undergoing implantation of a metal device. 1) **SUBJECTIVITY**: There is often a subjective nature to interpretation of the +1 to +3 dermal reaction results which are far from optimal given the number of different observer biases. 2) **CHALLENGE LOCATION**: Another concern is that antigen presenting cells (Langerhans cells) within the skin layers do not react in the same way as macrophages and dendritic cells located in the deep tissues around the implant. (This calls into question the results and correlations to orthopaedic implant performance.) 3) **SENSITIZATION**: Perhaps of most concern for orthopedic surgeons is that the method of patch testing involves mixing metal chlorides in petroleum jelly and applying them to the patient's skin for at least 48 hours. This same phenomenon (T-cell response) that provokes a response can theoretically induce sensitivity in people (as it has been shown to do in animal models) and while considered minimal, this risk has been consistently mentioned in the literature on the topic. Currently, the interpretation of the results of skin patch testing should be considered only in the context of the history and physical examination as well as the results of other diagnostic testing modalities.

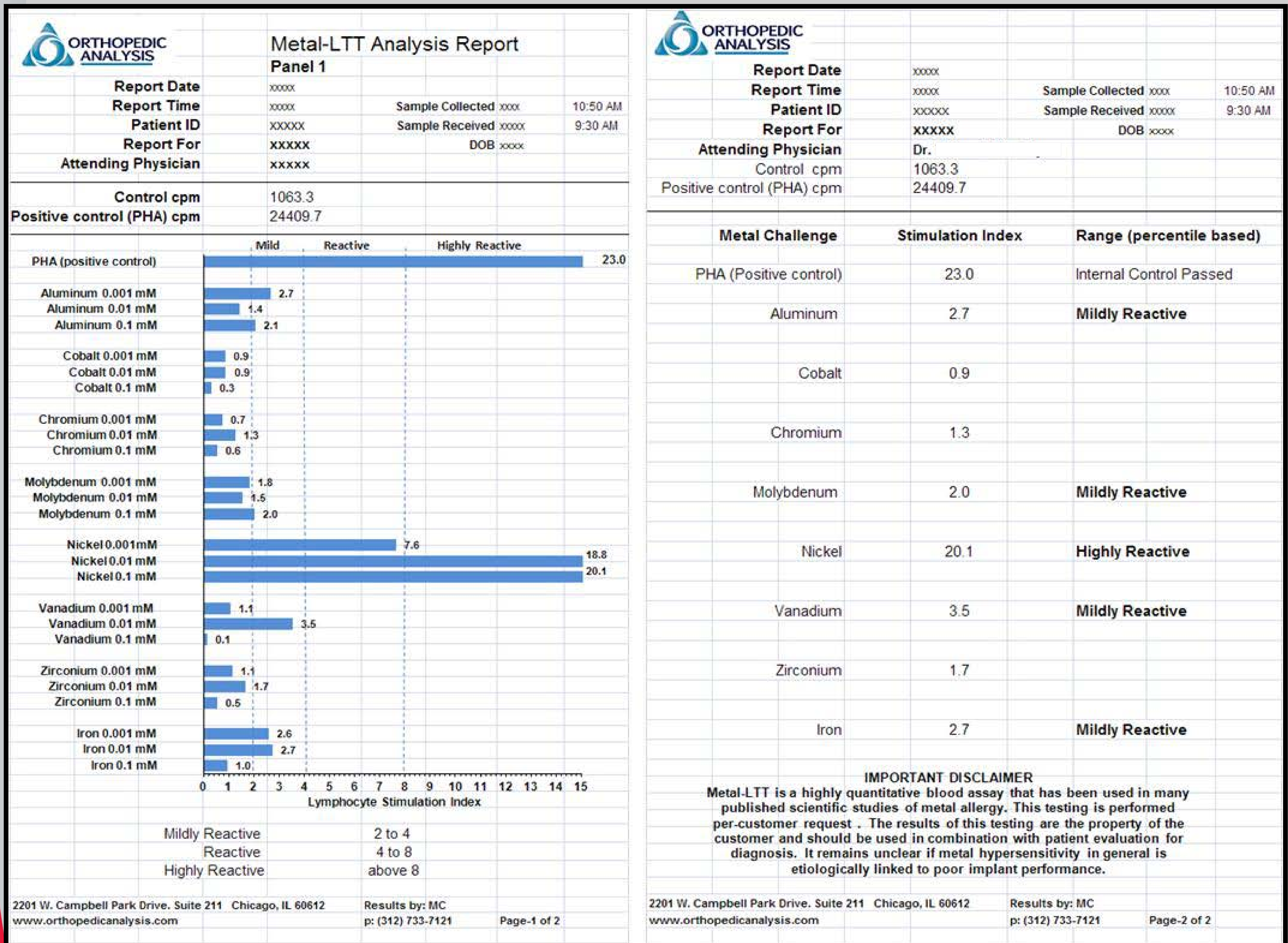


# LYMPHOCYTE TRANSFORMATION TEST (LTT)

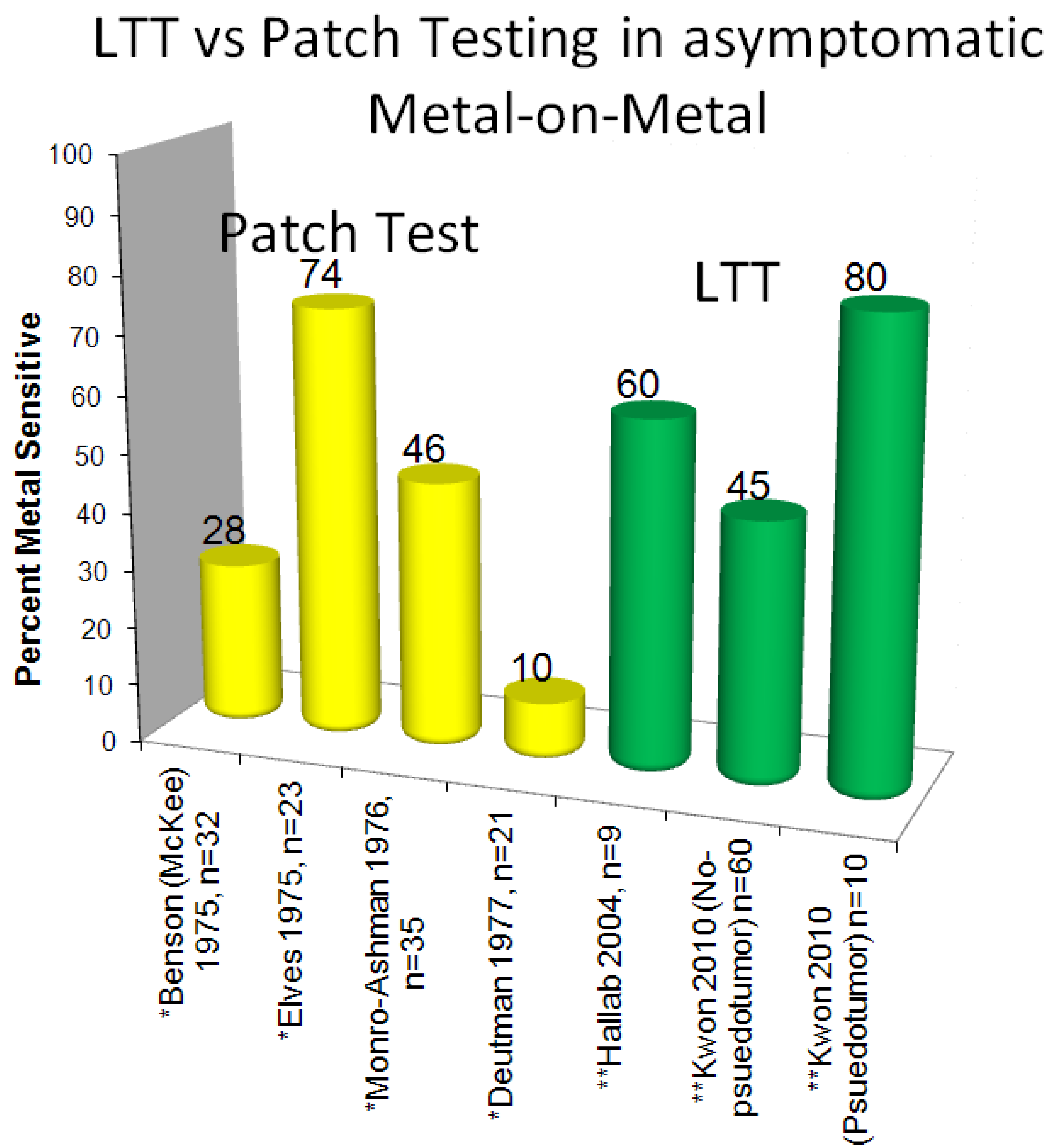
Soluble metals (Al, Co, Cr, Mo, V, Ni, Zr) quantified by a stimulation index

**Metal treated lymphocyte proliferation / 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.



Mild, Moderate, and High reactivity scores based on quartile squares and not clinical outcome



Lymphocyte Reactivity to Implant Metals Correlates with Reported High Pain Levels in Patients with Total Joint Arthroplasties: Implications for Pain-Related Hypersensitivity Responses. Caicedo, MS; Samelko, L; Ott, S; Hallab, NJ, *Trans Orthopedic Research Society*, 2012.



# REVIEW OF THE LITERATURE

- An analysis of the literature concerning patch testing in TJA was performed.
- The PubMed database was searched using combinations of the terms Arthroplasty, Hyper sensitivity, Patch Testing, and Allergy.
- Studies published in a foreign language, reviews and case reports were excluded.
- Prospective and retrospective studies were tabulated and summarized into each category.
- Ten retrospective reports were included in the summary (Table 1).
- Results revealed 33/138 patients revised for any reason had a positive skin patch test to an implant material (23.9% of revisions pre-op patch test positive).
- In 44/303 TJA surviving at the end of these studies had a positive skin patch test (14.5% of stable TJAs had a positive patch test).

TABLE 1: REVIEW OF RETROSPECTIVE STUDIES

MANUSCRIPT TITLE	JOURNAL	FIRST AUTHOR	SUMMARY OF RESULTS
Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty	Dtsch Med Wochenschr	Eben R	In cemented TJA: 22/66 Symptomatic pts patch +, asymptomatic patch + 3/26
Allergy to metals as a cause of orthopaedic implant failure	Int J Occup Med Environ Health	Krecisz B	14 poor implants, 8 patch + (7 Ni, 6 Cr), 3 underwent revision and improved
Early osteolysis following second-generation metal-on-metal hip replacement	J Bone Joint Surg Am	Park YS	8/9 MoM w/ osteolysis patch + to Co, 2/9 w/o osteolysis patch +; retrospective
Sensitivity to metal as a possible cause of sterile loosening after cobalt-chromium total hip-replacement arthroplasty	J Bone Joint Surg Am	Brown GC	0/20 loose MoM patch + (1977)
Metal sensitivity as a cause of bone necrosis and loosening of the hip prosthesis in total joint replacement	J Bone Joint Surg Br	Evans EM	9/14 w/ loose joints patch +, 0/24 w/ stable joints
Incidence of metal sensitivity in patients with total joint replacements	Br Med J	Elves MW	15/23 failed TJA patch +, 4/27 stable patch +, 8/13 w/ derm rxn were patch +
Dermatitis on the knee following knee replacement: a minority of cases contact allergy to chromate, cobalt, or nickel but a causal association is unproven	Contact Dermatitis	Verma SB	7 of 15 patients w/ cutaneous symptoms patch +
Metal sensitivity in patients with metal-to-plastic total hip arthroplasties	Acta Orthop Scand	Carlsson AS	13/134 MOP patch + post-op; unsure if hypersensitivity caused by THA, but in pts w/ hx of allergy, proceed w/ caution
Retrospective evaluation of patch testing before or after metal device implantation	Arch Dermatol	Reed KB	5/22 with history of hypersensitivity pre-op patch +, 0/22 referred for patch test post-op were patch +
Lymphocyte responses in patients with total hip arthroplasty	J Orthop Res	Hallab NJ	More + LTT and cytokine release in THA, and esp in loose THA
RETROSPECTIVE STUDY SUMMARY	Revised: 33/138 (23.9%) patch+, 44/303 (14.5%) patch + stable in TJA Failed/loose: 113/261 (43.3%) patch+, 32/146 (21.9%) patch+ in TJA Total: 146/399 (36.6%) patch+, 76/449 (16.9%) patch- 10/16 (62.5%) revised TJAs LTT+		



# REVIEW OF THE LITERATURE

- Ten prospective reports were included in the summary (Table 2).
- Combining results revealed that 9.1% of patients had a positive preoperative patch test out of 618 total patients.
- Postoperatively 14% of patients tested positive when results were combined.
- One study utilized allergen free type of implant for suspected hypersensitivity patients and resolved symptoms in 60% of patients.
- One study in *Archives of Dermatology* emphasized the need to patch tests patients before surgery with a positive history of metal hypersensitivity.

TABLE 2: REVIEW OF PROSPECTIVE STUDIES

MANUSCRIPT TITLE	JOURNAL	FIRST AUTHOR	SUMMARY OF RESULTS
Sensitivity to implant materials in patients undergoing total hip replacement	J Biomed Mater Res	Granchi D	Patch test unable to differentiate stable vs stable implants, equivalent lifespan in metal patch +; 10 yr survival for metal patch + 44% vs patch - 47%; POOR survival for cement patch +
Allergy to components of total hip arthroplasty before and after surgery	Ital J Orthop Traumatol	Cancilleri F	10/66THA patch + (1/12 w/ aseptic loosening patch +), 2/41 pre-op patch +; hypersensitivity may play role in loosening, but likely small
Metal sensitivity in patients with metal-to-plastic total hip arthroplasties	Acta Orthop Scand	Carlsson AS	9/112 patch + pre-, 12/112 patch + post-; All complications except 1/246 explained by reasons other than hypersensitivity
Allergy in hip arthroplasty	Contact Dermatitis	Waterman AH	13/85 patch + pre-op (13 metal), 25/85 patch + post-op (23 metal, 2 cement), 0/10 looseTHA patch +; no evidence to suggest loosening because of hypersensitivity
The development of metal hypersensitivity in patients with metal-to-plastic hip arthroplasties	Contact Dermatitis	Nater JP	0/66 patch + pre-op, 4/66 patch + MOP conversion post op; no clinical sequelae, no emphasized the need to test patients
Metal sensitivity in patients w/ orthopedic implants: a prospective study	Contact Dermatitis	Frigerio E	16/72 (22%) pre-op + patch or LTT, 19/72 (29%) post-op (5 conversions of 72 total); if pre-op history insufficient, rec for screening tests
Metal sensitivity before and after total hip arthroplasty	J Bone Joint Surg Am	Deutman R	10/173 patch + pre-op, 4/66 converted patch + post op MOP; no conclusion
Metal sensitivity in patients undergoing hip replacement	J Bone Joint Surg Br	Rooker GD	6/69 patch + pre-op MOP, only 1/54 patch + post-op; patch + may be effect not cause, no need to screen in MOP
The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants	Arch Dermatol	Atanaskova Mesinkovska N	31 with history of hypersensitivity pre-op, 21 patch +, all did well with "allergen-free" implants; 41 suspected of hypersensitivity w/ TJA, 10 patch +, 6/10 had resolution of symptoms with allergen free implant; recommend patch testing in those with history
Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty	Biomaterials	Niki Y	24/92TKA were mLST+ pre-op, 5/24 developed eczema, Cr + in eczema patients but not others; screening indicated
PROSPECTIVE STUDY SUMMARY	Pre-op patch/LTT+: 9.1%, Post-op: 14.0% Some studies included LTT and patch testing MOP = metal on polyethylene implant bearing		



# WHAT'S THE BOTTOM LINE?

The resulting question is - What to do with a patient prior to a primary TKA when they come into the office stating they are sensitive to a specific metal and want to know their options?

If the reactivity is high as determined by patch testing or LTT testing, then options for **avoidance of the reaction-producing metal(s)** in question, if possible, should be discussed with the patient. For example, if results of patch testing or LTT indicate high reactivity to a prominent implant metal such as Co or Cr, then using an implant comprised of a Cobalt alloy articulating surface may not be the optimal choice.

**Alternative bearing surfaces** that are comprised of metal(s) less environmentally prevalent, have the advantage of less pre-operative patient exposure. Some alternative bearing surfaces may also release less reactive metals and less metal in general, such as oxidized zirconium.

Other options include **titanium or zirconium nitride coatings**, and alumina (currently in PMA trials in the USA). Oxidized zirconium is a metal in which the surface is transformed into a ceramic layer. The element is in the same family as titanium in the periodic table but harder and forms a thick enough ceramic layer to be a more wear resistant surface compared to typical cobalt-chrome-molybdenum (Co-Cr-Mo) alloy TKA femoral components. Titanium nitride is coated onto the surface of a titanium-alloy femoral component facilitating improved wear performance while eliminating exposure to cobalt and chromium metals while zirconium nitride is a ceramic surface coating applied to a cobalt chrome alloy but encases the implant and significantly reduces the metal ion exposure. Therefore, if oxidized zirconium or a nitrided femoral component is used and an all polyethylene or titanium alloy/zirconium nitride coated tibial component is used, the risk of Co, Cr and/or Ni reaction in this patient is minimized. This does not preclude the risks associated with nickel and other metallic byproducts that could be emanating from the stainless steel instrumentation during implantation or issues with uncoated implants and titanium alloys.



## **REFERENCES**

[The lymphocyte response to nickel salt in patients with orthopedic implants.](#)

**Bjurholm A**, al-Tawil NA, Marcusson JA, Netz P.

Acta Orthop Scand. 1990 Jun;61(3):248-50.

[Metal determination in organic fluids of patients with stainless steel hip arthroplasty.](#)

**Pazzaglia UE**, Minoia C, Ceciliani L, Riccardi C.

Acta Orthop Scand. 1983 Aug;54(4):574-9.

[Cutaneous complications of orthopedic implants. A two-year prospective study.](#)

**Kubba R**, Taylor JS, Marks KE.

Arch Dermatol. 1981 Sep;117(9):554-60.

[Resurfacing knee arthroplasty in patients with allergic sensitivity to metals.](#)

**Pellengahr C**, Mayer W, Maier M, Müller PE, Schulz C, Dürr HR, Trouillier H, Steinborn M, Jansson V, Refior HJ.

Arch Orthop Trauma Surg. 2003 May;123(4):139-43.

[Study rationale and protocol: prospective randomized comparison of metal ion concentrations in the patient's plasma after implantation of coated and uncoated total knee prostheses.](#)

Lützner J, Dinnebier G, Hartmann A, Günther KP, Kirschner S.

BMC Musculoskelet Disord. 2009 Oct 14;10:128.

[Metal sensitivity in patients with joint replacement arthroplasties.](#)

**Benson MK**, Goodwin PG, Brostoff J.

Br Med J. 1975 Nov 15;4(5993):374-5.

[Considerations of allergy and mechanics in the selection of orthopaedic implant materials \[proceedings\].](#)

**Brown SA**, Merritt K, Mayor MB.

Bull Hosp Joint Dis. 1977 Oct;38(2):67-8.



[Metal sensitivity reactions to orthopedic implants.](#)

Merritt K, **Brown SA.**

Int J Dermatol. 1981 Mar;20(2):89-94. Review.

[Etiology of osteolysis around porous-coated cementless total hip arthroplasties.](#)

**Jasty M,** Bragdon C, Jiranek W, Chandler H, Maloney W, Harris WH.

Clin Orthop Relat Res. 1994 Nov;(308):111-26.

[Failed metal-on-metal hip arthroplasties: a spectrum of clinical presentations and operative findings.](#)

**Browne JA,** Bechtold CD, Berry DJ, Hanssen AD, Lewallen DG.

Clin Orthop Relat Res. 2010 Sep;468(9):2313-20.

[Nickel \(Ni\) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni.](#)

**Summer B,** Paul C, Mazoochian F, Rau C, Thomsen M, Banke I, Gollwitzer H, Dietrich KA, Mayer-Wagner S, Ruzicka T, Thomas P.

[The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants.](#)

Atanaskova Mesinkovska N, Tellez A, Molina L, Honari G, Sood A, Barsoum W, Taylor JS.

Arch Dermatol. 2012 Jun;148(6):687-93.

[Cutaneous and systemic hypersensitivity reactions to metallic implants.](#)

Basko-Plluska JL, Thyssen JP, Schalock PC.

**Dermatitis.** 2011 Mar-Apr;22(2):65-79.

[Benzoyl peroxide: is it a relevant bone cement allergen in patients with orthopaedic implants?](#)

Treudler R, Simon JC.

Contact **Dermatitis.** 2007 Sep;57(3):177-80.



[Metal sensitivity in patients with orthopaedic implants.](#)

Hallab N, Merritt K, Jacobs JJ.

J Bone Joint Surg Am. 2001 Mar;83-A(3):428-36.

[Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty.](#)

**Hallab** NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ.

J Arthroplasty. 2004 Dec;19(8 Suppl 3):88-93.

[A painful metal-on-metal total hip arthroplasty: a diagnostic dilemma.](#)

**Blumenfeld** TJ, Bargar WL, Campbell PA.

J Arthroplasty. 2010 Oct;25(7):1168.e1-4.

[Sensitivity to titanium. A cause of implant failure?](#)

**Lalor** PA, Revell PA, Gray AB, Wright S, Raiton GT, Freeman MA.

J Bone Joint Surg Br. 1991 Jan;73(1):25-8.

[Comparative Study of Clinical and Radiological Outcomes of Unconstrained Bicondylar Total Knee Endoprostheses with Anti-allergic Coating.](#)

**Bergschmidt** P, Bader R, Finze S, Schulze C, Kundt G, Mittelmeier W.

Open Orthop J. 2011;5:354-60.

[Failure modes of 433 metal-on-metal hip implants: how, why, and wear.](#)

**Ebramzadeh** E, Campbell PA, Takamura KM, Lu Z, Sangiorgio SN, Kalma JJ, De Smet KA, Amstutz HC.

Orthop Clin North Am. 2011 Apr;42(2):241-50, ix.

[Metal hypersensitivity in total knee arthroplasty: revision surgery using a ceramic femoral component - a case report.](#)

Bergschmidt P, **Bader** R, Mittelmeier W.

Knee. 2012 Mar;19(2):144-7.

[Metal sensitivity causing loosened joint prostheses.](#)

**Christiansen** K, Holmes K, Zilko PJ.

Ann Rheum Dis. 1980 Oct;39(5):476-80.



**Metal allergy and the surgical patient.**

Mayor MB, Merritt K, Brown SA.  
Am J Surg. 1980 Apr;139(4):477-9.

**Metal sensitivity in patients with joint replacement arthroplasties.**

Benson MK, Goodwin PG, Brostoff J.  
Br Med J. 1975 Nov 15;4(5993):374-5.

**An interesting case of joint prosthesis allergy.**

Beecker J, Gordon J, Pratt M.  
Dermatitis. 2009 Mar-Apr;20(2):E4-9.

**Metal sensitivity in a patient with a total knee replacement.**

Handa S, Dogra S, Prasad R.  
Contact Dermatitis. 2003 Nov;49(5):259-60.

**Metal allergy and second-generation metal-on-metal arthroplasties.**

Cousen PJ, Gawkrödger DJ.  
Contact Dermatitis. 2012 Feb;66(2):55-62.

**Allergy to endoprostheses.**

Milavec-Puretić V.  
Arh Hig Rada Toksikol. 2004 Jun;55(2-3):193-6.