# Hypersensitivity Reactions to Orthopedic Implants: What's All the Hype?

**Amber Reck Atwater, MD; Margo Reeder, MD**

## PRACTICE **POINTS**

- Common clinical presentations of orthopedic implant hypersensitivity reactions include localized cutaneous eruptions, generalized cutaneous eruptions, and noncutaneous reactions.
- Allergens implicated in orthopedic implant hypersensitivity reactions include metals and bone cement components.
- Routine preimplant patch testing for orthopedic hypersensitivity reactions is not recommended but can be performed when there is strong concern for metal allergy.
- Postimplant patch testing should be performed when symptoms are consistent with potential orthopedic implant hypersensitivity reactions.

Hypersensitivity reactions to orthopedic implanted materials exist but are rare. Potential allergens include metals and bone cement components. Clinical presentation can include localized or generalized cutaneous reactions and noncutaneous reactions. Preimplant patch testing for implant hypersensitivity reactions (IHRs) is only recommended if metal allergy is strongly suspected; postimplant patch testing to relevant allergens can be completed if symptoms are concerning for implant hypersensitivity. The decision to remove or revise an orthopedic implant should be made as a joint decision between the surgeon and patient.

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Hypersensitivity to metal implants remains a controversial field in contact dermatitis and patch testing. With positive reactions to nickel hovering around 20% in patch-tested populations,[1] the question remains whether metal-allergic patients can safely receive metal implants. Unfortunately, large controlled studies are lacking, in part due to ethical concerns of knowingly placing a metal implant in a metal-allergic patient. Much of the focus of implant hypersensitivity reactions (IHRs) has been on orthopedic joints including hips, knees, and shoulders, as well as fixed orthopedic implanted materials such as screws and plates. However, there have been reports of IHRs to cardiac devices including defibrillators, pacemakers, and intracardiac devices; dental hardware including implants, crowns, dentures, and braces; and neurologic and gynecologic devices. For the purposes of this review, we will focus on IHRs to orthopedic implants.

## Making the Case for IHRs

There are multiple case reports and series documenting likely orthopedic IHRs in the literature[2-5]; however, large prospective studies are lacking. Some of the largest series are from Danish registry studies. In 2009, Thyssen et al[6] reviewed 356 patients who had undergone both total hip arthroplasty and patch testing. Metal allergy frequencies were similar between patch-tested registry patients and patch test controls, showing no increase in positive patch tests to metals after receiving implants. Additionally, implant revision rates were comparable between registry patients with and without patch testing. The group concluded that the risk for revision after hip implantation in metal-allergic patients and the risk for development of metal allergy after implantation were both low.[6] In 2015, Münch et al[7] compared 327 patients who had undergone both total knee arthroplasty and patch testing and found that prevalence of allergy to nickel, cobalt, and chromium was similar between patients who had undergone revision surgery and those who had not; however, for patients who had 2 or more knee revisions, there was a higher prevalence of postimplant metal allergy. This study also showed that metal allergy identified before implantation did not increase the risk for postimplantation knee revision surgery or implant failure.[7] These larger studies suggest that although individual cases of IHR exist, it is likely quite rare.

Dr. Atwater is from the Department of Dermatology, Duke University School of Medicine, Durham, North Carolina. Dr. Reeder is from the Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madison.

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Correspondence: Amber Reck Atwater, MD, 5324 McFarland Rd #210, Durham, NC 27707 (amber.atwater@duke.edu).

Patients have been found to have increased levels of chromium (serum and urine) and titanium (serum) following total hip arthroplasty.[8] Additionally, metal wear particles have been identified in postmortem livers and spleens, which was more prevalent in patients with a history of failed hip arthroplasty.[9] It is difficult to determine the meaning of this data, as the presence of metal ions does not necessarily indicate allergy or IHR. In 2001, Hallab et al[10] pooled data from several implant cohort studies and concluded that in comparison to a baseline metal sensitivity prevalence of approximately 10%, patients with well-functioning implants had a metal sensitivity–weighted average of 25%, and those with poorly functioning implants had a weighted average of 60%. Again, positive patch testing to metals does not necessarily implicate allergy as the cause of implant failure.

Some small studies have shown that patients with evidence of metal hypersensitivity improve with revision. Zondervan et al[11] reviewed results of 46 orthopedic revisions following painful total knee arthroplasty. Patients with knee pain and lymphocyte transformation testing (LTT) positive for metals received hypoallergenic revisions, and those with LTT negative for metals received standard revisions. The group who received hypoallergenic revisions had more pain reduction compared to the standard revision group (37.8% reduction in pain vs 27%). However, this study was limited in that the diagnosis of metal allergy was made entirely on results of LTT.[11] In 2012, Atanaskova Mesinkovska et al[12] described 41 patients who underwent orthopedic patch testing following implantation for symptoms including pain, dermatitis, pruritus, joint loosening, edema, and impaired wound healing. Fifteen (37%) patients had positive patch test reactions to metals, and 10 (67%) of them had reactions to metals that were present in their implants. Six (60%) of these patients had their implants removed and their symptoms resolved; the remaining 4 continued to experience implant symptoms.[12] These studies support the existence of rare metal-related orthopedic IHRs and support the concept of proceeding with orthopedic implant revision when indicated, safe, and agreed upon by the surgeon and patient. However, as noted in the series by Zondervan et al,[11] not every patient with confirmed metal allergy who undergoes revision improves, so an informed conversation between the patient and surgeon is mandatory.

## Types of Orthopedic Implants

Orthopedic implanted materials consist of either dynamic (knees, hips) or static (screws, plates) components. Several generations of hip implants have evolved since the 1960s. First-generation implanted hips were metal-on-metal and had high rates of metal release and sensitization. Metal-on-plastic implants may be less likely to release metal but instead release large polyethylene wear particles. Second-generation metal-on-metal implants reportedly have lower wear rates. With these implants, wear particles are generated but are reportedly smaller than first-generation particles.[13]

## Allergens in IHRs

*Metals*—Metals are the most commonly implicated allergens in orthopedic IHRs. Potentially relevant metal alloys include 316L stainless steel, cobalt-chromium-molybdenum steel, Vitallium alloy, titanium alloy, titanium-tantalum-niobium alloy, and Oxinium (Smith & Nephew).[14,15] Each alloy contains several metals, which can include nickel, chromium, cobalt, manganese, molybdenum, iron, titanium, aluminum, vanadium, niobium, tantalum, and zirconium, among others. For example, 316L stainless steel contains iron, nickel, chromium, manganese, molybdenum, nitrogen, carbon, sulfur, silicon, and phosphorus, whereas Oxinium contains only oxidized zirconium and niobium.

*Bone Cement*—Bone cement also has been reported in cases of orthopedic IHRs and can contain several chemicals, including methyl methacrylate, N,N-dimethyl-p-toluidine, benzoyl peroxide, hydroquinone, and gentamicin.[14] Other potential exposures include adhesives (cyanoacrylates) and topical antibiotics.

## Clinical Presentation

Several clinical presentations of orthopedic IHRs have been described. Perhaps the most commonly recognized is a localized cutaneous eczematous eruption, with dermatitis typically overlying the site of the implanted material.[1,2,16] Generalized cutaneous eczematous IHRs also have been reported, including diffuse generalized dermatitis from a stainless steel orthopedic screw[4] and nummular dermatitis attributed to vanadium in an orthopedic plate.[5] Urticaria, vasculitis, and bullous cutaneous reactions, as well as extracutaneous complications, also have been reported.[14,15] Pain, edema, joint loosening or failure, and poor wound healing have been reported,[12] but it remains unclear whether these symptoms represent IHR.

## Patch Testing for IHR

Several groups have published recommended patch test series for IHR.[12,14,15] Common components of implant patch testing panels include metals, adhesives (acrylates, epoxy resins) and antibiotics. Importantly, obtaining product information from the manufacturer of the suspected implant can guide which allergens to include in patch testing. Implant and metal panels also are available for commercial purchase.

## Other Diagnostic Tests

We rarely (almost never) order LTTs in the workup for potential IHRs. This is an in vitro test that includes lymphocytes, metal ions, and the radioactive marker methyl-3H-thymidine. The goal of the test is to evaluate if patient lymphocytes are reactive or responsive to metal ions. A positive LTT suggests that lymphocytes can respond to the presence of metal ions but does not confirm allergy or the presence of IHR.

Typically, skin or tissue biopsies are not required to make a diagnosis of IHR; however, if performed, histopathology suggestive of IHR can support a suspected diagnosis. Typical findings include but are not limited to spongiotic dermatitis. Eosinophils may or may not be present. Metal disc testing has been utilized for orthopedic IHR but is not currently recommended due to low diagnostic yield. Prick testing rarely is used and also is not a primary method for diagnosis of IHR.[17]

## Preimplantation Patch Testing

Expert opinion guidelines published by the American Contact Dermatitis Society (ACDS) state that routine preimplantation patch testing is not necessary; however, for those patients with a clear history of contact reactions to metal, preimplantation patch testing can be considered.[17]

Patch test results can influence the orthopedic surgeon's choice of implant material. In one study, when preimplantation patch testing showed a positive patch test reaction to metals, the results influenced the surgeon's decision-making in all cases.[12]

## Postimplantation Patch Testing: Diagnostic Criteria for Metal IHR After Implantation

From 2012 to 2013, Schalock and Thyssen[18] surveyed expert attendees at meetings of the European Society of Contact Dermatitis and the ACDS for their opinions on proposed diagnostic criteria for metal IHRs. Based on these results (N=119), the authors stratified 4 major and 5 minor diagnostic criteria, which were defined based on overall responses of meeting attendees. Major criteria included (1) chronic dermatitis beginning weeks to months after metallic implantation, (2) complete recovery after removal of the offending implant, (3) eruption overlying the metal implant, and (4) positive patch test reaction to a metal used in the implant. Minor criteria included (1) histology consistent with allergic contact dermatitis, (2) morphology consistent with dermatitis (ie, erythema, induration, papules, vesicles), (3) positive in vitro test to metals (eg, lymphocyte transformation test), (4) systemic allergic dermatitis reaction, and (5) therapy-resistant dermatitis reaction. The authors did not describe a scoring system for evaluation and confirmation of a diagnosis of IHR. Instead, the criteria should be used as general guidelines when evaluating patients for possible IHRs. From a standpoint of available diagnostic tests for metal IHR, 86.1% of experts agreed that a positive patch test reaction to a metal used in the implant was suggestive of a diagnosis, whereas a positive in vitro test to metals (LTT) was suggestive of a diagnosis for only 32.2% of respondents. This study was designed specifically for metal IHRs and therefore is not necessarily generalizable for nonmetal IHRs.[18]

## Final Interpretation

We follow the 2016 ACDS guidelines[17] and complete preimplantation patch testing only in the setting of suspected metal allergy and postimplantation patch testing based on the guidelines described by Schalock and Thyssen.[18] However, an extended conversation is warranted prior to patch testing to ensure the patient fully understands the limitations of the test. Although we have both ordered the LTT, interpretation remains murky, and until this test is standardized, routine use is unlikely to benefit the patient. Until we are more reliably able to predict who will develop hypersensitivity to implanted metals, the decision to remove or revise an implant is one that should be made by a multidisciplinary team that includes the surgeon and the patient.

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