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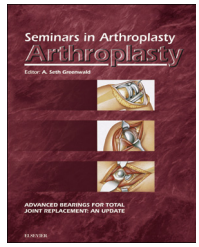

Hypersensitivity: "Doc, Am I Allergic to My Implant?"

Nicholas B. Frisch, MD, MBA, and Joshua J. Jacobs, MD*

Department of Orthopaedic Surgery, Rush University Medical Center, Adult Reconstruction, 1611 W. Harrison Ave, Chicago, IL 60612

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ABSTRACT

There is controversy regarding the clinical significance of metal hypersensitivity in total knee arthroplasty (TKA). Given the current state of the art, metal hypersensitivity, if it exists at all, is a diagnosis of exclusion. Clinical presentation may involve a cutaneous response, but current diagnostic methods do not have robust clinical validation and should be used with caution. The two most commonly used tests include cutaneous patch testing and in vitro lymphocyte transformation testing. Initially, conservative management is indicated and other more common causes of a symptomatic total knee replacement should be fully explored. In rare cases, device removal may be undertaken but this should be considered a last resort. Pre-operative testing prior to a primary total joint replacement may be helpful when there's a patient-reported history of intolerance to jewelry or of an allergic reaction to a prior metal implant, but routine lab screening is not supported by the literature.

Clinically significant allergic reactions to metallic orthopaedic implants has been a topic of concern since the advent of total joint allergy. There is controversy over whether clinically significant metal hypersensitivity even exists in total knee arthroplasty (TKA). If we posit that it does in fact exist, how prevalent is it? How might it present in the setting of a hip or knee arthroplasty? How do you make the diagnosis? Finally, how do you manage metal hypersensitivity?

There are several strands of evidence that suggest that clinically significant hypersensitivity to metallic orthopaedic implants exists. Case reports have been published illustrating the presence of hypersensitivity reactions in total joint arthroplasty [1–7]. Similar reports have been made regarding hypersensitivity in other medical devices, including cardiovascular [8–10], neurologic [11], plastic surgical [12,13], and dental implants [14–16]. Further, many have demonstrated an immune reaction and sensitivity after implantation of orthopaedic devices [17–24]. This temporal association between sensitization only after implantation supports the argument that an immune reaction to a metallic orthopaedic device is possible.

The prevalence of metal hypersensitivity in the general population has been estimated to range between 10% and 15% [25]. About 14% of the population are actually sensitive to nickel if you use patch testing as the diagnostic tool. Interestingly, if you have patients with well-functioning implants that range goes up to 25%, and with poorly functioning implants that can go up to 60%. However, this association has not been proved a causal effect. That is, people are not necessarily having painful or loose implants because of metal allergy. It could be the other way around. Taking the population as a whole there have been several reports suggesting

* *Corresponding author.*
E-mail address: nick@gafrisch.com (N.B. Frisch).

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cutaneous contact allergies to metals. In a cross-sectional study of 5 different European countries, Diepgen et al reported that 27% of patients tested demonstrated a positive reaction to at least one allergen, most commonly nickel (14.5%) and cobalt (2.2%) [26]. More specifically, epidemiologic studies suggest the prevalence to be 13.1% for nickel, 2.4% for cobalt, and 1% for chromium [27]. Perhaps one of the issues surgeons are facing now is that awareness of hypersensitivity reactions has grown in recent years and was not previously considered a real clinical entity. Goldenberg et al. reported on 18,251 adults with reported nickel sensitivity in the United States between 1962 and 2015. They demonstrated that between the 1960s and 1990s only 4.3% of cases were reported, compared to 64.3% between 2010 and 2015 [28]. The increased awareness by not only the medical community but also the population in recent years could explain this trend. Concurrently, the increased number of total joint arthroplasties performed annually lends to a larger group of patients being managed.

The mechanism of implant-induced metal hypersensitivity has been explored [19,23,29–33]. Metal debris, both particulate and ionic are generated from metal components, typically generated from mechanical wear and corrosion. These metal ions can complex with local serum proteins and activate the immune system. In general, there is a type IV hypersensitivity reaction, involving activation of specific T lymphocytes. These are cell-mediated, delayed-type sensitivity reactions that occur when sensitized T lymphocytes recognize an antigen and initiate a cascade that ultimately results in the release of cytokines that perpetuate an inflammatory response. There is also evidence of an innate immune response to implant-derived wear particles. This non-specific reaction is immediate and largely controlled by macrophages [33].

The presentation of metal hypersensitivity reactions may often be vague. Typically there will be a dermatitis (cutaneous reaction), urticaria or vasculitis [6,34–36]. Patients with non-specific pain and swelling, chronic effusion, stiffness or loss of function are, in general, a great challenge; it is conceivable, though quite difficult to prove, that these individuals are manifesting a form of metal sensitivity. It is helpful to determine if the patient has a history of any intolerance to metals, including jewelry. Nam et al. reported on 1495 patients undergoing total hip and total knee arthroplasty (THA and TKA respectively), of whom 1.7% self-reported metal allergy, increasing to 4% when directly asked about a metal allergy. Those with a reported metal allergy were associated with decreased functional outcomes after TKA and decreased mental health scores after THA when compared with patients not reporting a metal allergy [37].

The challenge with making a diagnosis of metal hypersensitivity is that aside from a dermatologic reaction, the other presenting features are relatively non-specific. Chronic effusion, stiffness or unexplained pain generate a broad differential diagnosis that includes periprosthetic joint infection, aseptic component loosening, mid-flexion instability, component malalignment with patellar maltracking, complex regional pain syndrome, crystalline arthropathy or potentially a psychological disorder [38,39]. It is essential to start with a detailed history and physical examination. Get any appropriate laboratory tests to rule out infection, including complete blood count (CBC) with differentials, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). If there is any additional concern for infection perform an arthrocentesis and send fluid for appropriate testing, including synovial white blood cell count and differential, crystal analysis to rule out crystalline arthropathy, and culture. Cultures can be held for longer time (>2 weeks) if necessary. Once infection is ruled out, based on clinical examination findings additional imaging may be necessary. Start with routine radiographs and if there is concern for component malalignment consider advanced imaging with CT scan to properly measure component rotation. A technetium bone scan can used to better assess potential aseptic component loosening.

After excluding other causes of chronic pain, specific workup for metal hypersensitivity can be performed. If the patient has a history of cutaneous response to metal jewelry or presents with a cutaneous reaction it would be reasonable to perform allergy testing. The two most commonly used tests include cutaneous patch testing and in vitro lymphocyte transformation testing. The advantages to patch testing, which has historically been the test of choice, are that it can be routinely performed by dermatologists without a special facility, is suitable for large-scale screening and allows simultaneous evaluation of many different immunologic substances [34,40]. The disadvantages to patch testing are that they are highly subjective, do not test the reactivity of deep tissue, involve a different mechanism of reactivity with Langerhans cells and the potential to induce sensitization [34,38]. Since the skin has a different immunologic milieu than the deep tissue, it remains unclear whether or not skin testing reflects a true representation of deep reaction. Furthermore there is a subset of patients that are anergic and will not respond to anything.

Granchi et al. performed patch testing on 20 candidates for TKA, 27 patients with well-functioning TKA, and 47 patients with loosening of TKA components to evaluate the frequency of sensitization in patients after TKA [41]. The frequency of positive skin reaction to metals increased significantly after TKA, regardless of implant stability. Additionally, they found a fourfold increase in TKA failure in patients who had symptoms of metal hypersensitivity before implantation. Bravo et al. [42], retrospectively, compared 161 TKA after skin patch testing for history of metal allergy to 161 TKA patients without any prior history of metal allergy and no patch testing to determine the relationship between positive patch testing results and complications, clinical outcomes and clinical survivorship. They found no difference in complication rates between positive or negative patch testing or controls. They found no difference in post-operative Knee Society Scores or survivorship free of reoperation and revision at mean 5.3-year follow-up. They did find an association between those with a reported history of metal hypersensitivity and a negative patch test with arthrofibrosis, however, noted that none required revision.

The lymphocyte transformation test (LTT) is an alternative to skin patch testing. In vitro testing takes advantage of the fact lymphocytes will proliferate when exposed to an antigen that they are sensitized to. The pro of this is the test assays

circulating lymphocytes and monocytes, thereby bypassing the skin and avoiding the confounding responses of epidermal Langerhans cells as well as the potential for sensitization with serial tests. Furthermore, these results are quite quantitative, which can be helpful in analysis. Compared to skin testing, LTT may have higher sensitivity [22]. However, it has many of the same cons of patch testing. That is, the applicability of challenge agents, the lack of robust clinical validation, and sometimes this technique is not readily available unless you are in academic medical centers [22,25,34,38].

Despite the increased awareness of metal hypersensitivity in the population and amongst surgeons, there appears to be a limited implementation of these two available diagnostic tests. Hallock et al. performed a survey of Orthopaedic surgeons regarding the question of metal hypersensitivity to orthopaedic implants. Only 6.8% of respondents reported they always screen and only 4.5% often screen, compared to 50% who rarely do [43]. Similarly, Razak et al. performed a survey regarding metal allergy screening prior to joint arthroplasty and demonstrated that 69% of respondents do not perform routine screening. In patients that were sent for testing, even if the patch test came back positive, 44% of surgeons would continue with standard implants [44]. While both of these surveys suffer from poor surgeon response, they demonstrate that there is no real consensus regarding the presence, or perhaps more-so the significance of metal hypersensitivity and therefore there is a low propensity to perform either patch testing or the LTT.

Given the current state of the art, metal hypersensitivity is a diagnosis of exclusion. There is no agreed upon clinically validated protocol for metal sensitivity testing. Some have attempted to create diagnostic criteria for metal hypersensitivity to metallic implants [45] but little consensus exists and the lack of large-scale prospective studies leaves many unanswered questions. In TKA candidates, it is reasonable to consider pre-operative metal hypersensitivity testing if the patient has a significant history of cutaneous sensitivity to jewelry or a purported history of an allergic reaction to a previous metal implant. Such testing may guide implant selection. In post-operative patients with persistent pain, swelling, dissatisfaction, or loss of function perform a thorough diagnostic workup to rule out the most common etiologies. If there is still concern, particularly if there are cutaneous manifestations, metal hypersensitivity testing can be employed, but these tests are difficult to interpret and should not be used as a sole indication for revision surgery. Given the aforementioned pros and cons of patch testing and LTT, some authors advocate combining tests to improve diagnostic accuracy [21,24]. Thomas et al. [18] advocate for a combined assessment including patch testing, LTT and periprosthetic histologic and cytokine assessment. Regardless, robust clinical validation is lacking.

If pre-operative testing is positive for cobalt or chromium sensitivity, there are a number of alternative bearing materials to choose from which either do not contain these elements or minimize the release of these elements. These include titanium alloy, zirconium–niobium alloy, or other ceramicized surface components. These systems may eliminate or minimize exposure to metals to which the patient has demonstrated sensitivity and result in exposure to less reactive metals. If pre-operative testing is positive for nickel sensitivity (found in approximately 15% of the general population), the issue is less clear. Standard cobalt–alloy implants contain less than 1% nickel, which in the bulk alloy is not in a bioavailable state. While one can avoid even this small amount of nickel by using titanium alloy or zirconium–niobium alloy components, some believe that traditional cobalt chromium/stainless steel implants are appropriate regardless of positive metal hypersensitivity testing [44,46]. The argument is that standard component use will result in more predictable results and that these implants have proven longevity in clinical practice. Munch et al. reviewed the Danish Knee Arthroplasty Registry and crossreferenced with a contact allergy patch test database to evaluate the association between metal allergy and revision surgery [47]. A total of 327 patients were identified who had both primary TKA and metal allergy patch testing. They did not find an association between metal allergy and revision surgery. Interestingly they noted that those patients who underwent two or more revisions had a higher prevalence of metal allergy, which they attributed to increased release of metal from wear and corrosion. There is no large study available to demonstrate that using alternative bearing surfaces results in improved long-term outcomes. Ultimately it is at the discretion of the surgeon and the patients as they engage in a shared decision-making process.

In our practice, standard cobalt–alloy bearings are avoided when possible in patients with suspected sensitivity to Co, Cr, and/or Ni. Although no large study demonstrates superiority of alternatives to cobalt–alloy bearings, there are several smaller studies that suggest good results [5,48]. Innocenti et al. reported on 24 patients with suspected metal allergy treated with Oxinium (oxygen diffusion-hardened zirconium–niobium alloy) femoral and all-poly tibial components [48]. They performed detailed medical history, patch testing and lab assays, ultimately showing 20.8% of patients were considered to have metal hypersensitivity. At mean follow-up of 79.2 months no patients reported any hypersensitivity reaction and there were no reported implant failures or patient-reported anterior knee pain. Furthermore, experience with revision surgery in both THA and TKA for presumed or documented metal hypersensitivity with non-cobalt–alloy bearings has resulted in improved outcomes [3,4,49].

Since there are only anecdotal case reports supporting revision surgery for metal allergy, this should only be considered a last resort for the persistently symptomatic patient who has failed other non-operative interventions. The informed consent process needs to convey that the outcome of such revisions is unpredictable. Trials of antihistamines and corticosteroids for skin reactions should be considered first. Revision surgery can be very challenging especially with well-fixed components and bone loss and carries with it additional post-operative risks. Furthermore, the use of non-cobalt–alloy bearings address the issue of the debris shed from the stainless steel surgical tools which contain approximately 10–14% nickel. Currently, non-stainless steel surgical tools are not readily available.

In summary, metal hypersensitivity to orthopaedic implants has been documented in isolated cases. The true prevalence is

unknown, but clinically significant symptomatology is very rare in total knee replacements. Clinical presentation typically involves a rash, and current diagnostic methods have not been clinically validated, so should be used with caution. Initially conservative management is indicated and in rare cases device removal may be undertaken, but should be considered a last resort. Finally, pre-operative testing prior to a primary total joint replacement is indicated when there is a patient-reported history of intolerance to jewelry or of a previous reaction to a metal implant, but routine lab screening is not supported by the literature.

Disclosures

Joshua J. Jacobs, MD is a consultant for Medtronic Sofamor Danek. He holds stock options with Implant Protection. He receives research or institutional support from Nuvasive, Medtronic Sofamor Danek and Zimmer. He is on the board of trustees at OREF, Treasurer of the Hip Society and Director of the ABOS.

Nicholas B Frisch, MD is a physician advisor and speaker for 3M. He holds stock or stock options in Vital Therapy and PeerWell. He is a reviewer for Journal of Arthroplasty.

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