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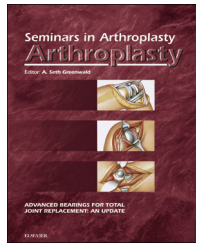

Hypersensitivity: "Doc, Am I Allergic to My Implant?"

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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

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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