

The Role of Patch Testing in the Evaluation of Orthopedic Implant-Related Adverse Effects: Current Evidence Does Not Support Broad Use

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Abstract: In recent years, there has been a growing interest in the use of skin patch testing to evaluate patients for orthopedic, implant-related adverse effects. This may be done preoperatively to avoid implanting a material to which an individual may be allergic or postoperatively to implicate sensitivity as a cause for implant failure. There is emerging evidence that patch testing might have utility in the workup of implant-related adverse events; however, the level of evidence at the present time is weak and based only on a collection of case reports, series, and retrospective cohort studies (level IV evidence as per United States Department of Health and Human Services guidelines); there are no randomized controlled trials (level I evidence) with which to guide medical decision making. Recent reports have advocated that patch testing be broadly used in the preoperative evaluation of all patients self-reporting a history of metal sensitivity. In addition, several authors have advocated that patch test results should guide preoperative implant selection and postoperative implant removal. It is the opinion of this author that these recommendations are premature, lacking robust clinical evidence, and unfeasible given the broad-reaching logistical impact and societal costs involved. More robust clinical data are

needed, and thorough cost-benefit analyses must be performed before such far-reaching and costly systematic practices should be broadly implemented.

HIP AND knee replacement surgeries are among the most common operations performed in the United States. More than 1 million procedures were performed in 2009,¹ and spending reached \$17.5 billion.² It is estimated that by 2030, 4.5 million procedures will be performed, representing \$50 billion in health care expenditures.³ Given these statistics, it is not surprising that there is such a strong interest in maximizing implant longevity and minimizing implant-related adverse effects, as implant failure results in substantial morbidity and societal cost.

Implants may fail for a variety of reasons, including aseptic osteolysis (75%), infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and surgical error (3%).⁴ It is theorized by many that aseptic loosening may be caused or accelerated by host immune sensitivity to metal (or nonmetal) substances within the implant. It is also theorized that skin patch testing may be an accurate test to identify this immune sensitivity and that this test can be used to guide implant material selection and the potential need for implant removal.⁵⁻⁷

Historically, the most prevalent metals in orthopedic implants include nickel, cobalt, chromium, titanium, tantalum, and vanadium. In addition, implants may contain other materials such as acrylic polymers (eg, polymethylmethacrylate). It is well established that external contact with these same substances can, in certain individuals, result in cutaneous immunologically based adverse effects (primarily manifesting as eczematous skin eruptions). In fact, skin sensitivity to metal is quite common in the general population; as many as 19% of patients undergoing patch testing demonstrate reactions to nickel.⁸ There is also evidence that there may be a relatively small subset of metal-sensitive individuals (particularly with regard to nickel) who may demonstrate immune reactions after systemic ingestion.^{9,10}

It would seem plausible, then, to hypothesize that internal exposure to these same materials after implant surgery could

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The author has no funding or conflicts of interest to declare.

Dr Crawford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr Crawford

Acquisition of data: Dr Crawford

Analysis and interpretation of data: Dr Crawford

Drafting of the manuscript: Dr Crawford

Critical revision of the manuscript for important intellectual content: Dr Crawford

Statistical analysis: Dr Crawford

Study supervision: Dr Crawford

DOI: 10.1097/DER.0b013e3182948251

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feasibly result in immunologically derived adverse effects. Over the past few decades, several cases and small series have presented supporting evidence for this theory, chronicling adverse events after orthopedic, cardiovascular, and dental implant procedures. These reports demonstrate compelling cases with temporal relationships between implantation and adverse events and corroborating positive patch test reactions to materials found within the implants.^{11–22} Several reports have even demonstrated improvement in symptoms after implant removal. Hallab et al²³ in 2009 pooled data from 12 retrospective cohort studies and demonstrated that patients with failing or poorly performing implants had very high levels of positive patch test reactions to metals (60%). It is through this logical progression that many have advocated the importance of patch testing in detecting immune sensitivity and in attributing the role of immune sensitivity as the cause of implant failure and implant-related adverse effects.

There are, however, several major problems with this analysis. It is possible (or even likely) that alternative nonspecific immunologic and nonimmunologic mechanisms are the dominant factors in implant failure. Specific immunologic mechanisms (such as delayed-type hypersensitivity) may at best play a role in a small minority of patients. Based on the background rates of metal sensitivity in the general population (which is close to 20% in some studies),⁸ if immune sensitivity had a dominant role in implant failure, one would expect much higher rates of implant-related problems. It has been shown that particulate and soluble debris derived from Cobalt-Chromium-Molybdenum alloy implants can (in an immunologically nonspecific manner) induce monocyte-macrophage activation and secretion of proinflammatory cytokines. This may result in stimulation of osteoclast activity/maturation and result in increased periprosthetic bone resorption.^{24,25}

It is known that through corrosion and degradation, implants release ions and molecules, and these substances are measurable in the body in increased concentrations after implant procedures.^{26–31} Although not typically capable of causing immune reactions on their own, these degradation/corrosion products may combine with native proteins and induce delayed-type hypersensitivity reactions. Although patch testing is certainly the standard for identifying delayed-type sensitivity in the skin to external allergens, whether this procedure accurately identifies sensitivity to internal materials is unknown. Patch testing involves the incorporation of an antigen into a carrier, followed by topical exposure for 48 hours, penetration of the antigen into the dermis, and presentation to the Langerhans cell (the cell currently accepted as the dominant cell responsible for antigen presentation in the skin). With regard to timing of most orthopedic implant failures, the duration of implant exposure is by comparison much longer (typically on the order of months or years), and the immunologic mechan-

isms of peri-implant osteolysis have not been accurately characterized. To highlight the inherent differences between the patch testing and the peri-implant environment, Summer et al³² evaluated 52 metal-allergic and 48 nonallergic controls by patch testing to stainless steel and Cobalt-Chromium-Molybdenum discs (similar to those used in orthopedic implants). None of the 52 metal-allergic patients reacted to the stainless steel discs and only 5 of the 52 patients reacted to the Cobalt-Chromium-Molybdenum discs.³² If skin patch testing accurately recreated the immunologic environment of internal periprosthetic tissue, then one would expect a much higher percentage of metal-sensitive patients in this study to react to these metal test discs. The environment under a patch test chamber is certainly quite different to what is found in the periprosthetic tissue; mechanical and chemical factors likely contribute to the degradation/corrosion of metal and nonmetal implant materials, and there are likely a range of divergent immunologic cells and pathways involved in this tissue.

Alternative mechanisms to assess for specific immune sensitization include *in vitro* tests such as the lymphocyte transformation test (LTT) and the leukocyte migration inhibition factor (MIF) test. These tests have been shown to effectively assess systemic sensitivity to metals; in fact, some studies suggest that they may actually offer increased sensitivity in comparison with patch testing.^{33–38} However, there are limitations that make large-scale implementation untenable at the present time, including increased expense (time, reagents, and biological materials), complexity, paucity of qualified laboratories, and the limited number of haptens that can be tested (resulting from the limited numbers of lymphocytes obtained from individuals for testing). The advantages of patch testing over currently available *in vitro* tests include lower cost, ability to simultaneously test more substances, broader availability, and somewhat standardized protocols. Despite these favorable aspects, the validity of patch testing in detecting sensitivity to internal/implanted materials has not yet been confirmed.

As mentioned previously, the pooling of data from several retrospective cohort studies suggests a correlation between implant-related problems and positive patch test reactions.²³ However, the validity of these findings can be questioned on a variety of grounds including the divergent patient populations, varied inclusion criteria, small sample sizes, disparate methodologies, and possible reporting bias. Two recent studies actually contradict the potential relationship between patch test reactions and implant failure. Granchi et al,³⁹ in a retrospective cohort study ($n = 223$), reported a rate of nickel sensitivity that was actually lower in the postimplant failure group. Similarly, Atanaskova et al⁷ retrospectively analyzed patients who had been patch tested for implant-related reasons ($n = 72$). In the preimplant group, 21 (68%) demonstrated

reactions to metals, whereas in the postimplantation group, 15 (37%) demonstrated metal reactions on patch testing.⁷ Again, causal relationships between metal sensitization and implant failure have not been proven, and sensitization may feasibly result from implant loosening, rather than be the cause of it.

One must also appreciate the enormity of scale pertaining to the number of implant procedures performed on the increasingly aging US population; the small sum-total of patients in the aforementioned reports over the past 3 decades pales in comparison with the more than 1 million knee and hip implant procedures performed in the United States annually. Nickel is a ubiquitous chemical, is the 22nd most abundant element on the earth, and is found in most foods. In fact, it is estimated that in the United States, the average daily intake of nickel is approximately 0.17 mg/d.⁴⁰ There is a recognized, albeit exceedingly small, subset of nickel-allergic patients who develop adverse effects from ingestion of nickel (the so-called baboon syndrome).^{9,10} However, most nickel-allergic individuals are able to tolerate nickel in their diets. There is very little evidence to support the implementation of nickel-avoidance diets in patients with nickel-related dermatitis.⁴¹ Consequently, if we do not arbitrarily recommend nickel-avoidance diets in all patients with a history of nickel allergy, then why would we broadly recommend avoidance of nickel-containing implants solely based on a history of external nickel sensitivity? Granchi et al³⁹ (n = 223) reported a subset of patients who had both positive patch test reactions to metals and a self-reported history of metal sensitivity (n < 15); these patients had decreased 10-year survival rates for their implants in comparison with controls (32% vs 51.5%).³⁹ Based on these results, one might attempt to conclude that prospectively, patients with a history of metal sensitivity will experience decreased implant longevity. However, the number of patients in each subgroup was very small; and the study was clearly not statistically powered to assess so many variables.

Despite the lack of robust evidence, patch testing is commonly used by physicians to guide selection of orthopedic implants. Atanaskova et al⁷ reported that in every one of their patients who demonstrated positive patch test reactions before surgery (n = 21), the surgeon chose an implant that did not have that metal as a component. This may seem to be an innocuous consequence; however, alternative (typically titanium-based) implants are much more expensive. The actual implant itself can represent close to 50% of the total health care cost of the procedure. Consequently, the rationale for choosing a specific implant must be based on evidence and include careful consideration of cost.

Unfortunately, at present, there is no proven method to prospectively identify (with any degree of certainty) individuals who will develop specific immunologically mediated

adverse reactions to their implants. The recommendation that all patients with history of metal sensitivities (which could represent as much as 20% of the general population) undergo an extended battery of patch tests before implantation lacks true evidentiary support and necessary cost-benefit analysis. If broadly implemented, preimplant testing in all individuals with histories of metal sensitivity would result in approximately 200,000 patch test procedures in the United States each year based on current estimates and closer to 1 million by 2030. This projection ignores the likely far-greater number of cardiovascular (eg, pacemaker, stents), dental, and other orthopedic implant (eg, hip, shoulder, internal fixation devices) procedures that are also performed every year. It is obvious that broad use of preimplant patch testing would result in an inevitable collision course between health care providers, patients, and payers.

After careful consideration of all of these factors and the available evidence, a few conclusions and recommendations can be made at the present time:

1. There may be a higher rate of positive patch test reactions to certain chemicals (eg, nickel, cobalt, chromium, and, to a lesser degree, titanium, vanadium, and acrylate polymers) in patients with implant-related symptoms (eg, pain) or failure (eg, loosening) in comparison with controls with functioning implants. However, there is no available data to reasonably conclude whether specific immune sensitivity is a causative factor or a confounding variable (ie, did the sensitivity result in the loosening or did the loosening result in the sensitivity).
2. There are anecdotal reports of individual patients with compelling histories to suggest that specific immune-mediated reactions against implant materials may have been causative. However, based on the monumental scale of implant procedures currently performed annually in the United States each year (ie, more than 1 million), in combination with the ubiquitous presence of metal sensitivity in the general population (as high as 20% in some studies), it is reasonable to conclude that the incidence of these specific immune-mediated implant-related complications is exceedingly rare.
3. Patch testing is the current standard to detect delayed-type hypersensitivity to chemicals that come in contact with the skin. At the present time, it is not known whether this test accurately reproduces the immunologic mechanisms in periprosthetic tissue. Given these uncertainties listed above, the cost, and the likelihood that specific immunologic reactions to implants are extremely rare, it is premature to broadly recommend a multitude of preimplant patch tests for all individuals who self-report history of metal sensitivity. Prospective studies and cost-benefit

analyses are needed before such a practice should be broadly implemented.

During the review process of this editorial, I was asked to provide some sort of practical recommendation to treating dermatologists who are faced with these clinical situations. Unfortunately, all available options require compromise with regard to the seemingly conflicting influences of “defensive medicine,” evidence-based medicine, and cost-effective care. The available options, associated problems, and several unanswered questions are listed below.

1. The dermatologist could refuse to do the testing, conserve health care dollars, and base this decision on the lack of robust published clinical evidence. However, in these cases, patients will only have surgery needlessly delayed or withheld because many surgeons mandate that patch testing take place before surgery. Furthermore, in consideration of the current malpractice climate, is there potential liability exposure for a treating dermatologist who refuses to perform preimplant testing, if later a patient develops a complication that is argued to have been preventable (eg, patient is later found to have a positive patch test reaction to a constituent material of the implant)?
2. The dermatologist could select a broad battery of patch tests and proceed with testing. In an attempt to provide practical recommendations, Thyssen et al⁶ have provided their criteria for preimplant testing as well as specific recommendations for allergen selection. The recommended battery includes several metals to which reactions are exceedingly unlikely (eg, titanium, vanadium, zirconium) and 1 metal where clinical relevance is extremely questionable (ie, gold). Using diagnostic tests in situations with exceedingly low pretest probabilities and tests for which sensitivities and specificities are not known is problematic. Most of the positive results in this scenario will be falsely positive and have low predictive value. How many false positive tests are acceptable to detect 1 patient at risk? How many at-risk patients need to be identified to prevent 1 adverse event?
3. Lastly, the dermatologist could proceed with limited testing based on a careful evaluation of pretest probability. In the vast majority of patients referred for preoperative testing (typically patients with self-reported intolerance to costume jewelry or metal-containing apparel), the salient clinical question is whether or not a patient is sensitive to nickel. It is entirely reasonable in many cases to apply a single patch test for nickel. Further, this single test for nickel does not necessarily have to be performed at a tertiary patch test referral center. In fact, at our institution, after having experienced an onslaught of semi-urgent patch test requests prior to angiographic stent procedures, we provided training to clinical teams to perform nickel

patch testing in their own department (reducing patient inconvenience, minimizing cost, and preventing undue delay prior to procedures). If there is compelling clinical information to prompt more extended testing, we will, on a case by case basis, consider other chemicals for testing based on that patient's prior exposures, unique clinical history, and a careful assessment of pretest probability.

From this discussion, it should be clear that the subject of preimplant patch testing is fraught with dilemmas and that no perfect solution currently exists. The competing desires to minimize societal cost, reduce liability exposure, and promote evidence-based medicine have created a difficult puzzle for us to navigate. It is my hope that this editorial stimulates discussion, research, and the future development of meaningful evidence-based guidelines.

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