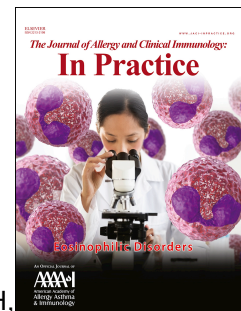


Journal Pre-proof

Sensitization to implant components is associated with joint replacement failure;
Identification and revision to non-allergenic hardware improves outcomes

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PII: S2213-2198(21)00305-6

DOI: <https://doi.org/10.1016/j.jaip.2020.12.068>

Reference: JAIP 3486

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 23 April 2020

Revised Date: 11 December 2020

Accepted Date: 29 December 2020

Please cite this article as: Mayer AS, Erb S, Kim RH, Dennis DA, Shirname-More L, Pratte KA, Barker EA, Maier LA, Pacheco KA, Sensitization to implant components is associated with joint replacement failure; Identification and revision to non-allergenic hardware improves outcomes *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2020.12.068>.

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Each author acknowledges that they have no conflict of interest regarding funding sources, consultant arrangements, speakers' bureau participation, stock or other equity ownership, patent licensing arrangements, support such as financial or materials grants for research, employment, or expert witness testimony, that would affect the contents of this manuscript.

Each author certifies that his/her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

Abstract

Background: Over 90% of 1 million yearly US joint replacements are highly successful. Nonetheless, 10% do poorly, attributed to infection or mechanical issues. Many implant components are sensitizers, and sensitization could also contribute to implant failure.

Objective: Determine the prevalence of implant sensitization in joint failure patients, their clinical characteristics, and implant revision outcomes. We hypothesized that sensitized patients should improve when revised with non-‘allergenic’ materials.

Methods: We prospectively enrolled n=105 joint failure patients referred by their orthopedic surgeon who had already excluded infection or mechanical causes. Patients provided informed consent, completed a history & physical exam, patch testing to metals and bone cement, and a Nickel lymphocyte proliferation test (Ni-LPT). A study coordinator was able to contact 64% (n=67) 9–12 months later to evaluate outcomes.

Results: 59% were sensitized to an implant component: 32% to metal and 37% to bone cement. The Ni-LPT was 60% sensitive and 96% specific in diagnosing nickel sensitization. Most sensitized subjects reported no or uncertain histories of reactions to the specific material(s). Implant sensitized patients were younger, reported previous eczema, joint itching, and implant loosening. 9-12 months later, most patients with a revised implant (‘revised’) described significant improvement (16/22 revised for sensitization, $p=0.0003$, vs. 9/13 revised without sensitization, $p=0.047$) compared to patients without implant revision). All revised patients with sensitization used components to which they were not sensitized. Pain ($p=0.001$), swelling ($p=0.035$), and instability ($p=0.006$) were significantly reduced in the revised sensitized group.

Conclusions: Sensitization to implant components is an important cause of unexplained joint replacement failure. Joint revisions based on sensitization information resulted in significant improvements.

Highlights:

1. What is already known about this topic?
Of the over 1 million joint replacements performed in the US each year, 10% will do poorly. Commonly considered causes include infection and mechanical issues related to the implant.
2. What does this article add to our knowledge?
Sensitization to implant hardware or bone cement is another cause of joint replacement failure, and should be assessed by patch or blood testing to implant components. Revision based on sensitization information leads to measurable improvement.
3. How does this study impact current management guidelines?
Testing for sensitization to implant components needs to be part of the routine evaluation of joint failure patients. Information obtained from such testing should be used to inform revision choices.

Keywords: joint replacement, joint replacement failure, implant sensitization, nickel sensitization, bone cement sensitization, joint revision

List of abbreviations:

NiLPT = nickel lymphocyte proliferation tests

CoCrMo = cobalt/chromium/molybdenum alloy

Ti alloy = Ti – 6Al – 4V or 90% titanium/6% aluminum/4% vanadium

Zr alloy = zirconium alloy = 97.5% zirconium/2.5% niobium

LPT = lymphocyte proliferation test

CRP = C-reactive protein

Ni patch = nickel patch

AIC = Akaike Information Criterion

ALVAL = aseptic lymphocyte-dominant vasculitis-associated lesion

Introduction:

Worldwide, the demand for joint replacements is growing with more advanced hardware and surgical procedures, as well as a physically active, aging, population (1, 2). In the US alone, over one million joint replacements are performed each year: most are highly successful and cost-effective (3). Up to ten percent of joint replacements, however, do poorly (1, 4), with well-studied causes in the orthopedic literature including infection (5), and mechanical issues such as incorrect size, spacer dimension, implant orientation, and aseptic loosening. Risk factors for failure include cigarette smoking (6), excess weight (7), hemarthrosis (8, 9), and osteopenia /osteoporosis with poor bone formation (10). As joint replacement constitutes the highest inpatient short-stay cost for Medicare (11, 12), the financial impact of joint replacement failure is substantial, in addition to the physical and psychological patient costs. Accurate identification of the cause of implant failure, thus, becomes critical to a successful revision.

Recognition is growing that sensitization to joint replacement components also contributes to poor replacement outcomes (13-18). There is biological plausibility for this concept, as a number of materials used in joint implants are established sensitizers. These include nickel, cobalt, chromium, and molybdenum in cobalt-chrome (CoCrMo) alloys. Although titanium, aluminum, and vanadium in titanium alloys (Ti-6Al-4V), and zirconium and niobium in zirconium alloys (Zr-alloy) have lower sensitization potential, they still are rarely reported to cause sensitization and joint failure. Allergens in bone cement include methyl methacrylate, benzoyl peroxide, hydroquinone, and n,n-dimethyl-p-toluidine. Immune responses to these metals and methacrylates have been documented in other populations exposed environmentally (19, 20), or occupationally (19). A growing number of reports of sensitization to these compounds in patients with prosthetic joint failure add to this body of evidence (21-23).

The clinical presentation of sensitization to implant components, however, is not different from other causes of implant failure. Dermatitis over the replaced joint is more easily recognized as related to implant sensitization, but is uncommon. More typically, joint failure presents as patient reports of chronic pain, swelling, recurrent effusions, and the sensation of prosthetic instability and loosening. However, these are symptoms common to many causes of implant failure, including infection and mechanical causes as well as implant sensitization.

Because the clinical presentation of joint replacement failure does not distinguish between causes, the precise role of sensitization in joint implant failure has been difficult to quantify (24, 25). The best method of diagnosing implant sensitization is also debated. Currently, patch testing remains the best established and accepted method of diagnosing delayed type hypersensitivity to metal (26, 27), and bone cement components (28, 29). Specific lymphocyte proliferation testing (LPT) is another approach, but while some LPTs have been validated against patch testing (30), others have not established normal reference values or been compared to other diagnostic tools (31), limiting their clinical relevance. Guidelines published in the dermatological literature (27, 32, 33) recommend that sensitization to joint replacement components be part of the differential diagnosis of joint failure, and evaluated when other common causes of joint failure have been excluded.

We have accumulated a large cohort of implant failure patients specifically referred for evaluation of implant sensitization as a cause. Our goals for this study were to describe the clinical characteristics and prevalence of sensitization to implant components in a subset of these patients. This population already has a higher *a priori* risk for this outcome, as the referring orthopedic surgeon had previously excluded infection and mechanical issues as the cause of joint failure. We measured the correspondence between a history of metal sensitization, and verification by patch testing and the Nickel LPT. We then hypothesized that if sensitization to implant components were, in fact, the cause of joint failure, then clinical improvement should be measurable if the joint were revised to an implant without the allergenic material.

Methods:

Study design and setting

The study protocol was approved by the National Jewish Health (NJH) Institutional Review Board. We selected a referral population of patients sent to us for immunological evaluation of joint replacement failure by their orthopaedic surgeons between October 1, 2010 and September 30, 2012. Subjects were sequentially enrolled after providing written informed consent, evaluated at the National Jewish Health campus, and contacted by phone 9 to 12 months after the initial evaluation.

Participants/study subjects

The surgeon provided information that common causes of joint replacement failure had already been ruled out, including infection by negative culture of the synovial fluid and/or use of the Synovasure assay, which measures the concentrations of alpha-defensins and CRP in synovial fluid with high sensitivity and specificity for prosthetic joint infection. Correct mechanical placement of the implant was based on x-ray and their clinical exam. Our study exclusion criteria were 1) age > 90 years, 2) pregnancy, and 3) treatment with more than 10 mg/day of prednisone which could not be tapered. Of the original n=130 patient who agreed to participate, we also excluded those in whom other causes of joint failure became evident, such as late infection or complex regional pain syndrome (n=7), those who did not complete all 3 visits for patch testing (n=3), those who had more than one affected joint (n=7), and those with instrumentation of non-major articular joints such as spinal vertebrae, or dental implants (n=8). We retrieved the operative reports to identify components, and verify them with the manufacturer.

Study Protocol

All patients underwent the same patch test series to components commonly used in orthopedic implants. All extracts were purchased from Allergeaze (Phoenix, AZ).

TABLE: All metal extracts were suspended in petrolatum except as noted. Extracts included aluminum hydroxide 10%, chromium sulphate 0.5%, chromium chloride 1%, cobalt sulphate 2.5%, cobalt chloride 1%, potassium chromate sulphate 2% (water), manganese chloride 0.5% (water), molybdenum chloride 0.5%, ammonium heptamolybdate 1% (water), nickel sulfate hexahydrate 2.5% and 5%, tantalum 1%, titanium 1%, titanium oxide 0.1%, vanadium 10%, and zirconium oxide 0.1%.

Components of bone cement included methyl and ethyl methacrylate derivatives, benzoyl peroxide, hydroquinone, and n,n-dimethyl-p-toluidine. Because the allergenic potency of commercial methacrylate extracts wanes quickly (34, 35), we included patch testing to bone cement itself, using Components A (liquid) alone, and A & B (liquid and powder), obtained from several manufacturers. All bone cements contain similar components, with minor differences in percentage of methacrylate subtypes, addition of antibiotics, and kind of dye.

Antibiotics such as bacitracin, neomycin, gentamicin, and tobramycin are known sensitizers, and are sometimes added to bone cement, or to surgical lavage fluid. This cohort was not tested to these.

A standard patch testing protocol was used (36). Conditions necessary for patch testing included the requirement that patients did not sunbathe or apply topical steroids to the skin within 2 weeks of the testing, and, if treated with oral steroids, were tapered to ≤ 10 mg/day before clinical evaluation.

The protocol and patch test readings were supervised by a board-certified allergist with experience in patch testing. Briefly, the patches were prepared just before placement on the skin of the upper back or volar forearms (Day 1). On Day 3, the patches were removed and the sites scored according to accepted guidelines (36). The final reading was performed on Day 4-5 (range 4 to 7 days, depending on patient and clinic availability). Patients who developed a late reaction after the final reading were asked to send in photos and return to clinic for definitive reading. All patch test sites were photographed and catalogued as a visual record. For analysis purposes, patch test responses were recorded as positive (1+, 2+, or 3+), negative (0) or irritant (IRR) on Day 5 (36).

A nickel LPT (NiLPT) developed and validated by our group (30) became available during the course of the study to test 90 (86%) of all participants as part of the clinical evaluation. Patients were considered sensitized to nickel if they showed a positive reaction to either the patch test or NiLPT.

Variables, outcome measures, data sources, and bias

Baseline data included age, gender, medical conditions, reported joint symptoms (swelling, burning, itching, pain, instability, loosening, and/or decreased range of motion), and a prior history of metal reactivity. Subjects spontaneously described a sensation of 'internal joint itching', although this may have referred to periarticular itching. Patch test reactions and the NiLPT were recorded. All patients consented to be contacted by telephone between 9 and 12 months after the initial evaluation. Follow-up participants completed a short symptom questionnaire using some of the questions included in the Knee Society Score and generalized to all implants, that was administered by a study coordinator (37, 38). Subjects were asked if the testing had revealed sensitization to an implant component, and those answers were verified against their original test results. They were also asked if they had undergone revision, and if the new implant excluded the materials to which they had been shown to be sensitized. If the joint had not been revised, they were queried if they had undergone any other surgery. The primary outcome of our study was the response to the question: "Overall how do you think you are doing compared to when you were here 9 to 12 months ago" using a 4-point scale: "a lot better", "moderately better", "a little better", or "not at all better". They were also asked similarly scored questions about joint pain, swelling, instability, decreased range of motion, burning, and itching. We focused on patient reported symptoms to assess responses to treatment, as these are increasingly used to support medical decision-making, as a quality measure, and the basis of reimbursement by CMS (39, 40).

Statistical analysis, study size

Statistical analyses were performed using JMP software 10.00 and SAS 9.4(SAS institute, Cary NC). Differences between groups and characteristics were evaluated using chi-square test, with a Fisher's exact test for small sample sizes. Continuous data were evaluated using t-test or Wilcoxon Rank Sum for non-normally distributed data. Two-tailed p-values were set at level of significance of 0.05. Sensitivity, specificity, predictive positive and negative values with 95% confident intervals were calculated between a self-reported history of metal allergies and a positive result from the metal patch tests or NiLPT compared to negative for both. A McNemar's chi square test examined the consistency between the matched results for the two tests (NiLPT and Ni Patch; and a self-reported history of metal allergies and positive metal patch test or NiLPT). We used multivariable logistic regression with manual backward elimination procedure to compare the characteristics associated with sensitization to at least one implant component versus having no such condition. Variables were selected from bivariate analyses on the basis of a p-value < 0.20, and without zero cell counts. At each step, Akaike's

Informative Criterion (AIC) reduction was assessed, and estimates were evaluated as to whether the removal of the covariate largely affected (>10%) the estimates of the remaining variables. Because the sample size for these analyses was small, we used a penalized likelihood method (FIRTH) for modelling to reduce bias. Covariates included in the model were initially evaluated for collinearity using Kendall's tau. To further assess collinearity, we evaluated the model using linear regression to obtain estimates of variance inflation factor and tolerance. If collinearity was identified, only one of the variables was included in the model. Extreme outliers were defined as observations that appear to be inconsistent with the rest of the data. In our analyses they were determined by diagnostic statistics and influence statistics (leverage a measure of how extreme an observation is; measures of changes in regression coefficient, deviance, Pearson chi-square with deletion of a particular observation; and measures of overall change in regression coefficients) provided in SAS logistic regression output. If observations were found influential, they were removed in a form of a sensitivity analysis and reported. Logistic regression was used to determine whether a significant difference in outcome symptoms was based on sensitization to implant components, and whether the subjects had undergone revision surgery.

Results:

Demographics, description of study population

130 of the joint failure patients evaluated during the study period met the entry criteria and consented to enrollment. We excluded $n=25$ based on criteria enumerated above, and limited this study to patients with symptomatic large joint failure (knees, hips, and shoulders) for a final study population of $n=105$ (Figure 1). The overall mean age was 61.4 years (range 33-83) and 55% were female (Table 1). Affected joints included 85 knees, of which 49 were right sided implants, 18 hips of which the majority ($n=15$) were right sided, and 2 shoulder replacements, both right.

Accounting for all patients / study subjects

We contacted all patients 9 to 12 months after initial enrollment to assess their outcomes, and were able to speak with 69 of them. The remainder had moved, or did not return two phone calls. We found no significant differences in the characteristics of those who responded to contact to those who were lost to follow-up (Table 1).

The pattern of Sensitization Corresponds to Joint Implant Materials.

Over half of the study population was sensitized to a joint replacement component (Table 2). A total of $n=61$ (59%) had a positive reaction to patch testing or the NiLPT: 33% to any metal, 37.5% to any bone cement component, and 11% to both (data not shown). Most were sensitized to a component of their implant: 36/39 (92%) of subjects sensitized to bone cement had bone cement used in their failed joint, and 28/34 (82%) of subjects sensitized to cobalt, chromium, or nickel had cobalt/chromium/nickel alloy hardware in place (Table 2). About 30% of the nickel allergic patients were also sensitized to cobalt, as has been reported previously (41, 42). Further details including the specifics of patch testing and the NiLPT results are found in Table E1.

The majority of subjects (90%, $n=95$) had at least one cobalt/chromium component, present in 94% of the knees, all hips, and none of the two shoulders. Interestingly, 25% of knees and 77% of hip implants had mixed cobalt/chromium and titanium/aluminum/vanadium components. Subjects without a Co/Cr/Ni implant were more likely to be sensitized to nickel ($p=0.051$), suggesting some pre-operative implant selection. Only one subject demonstrated sensitization to titanium, but did not have a titanium component. There were no reactions to either zirconium or niobium. Bone cement was used in 86 subjects (82%), and all knees. Those with cemented implants were significantly more likely to be sensitized to a component of bone cement than those without (42% vs. 16%, $p=0.038$).

Comparison of a history of metal sensitization to patch test and Nickel LPT (NiLPT)

Two-thirds of patients reporting a prior history of skin reactions to metal were documented to be metal sensitized with a positive test to nickel, cobalt, and/or chromium (Table 3), compared to 18/69 (26%) of those without such a history, and 6/21 (29%) of those not sure they were metal reactive. This indicates that a prior history of skin reactions to metal has reasonable predictive value for a documented sensitization. Seen another way, however, 71% (24/34) of patients with a positive test for metal sensitization had no prior history or uncertainty regarding metal reactivity, and may have developed the response after the implant was placed. McNemar's test shows a p -value of 0.0067, indicating that the two measures of metal sensitization, history and testing, were not concordant. When we examined the data separated by gender, 69% of women reporting a prior history of metal reactivity were sensitized to a metal, compared to 28% of those reporting no reactions, and 31% of those who were unsure ($p=0.03$).

A history of metal reactivity in men did not significantly discriminate between the groups (Table E2). We also enquired about occupational exposure to metal in 46 subjects of our cohort, of whom 8 (17%) reported exposure: 6 to nickel, 6 to chromium, 2 to cobalt, and 2 to titanium. However, only one of those exposed to nickel was sensitized to that metal (17%) and the rest were not.

The NiLPT improved our ability to diagnose nickel sensitization, and contributed an additional 3 subjects with nickel sensitization. The intensity of the nickel patch test reaction (0 – 3+) significantly correlated with the NiLPT peak stimulation index ($p < 0.0001$). Comparison of the nickel patch test with the NiLPT showed that the NiLPT was 60% sensitive and 96% specific in diagnosing nickel sensitization, with a McNemar's p -value of 0.13: non-significance indicating that the two measures of nickel sensitization have strong agreement (Table 3b).

Demographic and symptom differences between those with and without sensitization to implant components

We compared the characteristics of patients sensitized to implant components to those not sensitized, to identify attributes of either condition. In a univariate analysis (Table 4), those sensitized to their implant were significantly younger, 59.4 years vs. 64.2 years, $p = 0.025$, although gender was equally distributed (59% vs. 50% female, $p = 0.36$). Most co-morbid conditions were equally present in both groups, including allergies/hay fever, hypothyroidism, a connective tissue disease, diabetes, and hypertension (data not shown). Sensitized patients were somewhat more likely to have a history of eczema, reported by 7% of the component sensitized subjects and none of the non-sensitized subjects, and asthma. There were no significant differences in the joint involved or the implant components. Interestingly, those with implant sensitization were more likely to have had at least one revision surgery, compared to those without implant sensitization (41% vs 30%), although the differences were not significant (data not shown). The kinds of joint symptoms reported were similar in both groups, other than the sensation of internal itching described by 33% of the sensitized group compared to 11% of the non-sensitized group, $p = 0.012$, although this may have referred to periarticular itching. Symptoms of implant loosening were weakly increased in the sensitization group, 31% vs. 18%, $p = 0.13$. Blood tests showed no differences in markers of allergy, including eosinophil percentage and median IgE (data not shown) between the two groups.

Based on these data, we developed a preliminary multivariable model of factors associated with sensitization to implant components (Table 5). The most highly predictive variable for sensitization was the sensation of internal itching, described by study subjects as constant, and inside the joint. When implant loosening or instability were combined in the final model, with extreme outliers removed, the combined variable was also significantly associated with sensitization to implant components ($p = 0.044$).

Revision for implant failure improves outcomes, especially for those due to sensitization

Nine to 12 months later, we were able to re-contact 67 (64%) subjects to complete a follow-up phone survey. As shown in Table 1, there were no significant differences in age, gender, implant type, or sensitization results between the follow-up and lost to follow-up groups. A longer duration of the implant is another risk factor for joint failure. However, the mean age of the problem implant did not differ between sensitized and non-sensitized subjects (2.6 years vs 2.3 years, $p = 0.66$), nor did the mean number of revisions. Subject recall of sensitization was good, with 90% correctly recalling they had been

diagnosed with sensitization to their implant, and 96% correctly recalling they were not. At the time of follow up, 52% (n=35) of the total cohort had undergone revision surgery of the problem joint. Another 40% had no revision, and 8% underwent another procedure, either arthroscopy (n=4) or placement of a spinal cord stimulator (n=1). Of the 22 sensitized subjects who were revised to a different, non-allergenic implant, 13 were sensitized to an implant metal, 15 were sensitized to bone cement, and 6 were sensitized to both. When we compared outcome groups using a continuous measure of improvement (from 1=no change to 4=much better) we found the greatest amount of improvement in those sensitized to bone cement. Of the 26 non-sensitized patients, the 13 who were revised to a different implant did somewhat better than those not revised, $p=0.071$. The 9 of 18 sensitized to bone cement who were revised to a press-fit option did significantly better than those not revised, $p=0.02$. Seven of 14 patient sensitized to a metal were revised to titanium or oxinium alloy implants, with nearly significant improvement $p=0.06$. And 6 of the 7 patient sensitized to both a metal and to bone cement were revised to custom press-fit implants, and also did significantly better $p=0.0005$.

The overall percentage of reported improvement ("Overall doing better") was similar in the sensitized and non-sensitized groups who underwent surgery to replace the implant (73% vs 69%, $p=0.999$), and both revised groups were more likely to report doing a lot better than those who were not revised (73% vs. 8%, $p=0.0003$ in the sensitized group, and 69% vs. 25%, $p=0.047$ in the non-sensitized group respectively) (Table 6). However, we found significant differences in specific symptom improvement following revision in the sensitized group, but not the non-sensitized group. Those who underwent revision due to implant sensitization were significantly more likely to report no or mild pain (68% vs. 8%, $p=0.001$), no or mild swelling (64% versus 23%, $p=0.035$), and no or mild instability (73% vs 23%, $p=0.006$), with a trend towards better range of motion (59% vs. 23%, $p=0.078$) compared to those sensitized but not revised. Those without implant sensitization who underwent surgical replacement of a different implant also reported overall improvement in symptoms, but specific symptoms did not differ significantly from those who did not undergo surgery (Table 6.).

Discussion:

Given the large number of joint replacements performed yearly in the US, accurate assessment of the cause of a failed joint replacement is essential to improving the outcomes of the 10% who do not do well. Although infection and mechanical issues are commonly evaluated, there remains a group of patients who do not fit these parameters. A few, mostly case reports, have described sensitization to implant components as another cause for joint replacement failure (16, 43, 44). ALVAL (aseptic lymphocyte dominated vasculitis associated lesion) has been identified as type IV hypersensitivity reactions to metal debris derived from metal on metal hip articulations. In one small study, patients with ALVAL did not improve if their implant was changed to another metal on metal hip replacement, but all patients improved when the metal on metal implant was removed and replaced with a ceramic on ceramic bearing (45). Similar findings have more recently been reported for knee replacements (46). We have accumulated a large cohort of joint failure patients specifically referred by their orthopedic surgeon for possible implant sensitization, and report our findings on an early subset of them. We have also been able to follow some of these patients over time to determine if an immunological evaluation had a positive effect on patient outcomes.

Notably, this cohort of implant failure patients was *a priori* enriched for possible sensitization. Indeed, we found that over half of this selected population was sensitized to one or more components of their

joint replacements. The most common reaction was to nickel, found principally in cobalt/chromium implants and in stainless steel, and the most common contact allergen in the general population (47).

A common critique is that patients with joint replacements generally have a higher prevalence of positive metal patch tests compared to those without metal implants. However, it is important to note that such testing was performed independent of outcome. For example, Granchi D et al (48) found that patients with a stable knee replacement had a 48% rate of metal sensitization by patch testing, compared to 20% in patients evaluated preoperatively. However, the rate was 60% in those with a loose or failed knee replacement, and patients with a preoperative history of metal reactivity had a four-fold increased risk of joint replacement failure compared to those without such a history. She found similar results in patients with hip replacements (49). In a large meta-analysis, she compared results from 367 stable joint replacements to 297 failed replacements (50). When testing was performed in the context of the clinic history, the probability of metal sensitization was significantly higher in failed compared to stable joints, with an OR=2.76 (1.14, 6.70) $p=0.02$, and similar findings have been reported elsewhere (51). Taken together, these results indicate that metal sensitization is indeed a cause of implant failure, and reaffirms that patch testing is relevant only within the clinical context.

We found that a prior history of skin reactions to jewelry, watch bands, or jean snaps was about 67% sensitive in identifying subjects with metal sensitization by patch testing or NiLPT, similar to those reported by Mesinkovska et al (52), who found that 21/31 (68%) of patients with a prior history of metal reactivity were patch test positive to metal, and the majority, 15/21, were positive to two or more metals. But about one-quarter of our subjects without a prior history were also metal sensitized, as well as one-quarter of those who weren't sure. This suggests that a subset of patients may become sensitized to the implant after joint replacement surgery, independent of a prior history of metal reactivity. It also indicates that testing for metal sensitization may provide an answer in those patients with unexplained joint replacement failure.

We found several differences in patients with a failed joint due to sensitization that may be clinically useful. The medical condition that most distinguished the implant sensitized from non-sensitized subjects was a prior history of eczema, raising the issue of an incomplete skin barrier as a risk factor for sensitization. Null mutations in the Filaggrin gene, which codes for a histidine rich polypeptide essential for intact barrier function of the epidermis, are associated with both childhood eczema, and nickel sensitization (53, 54). One of our future goals is to evaluate the association of Filaggrin mutations with sensitization to implant components. Implant sensitized patients were also somewhat more likely to report a history of asthma, although other allergy markers were not predictive.

In terms of clinical presentation, significantly more implant sensitized patients reported itching, which they described as 'internal joint itching', than the non-sensitized patients. Pain, swelling, burning, instability and decreased range of motion were similar in both groups. The implant sensitized group was also somewhat more likely to report symptoms of loosening, and we speculate that a portion of patients diagnosed with aseptic loosening are, in fact, sensitized to their joint replacement, and the resultant local inflammation is the cause (55). Similarly, Mesinkovska et al (52) found that metal sensitized implant patients were more likely to report pruritus (20% vs 10%), and loosening (40% vs 13%) compared to non-sensitized implant patients.

One of the most important findings in this study was that revision for implant sensitization clearly improves outcomes. Although all revised patients improved, the sensitized group benefitted the most.

They reported significant improvements in reduced pain, swelling and instability, with a trend towards improved range of motion, compared to their sensitized counterparts who did not undergo implant change. Although the non-sensitized group undergoing implant revision also generally improved, they showed no significant differences in specific symptoms compared with their counterparts not undergoing surgery. Interestingly, non-sensitized patients also had higher rates of spontaneous improvement over time compared to the sensitized patients, although the numbers were small. In addition to revision to different metal implants based on metal sensitization, improvements were also noted in sensitized patients revised to press-fit implants due to sensitization to bone cement components. This adds to the positive findings reported in press-fit revision studies, despite concerns of resultant instability (56).

Other studies have found similar symptom improvement with revision to a different implant in sensitized implant patients (16, 43). A recent review of revision knee surgery found that patients sensitized to metal and revised to a different implant continued to show significant decreases in pain at 6 weeks, 5 months, and 1 year after revision (all $p < 0.001$), compared to sensitized patients who did not undergo implant change. Similar to our results, those patients without metal sensitization who were revised to a similar implant only showed significant decreases in pain at 6 weeks compared to those not undergoing revision surgery ($p < 0.03$), but had no further changes over time (44).

Notably, some orthopaedic surgeons are reluctant to revise implants due to failure from component sensitization. Nonetheless, our results and others indicate that many of these sensitized patients have better outcomes with revision, and little chance of improvement without.

Limitations

We acknowledge there are limitations to our study. The patient population was relatively small, and their results may not be representative. The follow-up time period was short, and more or other outcome differences may become apparent in a longer study (which is ongoing). We were only able to recontact 69 of the original cohort, although their characteristics did not differ from those lost to follow-up. Ninety out of 104 subjects were assessed for sensitization to nickel by both patch testing and LPT testing, which may have increased our case finding for nickel sensitization by methods that were not available for other implant components. As a result, sensitization to other metals may have been under-reported. Patients were not tested to sensitizing antibiotics commonly added to bone cement or to surgical irrigation fluid. However, these degrade rapidly after their addition, and are unlikely to cause long-term joint failure. All patients with a joint revision did better, regardless of their sensitization status, and thus the improvement could be related to surgical revision rather than material avoidance. However, the significant improvements across all symptom measures in the sensitized group revised to a different implant without the implicated material, compared to the rest of the sensitized group not undergoing surgical revision, strongly suggest that the change for the better was due to removal of the offending joint component(s). Our findings are based on patient responses to symptom questionnaires, and we were not able to include objective measures of implant function. Nonetheless, patient symptom improvement and satisfaction do not always correlate with objective measures of function, but may be more important. Increasingly, patient reported outcomes are used as a quality measure, to support medical decision-making, and form the basis of reimbursement by CMS (39, 40). As such, our results are informative for the treatment of implant sensitized patients.

Conclusions

Middleton et al (57) suggests that the diagnosis of sensitization related implant failure requires three components: 1) demonstration of T cell dominated immunohistopathology, 2) positive patch tests to implant derived allergens, and 3) healing upon exchange of the implant to a non-allergenic substitute. Our study has demonstrated, in a prospective fashion, two of these three conditions. Adding pathology of synovial tissue samples from revision surgery will strengthen our findings. Other future directions include replication of these outcomes in a larger cohort, and followed for a longer period of time. Better definition of risk factors for implant sensitization will help distinguish patients before surgery to avoid this outcome. Taken together, the financial burdens and personal expenses of revision surgery are high, and current reimbursement does not cover the full costs (58). Considering sensitization to implant components in the differential diagnosis of joint replacement failure, and including an evaluation for implant sensitization as part of the work-up, will help limit the number of revisions, reduce costs, and improve patient outcomes and satisfaction.

Acknowledgements

We thank Dr. Liz Regan for helpful comments and corrections to the manuscript, and Mrs. Stephanie Clancy for editorial aid and formatting. We also thank the patients who generously contributed to this research. The universal reason for participation was that each wanted to provide their experience, so that no one else would have to go through what they had.

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Legends**Figure 1.** Study Flow.**Table 1.** Study population and outcomes population**Table 2.** Sensitization results of study population.**Table 3****a.** Association of reported history of metal reactivity with verification by patch test or NiLPT.**b.** Comparison of nickel LPT and nickel patch test results.**Table 4.** Comparison of subjects with and without sensitization to implant components.**Table 5.** Model for sensitization to implant components.**Table 6.** Comparison of outcomes by sensitization status.

Table 1.	Study Population	Outcomes Population	
Variable	All n=105	Followed-up N=67	Lost to follow-up n=38
Age	61.4 (33-83)	61.8 (43-83)	60.7 (33-81.5)
Female	58 (55%)	37 (55%)	21 (55%)
Joint involved			
Knee	85 (81%)	52 (78%)	33 (87%)
Hip	18 (17%)	14 (21%)	4 (11%)
Shoulder	2 (2%)	1 (<1%)	1 (<1%)
Any patch test +	61 (59%)	40 (60%)	21 (55%)
Metal +	34 (33%)	22 (33%)	12 (32%)
Bone Cement +	39 (37.5%)	26 (39%)	13 (34%)
p-value = ns for comparisons between followed-up and lost to follow-up populations.			

Table 2. Sensitization test results of the study population	
Component	Percent (n) sensitized
Any	59% (n=61/104)
Any metal	33% (n=34/104)
Nickel	24% (25/104)
n=10 + by nickel patch test, n=3 + by NiLPT, n=12 + by patch & LPT. 14 subjects did not complete LPT testing.	
Cobalt	15% (16/104)
Chromium	1% (1/104)
Titanium	1% (1/104)
Bone cement	37.5% (n=39/104)
11% of subjects were sensitized to metal and bone cement.	

Table 3a. Association of reported history of metal reactivity with verification by patch test or NiLPT

	Metal allergy documented by patch or NiLPT		
Skin rash or itching to jewelry, watchbands, or jean snaps	Positive N (%) (n=34)	Negative N (%) (n=71)	Predictive Value
Yes (n=15)	10 (35.7%)	5 (8.9%)	Positive 66.7% (38-88%)
No (n=69)	18 (64.3%)	51 (91.1%)	Negative 73.9% (62-84%)
Sensitivity / Specificity	Sensitivity 35.7% (19-56%)	Specificity 91.1% (80-97%)	McNemar's p-value = 0.0067
Not Sure (n=21)	6 (17.7%)	15 (21.1%)	N=105

Table 3b. Comparison of nickel LPT and nickel patch test results

	Nickel Patch		
Nickel LPT	Positive N (%) (n=20)	Negative N (%) (n=70)	Predictive Value
Abnormal (n=15)	12 (60.0%)	3 (4.3%)	Positive 80% (52-96%)
Normal (n=65) or Borderline (n=10)	8 (40.0%)	67 (95.7%)	Negative 89% (80-95%)
Sensitivity / Specificity	Sensitivity 60.0% (35-81%)	Specificity 95.7% (88-99%)	McNemar's p-value = 0.13
			n=90

Table 4. Comparison of subjects with and without sensitization to implant components

Variable	Sensitized to at least one implant component (n=61)	No sensitization to any implant component (n=44)	p
<u>Demographics</u>			
Age (sd)	59.4 years (10.5)	64.2 years (10.6)	0.025
Gender (%Female)	36 (59%)	22 (50%)	0.359
<u>Other medical conditions</u>			
<i>History of eczema</i>	4 (7%)	0 (0%)	0.138
<i>Asthma</i>	11 (18%)	3 (7%)	0.145
<u>Implant duration/revisions</u>			
<i>Age of implant (sd)</i>	<i>2.6 years (3.21)</i>	<i>2.4 years (2.24)</i>	0.661
<i>Mean number revisions (sd)</i>	<i>1.5 (0.70)</i>	<i>1.4 (0.65)</i>	0.307
<u>Joint Implants</u>			
CoCrMo component	53 (90%)	42 (98%)	0.234
TiAlV component	24 (41%)	16 (37%)	0.723
Zr alloy component	1 (2%)	1 (2%)	0.999
Bone cement used	50 (82%)	36 (82%)	1.000
<u>Symptoms</u>			
Swelling	48 (79%)	33 (75%)	0.657
Pain	56 (92%)	39 (89%)	0.739
Itching	20 (33%)	5 (11%)	0.012
Burning	12 (20%)	9 (20%)	0.92
<i>Loose</i>	<i>19 (31%)</i>	<i>8 (18%)</i>	0.134
Unstable	21 (34%)	10 (23%)	0.195
Loose/unstable combined	29 (48%)	15 (34%)	0.170
Decreased ROM	13 (21%)	8 (18%)	0.692

Table 5. Model for sensitization to implant components (N=105).

Final model (C Statistic=0.72)			Final Model with extreme outliers removed (C Statistic=0.75)§		
Variables	OR (95% CI)	p	Variables	OR (95% CI)	p
Age (yrs)	0.97 (0.93-1.01)	0.124	Age (yrs)	0.96 (0.92 – 1.00)	0.047
Itching (Yes/No)	3.15 (1.06 - 9.44)	0.040	Itching (Yes/No)	5.47 (1.51 – 19.78)	0.008
Loose/Unstable* (Y/N)	1.88 (0.81 - 4.35)	0.140	Loose/Unstable (Y/N)*	2.49 (1.03 – 6.05)	0.044
* Instability and Loosening were combined as one variable.					
§ Two observations were extreme influential points that were removed.					

Table 6. Comparison of outcomes by sensitization status

Outcome	Implant Sensitization n=35			No Implant Sensitization n=26		
	Revision n=22	Other surgery or no Revision n=13	p	Revision n=13	Other surgery or no Revision n=13	p
No or mild Pain	15 (68%)	1 (8%)	0.001	6 (46%)	4 (31%)	0.688
No or mild Swelling	14 (64%)	3 (23%)	0.035	8 (62%)	6 (46%)	0.695
No or mild Instability	16 (73%)	3 (23%)	0.006	11 (85%)	7 (54%)	0.202
Good or better ROM	13 (59%)	3 (23%)	0.078	9 (69%)	5 (39%)	0.238
Overall doing better	16 (73%)	1 (8%)	0.0003	9 (69%)	3 (25%)	0.047

Figure 1. Study Flow