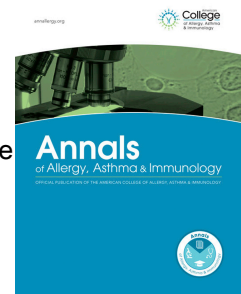


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The role of metal patch testing in evaluating patients for metallic prosthetic joint failure

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Background: Metal allergy may be an uncommon cause of prosthetic joint failure. There exists little data on patch testing to metals in this context and its impact on outcomes of joint revision in these patients.

Objective: Explore the utility and indications for metal patch testing in the evaluation of patients suspected of having metal allergy as a cause of failed joint replacements and clarify the outcomes of patients revised with alternative metallic joints because of positive patch testing.

Methods: A retrospective analysis from January 2016 to April 2020 was completed on a patient cohort referred for evaluation of metal hypersensitivity. Charts were reviewed for age, biological sex, referring specialty, patch testing results, joint, revision status, and outcome measures. Biostatistical analysis and descriptive statistics were performed to determine patch testing performance and functional outcome trends among this patient cohort.

Results: The sensitivity and specificity of patch testing, in general, is limited when evaluating patients with metallic joint replacements. However, the predictive value of testing appeared to improve with strongly positive patch testing results. Functional outcomes in patients when positive results were used to guide revision prosthesis demonstrated clinical improvement.

Conclusion: The attribution of metal allergy or hypersensitivity as a cause of failure in metal prosthetic joint replacement remains unproven. Some patients with positive histories and patch testing that were used to modify the implanted prosthesis had improved functional outcomes. These results suggest patch testing may be useful in patients with prior history of metal sensitivity and prosthetic failure.

1 Introduction

2
3 Hip and knee replacement with metallic implants is estimated to occur in
4 approximately 1.5 million patients in the United States in 2020. Additionally, hip
5 and knee replacements are anticipated to increase by 284% and 401%, respectively,
6 by 2040.¹ Allergic reactions to metals such as nickel, cobalt, and chromium are
7 common conditions affecting between 3% of males and 17% of females.² Over the
8 last several years a growing body of evidence has suggested that metal allergy may
9 be a cause of prosthetic failure in patients with metallic joint implants.³ Commonly
10 these metals were utilized in first generation replacements as metal-on-metal
11 prosthetic implants for total joint replacement.⁴ The primary mechanism of metal
12 sensitization is hypothesized to involve the physiologic reaction of metal ions
13 produced by small metal wear particles found within the joints of those with
14 evidence of prosthetic failure.⁵ There is likely systemic absorption of the ions which
15 activate dendritic cells, resulting in significant perivascular T cell activation and
16 infiltration within and around the synovial capsule.⁶ This is similar to the
17 pathophysiology of contact dermatitis to metals. The use of metal-on-plastic
18 prosthetics and ultimately the development of new second generation alloys proved
19 to be more durable and resulted in less metal release and resulting sensitization.⁷
20 However, there have been some reports of sensitization to modern, titanium based
21 products.⁸ Approximately five percent of total knee arthroplasty will require revision
22 in 10 years, and previous research has suggested that evaluation for metal allergy
23 should be part of the diagnostic algorithm for patients experiencing signs of

premature joint prosthetic failure. Metal allergy testing should be done after more common causes of failure have been excluded.^{9,10} A previous survey of professionals performing patch testing sought to determine perceptions of criteria for diagnosis of metal allergy. This study revealed that the presence of chronic dermatitis beginning weeks to months after metallic implantation, rash overlying the metal implant, positive patch test to a metal salt of the component of the implant, and complete clearing after removal of the potentially allergenic implant could each be major determinants of the diagnosis of metal sensitization. They also suggested that minor determinants could be systemic allergic dermatitis reaction, therapy-resistant dermatitis, morphology consistent with dermatitis, histology consistent with allergic contact dermatitis, and a positive in vitro test to metals.¹¹ Despite the relative paucity of research into the validity of patch testing for metal allergy, the use of patch testing to metals and other components of joint replacement is the standard method of evaluating metal allergy in these patients. This practice has been adopted based on the presence of metal sensitization discovered in patients that have had past joint prosthetic failure.^{12,13} Additionally, patch testing can have a significant role in helping guide the choice of implant. One such study evaluated the utility of patch testing patients with known metal allergy which resulted in placement of non-allergenic materials resulting in improved outcomes for these patients.¹⁴ A major critique of patch testing involves the anatomic segregation of the synovial compartment suggesting that dermatologic testing may not truly reflect synovial compartment reactions. Given the concerns that dermatologic testing may not truly represent the synovial manifestations of allergy, other assays such as the lymphocyte

transformation test in which metal salts are incubated with the patients lymphocytes are promising, however, have not been validated or widely incorporated into the standard of care.¹⁵ Given the scarcity of research regarding patch testing performance in these patients, we sought out to study the testing performance of patch testing in patients who were candidates for metallic implants and evaluate its effect on postoperative outcomes with the goal to help guide decisions on the utility of patch testing in these patients in the future.

Methods

A retrospective review of electronic medical records of patients encountered between 01/01/2016 – 04/15/2020 was completed to evaluate patch testing results in patients with previous metallic implants. Most were referred by their orthopedic surgeon in preparation for a knee implant or revision. Electronic health records were identified with the help of Health Data Compass, a University of Colorado affiliated data acquisition service. An associated diagnosis of irritant contact dermatitis to metals (ICD-10: L24.81) was used because several insurance companies required this diagnosis for reimbursement, and to isolate individuals who were specifically evaluated for metal allergy. It should be noted that this diagnosis was not pulled from a patient's past medical history, but from the associated visit diagnosis. Additional criteria for patient record selection included an encounter by the Department of Allergy and Clinical Immunology and having an associated procedure code for patch testing (72326). These records were then reviewed for

patient age, biologic sex, referring specialty, previous history of reaction to metals,
symptom of joint failure, type of metallic implant, patch testing results, revision
status, and surgical outcomes for hip and knee implant patients. The identification of
an individual's history of reactions to metals, separate from the diagnostic code
utilized in the initial data acquisition, was used to identify patients who would
represent true positive, and conversely true negative results by the presence or
absence of historical reactions to metals. Patients with isolated symptoms of joint
failure without dermatitis, and no previous reactions to metals were considered to
have no history of previous reactions to metals. Additionally, it is the practice
standard of referring surgeons to evaluate for all other etiologies of premature joint
prosthetic failure prior to metal allergy evaluation.

For patients who had hip or knee implants, validated objective preoperative and
postoperative outcome measures were obtained as part of a standard internal
registry. Chart review was then used to collect results documented in the health
record for the timed up and go, thirty second sit to stand, and 4-meter walk
tests.^{16,17,18} Symptom scores for hip and knee revision patients were obtained in a
similar fashion with collection of data from validated HOOS JR and KOOS JR
surveys.^{19,20} Descriptive statistics were performed on the functional outcome
measures to determine confidence intervals to assist with statistical significance
determination. Biostatistical analysis of patch testing was performed in regard to
patients reporting previous history of reactions to metals to aid in determination of

testing performance, as this was thought to be most similar to patients in which previous validation of patch testing was performed.

Statistical Methods

Biostatistical analysis was completed on patch testing results using standard methods of comparing frequency true positive and negative results with false positive and negative results to generate testing sensitivity and specificity. Positive likelihood ratios were generated from values of sensitivity and specificity of metal patch testing performance. True positive results were defined as those having a history of previous reactions to metals, and positive metal patch testing results. True negatives were defined as those without history of previous reactions to metals and negative patch testing. False negatives were assigned to those with previous reactions to metals and negative positive patch testing. False positives were assigned to those without previous reactions to metals and positive patch testing. Given that the patch testing system utilized in this study contained metals that are epidemiologically associated with a greater frequency of reactions, it was felt that those with history of previous reactions to metals would more uniformly react to the patch test panel allowing for more accurate statistical analysis. Subgroups of patients who underwent hip and knee replacement were additionally analyzed for sensitivity and specificity calculations. Additionally, using the data among orthopedic patients with previous reactions to metals; we stratified the testing performance calculating a true positive

rate and false positive rate to generate a receiver operating curve to better understand the testing performance of metal patch testing.

Descriptive statistics were performed using the assistance of statistical analysis tools embedded in Microsoft Excel[®]. Analysis was completed on preoperative data in patients compared to three months follow up data. One year follow up data was incomplete among patients enrolled within the study and excluded from analysis. Statistical analysis outputs resulted in values for data with minimums, maximums, medians, and mean values. Standard deviation of each dataset relating to each outcome measures were obtained and used to calculate 95% confidence intervals to assist with determining statistical significance.

Results

A total of 111 individual patients were returned from our initial query. A total of 94 patients within the initial query were identified as having undergone metal testing related to metallic implants and were the primary focus of this investigation. There were 43% (n=41) patients that had positive patch testing results. (Table 1, Figure 1) Most patients were planning to undergo replacement or revision to their previous implant. A female predisposition was found with 35 out of 72 females (48%) and were correlated with 85% of all positive results. (Table 2) History of previous reactions to metals, rash, and pain were more likely to be associated with positive patch testing results with 53% (n=19), 45% (n=5), and 37% (n=13) positive patch

tests, respectively. (Table 3). The majority of patients (n=55) were referred for evaluation of their hip or knee prosthesis. Patch test data revealed 47% (n=26) and 53% (n=29) of patients with hip or knee prosthesis had positive and negative results, respectively. Additionally, patients with hip or knee replacements with positive patch testing 80% (n=21) were more likely to undergo surgical revision as compared to those with negative patch results 55% (n=16) (Table 4). Nickel, cobalt, and potassium dichromate were most associated with positive patch tests. (Table 5) Post-operative outcome measures for patients with hip or knee revision were complete for 10 patients with positive patch results and 9 patients with negative patch test results.

Biostatistical analysis (in section: statistical methods) on all implant patients with “previous reactions to metals” indicated a sensitivity of patch testing of 53% and specificity of 62%. Isolating patients who had received either hip or knee replacement the sensitivity increased to 62% and specificity increased to 66%.

Interestingly, testing performance improved among patients with intermediate (++) and strong (+++) patch testing results when comparing true positive and false positive rates. (Figure 2) Metal patch testing, in general, revealed a positive likelihood ratio of approximately 2. When stratifying testing performance by the magnitude of reaction, we found that weak positive (+) reactions share a similar positive likelihood ratio, however, more strong positive reactions (++,+++) had a higher likelihood ratio of approximately 4. Descriptive statistics (in section: statistical methods.) were performed on functional outcome measures for orthopedics patients with hip or knee implants that went on to have their joints

revised. In the non-allergic revised group (n=9) there were slight, but not statistically significant improvements in the objective outcome measures timed 4-meter walk, 30 second sit to stand count, or timed up and go. In the metal allergic revised group (n=10) there is a statistically significant difference in the 30 second sit to stand measure with a mean increase in repetitions by 3.6 (95% CI 1.62:5.57). There were improvements that were not statistically significant in the metal allergic patients for the timed up and go or timed 4-meter walk tests. Additionally, patients within the allergic group had statistically significant improvement as compared to the non-allergic groups by a mean reduction of 8.4 points (95% CI -12.68:-4.11) versus 4 points (95% CI -7.04:-0.92). (Figure 3) It is the practice of our orthopedics department that all patients with positive patch testing results receive a prosthesis avoiding the metals involved in positive patch testing.

Discussion:

Many patients have garnered the increased quality of life associated with having a damaged joint replaced with a metallic joint prosthetic. However, these devices are not without rare complications such as septic arthritis, periprosthetic fracture, malalignment, and mechanical failure. With the availability of modern alternative prostheses, the development of validated diagnostics to better tailor revision strategies is needed. Previous studies suggest that total knee arthroplasty can result in upwards of 20% sensitization to implanted metals with stable joints and upwards of 60% with unstable joints²¹. This study also concluded that patch testing could not

delineate between stable and loose joints in symptomatic patients suggesting that
patch testing may have limited testing performance in patients with symptoms of
metallic joint failure. Our study additionally suggests that metal patch testing has
limited sensitivity and specificity in diagnosing metal allergy when evaluating those
with metallic implants and previous reactions to metals. Testing positive predictive
value did improve with intermediate and strong positive reactions and highlights the
challenges of interpreting patch testing results to diagnose metal hypersensitivity.
Previous literature has suggested that patch testing can have a diagnostic specificity
and sensitivity of approximately 70%-80%, however, is variable depending on the
material in question²² However, despite the limitations in testing, patients with patch
testing suggestive of metal allergy, were observed to have improved outcomes after
revision with a prosthesis avoiding the implicated metals as compared to those with
negative patch testing.

Although patch testing is relatively inexpensive and non-invasive it has several
limitations. These include provider interpretation bias, and limited testing
performance. Additionally, there is controversy regarding whether cutaneous
reactions are equivalent or are diagnostic of synovial reactions. These concerns have
been discussed by Schalock and Thyssen who agreed that metal patch testing
indicative of metal hypersensitivity is not adequate to make a diagnosis of metal
allergy, but other features such as dermatitis correlating with implantation would be
sufficient to make a diagnosis in conjunction with metal patch testing.¹⁰ Novel
diagnostics have been investigated and include lymphocyte transformation assays.

cytokine assays, and cellular microscopic techniques. However, neither of these
assays have been validated, often are discordant with patch testing, nor have
predictive values associated with their performance.²³ Previous studies have sought
to understand whether patch testing preoperatively or postoperatively after
development of symptoms of joint failure is preferred. The literature suggests that
testing prior to implantation, especially those with history suggestive of metal
hypersensitivity, will lead to selection of alternative implants and will reduce
complications related to metal allergy.²⁴

Limitations of our study include retrospective analysis of data within the patient
record. There likely exists a spectrum of patients within our group of patients with
previous reactions to metals, ranging from irritant reactions to true metal allergy, and
likely contributes to diminished testing performance. Despite a small cohort of
patients with complete functional outcome data, we were able to demonstrate
clinical improvement in patients with patch testing suggestive of metal allergy with
subsequent use of a revision prosthesis avoiding the implicated metals. It would be
interesting to observe with a larger cohort if the functional gains are observed long
term. Looking forward, it would be prudent to stratify patient's previous reactions to
metals, to evaluate testing performance in those patients with more severe reactions
to metals. Should patients develop worsening symptoms after revision, it would be
interesting to evaluate if any changes in metal patch testing are observed despite
having had an alternative implant avoiding metals implicated in patch testing placed.
Future investigations involving synovial tissue biopsy or synovial fluid cellular

analysis could be utilized to evaluate for evidence of hypersensitivity in these patients. Additionally, it would be interesting to involve comparisons to lymphocyte transformation assays or cytokine assays to draw further correlations between diagnostics, joint pathology, and metal hypersensitivity.

Ultimately, the decision to pursue referral for testing and eventual revision is between the surgeon and the patient. Typically, patients with concern for complications after total joint arthroplasty are first evaluated via standardized algorithms with laboratory testing, imaging, and joint aspiration to exclude the more common complications of joint implant failure.^{25,26,27,28} (eTable 1) Should this evaluation be unrevealing, the question of metal allergy as a cause of symptoms can arise. The existing literature and our study suggest that previous reactions to metals or history of dermatitis to metals are key features of metal allergy and testing could be considered in these patients. Our study would also indicate that symptoms such as pain or poor healing are less likely to result in patch testing indicative of metal allergy. Based on our current data and interpretation of available literature, it would be reasonable to pursue metal patch testing to evaluate patients for potential allergy to a metallic implant should other, more common, etiologies of prosthetic failure be excluded prior to metal allergy evaluation. Should the patient's history and evaluation be suggestive of hypersensitivity, revision with an alternative implant avoiding implicated metals could be pursued with the expectation of clinical improvement.

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Table 1: All patch test results

Patch Result	Count	Percent of Total
Negative	53	57%
1+	19	20%
2+	19	19%
3+	3	3%

Table 2: Patch test results correlated with biological sex

Biological Sex	Count	Average Age	Percent Positive	Percent Negative
Male	22	59.5	27%	73%
Female	72	60.2	48%	52%

Table 3: Patch test result correlated with presenting complaint

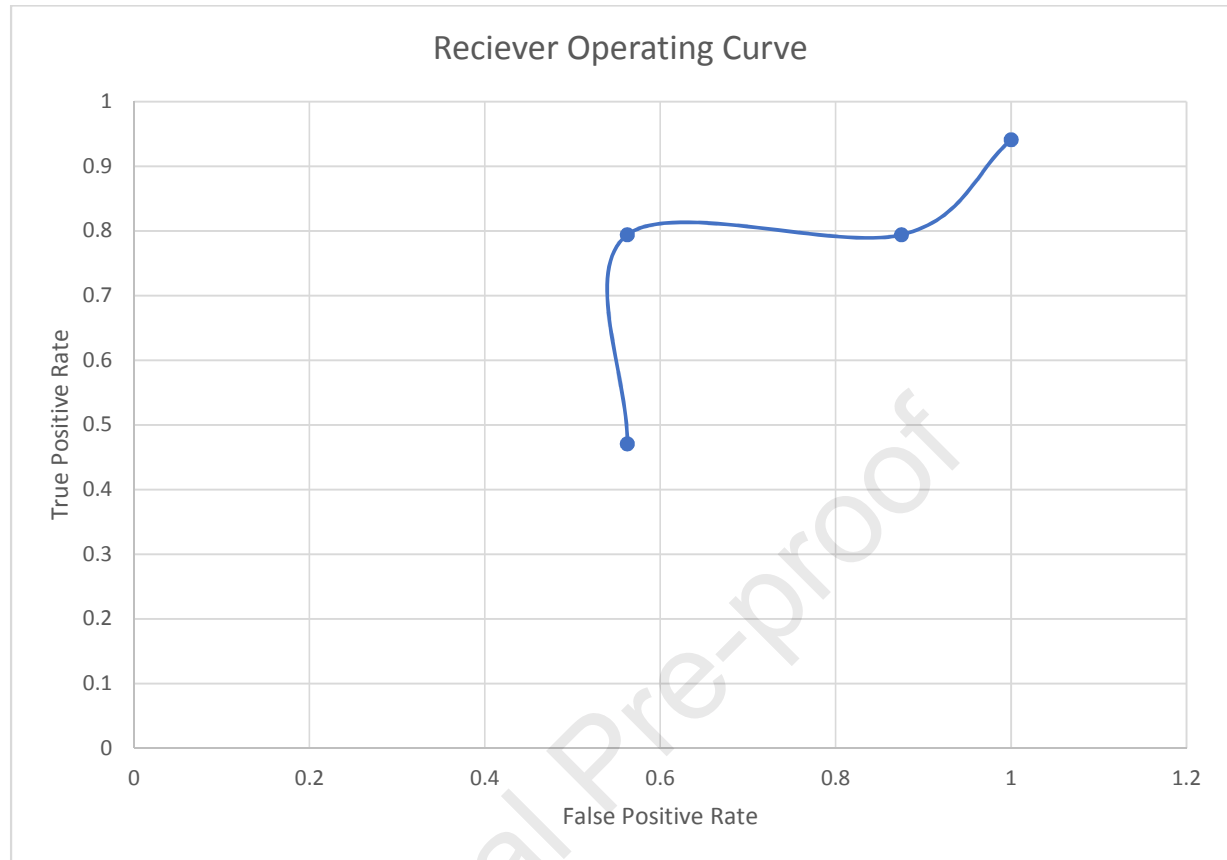
Complaint	Total	Patch Positive	Percent Positive	Percent Negative
Pain	35	13	37%	63%
Swelling	22	4	18%	82%
Rash	11	5	45%	55%
Impaired healing	4	0	0%	100%
Previous reaction to metals	36	19	53%	47%

Table 4: Hip and knee patch testing results and revision status.

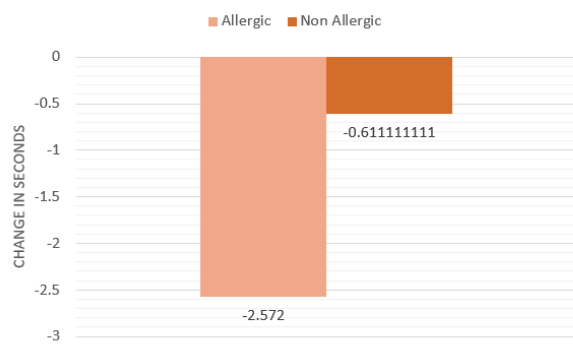
Hip/Knee Revision Data	Count	Percent	Patients Revised	Percent
Positive Patch Results	26	47%	21	81%
Negative Patch Results	29	53%	16	55%

Table 5: Metals Associated with Positive Patch Tests

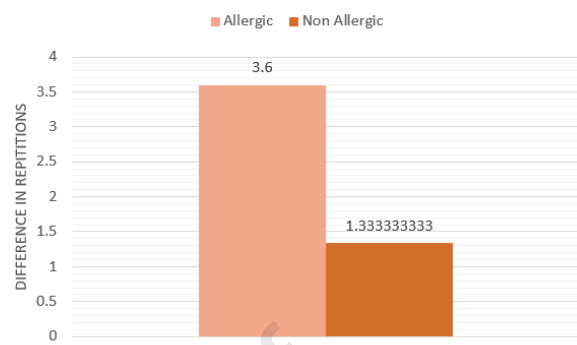
Metal	Count	Percent of Positive
ammonium tetrachloroplatinate	1	1%
niobium	1	1%
zirconium	1	1%
copper	2	3%
vanadium	2	3%
titanium	2	3%
tantalum	2	3%
manganese	2	3%
tungstein	2	3%
platinum	4	6%
gold	4	6%
zinc	5	7%
palladium	5	7%
potassium dichromate	6	9%
cobalt	7	10%
nickel	22	32%



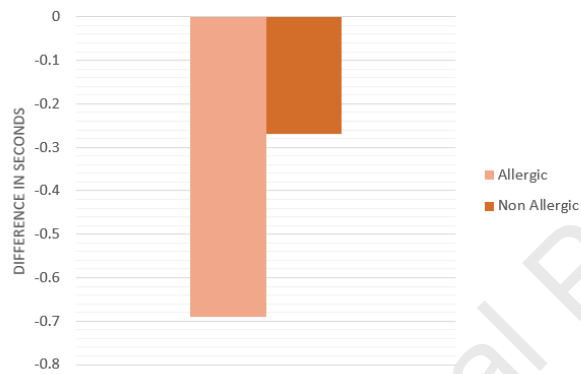
Timed Up and Go



Thirty Second Sit to Stand



Four Meter Walk



Symptom Score

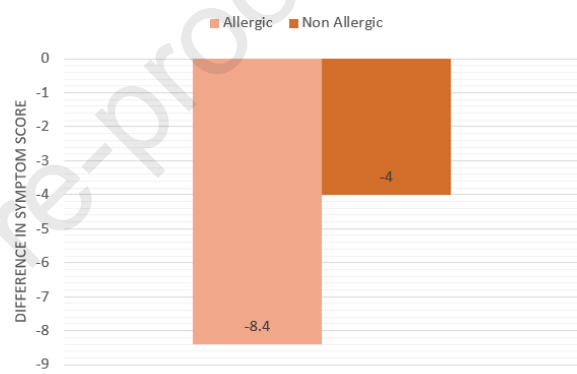


Figure 1: Example Results

1A: Strong reaction to aluminum, silver nitrate, intermediate reaction to cobalt, gold

1B: Strong reaction to nickel, intermediate reaction to palladium, weak reaction to vanadium and zinc.

1C: Strong reaction to cobalt, nickel, intermediate reaction to copper, weak reaction to wolfram, iridium, tantal, tin, manganese.

Figure 2: Receiver Operating Curve

False positive rate compared to true positive rate of metal patch testing results for patients with hip and/or knee arthroplasty.

Figure 3: Outcome Measure Graphs

Difference in preoperative and three-month postoperative outcome measures of patients with positive patch testing (Allergic) compared to patients with negative patch testing (Non Allergic).

Figure 1A



Figure 1B



Figure 1C



eTable 1: Common Causes of Prosthetic Joint Failure

Cause of Failure	Approximate Frequency
Intra-articular	40-50%
Infection	1-3%
Aseptic loosening	10%
Instability	1-2%
Malalignment	1-2%
Wear/Mechanism Failure	20%-30%
Peri-articular	20%-30%
Fracture	0-1%
Bursitis/Tendonitis	19%
Extra-articular	20%-30%
Distal/Proximal Joint Pathology	25%
Vascular Claudication	0-1%
Complex Regional Pain Syndrome	0-1%

Reviewer 1: 1/ A table of the common causes of joint failure would be useful to the reader

Response: See included eTable1, additional references 27/28 included for additional frequency data.

Table 6: Common Causes of Prosthetic Joint Failure

2/Did patients with a combination of rash, pain, and a prior reaction to metals have a higher positive predictive rate than each individually

Response: No. Analysis of that data as aggregate did not significantly change the analysis. This was related that the majority of patients with previous history of reactions to metals were presenting with symptoms of rash, pain more frequently than those without.

3/ Line 111 Reviewing... The sentence needs to be rewritten

Response: Line 127A total of 94 patients within the initial query were identified as having undergone metal testing related to metallic implants and were the primary focus of this investigation.

4/ Line 147 Regarding... The sentence needs to be rewritten

Response: (Line 165)Additionally, patients within the allergic group had statistically significant improvement as compared to the non-allergic groups by a mean reduction of 8.4 points (95% CI -12.68:-4.11) versus 4 points (95% CI -7.04:-0.92).

5/ Line 162 prostheses

Response: adopted revision (Line 180)

6/ What % of patients also had lymphocyte transformation testing?

Response: No patients underwent lymphocyte transformation testing within our cohort. Other researchers have addressed this (ref 15) and this would be an interesting aspect to evaluate prospectively.

7/ It would be interesting if combined use of patch testing combined with lymphocyte transformation testing (either blood or synovial fluid or both) would help sensitivity and specificity

Response: We agree and are looking into protocol designs to incorporate this.

Reviewer 2: Line 18- replace proved to me with "proved to be"

Response: adopted revision (Line 18)

Line 88- could the authors clarify why they assumed patients who had no "reactions" to metals and negative patch testing to be true negatives. As you describe true negatives were defined as those without history of previous reactions to metals and negative patch testing, however was this population not picked from "patients seen by the Department of Allergy and Clinical Immunology,

having an associated diagnosis of irritant contact dermatitis to metals"? Meaning that all the patients you reviewed had been deemed, by a physician, based on history, to have suspicion of joint replacement failure due to metal hypersensitivity. So if their patch testing was negative, what made the authors assume, that they were a true negative, considering the mere fact of being evaluated with the above codes, meant they had been deemed to have query metal allergies. Is it perhaps patients who only had pain and premature joint failure, where other causes were ruled out? If so can you clarify this. The authors even say, earlier in the article, that there are "concerns that dermatologic testing may not truly represent the synovial manifestations of allergy", so how can they go on to confidently describe the above patients as true negatives. I understand these are limitations to the study, but I think it would be important to address this, and how this affects the outcomes of the study. Also how do the sensitivity and specificity of this study compared to sensitivity and specificity of patch testing to other common allergens?

Response: Line 61 An associated diagnosis of irritant contact dermatitis to metals (ICD-10: L24.81) was used because several insurance companies required this diagnosis for reimbursement, and to isolate individuals who were specifically evaluated for metal allergy. It should be noted that this diagnosis was not pulled from a patient's past medical history, but from the associated visit diagnosis. Additional criteria for patient record selection included an encounter by the Department of Allergy and Clinical Immunology and having an associated procedure code for patch testing (72326). These records were then reviewed for patient age, biologic sex, referring specialty, previous history of reaction to metals, symptom of joint failure, type of metallic implant, patch testing results, revision status, and surgical outcomes for hip and knee implant patients. The identification of an individual's history of reactions to metals, separate from the diagnostic code utilized in the initial data acquisition, was used to identify patients who would represent true positive, and conversely true negative results by the presence or absence of historical reactions to metals. Patients with isolated symptoms of joint failure without dermatitis, and no previous reactions to metals were considered to have no history of previous reactions to metals. Additionally, it is the practice standard of referring surgeons to evaluate for all other etiologies of premature joint prosthetic failure prior to metal allergy evaluation.

Response Line 105: Given that the patch testing system utilized in this study contained metals that are epidemiologically associated with a greater frequency of reactions, it was felt that those with history of previous reactions to metals would more uniformly react to the patch test panel allowing for more accurate statistical analysis.

Response Line 191: Previous literature has suggested that patch testing can have a diagnostic specificity and sensitivity of approximately 70%-80%, however, is variable depending on the material in question.

Line114- remove where, should read "81% of patients (n=75) were referred by orthopedics with the remaining 7% (n=7) and 12% (n=12) referred by neurosurgery"

Response: removed sentence: 81% of patients (n=75) were referred by orthopedics with the remaining 7% (n=7) and 12% (n=12) were referred by neurosurgery or "other" (dental, cardiology) respectively.

Line 119- The study creates a nice profile of patients to consider for patch testing to metals, in prosthesis failure. The authors state that "history of previous reactions to metals, rash, and pain were more likely to be associated with positive patch testing results" Perhaps it would be prudent to mention positive likelihood ratios of patch testing in this population to predict post test odds? Something to consider if you feel this is an appropriate analysis tool.

Response: The positive likelihood ratios are LR+ 1.76 when looking at all individuals patch tested. When breaking down patch test results among the hip and knee cohort, isolating weak positive (1+) reactions to stronger positive reactions (2+/3+) the positive likelihood ratio is 2 and 4 respectively. See text:

Line 98: Positive likelihood ratios were generated from values of sensitivity and specificity of metal patch testing performance.

Line: 151: Metal patch testing, in general, revealed a positive likelihood ratio of approximately 2. When stratifying testing performance by the magnitude of reaction, we found that weak positive (+) reactions share a similar positive likelihood ratio, however, more strong positive reactions (++,+++) had a higher likelihood ratio of approximately 4.

Line 137- please define what is meant by "more strongly positive patch testing results". You also later mention that there is "lack of correlation of symptoms despite weak or strong patch test results", so what clinical utility does this have?

Sentence now reads: Line 150: Interestingly, it appeared that the testing performance improved among patients with intermediate (++) and strong (+++) patch testing results when comparing true positive and false positive rates.

Revision line 178: Goal of previous sentence was to highlight previous literature discussing poor predictive value of patch test to determine symptomatic joints. Now reads:

Line 200: Although patch testing is relatively inexpensive and non-invasive it has several limitations including bias related to the provider interpreting the patch testing results, limited testing performance of cutaneous patch testing, in general, and that metal sensitization has been observed more frequently in patients with unstable joints, however, is unable to accurately predict unstable joints in symptomatic patients.^{21,22}

Line 188 - sentence too long, would recommend breaking it up for clarity. Suggest. "Other modalities of aiding the diagnosis include; lymphocyte transformation assays, cytokine assays, and cellular

microscopic techniques. However, none of these assays have been validated, are often discordant with patch testing and do not have predictive values associated with their performance"

Response: adopted revision (Line 211)

Other modalities of aiding the diagnosis include lymphocyte transformation assays, cytokine assays, and cellular microscopic techniques. However, neither of these assays have been validated, often are discordant with patch testing, nor have predictive values associated with their performance.ⁱ

194-comma after hypersensitivity

Response: adopted revision (Line 218)
