Effect of Nickel Sensitivity on Patient Reported Outcomes after Total Knee Arthroplasty

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Research Protocol

Title: Effect of Patient-Reported Nickel Sensitivity on Patient Reported Outcomes after Total Knee Arthroplasty

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Purpose: The purpose of this study is to compare patient reported outcomes after total knee arthroplasty (TKA) in patients with self-reported metal/nickel sensitivity who receive standard of care cobalt chrome femoral implant vs standard of care nickel free oxidized zirconium femoral implants.

Hypothesis: There will be no difference in patient reported outcome scores in patients with self-reported metal sensitivity who receive standard cobalt chrome implant vs standard of care nickel free implant for primary total knee arthroplasty.

Background:

Metal implants are a mainstay of orthopedic treatment, and a variety of metal implants have been utilized for more than 40 years. Total knee replacement implants have been comprised of a variety of metal, ceramic, and plastic components. Current standard of care for TKA employs a cobalt chrome alloy femoral implant that articulates with the polyethylene surface of the tibial component. This cobalt chrome alloy can contain up to 1% nickel.1

While most patients report pain relief and satisfaction after TKA, there are a number of complications that can result. Infection, component loosening, polyethylene wear, and malalignment are common reasons for persistent pain after TKA. Metal sensitivity as a cause of persistent pain after total joint arthroplasty is a controversial topic. Cutaneous metal hypersensitivity has a prevalence of approximately 10-15% in the general population, with nickel being the most common metal sensitizer with a prevalence near 14%.2,3 Cross reactivity with cobalt chrome and nickel is very common. The role of metal allergy in orthopedic surgery and total joint arthroplasty is a poorly understood relationship. It is generally thought to be a Type IV hypersensitivity reaction

with delayed cell mediated response.4 The cause and effect relationship of this process has not been delineated – it is unclear if the immunogenic response causes implant failure, or implant failure releases happen particles with lead to a deep tissue reaction.5 The reaction occurs when wear osteolysis produces small metal ions that bind with host proteins, creating an immunogenic metal-peptide complex. Metal hypersensitivity after TKA is a rarely documented phenomenon without specific diagnostic criteria, and there is much debate on if this is even a true diagnosis.6,7 The two most commonly described presentations include 1) dermatitis or 2) persistent painful synovitis6,8 although these have only been described in case reports without defined diagnostic criteria. Few reports exist regarding the diagnosis and management of these conditions. There is no reliable or generally accepted test for allergy to total joint replacement components. Patient history of metal sensitivity is not a reliable indicator of TJA outcome, as 25% of patients with well-functioning TJA implants have a reported metal allergy.2 A nickel or metal sensitivity has not been statistically identified as a risk factor for any specific cutaneous or deep tissue reaction, complication, or poor outcome after TKA.

Typically, metal sensitivity patients are identified after having a superficial skin reaction after dermal contact with a metal. Nickel containing jewelry is a common precipitator. The true diagnosis of skin sensitivity to metal is diagnosed by cutaneous patch testing, often employed by dermatologists. This test is not specific or sensitive for the diagnosis of deep tissue metal sensitivity. In a case control study, Granchi et al followed 94 patients without metal implants, with stable painless TKA, and with TKA and evidence of loosening. The study found no predictive value in dermal patch testing for metal hypersensitivity and the stability of TKA implants.9 Verma et al followed 30 patients with dermatitis following TKA.6 Fifteen were available for patch testing, but only seven patients tested 1+ or 2+ reaction to a metal. Dermatitis in all patients cleared with topical steroid. The relationship between positive patch testing and clinically relevant deep tissue reactions has not been delineated.4

Lymphocyte transformation testing (LTT) or lymphocyte stimulation testing involves obtaining patient lymphocytes from a peripheral blood draw, and testing reactivity with a variety of antigens, including cobalt, nickel, and zirconium. Many argue that this test better replicates the sensitization that occurs in deep tissue

after TJA, but its correlation to outcomes after arthroplasty has never been shown.2,4,10 Niki et al preformed lymphocyte stimulating testing on 92 patients (108 knees) undergoing primary TKA. 24 patients tested positive for metal hypersensitivity. Ultimately only five went on to develop dermatitis.11 Thus the clinical significance of positive results of lymphocyte stimulation testing is still unknown.

Additionally, serum metal levels are often elevated in patients with well-functioning TKA, and thus this test is not recommended for diagnosis of metal sensitivity.4 As a result, other causes such as infection, malalignment, aseptic loosening, referred pain, or systemic pain syndromes should all evaluated in persistently painful TKA.

At this time, metal sensitivity is not considered a significant cause of TKA failure. As the literature is inconclusive on identification and management of patients with metal hypersensitivity there is currently no indication for metal allergy screening prior to TKA. No study has found that patients with a previously known metal sensitivity have an increase rate of failure or revision TKA compared to those without. None of the major academic orthopedic societies recommend routine use of nickel free implants. There is currently no data showing correlation between nickel allergy and poor outcomes after total joint replacement with nickel containing implants. While non-nickel containing TKA implants have been developed, there is no evidence-based criteria for their use in specific patient populations.1,12 The goal of this study is to compare Knee Society Scores in patients with self-reported metal allergy who receive standard of care nickel containing implants vs oxidized zirconium nickel free implants for primary TKA.

Study design: Prospective randomized controlled trial

Inclusion criteria: - Patients with self-reported nickel allergy

- Patients undergoing primary total knee arthroplasty

- Age > 18 years

Exclusion criteria:

- Patients undergoing revision TKA

- Non-English speaking patients

- Medical comorbidities preventing TKA

Patients and protocols: Patients will be recruited from the practices of three fellowship trained orthopedic surgeons at Rush University Medical Center. It is standard of care that patients undergoing total joint arthroplasty are asked to fill out a questionnaire prior to the first clinic visit. This includes a question regarding metal/nickel sensitivity. If patient's response is "yes" to this question, they will be eligible for the study. Patients will be presented the study in clinic and consented. Patients will be introduced to the study in the clinic and consented. However, for telemedicine visits or patients who sign up after the in-person visit, they will be contacted via telephone. An eConsent will be sent via Patient IQ, allowing ample time for the patient to accept or decline participation.

Patients enrolled in the study will be scheduled for TKA based on surgeon and patient availability and patient preference, per normal clinical practice. All patients will receive preoperative cutaneous patch testing and lymphocyte transformation testing for nickel reactivity, paid for by The Department of Orthopedics. No additional costs will be incurred by the patient. Patients will be randomized to receive a standard of care femoral implant (cobalt chromium) or an oxidized zirconium (nickel free) implant at the time of surgery. Operative technique will be unchanged. Surgical incisions will all be closed with sutures, not staples, as surgical grade staples can contain nickel. Patients will be blinded to the type of implant that they received.

Patients will attend their regularly scheduled clinical follow up appointments at 3 weeks, 6 weeks, 1 year, 2 years, 5 years, and 10 years. It is currently standard of care that patients complete the Knee Society Score (KSS) and Koos Jr patient reported outcome measures that these visits. These PROMs will be collected to compare outcomes for those patients who received standard implants vs nickel free implants. The nurses obtaining this PROMs will be blinded to the type of implant that the patient received.

Sample size:

The minimal clinically important difference for the KSS is 6 points. Power analysis based on detection of a minimum 6-point difference and assuming a standard deviation of 10 points, the study would require 45 patients per group (90 total) to

achieve 80% power. To account for 20% loss to follow up, a total of 54 patients per group (108 total) would be required.

Demographics/patient specifics: Age, sex, ASA score, medical co-morbidities, weight, height, preoperative pain scores, hospitalization days, BMI, postoperative pain scores All pain scores are measured as a part of the KOOS Jr Score

Primary outcome measure: Improvement from pre-operative to post-operative Knee Society Score

Secondary outcome measures:

1. Postoperative Inpatient Pain Scores
    a. KOOS Jr
2. Postoperative Outpatient Pain Scores
    a. KOOS Jr
3. Complications
    a. DVT or PE
    b. Return to the OR within 90 days
    c. Re-admission within 90 days
    d. Superficial infection
    e. Deep infection
    f. Dermatitis
    g. Periprosthetic fracture
    h. Cerebrovascular accident or Transient ischemic attack
    i. Dislocation

Outcome measurements will be assessed at the final preoperative visit as appropriate, prior to intervention, and postoperatively at 3 weeks, 6 weeks, and 1 year, 2 years, 5 years, and 10 years.

Risks/benefits: Cobalt chromium implants, which contain up to 1% nickel, are the standard of care implant used in all TKA patients, irrespective of self-reported metal sensitivity. A nickel or metal sensitivity has not been statistically identified as a risk factor for any specific allergic reaction, complication, or poor outcome after TKA. Therefore, participation in this study does not involve any additional implant specific risk. The rest of the surgical care, hospital stay, and rehabilitation protocol will be standard of care and not affected by the research study.

A risk inherent to every study is the potential for breach of confidentiality and/or privacy. Below is a description of the procedure for maintaining confidentiality. Patient may have improved outcome from a nickel free implant.

Procedures for maintaining confidentiality: A breach of confidentiality and/or privacy is a risk of this study. To prevent this, all collected data will be stored electronically in password-protected files to protect patient identity and information. All information will be collected and reviewed by the research team only. Data will be maintained on a password-protected computer that will be accessible only to the study team. No patient identifiers will be maintained in the database.

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