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Research Article

Clinical Multi-Directional Instability Associated with Metal Ion Allergy Mimicking Infection Following Primary Total Knee Arthroplasty

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Keywords

- Multi-Directional Instability (MDI)
- Primary TKA
- Hypersensitivity
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Abstract

Patients can experience multiple issues following a primary Total Knee Arthroplasty (TKA). The causes of pain and swelling include infection, component loosening, Multi-Directional Instability (MDI), and arthrofibrosis. MDI following a primary TKA is a clinical syndrome characterized by global ligament laxity, pain while getting up from a seated position, audible clunking of the implant, a feeling of instability in gait, and a warm knee effusion. Furthermore, patients with metal allergies may be at a higher risk for a failed primary TKA possibly secondary to arthrofibrosis. In this study, patients presenting with clinical MDI following a primary TKA were subject to a Metal-Lymphocyte Transformation Test (metal-LTT) to determine any hypersensitivities to specific metal ions commonly seen in primary total knees. Those patients with metal hypersensitivities who elected to have a total knee revision using a Zirconium or Niobium prosthesis were then included in the patient population in this study for statistical analyses. Current research has not yet elucidated a relationship between multi-directional instability following a primary TKA and metal allergies, however, of the 190 patients experiencing MDI, 157 patients tested positive for metal hypersensitivity to their implant. The Nickel allergy with MDI is gender specific. The p-value < .001 for both the nickel allergy and the gender. Metal hypersensitivities to knee implants potentially factor into the development of MDI in patients with primary TKA implants, however more research is necessary to elucidate a cause or effect relationship between metal hypersensitivity and MDI.

INTRODUCTION

Patients with problems related to their primary TKA most commonly present with stiffness, pain, and swelling [1] Additionally, the most common causes of the aforementioned problems are arthrofibrosis, infection, component loosening, and multidirectional instability (MDI) [2]. MDI of the knee joint is a clinical syndrome involving increased laxity of the MCL and LCL leading to effusion and hyperemia around the joint [2]. Clinical MDI following a primary TKA is characterized by increasing pain when standing from the seated position, audible clunking of the implant, feeling of instability by the patient and opening of the joint after varus and valgus stress. Furthermore, the degree of laxity of the knee joint is directly related to the level of force applied during varus and valgus stress testing [2]. To properly evaluate the cause of the problems with a primary TKA, CBC, X-ray (XR), CT, bone scan, White Blood Cell Scans (WBC Scan) and physical diagnostic exams should be conducted [3]. Problems associated with primary TKA that require surgical revision are uncommon.[3-5] Surgically, if a thickened plastic insert is placed, the instability symptoms recur shortly thereafter in this group of patients. Surgical fixation of the instability necessitates a hinged prosthesis to provide stability and promote functionality. Furthermore, MDI in patients following a primary TKA is clinically observed in 1-3% of patients [4-7]. The cause of MDI is important for proper treatment [1]. If MDI is left untreated, the symptoms will get worse ultimately leading to an exchange of the joint.[6] It is common for infection or component loosening to cause MDI, however if the subsequent treatment does not improve the condition, other etiologies, such as metal allergy, need to be explored as the causative reason [1].

Metal sensitivities appear in less than 10% of the general population with Nickel being the most common allergy [2,8,9]. Furthermore, the prevalence of hypersensitivity varies on where the allergen is present. For example, patients exhibiting hypersensitivity on their skin may not experience such a reaction when a prosthetic joint is implanted [8,9]. Patients hypersensitive

to the implant will exhibit a Type IV allergic reaction, otherwise known as delayed cell-mediated response [3]. The delayed cell-mediated response leads to T cell activation which results in pain and tissue inflammation in the hypersensitive area [3]. Therefore, the symptoms of the immune response in the hypersensitive area mimic symptoms of infection [1]. Modern technological advancements have made metal allergy tests quicker and more accurate, making the test an effective research tool with future promise for diagnostic purposes given the increased awareness of metal allergy in the orthopedic community [2]. Prostheses made from different metals are now available for patients given the growing data about metal allergies [3]. Furthermore, the anecdotal evidence is showing a positive patient response following the revision of the primary TKA with a metal the patient is not allergic[3].The purpose of this study is to highlight a correlation between patients experiencing MDI and metal allergy related to their TKA.

METHODS

Study design and setting

This study was retrospective and case controlled. Patients with issues regarding their primary TKA were referred to the author. Between December 2015 and May 2020, patients with clinical MDI of their primary TKA were given a metal allergy test (metal-LTT) and patients with hypersensitivity were recommended the use of a Zirconium or Niobium prosthesis. Any patients presenting with clinical MDI of their primary TKA associated with metal hypersensitivity were noted in the Electronic Health Record for data analysis.

Participants/studysubjects

Patient identification for the study was based on multiple criteria. First, all patients must have problems related to their primary TKA. Then, the patient must present with the clinical syndromes of MDI; pain when getting up, audible clunking in the primary TKA when walking in full extension, effusion with hypertrophic synovium, feelings of instability during gait, and medial and lateral opening of the prosthetic joint upon varus and valgus stress. Patients that met the above criteria were subjected to extensive evaluation including laboratory studies and diagnostic tests to rule out the possibility of infection and prosthetic loosening as the cause of the MDI.

Description of experiment, treatment, or surgery

Metal Allergy Test: Proliferation Assay (Lymphocyte Transformation Tests): Proliferation of cells is measured by [3H]-thymidine incorporation into DNA in a 96-well microplate. The average for each treatment is normalized to that

of the negative control (no treatment) producing a ratio, generally termed a proliferation factor/index/ratio or stimulation index (SI). The SI is used to compare lymphocyte reactivity among different metals. The lower limit of this stimulation index is zero indicating all cells stopped dividing before addition of [3H]-thymidine, after 5 days. Proliferation assays using Ficoll separated peripheral blood mononuclear cells (PBMCs) collected from 30-40 milliliters of peripheral blood. These isolated PBMCs are cultured in 96-well cell-culture plates (Sigma), at a density of 0.1-0.3x10^6 cells/well for a period of 6 days in 150 mL of DMEM/well, 10% autologous serum at 37degrees C and 0.5% CO_2, with metal treatments, a positive control (0.01 mg/ml PHA) and a negative control (untreated). Each treatment is conducted in triplicate (3 wells/treatment). [3H]-thymidine is added during the last 12 hours of incubation after 5 days of treatment. At day six [3H]-thymidine uptake (1 m Ci/culture well) is measured using liquid scintillation. SI is calculated using measured radiation counts per minute (cpm): Simulation Index = (mean cpm with treatment) / (mean cpm without treatment). Six days of incubation are chosen to reproduce the DTH response. Stimulation indices of 2-4 indicate mild reactivity, 5-8 moderate reactivity and above 8 high reactivity to metals [10].

Diagnosis: Primary TKA patients presenting with the clinical syndromes of MDI were evaluated with CBC, preoperative XR, CT, bone scan, and WBC Scan. These results, in addition to the metal-LTT were examined to rule out other pathologies that could account for the patient symptoms. For patients with MDI associated with a metal hypersensitivity, and no evidence of another cause of MDI, the patient was recommended a surgical revision of the prosthetic device with a total Zirconium or Niobium replacement. Post-operative XR taken to show proper fixation and positioning during follow-up. Figures 1 and 2 show the standard evaluation patients receive to work-up the diagnosis of MDI with metal allergy and postoperative imaging.

Surgical Revision: All of the primary joints were well cemented without evidence of loosening on x-ray or CT. The primary joints were removed followed by debridement and excision of the hypertrophic capsule. The inflamed collateral and cruciate ligaments were also excised. The metal implant, determined based on the individual patient's allergy, was revised with a revision hinge. All components but the patellar component were exchanged. Each component was fit specifically to the physical dimensions of bone loss caused by the revision in the patient.

Description of follow-up routine

Patients electing for the revision were placed on antibiotics for one day and followed up postoperatively two weeks, three months, six months, and one year. After which, the patient is followed up on a yearly basis.

Variables, outcome measures, data sources, and bias The variables studied were if the patient presented with MDI following a primary TKA, if the patient was hypersensitive to any metals, the gender distribution of the metal allergies, and the specific metal causing the hypersensitivity. Predictors of MDI are the following clinical syndromes: pain upon getting up, audible clunking of the prosthetic when walking, effusion with a hypertrophic synovium, feelings of instability during gait, and medial and lateral opening due to varus and valgus stress. Patients with these symptoms and a positive metal hypersensitivity were included in the study. A misdiagnosis of the cause of the MDI is the primary confounding variable. Metal hypersensitivity was determined based on metal allergy testing described above. In addition, CBC, XR, CT, WBC scans and bone scans were performed to rule out potential confounders (infection or prosthetic loosening). Complete physical exam, applied by board certified orthopedic surgeons, was used to determine the presence of symptoms associated with MDI. Multidirectional instability was diagnosed by accounting for each patient's history, symptoms, physical examinations, and diagnostic/laboratory reports.

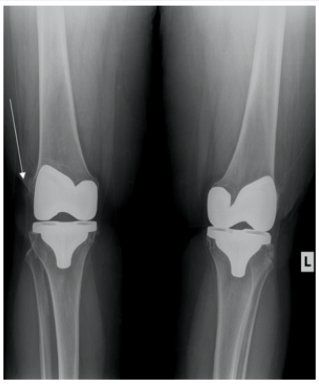

Figure 1a: Pre Op AP XR view of bilateral knee joints showing well-fixed components with heterotopic bone on the R knee* (arrow)

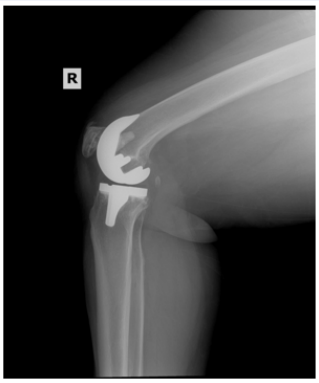

Figure 1b: Pre Op Lat XR view showing well-fixed components

*R knee was the symptomatic joint

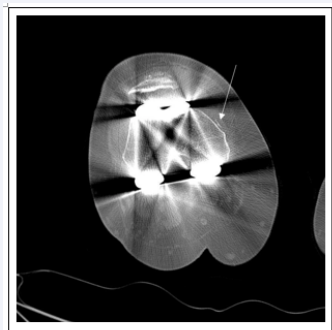

Figure 1c: CT femoral component showing adequate fixation with no signs of radiolucency and focal areas of calcification in the medial collateral ligament (arrow).

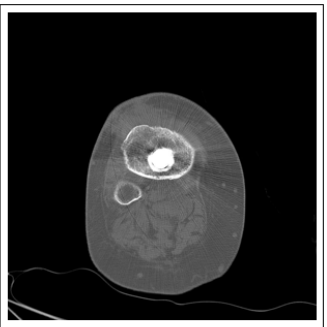

Figure 1d: CT Tibial component showing adequate fixation with no signs of radiolucency.

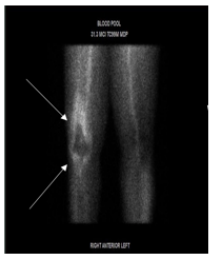

Figure 1e: Bone scan vascular phase demonstrating increased uptake and reaction in both the tibial and femoral components (arrows).

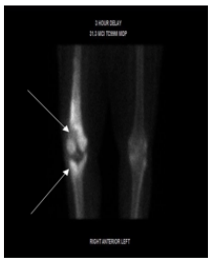

Figure 1f: Bone scan delayed phase demonstrating increased uptake and reaction in both tibial and femoral components (arrows).

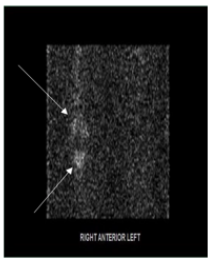

Figure 1g: Positive WBC Scan showing increased uptake in femoral and tibial components (arrows).

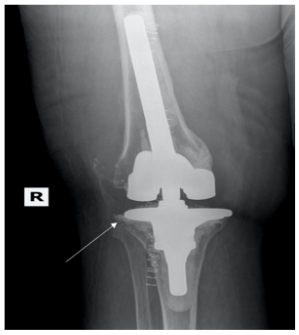

Figure 1h: Post op AP XR showing well-fixed prosthesis utilizing a hinge mechanism showing antibiotic pellets (arrow).

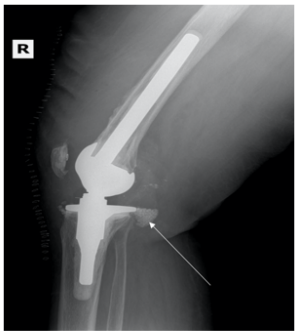

Figure 1i: Post op Lat XR showing well-fixed prosthesis utilizing a hinge mechanism showing antibiotic pellets (arrow).

Figure 1

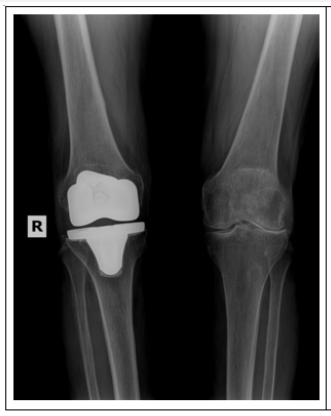

Figure 2a: Pre Op AP XR showing well-fixed prosthesis without bony deformities.

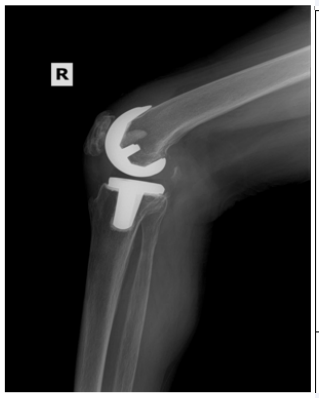

Figure 2b: Pre Op Lat XR showing well-fixed prosthesis without bony deformities.

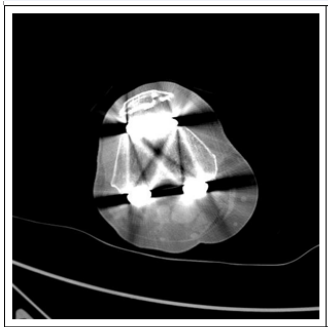

Figure 2c: CT femoral component showing no evidence of prosthetic loosening.

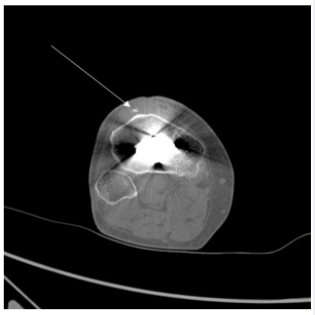

Figure 2d: CT tibial component showing adequate fixation with heterotopic bone and soft tissue reaction (arrow).

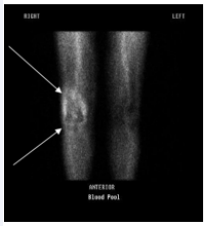

Figure 2e: Bone scan vascular phase showing increased uptake in femoral and tibial components (arrows).

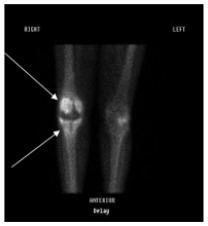

Figure 2f: Bone scan delayed phase showing increased uptake in femoral and tibial components (arrows).

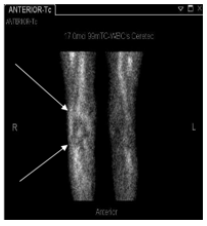

Figure 2g: Positive WBC scan showing increased uptake in femoral and tibial components (arrows).

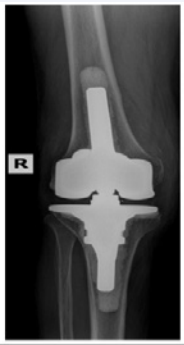

Figure 2h: Post Op AP XR showing well-fixed prosthesis utilizing a hinge mechanism.

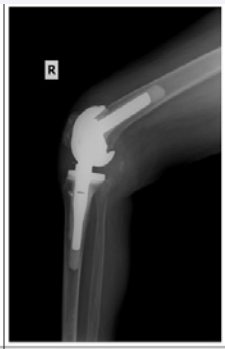

Figure 2i: Post Op Lat XR showing well-fixed prosthesis utilizing a hinge mechanism.

Figure 2

RESULTS

Of the 190 patients experiencing MDI following a primary TKA, 157 experienced a metal allergy to the prosthesis (n =190). Of the 157 patients experiencing MDI associated with metal allergies, 116 were Nickel, 8 were Vanadium, 7 were Aluminum, 7 were Zirconium, 7 were Molybdenum, 6 were Cobalt, 4 were Iron, and 2 were Chromium (n =157). Of the 157 patients experiencing MDI associated with metal allergies, 111 were female and 46 were male (n = 157).

DISCUSSION

Patients can experience complications following a primary TKA. The ability to accurately diagnose the root of the issue will lead to proper treatment and better patient quality of life. However, the most common symptoms, pain and swelling, can indicate a multitude of disorders which leads to misdiagnosis and improper treatment. MDI is one of the complications following a primary TKA and is recognized clinically as medial and lateral collateral ligament instability, pain when standing from the seated position, audible clunking of the implant, feelings of instability during gait, and opening of the joint after varus and valgus stress. Note, all patients were questioned extensively about their timeline of symptomology in this study in order to rule out other sources associated with implant failures. Almost all referrals to our institution were referred by fellowship trained total knee specialists. As a result, the patients represented in the data experienced problems associated with their primary TKA after periods of time without symptoms. Laboratory tests demonstrate normal red and white blood cell counts. Both the CT and XR do not reveal loosening of the prosthesis or disruption of the bone around the prosthesis, but effusion is seen around the area. The bone scan shows a hyper-vascular synovium represented by increased uptake on the vascular flow phase and delayed phase. Histologically, the ligaments have lymphocytic infiltrate with perivascular cuffing, chronic inflammation, and fibrosis. The gross appearance of the ligament is red due to hypervascularity and chronic inflammation. The synovium is hypervascular, again with chronic inflammation much like a polyethylene wear and debris response. For patients with MDI following a primary TKA, persistent problems and no indication of infection or prosthetic loosening could indicate a metal hypersensitivity to the implant. Intraoperatively, clinical MDI will present with medial and lateral ligament inflammation, hypertrophic synovium, and foreign bodies in the area of the prosthesis due to wear and debris. In this study, a significant correlation was found between the presentation of MDI and metal hypersensitivity in the patient population. Furthermore, a significant number of the metal hypersensitivities were nickel. The difficulty arises because the zirconium and niobium coated prostheses are not as readily available and more expensive than the nickel-alloy rotating hinges. This study found the prevalence of metal sensitivity in patients with MDI following a primary TKA to be 82.6%.This is similar to previous literature which found an average of 60% of patients experiencing poorly functioning implants with metal sensitivities [2,11] The data relating to the commonality of specific metals in patients with metal allergies also agreed with previous literature. Niki et al. (2005), Merritt et al. (1996), and Hallab et al. (2001) all found the most common sensitizer was Nickel, which our data resembles. However, previous literature has found chromium hypersensitivities to be common although very few of the patients in this study experiencing MDI registered a chromium hypersensitivity with metal-LTT [2,8,9] Regarding the type of implant used in the patients who received a revision procedure, it was in the opinion of the authors that a hinge system provided adequate stability and functionality for the patients with MDI. The data relating to the prevalence of a certain sex with metal allergy coincides with previous literature. In this study, 70.7% of the patients with MDI associated with a metal allergy were females. Previous literature noted that patients with implant issues after a primary TKA and metal hypersensitivities are a majority female [3,12-14] This could be the result of prior exposure to nickel-containing jewelry. The low prevalence of Zirconium allergy found in the patient cohort makes it a good candidate for metal prostheses in patients with metal hypersensitivities. More population-level data is needed for accurate statistical analysis of patients with aluminum, zirconium, and vanadium implants.

Recent studies have found metal-LTT as a highly sensitive test to determine allergy to an orthopedic implant [8,9,15-18] However, the metal-LTT is relatively new and does not have a foothold in standard clinical practice [15-17] Other tests are available for determining patient metal hypersensitivity, such as skin patch testing, but these tests are not sensitive for metal allergy to the orthopedic implant [8,9,15-18]. Some postulate the discrepancy in sensitivity between the metal-LTT and other tests for metal hypersensitivity, pertaining specifically to orthopedic implants, is due to a different biological environment between the skin and where the implant is fixated [15-17]. As a result, the metal-LTT measures the hypersensitivity reaction most closely related to the conditions the orthopedic implant is subjected [8,9,15-18] to It is pertinent to note that the metal-LTT is limited in terms of widespread availability and clinical applicability. Nonetheless, with regards to this specific study, the metal-LTT is the most suitable test for determining patient hypersensitivity to their orthopedic implant and allows the researchers to be more confident in the proposed correlation between metal hypersensitivity and MDI.

The bone scan and WBC Scan are important data points to consider when evaluating a patient for metal allergy versus infected TKA. Bone scans use a radiotracer that is related to blood flow with increased uptake signifying abnormal bone metabolism [19] Although not specific for the etiology of prosthetic failure, bone scans have high sensitivity for detecting a failed joint replacement [20]. WBC scans are nuclear medicine scans that show the degree of inflammation via the amount of nuclear radiotracer uptake from white blood cells in the area. Wanahita et al. (2007) found WBC scans to be highly specific for bone/joint inflammation and infection. The data found from the WBC scans support the hypothesis that metal hypersensitivity in patients with MDI of their primary TKA will mimic infection. Therefore, the high sensitivity of the bone scan paired with the high specificity of the WBC scan highlights that the patients with TKA presenting with MDI and a positive metal allergy have significant prosthetic failure and acute inflammation.

This study had a number of limitations. First, only one form of metal allergy test was performed. Other metal allergy tests involve using the dermis to test sensitivity, but the metal-LTT is believed to be the most representative of metal implant hypersensitivity since the test measures hypersensitivity in the

body and not on the dermis. Second, the patient could have been experiencing another problem with the TKA, like infection or prosthetic loosening, to compound the clinical syndrome of MDI. Nevertheless, multiple diagnostic studies were performed on each patient and interpreted by experts to minimize the potential for misdiagnosis. Thirdly, some patients with MDI following their primary TKA denied metal-LTT testing due to the associated costs. The additional patients would have increased the population size and added statistical significance. Additionally, the joint instability could be related to suboptimal ligament balancing with their primary TKA and not noticed the issues earlier on post-operatively. Also, hinged revisions generally provide more stability than other implants therefore the clinical improvement could potentially be from the hinged implant and not from removal of the offending allergen. Lastly, many of the patients did not follow-up post-operatively as extensively as the authors of the study preferred. As a result, post-operative questioning and functional evaluations were insufficient to represent the total patient population in this study.

Multiple problems can arise following a primary TKA and finding a correct diagnosis may be problematic since the symptoms associated with each problem are similar. In cases of MDI following a primary TKA, metal hypersensitivity could potentially exist as another etiology, especially when infection and prosthetic loosening are ruled out. In this study, a significant relationship was seen between patients with concomitant MDI and metal hypersensitivity. These results do not imply that metal allergies cause MDI, but that a relationship exists between hypersensitivity and MDI emphasizing the importance of continued research. These findings highlight the benefit of metal allergy testing before primary TKA and the benefit of using hypoallergenic prosthetics made from alternative metals, like Zirconium or Niobium, in order to optimize prosthetic implant success. This makes future research and design into a variety of prosthetic implants beneficial for the spectrum of patients with different metal hypersensitivities.

CONFLICTS OF INTEREST DECLARATION

Dr. Gerhard Maale: Smith and Nephew and Waldemar-Link

All other authors do not have conflicts of interest to disclose.

ETHICS APPROVAL

All procedures in this study were in accordance with the 1964 Helsinki Declaration (and its amendments) and the details of the Ethics Committee or institutional review board (IRB) which approved this study.

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