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Review article

Metal hypersensitivity in total hip and knee arthroplasty: Current concepts

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ABSTRACT

Metal hypersensitivity (MHS) is a rare complication of total joint arthroplasty that has been linked to prosthetic device failure when other potential causes have been ruled out. The purpose of this review was to conduct an analysis of existing literature in order to get a better understanding of the pathophysiology, presentation, diagnosis, and management of MHS. It has been described as a type IV hypersensitivity reaction to the metals comprising prosthetic implants, often nickel and cobalt-chromium. Patients suffering from this condition have reported periprosthetic joint pain and swelling as well as cutaneous, eczematous dermatitis. There is no standard for diagnosis MHS, but tests such as patch testing and lymphocyte transformation testing have demonstrated utility, among others. Treatment options that have demonstrated success include administration of steroids and revision surgery, in which the existing metal implant is replaced with one of less allergenic materials. Moreover, the definitive resolution of symptoms has most commonly required revision surgery with the use of different implants. However, more studies are needed in order to understand the complexity of this subject.

1. Introduction

Despite the high success rate of total hip (THA) and total knee arthroplasty (TKA),[1,2] it is estimated that 10% to 20% of lower extremity total joint arthroplasties (TJA) annually are revision surgeries due to implant failure.[3] The most common causes of failure include instability, infection, and stiffness for TKAs compared with dislocation and mechanical loosening for THAs.[4,5] However, in recent decades, attention has been drawn to metal hypersensitivity (MHS) as another possible cause of TJA failure.[6]

Metal hypersensitivity is a rare condition where the body develops an immunological reaction to the metallic portion of THA or TKA implants.[6,7] The frequency of cutaneous allergies to nickel, cobalt, and chromium in the general population, not related to arthroplasty, have been estimated to be 13%, 2%, and 1%, respectively, based on patch testing and blood analysis.[8] Moreover, since these are the same metals that many THA and TKA components are made of, it is possible that patients who have these particular allergies may develop a reaction to these implants postoperatively. Patients who have MHS may present with periprosthetic joint pain and effusions, as well as a cutaneous, eczematous rash;[9–12] however, MHS is a diagnosis of exclusion, since the current methods of testing lack adequate sensitivity and validity.[7]

Although the condition is rare, the number of TJA patients that test positive for MHS has increased over the past two decades.[1] The prevalence of cutaneous MHS in the general population is estimated to be 10% to 15%, while prevalence in patients with metallic implants may be as high as 25%.[13,14]. Furthermore, the prevalence of cutaneous MHS in patients who had a malfunctioning prosthesis was estimated to be as high as 60%.[13] However, the degree of association between MHS and TJA failure is currently unclear.[15] Therefore, the purpose of this review was to evaluate the current literature for MHS related to TJA, specifically focusing on general allergic hypersensitivity reactions, in order to provide a better understanding of the pathology. We specifically reviewed: 1) basic science; 2) clinical syndromes; 3) diagnostic measures; and 4) management of TJA-related MHS.

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1.1. Basic science

All metals experience some degree of corrosion when placed in contact with biological systems.[13] Osteoclasts have been observed to proliferate and differentiate while adsorbed to prosthetic metallic surfaces, actively degrading the material and releasing ions into surrounding tissues and joint space.[16] Metallic ions may then act as haptens, which interact with proteins to form antigenic complexes that stimulate the body's inflammatory response.[1]

Metal hypersensitivity is defined as a type IV hypersensitivity reaction, which means that the body's response is through a delayed cell-mediated response,[1] where the antigenic complexes are first processed and presented to CD4+ T-lymphocytes by antigen presenting cells (APCs), which includes endothelial cells, macrophages, dendritic cells, or other immune cells found within synovial tissue.[13,14] The interaction between APCs and T-helper cells results in the subsequent activation of both CD4+ and CD8+ cells, as well as macrophages that release pro-inflammatory cytokines, including interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ,[14,17] which results in an adaptive immune response that may damage tissues and result in the symptoms associated with MHS.[6] This mechanism of MHS differs from those seen with aseptic lymphocyte-dominated vasculitis-associated lesions and pseudotumors that occurs with adverse local tissue reactions that result from metal-on-metal THA implants.[18,19]

Synovial fluid analysis of patients who have presented with MHS have been reported to have an increased concentrations of macrophages, polymorphonuclear leukocytes, and lymphocytes.[20] Moreover, histologic analysis of the synovial membrane can demonstrate granulation tissue and fibrosis, along with numerous giant cells and calcification.[20] Lymphocytic and plasma cell infiltrates in the surrounding synovial tissue have also been reported, and are indicative of a chronic inflammatory response that can be consistent with synovitis.[7]

1.2. Clinical syndromes

Metal hypersensitivity has been reported to be more common in women, and has been shown to occur between two months and two years postoperatively.[6,7] Patients typically present with periprosthetic synovitis and swelling, and less frequently with an eczematous dermatitis that may be local or generalized.[7,9,10] The synovitis may present as pain that may be of burning quality, effusion, swelling, stiffness, and/or limited range of motion[7,9] and the dermatitis can be characterized as an erythematous, papular, pruritic, and scaly rash that may produce exudate.[6,11,12]

A study by Verma et al.[12] reported on 15 TKA patients who developed cutaneous eczematic eruptions within 3 months of TKA. The rash was contained to the outer aspect of the knee in all cases, just lateral to the anterior midline incision.[12] Similarly, Gao et al.[21] reported on a case in which a TKA patient developed eczematous lesions on the skin surrounding the operative scar within 6 months after surgery. Given that these symptoms appeared postoperatively and all other potential causes had been ruled out, MHS was suspected.[21] The lesions subsequently spread to the neck, buttocks, upper extremities, and ankles over the subsequent 3 months, and resulted in a chronic and recurrent dermatitis.[21] Interestingly, there has been one reported case of a systemic response in which a TKA patient with suspected MHS developed a full-body dermatitis and alopecia.[22]

Although both TKA and THA patients may present with joint pain and swelling, the cutaneous reaction is not common among THA patients.[23,24] In a study that reported on 4 THA patients who had a suspected MHS, symptoms ranged from localized swelling to groin pain that worsened with walking.[25] Additionally, osteolytic lesions in the proximity of the hip or knee implant may also be appreciated on radiographic images as a result of the inflammatory response and might result in aseptic loosening of the implant.[6,20,24]

1.3. Diagnosis

Metal hypersensitivity has been reported to be a diagnosis of exclusion,[26] and should be considered when other causes of implant failure, including but not limited to infection and aseptic loosening, have been ruled out and inflammatory markers (CRP and ESR) and joint aspiration have demonstrated negative results.[7,27] Although no established standard for diagnosing MHS exists, skin patch testing, lymphocyte transformation testing, modified lymphocyte stimulation testing, and leukocyte migration inhibition testing have shown utility.[1,10,13]

Skin patch testing is performed *in vivo* by preparing aqueous solutions of various metals, incorporating each into petroleum jelly and each mixture is applied to patients' skin via adhesive tape for up to 4 days.[27] Then, the patches are removed and cutaneous reactions are graded on a severity scale based on the presence of erythema, edema, papules, or vesicles.[28] In its ability to detect an allergy, patch testing has been shown to have a sensitivity and specificity of 77% and 71%, respectively.[29] However, there are several drawbacks to skin patch testing, such as the immunologic response elicited in patch testing is mediated by intradermal Langerhans cells, whereas the MHS reaction in the joint space is mediated by lymphocytes and macrophages.[27] Thus, it may not reliably predict the outcomes associated with TJA.[1] For instance, there have been cases in which patch testing revealed that patients who had received conventional CoCr implants became sensitized to the component metals, and yet, did not display any symptoms of MHS.[30] In addition, the results of skin patch testing are subjective, and therefore, the interpretation of the results can be difficult in terms of diagnosing MHS.[20] Moreover, *in vivo* performance of this test may sensitize the patient to the tested metals.[31] Despite these limitations, there is a consensus that preoperative screening should be performed in patients who have a history of metal allergy, such as through contact with jewelry or clothing accessories,[1,6] and if the patient tests positive for a metal that is present in the prosthetic component that is planned to be used, the use of a component made of hypoallergenic materials, such as titanium, zirconium or other ceramics, has been recommended.[1,32]

Lymphocyte transformation testing (LTT) is an *in vitro* alternative to skin patch testing and is performed by adding the potential allergen to a sample of the patient's blood and measuring the proliferation of lymphocytes in response.[33] The principle advantage of LTT over patch testing is a higher sensitivity, which has been estimated to be between 55% and 95%.[34,35] Lymphocyte transformation testing also has no potential risk for sensitization as it is performed outside the body, and it produces a quantitative set of results, which offers more objectivity.[6] Yet, there are several drawbacks to LTT such that it has been shown to have a limited specificity with no consensus as to the degree of specificity, despite the higher sensitivity relative to patch testing.[31] In addition, LTT is also limited in the number of allergens that can be assessed at one time.[33] Furthermore, while both skin patch testing and LTT are useful for evaluating patients for specific MHSs, they have not been shown to be reliable predictors of whether or not a patient will develop MHS following TJA.[1] There is also no data on their reliability in predicting success of revision TJA using hypoallergenic materials in patients with symptomatic prosthetic joints who have tested positive for MHS using these tests.

Other *in vitro* tests that have been used to detect MHS include the modified lymphocyte stimulation test (mLST) and the leukocyte migration inhibition test.[10,13] The mLST is similar to LTT in that the proliferation of leukocytes is measured upon

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