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Metal Hypersensitivity and Contact Dermatitis in Orthopedic Hardware and Biocompatible Implants

*Alyssa Cevetello[1], Janae Rasmussen[2], Rachael Larkin[3], Brandon Baek[4], Rachel Palet[5], Faaiz Ibrahim[6], Devri Langhelm[7], Kelly Frasier[8]**

[1]Touro College of Osteopathic Medicine, Middletown, NY, USA

[2]Valley Consortium for Medical Education, Modesto, CA, USA

[3]Edward Via College of Osteopathic Medicine, Blacksburg, VA, USA

[4]Touro College of Osteopathic Medicine, Middletown, NY, USA

[5]University of North Texas Health Science Center Fort Worth - Texas College of Osteopathic Medicine, USA

[6]Touro College of Osteopathic Medicine, CA, USA

[7]A.T. Still University School of Osteopathic Medicine in Arizona, Mesa, AZ, USA

[8]Department of Dermatology, Northwell Health, New Hyde Park, NY, USA

[*]Corresponding author:

Kelly Frasier
DO, MS, Department of Dermatology, Northwell Health, New Hyde Park, NY, USA, Phone: 3105956882, Email: kellymariefrasier@gmail.com

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ABSTRACT

Metal hypersensitivity is a type IV hypersensitivity reaction, which can affect hardware used in orthopedic procedures, such as total joint arthroplasty and fracture fixation using open reduction and internal fixation (ORIF). Metal hypersensitivity reactions are typically seen in orthopedic hardware containing nickel, titanium, cobalt, or chromium, as these metals have often been associated with allergies. Metal hypersensitivity reactions may present as dermatitis on the skin or as edema, which can hinder a patient's range of motion, typically localized to the affected area or joint. Often, individuals with periprosthetic joint infections or other orthopedic-related infections can present with similar dermatologic symptoms to metal hypersensitivity. Therefore, diagnosis of metal hypersensitivity is one of exclusion and has a rare reported occurrence. Treatment options for metal hypersensitivity from orthopedic hardware depends on the symptoms, types of hardware utilized (e.g. hardware utilized in fracture fixation that can be removed once the fracture heals) ranging from topical treatments for dermatitis, steroids for inflammation, and hardware removal or arthroplasty revisions. This literature review aims to further investigate reported metal hypersensitivity reactions from orthopedic hardware following total joint arthroplasty and ORIF procedures.

Keywords: Metal Hypersensitivity, Dermatitis, Orthopedic

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Hardware, Implants, Total Joint Arthroplasty

INTRODUCTION

Metal hypersensitivity is a delayed immunological response resulting from repeated exposure to certain metals. In orthopedics, metal hypersensitivity reactions may compromise the surgical hardware used in common orthopedic procedures, such as total joint arthroplasty (TJA) and open reduction internal fixation (ORIF). The immunological response seen in metal hypersensitivity reactions differs from the characteristic allergic reactions seen in those with an allergy to allergens in the environment, in food, or drugs [1]. Allergic reactions are type I hypersensitivity reactions, where there is recognition of an allergen leading to an immediate histamine release, which attracts inflammatory cells to cause an immediate inflammatory response [2]. Metal hypersensitivities (MHS) are described as type IV hypersensitivity reactions, which are mediated by delayed T-cell activation after initial sensitization to metal antigens [2]. A type IV hypersensitivity reaction is a delayed response that can occur hours to days after repeated exposure [2]. T-helper cells produce inflammatory cytokines, resulting in the recruitment and activation of macrophages [3]. MHS can present with symptoms of edema, dermatitis, loosening of hardware from osteolysis, or unexplained pain surrounding the location of the hardware [4]. MHS can occur in deeper tissues localized to where hardware is stabilized to the bone [5]. Reactions that take place in these areas can present with symptoms of pain, localized swelling, loss of range of motion, and joint effusions [5].

In TJA and ORIF, orthopedic hardware used are typically either stainless steel, cobalt-based alloys, or titanium alloys [6]. Each has its own unique properties that lead to advantages and disadvantages depending on their utilization in an orthopedic procedure. In the case of TJA, titanium is commonly utilized because of its ability to predictably oxidize and coat the implant, making it biologically inert [6]. Pairing titanium, which lies at the bone-interface, with cobalt-chrome alloys, which lie at the weight bearing surface, allows for the desirable smoothness intended in arthroplasty [6]. Stainless steel alloy implants continue to be used in a wide variety of orthopedic cases, such as ORIF, where plates and screws are utilized to fixate fractures. Titanium has a similar Young's modulus of elasticity to bone, which helps reduce stress shielding, and can help with osseous healing after uncemented arthroplasty or fracture fixation [7]. Nickel is clinically relevant in orthopedics as it can lead to MHS, and is commonly used as an alloy for stainless steel [6]. Other alloys used with stainless steel are iron, chromium, and molybdenum [6]. Stainless steel is widely utilized because of its ability to deform under stress, making it favorable for stabilizing fractures [6]. Understanding the clinical and biomechanical considerations for different materials helps improve orthopedic hardware with appropriate utilization.

The prevalence of MHS that presents as cutaneous reactions is estimated to be around 10% to 15% in the general population [8]. Allergic contact dermatitis is a form of MHS reactions, which is most commonly seen with cobalt, nickel, and chromium [9]. Notably, nickel has the highest prevalence of MHS estimated at 14% in the general population [9]. While there are documented manifestations of MHS reactions that occur cutaneously like allergic contact dermatitis or edema, there can also be a diffuse immunological response [10]. Histologic assessment of deeper tissues classically demonstrates the presence of lymphocytic infiltrate and fibrotic tissue responses [10]. Orthopedic hardware undergoes some degree of corrosion when the metal component comes in contact with surrounding tissue, leading to the release of metal ions, possibly contributing to a delayed hypersensitivity response seen in MHS [10]. The non-specific symptoms evoked from MHS reactions are nearly identical to other possible causes such as joint infections, prosthetic loosening, and mechanical failure making it difficult to distinguish one from the other. It is essential for an orthopedic surgeon to rule out other possible sources of hardware failure of cutaneous inflammatory reactions prior to a diagnosis of MHS.

This literature review aims to explore reported metal hypersensitivity reactions with its clinical impact and patient outcomes, focusing on TJA and ORIF procedures. The incidence of MHS is estimated to be lower than 1%, but given the variable criteria needed to make this diagnosis of exclusion, it raises the possibility of the true prevalence being underestimated [11]. This review will also examine case presentations to further illustrate the extent to which MHS is overlooked as a differential diagnosis of postoperative TJA and ORIF complications.

METHODS

This analysis was completed through database searches of journal articles published in the last 20 years. The databases that were used include PubMed, National Library of Medicine, Google Scholar, and ClinicalKey. This literature review included case reports, concept reviews, literature reviews, and case

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series. Keywords that were used in these searches included "metal hypersensitivity," "nickel allergy," "allergic contact dermatitis," "implant reactions," "metal inflammation," and "total joint arthroplasty." Articles were included in our analysis if they discussed contact dermatitis with the presence or absence of metal hypersensitivity reactions following total joint arthroplasty or open reduction and internal fixation procedures. In an attempt to limit biases, we searched for articles that provided current and supporting practices.

Clinical Implications and Outcomes

Metal hypersensitivity (MHS) in the context of total joint arthroplasty (TJA) and open reduction and internal fixation (ORIF) for fracture fixation has variable presentations. Reports of MHS following TJA or ORIF include skin involvement localized to the region of the hardware to systemic reactions. The most commonly reported presentation is a localized, periprosthetic cutaneous manifestation. Verma et al. reported thirty patients who developed an erythematous, papular, and scaly eczema localized to the outer aspect of the knee proximal to the anterior midline incision following TKA [12]. Researchers included that the dermatitis reactions observed erupted within 3 months following TKA [12]. Similar localized cutaneous manifestations have been reported in the context of ORIF as well. A case series by Bauman et al. reported four cases of MHS associated failures in patients who underwent ORIF throughout a duration spanning from 5 weeks post-surgery to 4 years post-surgery [9]. The authors found the most common symptom to be localized soft tissue reactions, such as delayed wound healing, with one patient presenting with a psoriatic rash 4 years following surgery [9]. Dermatologic presentations extending beyond the local soft tissue have also been reported. Phedy et al. reports a case of a systematic dermatologic manifestation associated with MHS following an ORIF [13]. The patient presented with psoriatic erythroderma involving their scalp, trunk, and upper and lower extremities in addition to the surgical wound site [13]. The author reports five episodes of such cutaneous eruptions during 7 months of postoperative follow up, each resolving within several days following topical and low-dose systemic steroids [13]. Although a causative relationship was not established, suspected MHS cases have been reported as systemic manifestations, with reactions extending beyond dermatological lesions. Kruckeberg et al. reports a patient who developed systemic hives, perioral swelling, and difficulty breathing 10 days following ORIF of an ankle fracture [14]. The author reports the patient had complete resolution of symptoms following hardware removal at 2 week, 6 week, and 12 month follow up [14]. Cases, such as the one discussed by Kruckeberg et al., underscore the importance of reviewing MHS reactions resulting from orthopedic hardware. The variability in presentation poses difficulties in deducing a diagnosis of MHS as well, which highlights the need for further investigation of the topic.

In the studies mentioned previously, treatment modality was dependent on patient presentation and the context of the orthopedic surgery. For cutaneous MHS manifestations, topical and systemic steroid use was prevalent. In cases where steroids were insufficient, hardware revision with hypoallergenic components was employed in TKAs, while hardware was removed in the context of ORIF. None of the treatment modalities are novel or specific to MHS. Treatment of MHS can pose difficulties as there remains a lack of consensus on treatment guidelines in suspected MHS following orthopedic surgery with hardware placement. One of the challenges in establishing a management guideline may be due to a lack of a reliable screening or diagnostic modalities in patients with a history of MHS or those with suspected MHS following TJA and ORIF.

Patch testing (PT) is a well-established diagnostic tool utilized to identify the etiologic agent in allergic contact dermatitis. As such, PT is the most accessible form of pre-implant testing in suspected MHS. However, limitations remain as PT lacks the ability to mimic the actual conditions of an orthopedic implant [15]. Granchi et al. demonstrated that PT provided no prognostic value prior to TKA as a positive PT was not able to distinguish between loose or a stable joint following TKA [16]. The same study did report TKA failure was fourfold more likely in patients with a known history of metal allergies prior to TKA, alluding to the fact that patient history may provide more clinically relevant predictive value [16]. A retrospective study by Keller et al. reported the predictive value of PT increased with a more robust positive PT test [17].

Another testing modality commonly encountered in MHS is lymphocyte transformation testing (LTT), which measures the proliferation of peripheral lymphocytes in response to a potential allergen after an incubation period [18]. LTT may provide greater sensitivity as it may help detect systemic hypersensitivity reactions. However, Yang et al. found no correlation between LTT scores and periprosthetic histopathologies measured by aseptic-lymphocyte-dominated-vasculitis-associated-lesion (ALVAL), suggesting LTT alone may not be a reliable diagnostic predictor of TKA failure secondary to MHS [19]. The

lack of definitive testing modalities may continue to pose a challenge in diagnosing MHS as well as establishing a treatment guideline in MHS following TJA and ORIF. There remains a lack of a consensus on a reliable testing modalities for metal hypersensitivities in orthopedics.

In the absence of other common causes of complications following TJA or ORIF such as infection, instability, or malalignment, MHS can be reasonably suspected. Diagnosis of MHS may require revisions to achieve optimal patient outcomes, but come with the associated risks of additional surgery. Zondervan et al. studied patients with pain following TKA with assessing patient outcomes following TKA revision with hypoallergenic components in patients with positive metal LTTs and patients with negative metal LTTs [20]. Researchers found that patients with positive metal LTT results had improved pain scores, walking function, and range of motion following revision, whereas patients with negative metal LTT results did not have significant improvements in their scores [20]. This renders some support for preoperative testing and use of hypoallergenic prosthetics, but there remain limitations in the generalizations of similar studies. Another similar retrospective study by Bracey et al. demonstrated contrasting results [18]. Bracey et al. reported worse outcomes measured by range of motion (ROM), Knee Society Scores (KSS), and Veterans RAND 12 (VR-12) in patients with suspected metal hypersensitivity despite use of hypoallergenic components utilized for primary TKA compared to those without MHS [18]. Researchers employed multiple testing modalities for MHS including PT, LTT, LPT, and MELISA [18]. Bracey et al. reported similar findings in patients undergoing revisional TKAs with MHS compared to those without MHS [18]. Despite the questionable predictive value of the two testing modalities, the retrospective study by Keller et al reported improved functional outcome when positive history and PT were used to guide revision in TJA [17]. These noted studies emphasize the inconsistencies in metal hypersensitivity testing modalities. They also question the utility of preoperative hypersensitivity testing modalities in clinical decision making.

Challenges and Limitations

In the setting of orthopedic hardware and biocompatible implants, metal hypersensitivity and contact dermatitis present significant challenges, especially in the accurate diagnosis of metal hypersensitivity reactions. This requires consideration of the nonspecific presentation of symptoms that usually overlap with more common postoperative complications, and has significant variability between individuals. The common postoperative complications often confusing the clinical picture include infection and mechanical failure [21,22]. Pain, erythema, and effusion are symptoms that broaden a differential to necessitate thorough diagnostic investigation, ultimately delaying treatment. This delay can also lead to unnecessary interventions, such as prolonged antibiotic therapy when an infection can't be ruled out, which will in turn complicate patient care and outcomes. Patch testing (PT) and lymphocyte transformation tests are diagnostic tools that have limited predictive value, leading to uncertainty in identifying at-risk patients [23]. Despite PT's ability to identify certain metals, it has not been trusted to predict post-implantation reactions. This unreliability is based upon differences between skin exposure and systemic immune reactions triggered by orthopedic hardware. Furthermore, underreporting and misdiagnosing is the diagnostic reality of metal hypersensitivity due to absence of standardized criteria [24]. When the literature and clinicians can confidently provide clarity to the definitive diagnoses and effective management, metal hypersensitivity outcomes will significantly improve.

The variability in patient responses to metal implants presents another challenge in metal hypersensitivity cases. Titanium is an example of a metal considered biocompatible with similar Young's modulus of elasticity to bone, yet has been correlated to some cases of allergic reactions [5,25]. Though rarely reported, these cases challenge the universal acceptance of titanium's safety, and should be a call to action for researchers and patients to advocate for answers to unexplained postoperative symptoms. This can be applied to cobalt, nickel, and chromium, as they are more commonly known to cause hypersensitivity reactions but not always develop symptoms in the patient [5]. Genetic predisposition, immune system discrepancies, or degree of metal ion release from orthopedic hardware can all contribute to the variability of symptoms. Notably, metal ions can be released into the bloodstream not only from the implant itself but also during the surgical process of inserting hardware, including drilling, cutting, and other manipulations [26]. Such intraoperative release may contribute to early sensitization in some patients [26]. This makes preoperative decision making difficult to navigate and puts the utility of preoperative screening in question. While some experts advocate for PT in patients with a history of metal allergies, others argue that it is unnecessary for asymptomatic individuals due to its limited ability to predict postoperative reactions

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[16,27]. This debate reveals the hardship in adopting preventive measures in the low prevalence of clinical significance of hypersensitivity. Additionally, the uninvestigated progression of metal hypersensitivity reactions limits the understanding of patient predicted outcomes over time, whether it worsens with prolonged exposure or remains stable [28]. Implants fail for many reasons, often involving mechanical errors, infection, or hypersensitivity, creating a multifactorial challenge to isolate the specific role of hypersensitivity in poor outcomes [28]. Management strategies are also faced with the chance of a systemic etiology, though rare [28]. Hypersensitivity caused by systemic reactions paint a non-localized clinical picture due to broad immune activation, compounding the challenge of diagnosis and treatment. Personalized treatment approaches would offer a solution to hypersensitivity patients if the future of research could clarify the multifaceted nature of implant failure and complexity of managing metal hypersensitivity.

Treatment options for metal hypersensitivity also face limitations. Localized dermatitis may be managed with topical agents or corticosteroids, whereas severe cases often require surgical intervention, such as implant revision with alternative materials [29]. While topical treatments can provide relief for mild cases, they are deemed insufficient when hypersensitivity reactions compromise the functionality of the hardware or lead to systemic symptoms. Revision surgeries, though an essential option in such scenarios, introduce significant risks and potential complications [30]. Grammatopoulos et al. compared patients who underwent revision hip replacement due to metal hypersensitivity to those who had revision hip replacement from fractures, loosening, infection, avascular necrosis, and recurrent dislocations [30]. They found an increased rate of complications for the hypersensitivity group using the Oxford hip score [30]. Fary et al. highlight how hypersensitivity and metal debris can exacerbate local tissue inflammation, leading to osteolysis and further soft tissue damage [31]. The accumulation of metal ions and wear debris from orthopedic hardware initiates an immune response, and perpetuates a cycle of inflammation and tissue destruction, which worsens surgical outcomes if left unaddressed prior to a revision surgery [31]. The lack of robust evidence-based guidelines for managing metal hypersensitivity reactions creates inconsistencies in clinical practice. For instance, while some clinicians may opt for titanium-based alternatives in patients with suspected allergies, others may not consider preemptive measures due to insufficient data supporting their efficacy [27,32]. In the setting of shoulder arthroplasty in metal-sensitive patients, Morwood et al. found titanium implants were preferred over nickel in subjects with a known history of cutaneous metal allergy, due to similar cost and lower chance of sensitization [32]. Addressing the limitations in treatment options requires a concerted effort to develop more effective and standardized management strategies for metal hypersensitivity reactions in orthopedic implants.

Future Directions

As the understanding of metal hypersensitivity (MHS) reactions associated with orthopedic hardware evolves, knowledge gaps in awareness, diagnosis, treatment, and prevention options remain. Beyond orthopedic uses, metal hypersensitivity can present in procedures in a variety of specialties, all leading to the possibility of poor patient outcomes. Dordunoo et al. conducted a study in which 90% of frontline health care workers did not routinely evaluate MHS risks when obtaining allergy history [33]. They found that 86% of these health care workers were unaware of associations between MHS and poor patient outcomes [33]. Common barriers reported by respondents included "Standards of Practice, Knowledge, and Futility of Screening" [33]. Standardized protocols are not established in screening for patients with metal allergies preoperatively, largely due to healthcare costs, and limited sensitivity and specificity of screening tools. Current protocols suggest preoperative screening should be reserved for patients with a history of metal allergy of previous aseptic implant failure [28]. Further studies may aim to determine if preoperative screening improves surgical outcomes, and conduct cost analysis of the feasibility of routine screening.

Current diagnostic methods are inadequate, with inconclusive evidence to support predictive values of screening tools, such as Patch Testing (PT) and Lymphocyte Transformation Testing (LTT) in screening for MHS [34]. PT may be most beneficial in patients with a known history of MHS, giving more predictive values with strongly positive PT results guiding clinical decision making and outcomes [17]. Future studies may focus on novel methods of detecting MHS, such as identification of specific biomarkers [35]. The use of biomarkers may guide risk assessment for MHS and enable personalized treatment options for patients undergoing procedures with metal implants.

Further advancements in development of metal implants with reduced associations with MHS may offer alternative options for improving outcomes. Ceramic coated implants are being used to reduce metal ion release into periprosthetic tissue

[36]. Lützner et al. demonstrated that plasma metal ion concentrations were not elevated one-year postoperatively in patients with total knee arthroplasty (TKA) with both CoCrMo alloy coated and uncoated implants [37]. In a noveler approach, alternative coatings are also being studied in comparison to traditional metals. Tantalum-based alloys may produce an alternative avenue based on their biocompatibility and corrosion resistance [38]. Further exploration is needed to investigate the long-term durability, safety, and efficacy of these alternative implant options for those with metal allergies.

Another orthopedic implant alternative emerging is carbon fiber, with particular implications in orthopedic oncology [39]. It has favorable radiolucency with minimal scatter or susceptibility artifact on magnetic resonance imaging (MRI) and computed tomography (CT) imaging. Thus, it is an advantageous implant option for tumor surveillance and osseous healing. Further beneficial properties include biocompatibility, high strength-to-weight ratio, and an elastic modulus similar to that of bone. One study examined outcomes in patients with TKA revisions due to failure of Carbon Fiber-Reinforced Poly-Ether-Ether-Ketone (CFR-PEEK) implants. Of 84 patients with a CFR-PEEK implant, 22 implants failed (26% failure rate) with an average time to failure of 25 months [40]. The authors attributed this to carbon fiber debris, which induces inflammatory responses leading to component loosening and implant failure. There is minimal research currently on carbon fiber's possible soft tissue reactions, which requires further investigation. As carbon fiber becomes more utilized, further exploration of long-term implant survival, complications, and clinical outcomes is needed.

Finally, given the low incidence rate of MHS and potentially underestimated prevalence due to diagnosis criteria, further longitudinal studies are needed to assess the long-term impacts of MHS on patient outcomes [11]. Larger cohort studies could track patients before and after implants to further investigate MHS adverse reaction incidence rates and clinical outcomes. Randomized controlled trials can also focus on comparing outcomes between alternative metal implants and MHS treatment approaches. Development of management protocol for MHS patients will depend on changes in screening and diagnostic criteria, development of hypoallergenic materials, and establishing personalized treatment options.

CONCLUSION

Metal hypersensitivity (MHS) remains a complex and largely underdiagnosed condition in orthopedic surgery, presenting with a variety of adverse events and patient outcomes including dermatologic manifestations, limited mobility, and implant loosening or failure [27]. This review highlights challenges in diagnosing MHS due to its presentation being reflective of alternative differential diagnoses, such as infections or complications with orthopedic hardware. There are additional difficulties in deducing a diagnosis of MHS, as well as managing symptoms as there are discrepancies in diagnostic testing, management protocol, and treatment options. Given the current understanding of MHS, improvements in screening and diagnostic methods, innovation of alternative implant materials, and personalized treatment approaches must be further investigated to serve this patient population. Standardization of evidence-based management strategies are required to guide patient care in clinical practice. In the interim, heightened awareness is critical in ensuring early recognition of MHS and appropriate intervention for patients at high risk of metal hypersensitivity reactions.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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