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Review Article

Metal Hypersensitivity in Total Joint Arthroplasty

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Abstract

Background: Failed total joint arthroplasty (TJA) is a multifactorial problem and one potential cause of failed TJA has been attributed to allergic reaction to the metallic components of the implants. The pathophysiology of implant function failure due to allergy has been postulated but is poorly understood. This review explores recent literature on the topic of metal hypersensitivity in TJA and human implantation in general to clarify the current state of understanding on this topic.

Methods: A literature search was completed via PubMed for all articles published related to implant failure in TJA due to metallic allergic reaction. The information was then sorted for relevance on basic science as well as clinical outcomes attributed to metal allergy in TJA.

Results: This review found that previous works attribute 5% of failed TJA to metal hypersensitivity reactions, no single test or finding has been found to be predictive of patients who will experience a failed TJA due to metal hypersensitivity, and there is no clear relationship between metal hypersensitivity and poor clinical outcomes in TJA although many theories have been presented.

Discussion: While evidence-based evaluation and management is desired for metal hypersensitivity, no clear consensus exists. Even routine pre-implantation testing has not shown to be of benefit. Furthermore, no test or finding has been shown to be diagnostic of metal allergy as a cause of failed TJA after implantation. Based on review of the published literature, this review article finds no objective evidence of metal allergy as a cause of TJA failure and therefore cannot conclude that metal allergic reaction is a mode of failure in TJA.

Keywords: Metal Hypersensitivity; Metal Allergy; Metal Ions; Allergic Reaction; Joint Arthroplasty

Abbreviations

TJA: Total Joint Arthroplasty; THA: Total Hip Arthroplasty; TKA: Total Knee Arthroplasty; MHR: Metal Hypersensitivity Reaction; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ASIA: Autoimmune/Inflammatory Syndrome Induced by Adjuvants; LTT: Lymphocyte Transformation Testing; MELISA: Memory Lymphocyte Immunostimulation Assay; ALTR: Adverse Local Tissue Reaction; ALVAL: Aseptic Lymphocyte-Dominated Vasculitis-Associated Lesion; PMMA: Poly Methyl Methacrylate; PE: Polyethylene; ELISA: Enyzme-Linked Immunosorbent Assay

Introduction

Total Joint Arthroplasty (TJA) has become some of the most commonly performed elective surgical procedures in the United States. Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) have been clinically cost-effective procedures for the treatment of end stage arthritis for the last 4 decades. Primary THA has been described as one of the greatest advances in healthcare in the 20th century. TJA has been shown to relieve pain, improve function, and improve quality of life in the majority of patients treated [1].

According to the National Inpatient Sample of 2014, there were 370,770 THA and 680,150 TKA procedures completed. By the year

2030 THA is projected to grow 171%, while TKA is projected to grow 189% over current case rates. Stated in terms of estimated numbers, THA will increase to 635,000 cases per year, while TKA will increase to 1.28 million cases per year by the year 2030 [2]. The general 10-year survival rate for TKA is considered to be 90 to 98%, with some studies reporting 15 to 20-year survival rates as high as 96%. While THA has greater than a 95% success rates at 10 years in reported studies [3].

Despite excellent 10 year survival rates, revision TJA now comes close to 25% of all total joint procedures completed in the United States [4]. As the demand for TJA increases, the costs associated with revision procedures will create a financial burden on the healthcare system that the orthopedic community should seek to reduce. Potential causes of revision TJA can be stratified into three groups: patient-related factors, implant-related factors, and failures related to surgical technique.

Unfortunately, up to 20% of TKA patients and 15% of THA patients are dissatisfied following surgery [5]. The most common presenting complaint in these patients following TJA was pain and/or stiffness. The reasons for these complaints can be multifactorial. General reported causes of TJA failures include polyethylene wear, infection, aseptic loosening, arthrofibrosis, malalignment, osteolysis, periprosthetic fracture, poor bone quality, allergy to metal, and some patients with a painful TJA have no clear explanation for the pain that can be found [6].

The first reported case of metal allergy to an orthopedic device was published in 1966, although at that time this was considered to be an insignificant issue. Today, the association between metal allergy and implant failure is well documented but poorly understood. Metal hypersensitivity is unpredictable and is highly debated as a cause of failure in revision TJA. Currently, there is a lack of consensus among orthopedic surgeons regarding the evaluation and management of a metal hypersensitivity reaction (MHR) [7]. This review explores the most up-to-date literature pertaining to metal hypersensitivity in orthopedic surgery to clarify its importance or lack thereof.

Metal allergy in the general population

It is estimated that 10 to 15% of the human population has some form of a metal hypersensitivity. Although various metals are known to cause allergic reactions, nickel is the most frequent cause of metal allergy. It is estimated that roughly 17% of females and 3% of males are allergic to nickel. Those who have known nickel hypersensitivity have been shown to have cross reactivity with other metals as well. Cobalt and chromium allergies are reported to occur in 1% of men and 3% of women [8].

Patients with autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome have been shown to have increased frequency of metal allergies. It has been theorized that a metal allergy can lead to over stimulation of the immune system and cause an autoimmune disorder [9]. Chronic fatigue syndrome, fibromyalgia, and autoimmune/inflammatory syndrome induced by adjuvants (ASIA) may be caused by a metal allergy. Patients with ASIA have also been shown to have increased allergies to food and other common allergens. In spite of this relatively high prevalence of metal hypersensitivity found in the population, metal allergies have only been reported to be the attributed cause of 5% of failures in TJA literature [10].

Should pre-operative allergy testing be performed?

No study published to date has supported pre-surgical metal allergy evaluation. No single test or physical finding has been reported as predictive for failure in TJA due to a metal hypersensitivity reaction (MHR). Further, there is no clear relationship between metal hypersensitivity and clinical outcomes.

The mental health and attitude of patients, however, has been documented to have a strong influence on clinical outcomes [11]. A patient who reports a pre-implantation history of MHR has been associated with poorer functional outcomes in TKA and poorer mental health scores following THA [12]. It has recently been reported that allergy diseases are associated with a 1.66 increased risk of having a psychiatric disorder [13]. An additional study demonstrated that mental well-being and self-reported health significantly predicted TJA outcomes regardless of physical health [14]. It is well-documented that clinical-depression increases early postoperative morbidity after TJA [15]. Thus, a patient with a psychiatric illness places them at significantly greater risk of postoperative complications versus patients with isolated, pre-existing metal allergy, alone.

Diagnostic evaluation of painful TJA

The diagnosis of MHR as the cause of a painful TJA is a diagnosis of exclusion at this time. The treating surgeon must work through the list of potential modes of failure as no reliable test currently exists to definitively confirm that a patient's symptoms have been caused by an allergic reaction. The patient frequently will have a history of prior reactions to metal devices such as jewelry, watches, cell phones, and clothing against the skin. The reactions can be widely varied but typically include itching, rash, and induration at the point of skin contact with metal. The reaction typically resolves once the metal contact is terminated.

Physical examination

MHR in the setting of TJA can manifest with multiple physical findings. Dermatitis adjacent to an implant can be associated with

a MHR. Local erythema, generalized urticarial, and cutaneous vasculitis have also been reported. These findings can be observed in both arthroplasty and static musculoskeletal implant settings. Other physical findings associated with failed TJA in the setting of MHR include device subsidence, chronic inflammation, pain, stiffness/arthrofibrosis, and loosening of prosthetic fixation to bone [16].

Infection

When evaluating a painful TJA the work up should begin with imaging and laboratory studies to detect or rule out the presence of an infection. Though not the focus of this review, infected TJA is likely far more common than MHR as a cause of failure. The incidence of infection in TKA has been reported to occur at 0.8% to 1.9%, while the incidence of infection in THA has been reported to occur at 0.3% to 1.7% of cases [17]. C-Reactive Protein, Erythrocyte Sedimentation Rate, D-Dimer, and White Blood Cell count with differential analysis of circulating blood are the basic values utilized when considering an infection etiology. Joint aspiration with synovial fluid analysis and cultures for aerobic and anaerobic organisms are required to rule out an infected TJA. The cultures should be held for up to 3 weeks to evaluate for the growth of atypical bacteria that would have otherwise been missed under standard culture protocols. Some authors have advocated a second aspiration and culture before excluding infection as the cause of a painful TJA if the first aspiration failed to grow any specific bacteria [18].

Tissue Ion levels

Serum levels of chromium, cobalt, and titanium are typically elevated in patients with functioning TJA [19]. Elevated metal ion concentrations have been reported in patients with TJA including elevations of ions in serum, erythrocytes, urine, whole blood, tissue, and organs [20]. Elevated serum metal levels are of unknown significance and have no clear meaning in the setting of a painful TJA. Part of the source of this confusion is the lack of a standard consensus on the measure or reporting of metal ion levels; no safe or conversely unsafe levels have been established.

Imaging findings

Imaging studies used to evaluate the painful TJA include plain film radiographs, CT scans, MRIs, and bone scans. Plain film radiographs and CT scans may show evidence of subsidence or loosening [21]. However, there is no single pathognomonic image finding which associates implant failure with MHR. As a result, the images may appear negative with no evidence of cause for pain.

Available allergy testing methods.

Patch testing

Patch testing is routinely performed by an allergist-immunologist and/or dermatologist to evaluate possible topical allergens [22]. The interpretation of the test result is subjective as this is a complex process which requires extensive training and expertise. Patch testing remains problematic for surgeons as studies do not definitively support its use in the diagnosis of metal hypersensitivity.

Each allergen is placed in a suitable media within a chamber to keep the allergen stable. The chamber is then placed on the patient's back and held with adhesive tape (Figure 1a and 1b). The allergen is removed at 48 hours and the reaction is outlined with a pen on the patient's back (Figure 1c). A second reading is later performed at 72 to 96 hours with the most important read being at the 96-hour time interval (Figure 1d) [22]. The readings are based on the strength of the reaction observed, ranging from a doubtful reaction to a very strong reaction with intense erythema, infiltration, and coalescing vesicles. Patch testing is somewhat subjective and has no clear meaningful use in the setting of orthopedic metal hypersensitivity detection.

Figure 1: a (top left): Allergy application with sharpie markings in the event the application is dislodged. b (top right): Paper tape to supplement the adhesive on the patch. c (bottom left): at 48 hours the patch was removed and demonstrated a positive nickel allergy (black arrow) and disperse blue dye allergy (blue arrow), d (bottom right): at 96 hours the patch was removed a second time and demonstrated another nickel allergy (red arrow) and more significant original nickel allergy (yellow arrow).

Bravo., *et al*. compared patients who underwent a TKA with and without pre-procedural patch testing. They found that patients with a positive patch test did not have a higher complication, reoperation, or revision rate when compared to negative patch tests. They concluded that patch testing cannot be strongly recommended as a method to guide implant selection [23]. On the other hand, Granchi., *et al.* found that at least one metal allergen on patch test with a positive medical history decreased THA lifespan. They showed that median implant survival decreased to 78 months for a positive test while implants survived to 120 months for a negative test. Grachi., *et al*. concluded that a positive patch test supports the theory of implant material sensitivity in implant failure [24].

To confuse issues further a report has been published on patients with pre-surgical confirmed nickel allergy by history and patch testing. Nickel containing TKA components were implanted and the patients were followed for over 6 years without the development of physical signs or symptoms of MHR or problems related to the TKA [25]. Additionally, another study reported no correlation between allergy, loosening, or pain associated with a TKA on patients with positive skin patch tests to the metal constituent components of the implanted device [26].

Lymphocyte transformation test

Lymphocyte transformation testing (LTT) is an alternative diagnostic aid for metal allergies. Unlike patch testing, LTT is performed *in vitro* to quantifiably measure the proliferation of T-cells to an allergen. Current research is inconclusive; it is unclear if T-cell proliferation actually indicates metal hypersensitivity which can be attributed to the cause of an implant failure. LTT is more expensive and not as readily available as patch testing. The basic premise of the LTT assay is to take sensitized memory T-cells from the patient's blood, introduce a specific metal allergen, and measure the proliferation of T-cells after 6 days. The proliferation is compared to blood not exposed to a metal allergen and is reported as a stimulation index, with a result of 2 to 4 indicating mild reactivity; 5 to 8 indicating moderate reactivity; and a value greater than 8 indicating high reactivity to metals [27].

Ständer., *et al*. directly compared patching testing to LTT patients with and without a self-reported nickel allergy. The authors calculated LTT to have an 88% sensitivity and 96% specificity. They concluded that performing LTT with optimized stimulating conditions may be a useful diagnostic aid [28]. Thomas., *et al*. evaluated patients without implants, arthroplasty patients without complications, and arthroplasty patients with complications using both patch testing and LTT. They found that patients with arthroplasty implants had a higher percentage of metal hypersensitivity than patients that were implant free. They also validated that patients with a poorly functioning implant have the highest chance of implant hypersensitivity [29].

Even though there are literature reports supporting LTTs ability for MHR diagnosis, LTT is only capable of testing a limited number of allergens and the test is not widely available.

MELISA Test

The MELISA (Memory Lymphocyte Immunostimulation Assay) test is a modified lymphocyte transformation test with improved specificity and sensitivity that is mostly available in Germany. Some of the differences include the use of a greater quantity of lymphocytes per test, the metal concentrations are optimized to be non-mitogenic and non-toxic; and macrophages are partially deleted to restore the lymphocyte-monocyte balance to more closely resemble *in vivo* blood. Also, proliferated lymphocytes are morphologically examined as an addition to the standard quantifiable calculation of lymphocytes. Valentine-Thon., *et al*. tested patients' blood with MELISA against 20 different metals in two to three different concentrations. They found that nickel had the greatest likelihood of reactivity and calculated a reproducibility rate of 94% using a stimulation index 3, and a reproducibility rate of 99% using a stimulation index 5. The authors concluded that the MELISA test is reproducible, sensitive, specific, and reliable for detecting metal sensitivity in metal-sensitive patients [30]. Valentine-Thon., *et al*. later published an additional series of patients tested with MELISA against 26 different metals. They demonstrated a 94.9% reproducibility rate and found a significant reduction or a normal MELISA test was obtained after removal of the prostheses which contained the allergenic metal. The authors concluded that the MELISA test is a clinically useful and reliable test for identifying and monitoring metal sensitization in symptomatic metal-exposed patients [31].

The MELISA may show promise for the diagnosis of a MHR, but it remains near impossible to use on a large scale due to its limited availability and significant cost

Type IV Delayed Hypersensitivity Reaction

Metal ions act as antigens and bind to serum proteins to form a complex. It is this metal-bound protein complex that may initiate an immune response. If the patient has a metal allergy a hypersensitivity reaction can occur, this is known as a T-cell mediated or type IV delayed hypersensitivity reaction. For this hypersensitivity reaction to occur the metal-bound protein complex must get picked up and presented to a T-helper cell (Figure 2). Further

Figure 2: Type IV Delayed Hypersensitivity Reaction.

interaction between the antigen presenting cell, T-helper cell, and macrophage leads to the secretion of inflammatory cytokines and lysosomal enzymes causing edema, erythema, tissue damage, and a fever. A T-helper cell may also differentiate into a killer T-cell releasing perforin and granzymes to directly induce apoptosis of the targeted. This type IV delayed hypersensitivity reaction ultimately causes an adverse local tissue reaction (ALTR) with inflammatory mass formation, osteolysis, tissue necrosis, and pain [32].

To further point out that the diagnosis of an implant-related allergy is nearly impossible, the type IV delayed hypersensitivity reaction seen from metal ion exposure of an implant may be completely different from the reaction seen in available allergy testing methods. It is known that the cutaneous reaction observed in patch testing is the result of Langerhan cells acting as antigen presenting cells in the dermal layer. However, it remains unknown which specific antigen presenting cells are responsible for intra-articular and extra-articular symptoms observed in TJA.

Findings at the time of revision

Metallosis

Revision surgery for prosthetic TJA failure due to a MHR will demonstrate metallosis. Metallosis (metallic debris) is the metallic staining of surrounding synovium and tissues about an implant or prosthetic TJA, which has failed due to a MHR.

Histology demonstrating aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL)

The histology observed from a synovial tissue biopsy at the time of revision surgery for painful synovitis has been reported to have characteristic findings of chronic inflammation, with lymphocyte and plasma cell predominance. The inflammatory response has been named an adverse local tissue reaction (ALTR) and has been well described in literature as a complication of metal implants. It is well known that histological specimen evaluation may be used to diagnose an aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), which is considered pathognomonic for a MHR. The histology demonstrates a dense perivascular infiltrate containing T-cell lymphocytes, B-cell lymphocytes, plasma cells, and macrophages, which is in contrast to a periprosthetic infection that demonstrates an abundance of neutrophils [33].

Some authors have suggested intraoperative histology evaluation prior to metal implantation, while others have suggested an arthroscopic biopsy when metal hypersensitivity is suspected after implantation. Even though the diagnosis of ALVAL may be considered pathognomonic for MHR, the absolute diagnosis of implant related allergy is almost impossible. Middleton., *et al*. report that this diagnosis requires abundant T-cells in the histology, a positive patch test, and the improvement of symptoms after revision to a hypoallergenic implant [34].

Treatment of painful TJA

Traditionally type IV delayed hypersensitivity reactions are treated by corticosteroids and removal of the trigger. However, there are no current standardized clinical guidelines for treating patients suspected of having a metal allergy. If the work up for infection is negative then the patient may initially be treated non-operatively. If non-operative management fails, the treating surgeon shall consider patch testing and lymphocyte transformation testing. If these tests are positive, the surgeon may consider revision surgery [35].

Traditional implants

Orthopedic implants are typically composed of nickel, cobalt, chromium, molybdenum, zirconium and/or titanium alloys. Most TKA implants are fabricated from chrome (Cr) cobalt (Co) metal alloys for the femoral component which articulates with a polyethylene (PE) bearing surface. The PE bearing surface is secured to a

metallic tray on the tibia or affixed directly to the tibia with poly methyl methacrylate (PMMA) cement in a so called all "poly tibia" configuration. The metal can be fixed to the bone by PMMA bone cement or by porous ingrowth surfaces of the metal device.

THA implants are fabricated and implanted under similar constructs. The acetabulum component of a THA contains a metal cup with a PE liner secured with PMMA or by a porous ingrowth surface at the bone implant interface. The femoral stem of a THA implant can be constructed of CrCo or titanium (Ti), which is secured via PMMA or a porous ingrowth surface in a so-called "press fit" fixation. The bearing surfaces in THA can be metal-on-metal, metal-on-PE, ceramic-on-ceramic, or ceramic-on-PE. Metal-on-metal articulation has been problematic and has largely fallen out of favor due to the increased release of metal ions causing metal hypersensitivity and pseudotumor formation.

Hypoallergenic implants for TJA

Recent developments in the manufacture of TJA implants have included the development of hypoallergenic surface treatments. Implants have been fabricated with the goal of minimizing exposure to the known sensitizing ions Ni, Cr, and Co. The base implants are fabricated using standard chrome cobalt stainless steel, and then sealed with various proprietary surface treatments. The exact metallurgy of all manufacturer's implants is not in the public domain due to the commercial competitive advantage.

Smith and Nephew's trademark "Oxinium™" is an oxidized zirconium metal surface treatment applied in hip and knee prosthetic implants. Oxinium™ is a nickel-free metal alloy that contains an outer oxide layer. This provides bearing properties similar to a ceramic without the fracture risk associated with ceramic brittleness. Oxinium™ uses a zirconium alloy metal base with an oxidized surface coating composed of 97.5% zirconium and 2.5% niobium. The outer layer of Oxinium™ seals the underlying metal of the implant, thereby preventing an ion release bioreaction and resulting type IV hypersensitivity reaction [36].

Aesculap implant systems developed a 7-layer "Advanced Surface Technology" which consists of a top layer, five transition layers, and a bond barrier layer on top of their standard cobalt chrome molybdenum implant. The top layer is composed of zirconium nitride, a material similar to ceramic with a low friction and high resistance to wear. The 5 transitions layers are made from chrome nitride, a hard anticorrosive material. The final layer is a chemical bond which holds the other layers to the cobalt chrome molybdenum implant. The surface treatment then seals the underlying chrome cobalt implant and prevents corrosion and ion release into synovial fluids [37].

Medacta International's implant "SensiTiN" consists of a ceramic-like coating of titanium nitride (TiN) which overlies the surface of the implant to reduce metal ion release. The SensiTiN titanium nitride layer is applied through a special process called physical vapor deposition, which creates a durable bond between the titanium nitride layer and the implant which aids in decreasing metal ion release. One study found that SensiTiN decreased the release of cobalt (Co), chromium (Cr), nickel (Ni), and molybdenum (Mo) by up to 90%. In addition to reducing metal ion release, the SensiTiN coating provides enhanced surface properties, such as increased surface hardness; improved surface wettability; low surface roughness; and decreased wear rates of the polyethylene inserted with the SensiTiN implant. Medecta International offers SensiTiN implants for total knee arthroplasty, partial knee arthroplasty, and revision knee arthroplasty [38].

MicroPort Orthopedics trademark "Evolution NitrX™" is a medial-pivot TKA containing a titanium niobium nitride (TiNbN) coating. Similar to the other sealed implants, this TiNbN coating creates a barrier to reduce the release of Co, Cr, Ni, and Mb ions. The coating also provides great wear properties with an increased surface hardness of 2450 Hv when compared to 300 Hv for CoCr [39].

CeramTec makes BIOLOX Ceramic implants primary used in Europe. Different from the other companies as their components are not sealed metal, instead they are completely composed of ceramic. They currently manufacture femoral heads, acetabular monoblock cup inserts, acetabular modular cup inserts, TKA femoral components, TKA femoral trays, and humeral heads. These ceramic implants are bioinert with an extremely hard and smooth surface to minimize polyethylene wear and type IV hypersensitivity reactions [40].

There are a few alternative strategies to using sealed chrome cobalt implants. One alternative has been to fabricate the implant from Ti alloy, which is felt to be less likely to stimulate an MHR. Another alternative is the use of a complete ceramic component. Alumina and zirconia are ceramic materials that are widely used in TJA applications and have been shown to have no allergic reaction potential. Ceramic prosthetic modular femoral heads have been used in total hip arthroplasty for many years. Studies now demonstrate successful short-term outcomes of complete ceramic femoral components in TKA [41]. Lastly, all-polyethylene tibial components in TKA remain a viable option to minimize metal ion exposure [42].

Even hypoallergenic implants release metal ions

All metals in a biologic system undergo corrosion, resulting in the release of ions. The free ions then form complexes with native

proteins. These new metal-bound protein complexes then act as antigens causing an immune response. In the case of a total joint the metal ions are most highly concentrated in the synovium of the prosthetic joint. Other potential antigens found in total joint systems occur in the form of polyethylene (PE) and poly methyl methacrylate (PMMA). However, both PE and PMMA are large molecules and are therefore unlikely to elicit the same reaction as an atom size particle created by metal ions [43].

Despite the use of hypoallergenic implants patients are still exposed to metallic debris at time of implantation. Sources of bio-reactive metallic debris during TJA surgery beyond the implants have been reported. Surgical instruments and saw blades are generally fabricated from 316L grade stainless-steel and contain 10 to 14% nickel. The metal TKA cutting blocks are held in place by metal pins, both of which are not sealed with a hypoallergenic coating and will leave metal ions behind. The use of an oscillating saw in the cutting block will inevitably shed metallic fragments [44]. As a result, this exposure will sensitize the patient leading to a MHR if they are truly metal hypersensitive. Hypoallergenic chrome cobalt sealed implants also possess the risk of future metal exposure if part of the sealed coating wears off over time [34].

Pending allergy testing in development

Currently there isn't a gold standard for MHR detection. Ongoing research is being performed to develop the ideal testing platform. Testing modalities available or under development include the leukocyte migration inhibition test and cytokine assessment.

The leukocyte migration inhibition test is an *in vitro* test that may be performed via four different methods, this includes the Boyden chamber membrane migration, a capillary tube, the leukocyte migration using the agarose technique, or via the use of collagen gels. A diagnosis of severe MHR is found when no cell migration is observed. Hallab., *et al*. concluded that migration inhibition testing has the potential to predict complications and the outcomes for patients receiving metal implants. These authors believe that migration inhibition testing used alone or in combination with other tests will improve the assessment of patients with suspected MHRs [45]. Another study implanted stainless steel implants into the bone of nickel sensitized and unsensitized New Zealand white rabbits. The nickel sensitized group demonstrated positive patch testing and positive leukocyte migration inhibition testing. The authors concluded that leukocyte migration inhibition testing is effective for hypersensitivity testing without the risk of sensitization associated with skin testing [46].

A cytokine assessment test analyzes cytokine expression to a potential allergen, IL-6 being the cytokine of particular importance after a patient develops symptoms of an allergy. Analysis may be performed with historic methods such as an ELISA (enyzme-linked immunosorbent assay), or with more recent technology such as the Luminex Cytokine Assay. The Luminex Cytokine Assay evaluates the proliferation of many cytokines from the patient's serum, plasma, cell culture supernatant, milk, saliva, or urine. One study compared ELISA to the Luminex Cytokine Assay on 96 pregnant women over the course of their pregnancy and calculated a similar Pearson correlation coefficient (r). They concluded that the Luminex Cytokine Assay is a valid alternative to ELISA and provides a higher throughput, requires a smaller sample volume, and costs less [47]. Another study analyzed patients with painful metal prostheses using patch testing, lymphocyte transformation testing (LTT), and the Luminex Cytokine Assay. Overall, the patch test and LTT results only agreed 60% of the time, and the Luminex Cytokine Assay only reached statistically significant levels some of the time. The authors stated that the Luminex Cytokine Assay may potentially be used to identify patients with metal hypersensitivity and for early markers of aseptic loosening. However, they concluded that the LTT remains the most suitable method for testing systemic allergies. They recommend the combined use of the patch test, LTT, and a cytokine assessment test in the preventive evaluation of immune reactivity in patients undergoing primary joint replacement and for monitoring metal hypersensitivity in patients with implants [48].

Conclusion

A review of up-to-date literature revealed that evidence based evaluation and management is desired, but no consensus opinion exists. Though reactions to orthopedic implants are well documented, routine pre-implantation testing is not shown to be of benefit and is not indicated. Instead, MHR currently is a phenomenon that appears to stem from media without significant factually information or consensus among orthopedic surgeons. More extensive research needs to be completed to determine the exact relationship between metal ions and a MHR, as well as how to prevent and treat an implant-related MHR.

Bibliography

1. Ulrich Slif D., *et al.* "Total hip arthroplasties: what are the reasons for revision?" *International Orthopaedics* 32.5 (2008): 597-604.

2. Sloan Matthew., *et al.* "Projected volume of primary total joint arthroplasty in the US, 2014 to 2030". *JBJS* 100.17 (2018): 1455-1460.

3. Heyse Thomas J., *et al.* "Total knee arthroplasty in patients with juvenile idiopathic arthritis". *Clinical Orthopaedics and Related Research®* 472.1 (2014): 147-154.

4. Mahomed Nizar N., *et al.* "Rates and outcomes of primary and revision total hip replacement in the United States medicare population". *JBJS* 85.1 (2003): 27-32.

5. Bourne Robert B., *et al.* "Patient satisfaction after total knee arthroplasty: who is satisfied and who is not?" *Clinical Orthopaedics and Related Research*® 468.1 (2010): 57-63.

6. Jones C Allyson., *et al.* "Total joint arthroplasties: current concepts of patient outcomes after surgery". *Rheumatic Disease Clinics of North America* 33.1 (2007): 71-86.

7. Kręcisz Beata Marta Kieć-Świerczyńska and Dorota Chomiczewska-Skóra. "Allergy to orthopedic metal implants-a prospective study". *International Journal of Occupational Medicine and Environmental Health* 25.4 (2012): 463-469.

8. Büdinger Lioba., *et al.* "Immunologic mechanisms in hypersensitivity reactions to metal ions: an overview". *Allergy* 55.2 (2000): 108-115.

9. Loyo Esthela., *et al.* "Autoimmunity in connection with a metal implant: a case of autoimmune/autoinflammatory syndrome induced by adjuvants". *Autoimmunity Highlights* 4.1 (2013): 33-38.

10. Basko-Plluska Juliana L., *et al.* "Cutaneous and systemic hypersensitivity reactions to metallic implants". *Dermatitis* 22.2 (2011): 65-79.

11. Giesinger Johannes M., *et al.* "Association of psychological status and patient-reported physical outcome measures in joint arthroplasty: a lack of divergent validity". *Health and Quality of Life Outcomes* 11.1 (2013): 1-6.

12. Nam, Denis, *et al.* "Patient-reported metal allergy: a risk factor for poor outcomes after total joint arthroplasty?". *The Journal of Arthroplasty* 31.9 (2016): 1910-1915.

13. Tzeng Nian-Sheng., *et al.* "Increased risk of psychiatric disorders in allergic diseases: a nationwide, population-based, cohort study". *Frontiers in Psychiatry* (2018): 133.

14. Perruccio Anthony V., *et al.* "Importance of self-rated health and mental well-being in predicting health outcomes following total joint replacement surgery for osteoarthritis". *Arthritis Care and Research* 63.7 (2011): 973-981.

15. Browne James A., *et al.* "Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study". *The Journal of Arthroplasty* 29.3 (2014): 481-483.

16. Munro-Ashman D and AJ Miller. "Rejection of metal to metal prosthesis and skin sensitivity to cobalt". *Contact Dermatitis* 2.2 (1976): 65-67.

17. Phillips JE., *et al.* "The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey". *The Journal of bone and joint surgery. British Volume* 88.7 (2006): 943-948.

18. Betsch Belinda Y., *et al.* "Treatment of joint prosthesis infection in accordance with current recommendations improves outcome". *Clinical Infectious Diseases* 46.8 (2008): 1221-1226.

19. Luetzner Joerg., *et al.* "Serum metal ion exposure after total knee arthroplasty". *Clinical Orthopaedics and Related Research (1976-2007)* 461 (2007): 136-142.

20. Hennig FF., *et al.* "Nickel-, chrom-and cobalt-concentrations in human tissue and body fluids of hip prosthesis patients". *Journal of Trace Elements and Electrolytes in Health and Disease* 6.4 (1992): 239-243.

21. Innocenti Massimo., *et al.* "Total knee arthroplasty in patients with hypersensitivity to metals". *International Orthopaedics* 38.2 (2014): 329-333.

22. Lazzarini., *et al.* "Patch tests". *Anais Brasileiros De Dermatologia* 88 (2013): 879-888.

23. Bravo Dalibel., *et al.* "No increased risk of knee arthroplasty failure in patients with positive skin patch testing for metal hypersensitivity: a matched cohort study". *The Journal of Arthroplasty* 31.8 (2016): 1717-1721.

24. Granchi Donatella., *et al.* "Sensitivity to implant materials in patients undergoing total hip replacement". *Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* 77.2 (2006): 257-264.

25. Carlsson A and H Möller. "Implantation of orthopaedic devices in patients with metal allergy". *Acta Dermato-Venereologica* 69.1 (1989): 62-66.

26. Webley M., *et al.* "Metal sensitivity in patients with a hinge arthroplasty of the knee". *Annals of the Rheumatic Diseases* 37.4 (1978): 373-375.

27. Pichler WJ and J Tilch. "The lymphocyte transformation test in the diagnosis of drug hypersensitivity". *Allergy* 59.8 (2004): 809-820.

28. Ständer Sascha., *et al.* "Evaluation of lymphocyte transformation tests as compared with patch tests in nickel allergy diagnosis". *Contact Dermatitis* 76.4 (2017): 228-234.

29. Thomas Peter., *et al.* "Arthroplasty patients and nickel sensitization: What do patch test and lymphocyte transformation test tell us". *Seminars in Arthroplasty* 24.4 (2013).

30. Valentine-Thon., *et al.* "Validity of MELISA® for metal sensitivity testing". *Neuroendocrinology Letters* 24.1/2 (2003): 57-64.

31. Valentine-Thon., *et al.* "LTT-MELISA (R) is clinically relevant for detecting and monitoring metal sensitivity". *Neuroendocrinology Letters* 27.1 (2006): 17-24.

32. King TC. "Inflammation, Inflammatory Mediators, and Immune-Mediated Disease-ScienceDirect". (2007): 21-57.

33. Black J., *et al.* "Metallosis associated with a stable titanium-alloy femoral component in total hip replacement. A case report". *JBJS* 72.1 (1990): 126-130.

34. Watters Tyler Steven., *et al.* "Aseptic lymphocyte-dominated vasculitis-associated lesion: a clinicopathologic review of an underrecognized cause of prosthetic failure". *American Journal of Clinical Pathology* 134.6 (2010): 886-893.

35. Middleton S and Andrew Toms. "Allergy in total knee arthroplasty: a review of the facts". *The Bone and Joint Journal* 98.4 (2016): 437-441.

36. Verilast - Oxidized Zirconium with XLPE". *Smith and Nephew, Inc.* (2014).

37. Advanced Surface Technology. *Aesculap Implant Systems* (2023).

38. Medacta SesiniTiN data on file. *Medacta International* (2023).

39. DOT America Medical Implant Solutions (2022).

40. Ceramic ball heads. *BIOLOX Inside* (2017).

41. Bergschmidt Philipp., *et al.* "Ceramic femoral components in total knee arthroplasty-two year follow-up results of an international prospective multi-centre study". *The Open Orthopaedics Journal* 6 (2012): 172.

42. Ajwani Sanil Harji and Charalambos P Charalambous. "Availability of total knee arthroplasty implants for metal hypersensitivity patients". *Knee Surgery and Related Research* 28.4 (2016): 312.

43. Merritt Katharine and Juan J Rodrigo. "Immune response to synthetic materials: sensitization of patients receiving orthopaedic implants". *Clinical Orthopaedics and Related Research (1976-2007)* 326 (1996): 71-79.

44. Klontz Karl C and William I Smith. "Acute Metallosis Following Total Knee Replacement-A Case Report". *Journal of Orthopaedic Case Reports* 4.1 (2014): 21.

45. Hallab Nadim., *et al.* "Hypersensitivity to metallic biomaterials: a review of leukocyte migration inhibition assays". *Biomaterials* 21.13 (2000): 1301-1314.

46. Merritt Katharine and Stanley A Brown. "Tissue reaction and metal sensitivity: an animal study". *Acta Orthopaedica Scandinavica* 51.1-6 (1980): 403-411.

47. Wang Kehui., *et al.* "Validation and comparison of luminex multiplex cytokine analysis kits with ELISA: determinations of a panel of nine cytokines in clinical sample culture supernatants". *Journal of Reproductive Immunology* 66.2 (2005): 175-191.

48. Carossino Anna Maria., *et al.* "Hypersensitivity reactions to metal implants: laboratory options". *BMC Musculoskeletal Disorders* 17.1 (2016): 1-14.