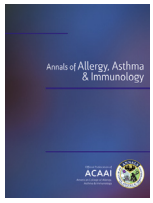
Ann Allergy Asthma Immunol xxx (2014) 1–6

Contents lists available at ScienceDirect



Review

Metal hypersensitivity in total joint arthroplasty

Michelle L. Pinson, MD; Christopher A. Coop, MD; and Charles N. Webb, MD

Department of Medicine, Allergy/Immunology Division, Wilford Hall Ambulatory Surgical Center, San Antonio, Texas

ARTICLE INFO

Article history:
Received for publication March 19, 2014.
Received in revised form May 13, 2014.
Accepted for publication May 15, 2014.

ABSTRACT

Objective: To review the clinical manifestations, testing methods, and treatment options for hypersensitivity reactions to total joint arthroplasty procedures.
Data Sources: Studies were identified using MEDLINE and reference lists of key articles.
Study Selections: Randomized controlled trials were selected when available. Systematic reviews and meta-analyses of peer-reviewed literature were included, as were case series and observational studies of clinical interest.
Results: Total joint arthroplasty procedures are increasing, as are the hypersensitivity reactions to these implants. Evidence is not conclusive as to whether metal joint implants increase metal sensitivity or whether metal sensitivity leads to prosthesis failure. Currently, patch testing is still the most widely used method for determining metal hypersensitivity; however, there are no standardized commercial panels specific for total joint replacements available currently. In vitro testing has shown comparable results in some studies, but its use in the clinical setting may be limited by the cost and need for specialized laboratories. Hypersensitivity testing is generally recommended before surgery for patients with a reported history of metal sensitivity. In cases of metal hypersensitivity-related joint failure, surgical revision ultimately may be required. Knowledge about joint replacement hypersensitivity reactions becomes vital because the approach to the evaluation depends on appropriate testing to guide recommendations for future arthroplasty procedures.
Conclusion: Evaluation of hypersensitivity reactions after total joint arthroplasty requires a systematic approach, including a careful history, targeted evaluation with skin testing, and in vitro studies.

Introduction

In the United States and worldwide, the incidence of total joint arthroplasty (TJA) procedures is increasing.[1–3] In the United States alone, primary total hip arthroplasties (THAs) are estimated to increase by 174% to 572,000 procedures and TKAs are expected to increase by 673% to 3.48 million procedures by 2030.[4] Revisions of joint replacements also are increasing and are projected to increase by 173% for hip implants and 601% for knee implants from 2005 to 2030.[4] A significant proportion of these patients undergoing arthroplasty have metal sensitivity and may react to their prosthesis. With the increasing number of metal joint prostheses being implanted, the incidence of metal sensitivity leading to implant failure also is likely to increase. These patients with metal sensitivity will need to be referred for allergy testing to help determine which material is triggering their reaction. This information will be helpful to patients for future arthroplasty revisions to avoid the material to which they are sensitive.

Total Hip and Knee Arthroplasty

The early prosthetic joints used for THA were metal-on-metal (MoM), meaning the metal femoral head articulated with the metal hip socket or cup. These early MoM implants had increased wear and shed metal debris into local tissues, resulting in the release of cobalt and chromium into the blood, hair, and urine.[5] Some complications include metal sensitization and prosthesis loosening.[6] Subsequently, orthopedic surgeons began using metal-on-polyethylene (MoP) prostheses, which consist of a metal femoral head articulating with a polyethylene socket. These MoP implants have yielded fewer complications associated with metal sensitivity. Recently, newer generations of MoM bearings have gained popularity because of their improvements in strength and durability. In the United States, the most common bearing-type implanted is MoP (51%) followed by MoM (35%) and ceramic-on-ceramic (14%).[7]

Reprints: Michelle L. Pinson, MD, Allergy/Immunology, 2200 Bergquist Drive, Suite 1, Lackland AFB, TX 78236; E-mail: michelle.pinson.1@us.af.mil.
Disclosure: Authors have nothing to disclose.
Disclaimer: The opinions expressed on this document are solely those of the authors and do not represent an endorsement by or the views of the United States Air Force, the Department of Defense, or the United States Government. No federal endorsement intended.
Funding: This work did not receive external commercial support.

http://dx.doi.org/10.1016/j.anai.2014.05.012
1081-1206/

Table 1
Materials commonly used in total joint replacements

Metals[9]: cobalt, chromium, molybdenum, nickel, tungsten, manganese, titanium, aluminum, vanadium	Cement components[16,17]: acrylates (monomeric methyl methacrylate), benzoyl peroxide, N,N-dimethyl-*p*-toluidine, hydroquinone, gentamicin or other antibiotics, chlorophyll, zirconium oxide, barium sulfate
Polyethylene	
Ceramic alloys: niobium, zirconium	

The articulating surface of joint replacements is designed to endure contact stress. There are varying rates of complications and the chance of revision is based on the type and design of the articulating surface. Because of the association with lower rates of revision,[8] MoP implants are not believed to induce metal allergy, but their plastic wear products produce a foreign body reaction in the bone.[9] This bone reaction may lead to aseptic loosening of the joint.[9] This is one of the reasons why surgeons are implanting more MoM joint replacements, particularly for younger patients. Some evidence suggests the newer generations of MoM have less wear debris and less aseptic loosening,[9] and there is a decreased risk of dislocation.[8,10] In contrast, MoM implants are associated with more metal hypersensitivity.[11] In addition, a higher rate of MoM prosthesis revision attributed to loosening, infection, and metal sensitivity is seen in the more stable joint that uses the larger femoral head.[12] Studies also have shown that primary[2,3,13] and revision[2,3,12,13] operations are more common in women than in men.

In knee replacements, similar problems have been seen. In TKA, the metal tibial component has a polyethylene cushion or polyethylene will be directly attached to the tibia. The tibial component articulates with the metal femoral component. There is no MoM contact between the femoral and tibial components.[14,15] The total knee prosthesis can have a cemented or an uncemented fixation. These uncemented designs use bioactive surfaces to attract new bone growth into the surface of the implant.[15] As with hypersensitivity to metal components, patients may have complications related to the components found in bone cement. There are case reports of benzoyl peroxide in bone cement as a cause of allergic complications after joint implantation.[16] However, systemic allergic contact dermatitis and other hypersensitivity reactions appear to be less common in knee replacements compared with hip arthroplasty, because there is no MoM contact between the femoral and tibial components.[14]

Materials commonly used in total joint replacements (TJRs) are listed in Table 1.[9,16,17] In general, there are more case reports of hypersensitivity reactions to stainless-steel (which contains nickel, chromium, molybdenum, manganese) and cobalt-alloy components compared with titanium-alloy components.[17]

Pathophysiology

All metals in contact with biological systems undergo corrosion.[17] Metal ions or haptens released from corrosion or wear debris are considered incomplete antigens that can only stimulate the immune system by binding with native proteins.[17,18] Moreover, these metal ion-bound protein complexes can elicit hypersensitivity responses.[19,20] Little is known about the short- and long-term pharmacodynamics and bioavailability of circulating metal degradation products in vivo.[19]

Some investigators believe that cell-mediated hypersensitivity plays a key role in influencing prosthesis performance and may contribute to acceleration of events that lead to implant failure.[17,18] Evans et al[6] found in metal-sensitive patients a release of metal ions from the prosthesis to the tissues that produced changes in local blood vessels. These vascular changes lead to interruptions of the blood supply and subsequent necrosis of the bone and soft tissues.[6]

One study showed that although a total hip prosthesis usually has a mean lifespan of approximately 120 months, the implant lifespan is decreased to 78 months in patients with positive test results and/or with a history of allergic contact dermatitis caused by metals.[18] This shortened lifespan of a total hip prosthesis in patients with metal allergy emphasizes the pertinent role of metal hypersensitivity in implant failure.

Metal Sensitization after TJA

In the general population, 10% to 15% have metal hypersensitivity.[17,19] The prevalence of delayed-type hypersensitivity and its related testing has increased over the past 4 decades.[11] A systematic review and meta-analysis showed a higher probability of developing a metal allergy after TJR compared with patients without an implant.[11] Another systematic review found the prevalence of metal sensitization was approximately 25% in patients with stable hip arthroplasties and 60% in patients with failed or poorly functioning implants.[17] In a similar trend, there is an increased probability of metal allergy in failed TJRs compared with stable TJRs.[11] Browne et al[21] showed that of the 37 patients with MoM total hip or resurfacing arthroplasties who underwent revision over a 3-year period, 27% (10) underwent revision for presumed metal hypersensitivity. For 1 orthopedic surgery practice, metal hypersensitivity reactions accounted for 5.2% of all hip resurfacing revisions.[22] In Australia, the cumulative incidence of metal sensitivity at 9 years after primary THA of MoM implantation was 0.1% to 1.6%. However, the investigators suspected the incidence of metal sensitivity was potentially higher but was underdiagnosed.[12]

Although several studies have shown that metal sensitivity increases after joint replacement, there are a few studies showing no correlation between TJA and metal sensitivity. For instance, a study from Denmark found that the prevalence of positive patch testing results to nickel, cobalt, and chromium was similar in patients who did and those who did not have a THA.[23] This study reviewed the Danish Hip Arthroplasty Registry and the Gentofte patch test database by comparing the prevalence and cause of revisions after THA in patients with dermatitis suspected of having contact allergy and in patients in general with THA. They also compared the prevalence of metal allergy in patients with dermatitis with and without THA. Moreover, they demonstrated the risk of surgical revision was not increased in metal-allergic patients with THA compared with "ordinary" patients with THA who did not have positive metal sensitivity testing results. In addition, Summer et al[24] demonstrated in a study of 15 patients that levels of the inflammatory marker interleukin-17 were increased only in those patients with nickel-containing replacement joints who had a positive patch test result to nickel and complaints of joint pain. Interleukin-17 levels were not increased in patients with a positive patch test result to nickel who did not complain of joint pain.[24] Furthermore, Waterman and Schrik[25] performed a prospective study of preoperative and postoperative patch testing in 85 patients in whom MoP hip prostheses were implanted. All 14 patients who had negative preoperative patch testing results and postoperatively developed positive reactions to metals and methylmethacrylate did not have loosening of the prosthesis. These patients had stable joint replacements despite having developed sensitization to their inserted prosthetic material. Conversely, in the 10 patients in whom prosthesis loosening was observed, no evidence of contact allergy to constituents of the prosthetic material was found.[25] These studies weaken the argument that metal sensitivity can lead to TJR complications and implant failure in patients with and without previous metal sensitization.

Overall, there is conflicting evidence as to whether sensitivity to implanted materials increases after joint replacement and whether

this metal sensitivity causes patients to have a higher likelihood of joint implant failure.

Development of Tolerance

Of 6 patients with preoperative positive patch test results, Rooker and Wilkinson[26] found 5 patients with postoperative negative results. These included 2 cases of chromate allergy, 2 cases of cobalt allergy, and 2 cases of nickel allergy (1 patient had a combined nickel-chromate allergy). The investigators suggested that immunologic tolerance can develop after MoP hip implantation.[26]

Symptoms and Intraoperative Findings

Within 3 years after arthroplasty, patients with failed joints or joint replacement-related symptoms typically can present with any one or several of these symptoms: pain, joint effusions, and joint dislocations. Dermatologic symptoms may be localized and/or generalized manifestations and can consist of erythema, induration, papules, vesicles,[27,28] warmth, effusion, or less commonly urticarial, bullous, or vasculitic eruptions.[29,30] Periarticular dermatologic eruption and chronic dermatitis beginning weeks to months after implantation are associated more often with metal hypersensitivity reactions.[27] Later findings include osteolysis and loosening of the implanted joint.[30]

Sometimes there are tissue changes found during joint implant revision that indicate a delayed-type hypersensitivity reaction has contributed to the current prosthesis failure. Intraoperatively, the surgeon may confirm the diagnosis of pseudotumor or diagnose aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) based on the appearance of the tissues surrounding the joint implant. The term *ALVAL* was coined by Willert et al[30] to describe an intense perivascular lymphatic infiltration that occurs around certain MoM devices. Its histologic appearance is similar to, but not necessarily diagnostic of, a delayed-type hypersensitivity response. Although ALVAL is not unique to tissues surrounding MoM implants, the intensity of lymphocytic infiltrate is often greater in association with MoM implants than with other bearing surfaces.[30] Pseudotumors are a rare complication of MoM hip arthroplasty. They are usually a reaction to increased wear debris[31] that develops into a nonmalignant, noninfectious soft tissue mass associated with the implant.[32] Symptoms related to a pseudotumor include hip discomfort, spontaneous dislocation, nerve palsy, a noticeable mass, or dermatitis.[32] Imaging with plain x-ray films can display subtle changes suggestive of the presence of pseudotumor in most cases. The pathogenesis of pseudotumors and implant failure may involve cytotoxic and delayed hypersensitivity responses to metal particles found in periprosthetic soft tissues.[33] However, in a study of 92 patients with and without pseudotumor, the lymphocyte transformation test (LTT) results to cobalt, chromium, and nickel did not differ significantly in patients with pseudotumors from patients without pseudotumors.[34] This suggests that systemic delayed-type hypersensitivity reactions, as measured by the LTT, may not be the dominant biological reaction involved in the occurrence of soft tissue pseudotumors. Because the ALVAL and pseudotumor diagnoses are often made during surgical revision of the prosthesis, they are not helpful in determining whether hypersensitivity reactions are the cause of joint implant failure before revision.

High Serum Levels of Metal Ions

There are case reports of patients who had high serum levels of metal ions after MoM and MoP hip replacements and later developed symptoms of systemic metal toxicity,[35] including cardiomyopathy.[36,37] However, there is no evidence of a widespread systemic problem of high levels of serum metal ions and the symptoms that are reported are largely nonspecific.[12] There is no evidence that there is a causal relation between high serum ion levels and metal hypersensitivity.[14,20]

Table 2
Recommendations for patch testing antigens[a]

Metals	Polyethylene disc
Cobalt (II) chloride hexahydrate, 1% pet[b]	Ceramic alloys
Nickel sulfate hexahydrate, 2.5% or 5% pet[b]	Niobium (V) chloride, 0.2% pet
Chromium (potassium dichromate, 0.5% or 0.25% pet; chromium trichloride, 2% pet)[b]	Zirconium (IV) oxide, 0.1% pet
Gold sodium thiosulfate, 0.5% pet[b]	Cement components
Potassium dicyanoaurate	Methyl methacrylate, 2% pet[b]
Ammonium tetrachloroplatinate, 0.25% pet	Benzoyl peroxide, 1% pet[b]
Mercury	Gentamicin sulfate, 20% pet[b]
Copper sulfate, 2% pet	Mupirocin
Tin	
Aluminum chloride hexahydrate, 10% pet	
Palladium chloride, 2% pet[b]	
Molybdenum (V) chloride, 5% pet	
Vanadium, 5% pet	
Titanium (titanium powder, 1% pet; titanium dioxide, 10% pet, titanium [IV] oxide, 0.1% pet; titanium disc)	
Manganese chloride, 2% aq	

[a]Table 2 adapted from tables by Thyssen et al[28] and Atanaskova Mesinkovska et al.[43]
[b]Antigens were associated with positive patch test results from a study by Atanaskova Mesinkovska et al.[43]

Diagnostic Methods

After infection and mechanical failure have been ruled out, the main delayed-type hypersensitivity diagnostic tools used to determine metal hypersensitivity include in vivo testing using patch testing and in vitro methods such as the LTT, the leukocyte migration inhibition factor test, and the lymphocyte activation test (LAT).

In Vivo Testing

Patch testing is considered the reference method for diagnosing contact allergy. However, some investigators believe patch testing in detecting hypersensitivity to implant materials is controversial because the closed periprosthetic environment is different from the open-testing dermal contact used in patch testing.[17,38,39] At cutaneous exposure, metal ions are taken up by Langerhans cells as the antigen-presenting cells.[17] Conversely, in the joint space, tissue macrophages and dendritic cells perform this function.[17] Despite the debate, patch testing is still the most common method for evaluating delayed-type hypersensitivity in TJA.

Patch testing with the Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E. test; Mekos Laboratories A/S, Hillerød, Denmark), the only Food and Drug Administration–approved patch test in the United States, is often used for initial screening in contact dermatitis. In allergy and dermatology practices, patch testing with T.R.U.E. test alone showed positive allergens were missed in 12.5% of patients with contact dermatitis.[40] In over a thousand patients who were tested over a ten-year period of time at the Mayo Clinic, Davis et al[41] found that their own standard series for patch testing did not include many metals that were associated with positive allergic patch-test reactions. These studies indicate that standard patch testing series may not encompass all the possible metals that patients are sensitized to but are helpful as initial screening tools.

Patch testing options include the T.R.U.E. test, the metal series patch test panel from DORMER Laboratories, Inc (Rexdale, Ontario, Canada),[42] or using Finn chambers for specific testing. Commonly used in contact dermatitis evaluations, the T.R.U.E. test contains nickel, cobalt, and chromium but lacks several of the other common materials that have been recently reported as triggering hypersensitivity reactions in TJA. The DORMER Laboratories Metal Series

patch testing kit includes 43 metal haptens but does not include other components commonly used in TJA, such as cobalt, niobium, potassium dichromate, benzoyl peroxide, gentamycin, or mupirocin. Nickel is available in separate DORMER Laboratories patch testing kits.

For developing a screening panel for metal hypersensitivity, we recommend testing for cobalt, nickel, potassium dichromate, sodium thiosulfate (gold), potassium dicyanoaurate, platinum, mercury, copper, tin, aluminum, and palladium. In addition, a more focused orthopedic prosthesis patch testing panel could include nickel, cobalt, potassium dichromate, molybdenum, palladium, sodium thiosulfate, vanadium, titanium, manganese, niobium, zirconium, methyl methacrylate, benzoyl peroxide, gentamycin, and mupirocin (Table 2).[28,43]

The variability of results in patch testing to specific compounds may be due to dose, size, counter ions, polarity, valence, and pH applied to the skin.[5] Evans et al[6] reported they specifically used nickel, chromium, and cobalt in their soluble forms as opposed to their insoluble forms as the parent alloy for their patch testing.[6] In the special case of titanium, sensitivity to titanium in the general population is low, and testing methods may not have a high-enough sensitivity to capture all patients with titanium sensitivity. Lalor et al[44] presented a case series of joint implant loosening attributed to titanium sensitivity. In 5 patients who underwent revision operations for failed total hip replacements, tissue specimens were found to contain large quantities of titanium, abundant macrophages, and T lymphocytes with no B lymphocytes, suggesting sensitization to titanium. The tissues did not demonstrate any other metals at electron microscopy analysis with energy-dispersive x-ray microanalysis. Patch testing results with dilute solutions of titanium salts were negative in all 5 patients. However, 2 of the patients had positive patch test results to a titanium-containing ointment.[44] Titanium patch testing might be less suitable for titanium allergy, because titanium dioxide salts and the titanium metal used are not soluble and therefore cannot penetrate the skin under the conditions of patch testing.[45]

Overall, patch testing is still the most widely used method for diagnosing metal sensitivity related to joint prosthesis. The usefulness of patch testing may be improved with larger panels encompassing more materials specific to the patients' implant, because testing for more haptens has shown a higher frequency of positive patch test results.[11,18]

In Vitro Testing

Some investigators have proposed that in vitro testing in prosthesis-related metal sensitivity is equal to or better than patch testing for assessment of implant-related allergy.[17] In vitro methods include the LTT, the leukocyte migration inhibition factor test, and the LAT.

The LTT, as described by Christiansen et al,[46] is an antigen-dependent oligoclonal T-cell expansion test. It is used to characterize clinical hypersensitivity reactions.[47] In the study by Christiansen et al, the LTT results to chromium, cobalt, and nickel were measured in 24 patients undergoing revision surgery for a painful or loose MoP prosthesis. They were compared with a control group of 11 patients who had stable total hip replacements for at least 2 years after surgery. An LTT positive response was a lymphocyte stimulation index higher than 3. This was found in 17 (71%) of the revision group compared with 1 (9%) of the control group ($P < .01$). Of the failed-prosthesis group, 15, 7, and 5 showed positive reactions to chromium, nickel, and cobalt, respectively. The 1 patient in the control group who exhibited positivity had a positive reaction to chromium.[46] A modification of the LTT, the memory lymphocyte immunostimulation assay (MELISA) test (MELISA Diagnostics, Ltd, London, United Kingdom), has been used for detecting metal hypersensitivity.[45] The MELISA test result was positive in 15 patients with confirmed or suspected nickel allergy. In patients without suspicion of nickel allergy, the MELISA test results was negative (6 patients) or very low positive (4 patients).[45] The LTT uses metals in the form of water-soluble salts, except for titanium dioxide, which is water insoluble. In vitro testing for titanium should be considered because patch testing may not be as sensitive.[44,45]

Some investigators have shown that in vitro testing, specifically the LTT, is comparable to patch testing.[17,48] Thomas et al[48] reviewed the role of metal hypersensitivity testing by patch testing and the LTT. In the 16 patients undergoing revision surgery, 13 patients (81%) had systemic metal sensitivity based on positive patch testing results and/or positive LTT responses. Patch test reactions were seen in 11 of 16 patients (69%). Ten of 16 patients (62%) showed positive LTT reactivity to metals. Concomitant evidence of periimplant lymphocytic inflammation suggestive of metal sensitivity was seen in 8 patients with positive patch testing reactivity and positive LTT response, in 3 patients with positive patch testing reactivity only, and in another 2 with positive LTT response only. In only 3 of 16 patients, the histomorphology was not reflected by positive patch testing or the enhanced LTT reactivity.[48]

The LAT was used by Granchi et al[18] to evaluate sensitization to metals in patients with cobalt-chromium hip prosthesis. Peripheral blood mononuclear cells were collected from 14 healthy donors, 10 candidates for primary TJR, 11 patients with well-fixed implants, and 13 patients with aseptic loosening of the hip prosthesis. Peripheral blood mononuclear cells were cultured with the metal ions used for implant manufacturing and the expression of CD69 activation antigen on CD3-T lymphocytes was detected by flow cytometry. Chromium extract significantly increased the expression of the CD3-CD69 phenotype in patients with loosening of the hip prosthesis. The chromium-induced "activation index" was higher in patients with loosening of the hip prosthesis than in healthy donors and in patients before implantation. The cobalt-stimulated peripheral blood mononuclear cells of patients with a well-fixed or a loosened prosthesis had an "activation index" significantly higher than those of healthy donors. The investigators recommended the LAT to be an easy and reliable method for monitoring hypersensitivity in patients with metal prostheses.[18]

Leukocyte migration inhibition factor testing involves the measurement of mixed-population leukocyte migration activity. In the presence of a sensitizing antigen, leukocytes migrate more slowly, losing the ability to recognize chemoattractants, and are said to be migration inhibited.[17,38] This type of testing may lack sensitivity for detecting delayed-type hypersensitivity responses at certain times over the course of a hypersensitivity reaction.[17] Therefore, if leukocyte migration inhibition factor testing is used alone to diagnose metal sensitivity, it may underestimate the number of patients with metal sensitivity.[17]

Overall, in vitro testing has been a clinically unpopular means of hypersensitivity testing and there are some limitations to the large-scale application of in vitro testing, including the cost and the need for specialized laboratories.[11]

In a meta-analysis of the peer-reviewed literature focusing on metal sensitivity testing (patch testing and in vitro testing) in patients undergoing joint replacement, Granchi et al[11] noted that although the proportion of positive reactions seemed to be larger when in vitro methods were used, the comparison with in vivo testing did not show significant results.[11]

Usefulness of Presurgical Hypersensitivity Testing

Some investigators have advocated for metal hypersensitivity testing before initial TJA procedures.[6,43,49–51] In a survey of

orthopedic surgeons in Scotland, Campbell[52] reported that 72% of surgeons would use a nickel-free implant if they knew the patient was allergic to nickel. Campbell commented that the variation in practice likely reflected the lack of evidence and guidance on this topic. In another study, positive patch testing results led the surgeon to choose a joint without the offending allergic metals, and patients did not develop joint failure or pain.[43] However, this study lacked information about whether surgeons would continue with the planned joint components irrelevant to the hypersensitivity testing results.[43] Conversely, some investigators do not recommend hypersensitivity testing before primary TJA.[25,26] Granchi et al[11] demonstrated that hypersensitivity testing could not discriminate between stable and failed TJRs, because its predictive value was not statistically proved.

Overall, patients who report a history of metal allergy, such as reaction to jewelry, should be considered for delayed-type hypersensitivity testing before surgery. Although Frigerio et al[50] demonstrated that history taking was far less reliable than patch testing for ascertaining metal sensitivity, not every potential TJA candidate requires hypersensitivity testing. Therefore, most investigators have suggested that in patients who report a history of metal allergy, hypersensitivity testing before surgery should be considered.[11,43] Hypersensitivity testing also should be performed in patients with failed TJRs, especially with MoM implants, and when the cause of loosening is unknown.[11] In general, hypersensitivity testing results may guide surgeons to consider implants with no or minimal amounts of the metals to which the patient positively reacted, especially in the case of joint implant revisions.[6,43,49–51]

Metal Polysensitization

Metal co-sensitization may play a role in positive patch testing results and positive in vitro studies. Metal concomitant sensitization is most common with nickel and cobalt.[5,19] In a study of 11,516 patch-tested patients, 79%, 39%, and 95% of patients allergic to cobalt, chromium, and palladium, respectively, also were reactive to nickel.[5,53] In addition, 23%, 31%, and 36% of patients allergic to nickel, chromium, and palladium, respectively, also were reactive to cobalt. In another study, all patients who reacted positively to cobalt, chromium, or palladium also reacted positively to nickel at patch testing or MELISA testing.[50] Palladium allergy prevalence is high but is mainly a result of cross-sensitization to nickel.[5]

Treatment Options

Currently, there is no consensus on how to treat joint failure from suspected allergic reactions. Some considerations include pain management with nonsteroidal anti-inflammatory drugs, physical therapy, and steroid injections for symptomatic joint implants. If only cutaneous symptoms develop temporally associated with implant placement, therapeutic options for allergic contact dermatitis, such as topical corticosteroids, topical calcineurin inhibitors, and systemic corticosteroids, could be considered. However, if pain, joint swelling, and cutaneous symptoms are not responsive to conservative therapies, or if there is joint implant loosening, revision of the TJA with components to which the patient is not sensitized has been shown to resolve patient symptoms.[14,16,54]

There may be a role of desensitization in the future. Bonamonte et al[55] evaluated the efficacy of oral hyposensitization of 26 patients allergic to nickel. These patients were given a daily dose of 50 μg of elemental nickel in cellulose capsules for 3 months. Patients had alleviation of contact dermatitis symptoms during the trial despite continued nickel exposures; however, 50% of patients had relapses of clinical manifestation at sites of topical exposure to nickel at the 1-year follow-up.

Conclusion

Total joint arthroplasty procedures are increasing. Although delayed-type hypersensitivity reactions are not a common cause of joint implant failure, it is likely more patients will be referred for hypersensitivity testing as part of the evaluation of a poorly performing prosthesis or implant failure. The MoM implants are associated with more metal hypersensitivity compared with MoP or ceramic-on-ceramic prostheses. Evidence is not conclusive as to whether metal joint implants increase metal sensitivity or if metal sensitivity leads to prosthesis failure. Currently, patch testing is still the most widely used method for determining metal hypersensitivity; however, there are no standardized commercial panels specific for TJR available currently. Testing to a wider selection of materials common to orthopedic implants may improve the usefulness of patch testing. In vitro testing has shown comparable results in some studies, but its use in the clinical setting may be limited by the cost and need for specialized laboratories. Hypersensitivity testing is generally recommended before surgery for patients with a reported history of metal sensitivity. In cases of metal hypersensitivity-related joint failure, surgical revision may ultimately be required. It is recommended that the revised implant not contain metals or other material to which the patient is sensitized to decrease the risk of hypersensitivity reactions leading to prosthesis failure.

References

[1] Bini SA, Sidney S, Sorel M. Slowing demand for total joint arthroplasty in a population of 3.2 million. *J Arthroplasty*. 2011;26:124–128.
[2] Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. *Ann Rheum Dis*. 2004;63:825–830.
[3] Singh JA, Vessely MB, Harmsen WS, et al. A population-based study of trends in the use of total hip and total knee arthroplasty, 1969–2008. *Mayo Clin Proc*. 2010;85:898–904.
[4] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89:780–785.
[5] Thyssen JP, Menne T. Metal allergy—a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem Res Toxicol*. 2010;23:309–318.
[6] Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg Br*. 1974;56-B:626–642.
[7] Bozic KJ, Morshed S, Silverstein MD, Rubash HE, Kahn JG. Use of cost-effectiveness analysis to evaluate new technologies in orthopaedics. The case of alternative bearing surfaces in total hip arthroplasty. *J Bone Joint Surg Am*. 2006;88:706–714.
[8] Sedrakyan A, Normand SL, Dabic S, Jacobs S, Graves S, Marinac-Dabic D. Comparative assessment of implantable hip devices with different bearing surfaces: systematic appraisal of evidence. *BMJ*. 2011;343:d7434.
[9] Gawkrodger DJ. Metal sensitivities and orthopaedic implants revisited: the potential for metal allergy with the new metal-on-metal joint prostheses. *Br J Dermatol*. 2003;148:1089–1093.
[10] Cuckler JM, Moore KD, Lombardi AV Jr, McPherson E, Emerson R. Large versus small femoral heads in metal-on-metal total hip arthroplasty. *J Arthroplasty*. 2004;19:41–44.
[11] Granchi D, Cenni E, Giunti A, Baldini N. Metal hypersensitivity testing in patients undergoing joint replacement: a systematic review. *J Bone Joint Surg Br*. 2012;94:1126–1134.
[12] Graves SE, Rothwell A, Tucker K, Jacobs JJ, Sedrakyan A. A multinational assessment of metal-on-metal bearings in hip replacement. *J Bone Joint Surg Am*. 2011;93(suppl 3):43–47.
[13] Mahomed NN, Barrett JA, Katz JN, et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. *J Bone Joint Surg Am*. 2003;85-A:27–32.
[14] Gao X, He RX, Yan SG, Wu LD. Dermatitis associated with chromium following total knee arthroplasty. *J Arthroplasty*. 2011;26:665.e13–e16.
[15] American Academy of Orthopaedic Surgeons. OrthoInfo: total knee replacement. Cited April 12, 2013. http://orthoinfo.aaos.org/topic.cfm?topic=A00389. Accessed April 12, 2013.
[16] Bircher A, Friederich NF, Seelig W, Scherer K. Allergic complications from orthopaedic joint implants: the role of delayed hypersensitivity to benzoyl peroxide in bone cement. *Contact Dermatitis*. 2012;66:20–26.
[17] Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am*. 2001;83-A:428–436.
[18] Granchi D, Cenni E, Trisolino G, Giunti A, Baldini N. Sensitivity to implant materials in patients undergoing total hip replacement. *J Biomed Mater Res B Appl Biomater*. 2006;77:257–264.

[19] Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin Orthop Relat Res*. 1996;326:71–79.

[20] Budinger L, Hertl M. Immunologic mechanisms in hypersensitivity reactions to metal ions: an overview. *Allergy*. 2000;55:108–115.

[21] Browne JA, Bechtold CD, Berry DJ, Hanssen AD, Lewallen DG. Failed metal-on-metal hip arthroplasties: a spectrum of clinical presentations and operative findings. *Clin Orthop Relat Res*. 2010;468:2313–2320.

[22] De Smet KA, Van Der Straeten C, Van Orsouw M, Doubi R, Backers K, Grammatopoulos G. Revisions of metal-on-metal hip resurfacing: lessons learned and improved outcome. *Orthop Clin North Am*. 2011;42:259–269, ix.

[23] Thyssen JP, Jakobsen SS, Engkilde K, Johansen JD, Soballe K, Menne T. The association between metal allergy, total hip arthroplasty, and revision. *Acta Orthop*. 2009;80:646–652.

[24] Summer B, Paul C, Mazoochian F, et al. Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni. *Contact Dermatitis*. 2010;63:15–22.

[25] Waterman AH, Schrik JJ. Allergy in hip arthroplasty. *Contact Dermatitis*. 1985;13:294–301.

[26] Rooker GD, Wilkinson JD. Metal sensitivity in patients undergoing hip replacement. A prospective study. *J Bone Joint Surg Br*. 1980;62-B:502–505.

[27] Schalock PC, Thyssen JP. Metal hypersensitivity reactions to implants: opinions and practices of patch testing dermatologists. *Dermatitis*. 2013;24:313–320.

[28] Thyssen JP, Menne T, Schalock PC, Taylor JS, Maibach HI. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol*. 2011;164:473–478.

[29] Basko-Plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. *Dermatitis*. 2011;22:65–79.

[30] Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am*. 2005;87:28–36.

[31] Grammatopoulos G, Beard D, Gibbons C, et al. Outcome of failed hip resurfacing revised to THR depends on revision indication. *J Bone Joint Surg Br*. 2010;92-B:517.

[32] Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br*. 2008;90:847–851.

[33] Mahendra G, Pandit H, Kliskey K, Murray D, Gill HS, Athanasou N. Necrotic and inflammatory changes in metal-on-metal resurfacing hip arthroplasties. *Acta Orthop*. 2009;80:653–659.

[34] Kwon YM, Thomas P, Summer B, et al. Lymphocyte proliferation responses in patients with pseudotumors following metal-on-metal hip resurfacing arthroplasty. *J Orthop Res*. 2010;28:444–450.

[35] Tower SS. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. *J Bone Joint Surg Am*. 2010;92:2847–2851.

[36] Gilbert CJ, Cheung A, Butany J, et al. Hip pain and heart failure: the missing link. *Can J Cardiol*. 2013;29:639.e1–639.e2.

[37] Dahms K, Sharkova Y, Heitland P, Pankuweit S, Schaefer JR. Cobalt intoxication diagnosed with the help of Dr House. *Lancet*. 2014;383:574.

[38] Mayor MB, Merritt K, Brown SA. Metal allergy and the surgical patient. *Am J Surg*. 1980;139:477–479.

[39] Cousen PJ, Gawkrodger DJ. Metal allergy and second-generation metal-on-metal arthroplasties. *Contact Dermatitis*. 2012;66:55–62.

[40] Camacho-Halili M, Axelrod S, Michelis MA, et al. A multi-center, retrospective review of patch testing for contact dermatitis in allergy practices. *Ann Allergy Asthma Immunol*. 2011;107:487–492.

[41] Davis MD, Wang MZ, Yiannias JA, et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. *Dermatitis*. 2011;22:256–271.

[42] DORMER Laboratories. MET-1000 (metal series) patch testing. Cited April 12, 2013. http://www.dormer.ca/Chemosite/SeriesDetails.aspx?Series=MET-1000. Accessed April 12, 2013.

[43] Atanaskova Mesinkovska N, Tellez A, Molina L, et al. The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. *Arch Dermatol*. 2012;148:687–693.

[44] Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA. Sensitivity to titanium. A cause of implant failure? *J Bone Joint Surg Br*. 1991;73:25–28.

[45] Valentine-Thon E, Schiwara HW. Validity of MELISA for metal sensitivity testing. *Neuroendocrinol Lett*. 2003;24:57–64.

[46] Christiansen K, Holmes K, Zilko PJ. Metal sensitivity causing loosened joint prostheses. *Ann Rheum Dis*. 1979;38:476–480.

[47] Summer B, Sander CA, Przybilla B, Thomas P. Molecular analysis of T-cell clonality with concomitant specific T-cell proliferation in vitro in nickel-allergic individuals. *Allergy*. 2001;56:767–770.

[48] Thomas P, Braathen LR, Dorig M, et al. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy*. 2009;64:1157–1165.

[49] Beecker J, Gordon J, Pratt M. An interesting case of joint prosthesis allergy. *Dermatitis*. 2009;20:E4–E9.

[50] Frigerio E, Pigatto PD, Guzzi G, Altomare G. Metal sensitivity in patients with orthopaedic implants: a prospective study. *Contact Dermatitis*. 2011;64:273–279.

[51] Fox S. Case series: identification of patients at risk for arthroplasty failure. *J Allergy Clin Immunol*. 2009;123:S63.

[52] Campbell A. Nickel allergy and nickel free implants in joint replacement surgery: an analysis of current practice in Scotland. *J Orthop*. 2010;7:e5.

[53] Kranke B, Aberer W. Multiple sensitivities to metals. *Contact Dermatitis*. 1996;34:225.

[54] Campbell P, Shimmin A, Walter L, Solomon M. Metal sensitivity as a cause of groin pain in metal-on-metal hip resurfacing. *J Arthroplasty*. 2008;23:1080–1085.

[55] Bonamonte D, Cristaudo A, Nasorri F, et al. Efficacy of oral hyposensitization in allergic contact dermatitis caused by nickel. *Contact Dermatitis*. 2011;65:293–301.