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REVIEW ARTICLE

Shoulder arthroplasty in the patient with metal hypersensitivity

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Background: The in vivo effects of metal hypersensitivity remain a topic of much debate. At the core of this debate is the possible, although still hotly contested, link between metal hypersensitivity and poorly functioning or failing implants. There are multiple studies on this topic in the hip and knee arthroplasty literature, but the applicability of this experience to shoulder arthroplasty remains unclear. Although how often metal hypersensitivity affects shoulder arthroplasty patients remains uncertain, a multitude of case reports have implicated metallic implants as a source of local and systemic allergic reactions. We recommend a cautious approach to patients with a history of metal hypersensitivity, including a careful evaluation of suspected metal hypersensitivities in all patients undergoing shoulder arthroplasty. If available, we recommend a metallic implant with low to no nickel content in patients with metal hypersensitivity. Given the large and increasing, number of total shoulder arthroplasty procedures and the high percentage of the population having a known or suspected metal hypersensitivity, this review is intended to guide and educate the shoulder surgeon in the evaluation and treatment of this patient population and to point out the areas where evidence-based recommendations are lacking.

Level of evidence: Narrative Review.

Keywords: Shoulder arthroplasty; metal hypersensitivity; orthopedic metal composition; osteolysis; wear debris; hypoallergenic implant options

The incidence of total shoulder arthroplasty (TSA) is steadily increasing: approximately 10,000 such procedures were performed in the United States in 2002, increasing to nearly 27,000 in 2008.[27] Part of this recent increase can be attributed to expanded options for patients with a wide range of shoulder pathology. Specifically, the reverse shoulder prosthesis, which was approved by the U.S. Food and Drug Administration in 2003 for use in the United States, allows effective treatment of a broader range of shoulder pathology, including rotator cuff tear arthropathy, fracture sequelae, revision shoulder arthroplasty, tumor resection, acute fracture, and chronic fracture sequelae.[31,47]

Successful, long-lasting implantation of a metal and plastic joint replacement requires the surgeon to understand not only the mechanical effects on the prosthesis in vivo but also any potential biologic response. One such issue involves the patient with a suspected or known metal hypersensitivity. Dermal manifestations of metal hypersensitivity are relatively common, affecting approximately 10% to 15% the general population.[20] Specifically, sensitization to nickel alone is estimated at approximately 10% of the population. Other metals that are known to cause a reaction

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are beryllium, cobalt, and chromium.[20] Clinical findings in such hypersensitivity reactions include dermatitis, rash, and erythema. Rarely, systemic signs have been appreciated, including generalized pruritus and dyspnea.[14,23] In contrast to these topical metal reactions, the potential for hypersensitivity to metal implanted deeper in the body is not as well understood.

One of the first case reports of presumed in vivo hypersensitivity to metallic orthopedic implants was reported in the *Journal of the American Medical Association* in 1975. Barranco et al[2] described a 20-year-old woman seen with extensive eczematous dermatitis on the chest and back 5 months after stainless steel screws had been implanted to treat a chronic patellar dislocation. The patient's dermatologic condition persisted despite extensive topical steroid administration. The day after the screws were removed, the erythema and pruritus markedly subsided. The authors noted the composition of the stainless steel screws included significant amounts of chromium (20%), nickel (14%), and molybdenum (4%).

More recently, Gao et al[14] reported a case of systemic dermatitis after implantation of a cobalt-chromium-molybdenum total knee arthroplasty (TKA). The authors reported the patient developed eczema near the operative scar at 6 months postoperatively. During the next 3 months, the eczema spread and became chronic over a period of 1 year. The dermatitis was diffuse, with lesions at the neck, wrist, hand, ankle, and buttock, with corresponding severe pruritus. These lesions, as well as the pruritus, were refractory to antihistamines and corticosteroids, although whether these were oral or topical is unclear from the description. A skin biopsy specimen showed a nonspecific perivascular lymphocyte and eosinophil infiltration of the upper dermis, suggestive of a type IV delayed-type hypersensitivity (DTH) reaction. A patch test result was highly positive for chromium sensitivity (++++). Given these data, the patient was diagnosed with chromium hypersensitivity, and a revision TKA was performed with a zirconium-niobium (Smith and Nephew, London, United Kingdom) implant. The authors reported the resolution of pruritus at 3 days and eczema at 2 months postoperatively, with no recurrence of symptoms at the 1-year follow-up. Two other case reports of similar dermal manifestations of metal hypersensitivity after TKA have also been reported,[4,21] although the authors did not report whether the dermatitis resolved with removal of the offending implants.

Many orthopedic implants contain large percentages of nickel as well as other trace metals (Table I). Stainless steel is less commonly used in today's arthroplasty implants; however, most screws are made of this composite metal. As reported in Table I, most stainless steel alloys contain a large percentage of nickel.[11,20] Cobalt alloy, frequently used for total joint arthroplasty, has approximately 1% nickel content.[20] It is pertinent to note that titanium alloy has no appreciable nickel content, although there has been evidence to suggest even titanium ions can rarely provoke a relevant immunologic reaction.[28]

Given the large, and increasing, number of TSA procedures and the high percentage of the population having a known or suspected metal hypersensitivity, this review is intended to guide and educate the shoulder surgeon in the evaluation and treatment of this patient population and highlight the areas where evidence-based recommendations are lacking.

Basic science of metal ion hypersensitivity

All metals that come into contact with biologic systems corrode, thereby releasing ions.[20,24] These ions can then activate an immune response by forming a complex with native proteins. This metal-protein complex becomes the "allergen" because the combination of the metal with the patient's own protein is no longer recognizable by the immune system as "self," and an inflammatory reaction ensues.[20] Hypersensitivity can be an immediate (within minutes) humoral response initiated by an antibody or a delayed (within hours to days) cell-mediated response. Implant-related reactions are generally believed to be DTH reactions.[14,16,20] Cell-mediated DTH is characterized by activation of sensitized lymphocytes by an antigen, release of various cytokines, and finally, recruitment and activation of macrophages. In the dermis, the Langerhans cell, part of the monocyte cell line and similar in function to macrophages, is the primary antigen-presenting cell (APC) associated with dermal hypersensitivity.[15,41] In subcutaneous/periprosthetic tissue, the dominant APC responsible for mediating an implant-related hypersensitivity response remains unknown. There are several proposed candidate APCs in the periprosthetic region, however, including macrophages, endothelial cells, lymphocytes, Langerhans cells, and dendritic cells.[20,35,48]

Experience in hip and knee arthroplasty

No prospective or retrospective studies have evaluated the link between metal hypersensitivity and aseptic loosening of humeral or glenoid components in TSA, although an abundance of literature has been devoted to this topic in the hip and knee, which may give some insight into the care of TSA patients. In 2001, Hallab et al[20] reviewed multiple studies performed in the 1970s and 1980s that attempted to find a correlation between metal sensitivity and premature implant failure. Fifteen studies were included and summarized in their review. These reports found a weighted mean prevalence of sensitivity to nickel, cobalt, or chromium of 25% in patients with a well-functioning implant, which was approximately twice that of the general population.[3,20] When looking at patients with a "failed or poorly functioning" implant, the prevalence of metal

Table I Metal composition of common orthopaedic alloys (in percentages)*

Implant alloy	Nickel	Cobalt	Chromium	Titanium	Molybdenum	Aluminum	Vanadium
Stainless steel	13-15.5	—	17-19	—	2-4	—	—
Cobalt alloy	1	62-67	27-30	—	5-7	—	—
Titanium alloy	—	—	—	89-91	—	5.5-6.5	3.5-4.5

* Adapted from Hallab et al[20] and Disegi and Eschbach.[11]

hypersensitivity was 60%, nearly 4 times greater than the population at large. The authors were quick to note, however, that all of the reported studies were performed on heterogeneous patient populations and used different strategies to test metal sensitivity. Neither the original articles' authors nor the reviewers came to the conclusion that a direct cause-and-effect relationship exists between metal hypersensitivity and implant failure. Instead, the question remains: whether the poorly functioning implants failed due to a pre-existing metal hypersensitivity causing loosening, or perhaps the patients were sensitized *because* the device failed, subsequently causing a greater metal ion burden. This unanswered question remains at the center of the discussion on the role of metal hypersensitivity in clinical outcomes of orthopedic implants.

Adding to the hypothesis that metal hypersensitivity may play a significant role in early implant failure, Granchi et al[18] showed that the median survival of total hip arthroplasty (THA) implants was 120 months in patients who had no skin reaction to patch testing, whereas THA failure occurred significantly earlier (78 months) in their patients with positive patch testing. The authors concluded that although a direct cause-and-effect relationship between sensitization and early implant failure could not be established, the shorter lifespan of THA implants in patients who had a positive patch testing supported the significant role of metal hypersensitivity in contributing to implant failure. Furthermore, a systematic review and meta-analysis by the same group in 2012 showed a higher probability of developing a metal allergy after THA when failed prostheses were compared with stable prostheses (odds ratio, 2.76; 95% confidence interval, 1.14-6.70).[17]

Most of the particulate wear debris is generated at the joint articulation, and different bearing surfaces certainly affect the type and amount of wear that is generated.[36] For example, metal-on-metal (MoM) hip replacement has been extensively studied due to the reports of adverse local tissue effects. In one of the seminal works on this topic, Willert et al[48] looked at the clinical data and histologic specimens of 19 revisions of MoM THAs. They used histologic specimens from 3 other groups, 2 of which had non-MoM THA, as controls. They found several characteristic histologic features of patients with an MoM implant, which included diffuse and perivascular infiltrates of T and B lymphocytes and plasma cells, high endothelial venules, massive fibrin exudation, accumulation of macrophages, and infiltrates of eosinophilic granulocytes and necrosis.[48] The control tissues did not show similar signs of immune reactions. Of note, 5 of 19 revision cases were reimplanted with a second-generation MoM implant. Clinically, none of perioperative symptoms resolved in the 5 patients who were revised with another MoM prosthesis. The authors reported resolution in 2 of these 5 only once a second revision was performed to a non-MoM implant and suggested the patients had been sensitized to the components of an all-metal bearing.

The authors coined the term "aseptic lymphocyte-dominated vasculitis-associated lesion," or ALDVAL, to describe this characteristic tissue pattern. They concluded that there was certainly a real, demonstrable, periprosthetic tissue reaction, but the overall prevalence of this reaction appeared very low. Furthermore, a connection between the extent of the immunologic response and the amount of metal contained in the tissue could not be established.[48] Finally, they did not comment on the possibility of a direct cause-and-effect relationship of metal sensitivity and implant failure, although their clinical data would suggest at least an association.

Although a direct causal relationship between metal hypersensitivity and implant failure has not been shown to date, there is evidence that local metal ion reactions can directly influence bone and soft tissue metabolism. Cadosch et al[5] reviewed the relationship between metal ions released through biocorrosion and bone cell metabolism. Through in vitro studies, they suggest a direct relationship between released metal ions and increased differentiation and activation of osteoclast precursors, a likely source for increased periprosthetic osteolysis. Furthermore, they summarized several studies that suggest high local concentrations of metal ions may affect the differentiation and function of osteoblasts, thereby inhibiting periprosthetic bony growth.[12,44,50]

Appropriate history and evaluation to identify the at-risk patient

The workup of a preoperative patient with a suspected metal sensitivity begins with a thorough medical history, including asking specifically about all instances of dermal or generalized reactions to metals. Many patients may report a reaction to inexpensive silver. By law, sterling silver must contain at least 92.5% silver, with copper

Table II Metal composition of common, noncustom, Food and Drug Administration-approved shoulder implant systems

Implant system	Component	Metal composition	Contains nickel? (Yes/No)
Anatomic			
Tornier Aequalis*	Stem	Titanium alloy	No
	Head	Titanium alloy	No
	Head	Cobalt chrome	Yes
Tornier Ascend	Stem	Titanium alloy	No
	Head	Cobalt chrome	Yes
Tornier Affinity	Stem	Titanium alloy	No
	Head	Cobalt chrome	Yes
Biomet Comprehensive*	Stem	Cobalt chrome	Yes
	Stem	Titanium alloy	No
	Head	Titanium alloy	No
	Head	Cobalt chrome	Yes
Stryker Solar	Stem	Titanium alloy	No
	Head	Cobalt chrome	Yes
Zimmer Anatomic	Stem	Titanium alloy	No
	Head	Cobalt chrome	Yes
Zimmer Bigliani/Flatow Complete	Stem	Titanium and tantalum	No
	Head	Cobalt chrome	Yes
DePuy Global	Stem	Titanium	No
	Head	Cobalt chrome	Yes
Reverse			
Tornier Aequalis Reverse*	Cemented stem	Cobalt chrome	Yes
	Cementless stem	Titanium alloy	No
	Baseplate	Titanium alloy	No
	Glenosphere	Cobalt chrome	Yes
	Glenosphere	Titanium alloy	No
Biomet Comprehensive Reverse	Stem	Cobalt chrome	Yes
	Glenosphere	Titanium alloy	No
	Glenosphere	Cobalt chrome	Yes
	Humeral tray	Titanium alloy	No
	Humeral tray	Cobalt chrome	Yes
Biomet BioModular Reverse*	Stem	Titanium alloy	No
	Humeral tray	Titanium alloy	No
	Glenosphere	Titanium alloy	No
DePuy Delta Xtend	Cemented stem	Cobalt chrome	Yes
	Cementless stem	Titanium alloy	No
	Metaglene	Titanium alloy	No
	Glenosphere	Cobalt chrome	Yes
Zimmer Trabecular Metal Reverse	Stem	Titanium and tantalum	No
	Glenosphere	Cobalt chrome	Yes

Biomet Inc, Warsaw, IN, USA; DePuy Orthopaedics, Warsaw, IN, USA; Stryker, Rutherford, NJ, USA; Tornier, Edina, MN, USA; Zimmer, Warsaw, IN, USA.
* Complete nickel-free implant available.

generally making up the remaining metal in this relatively bio-inert alloy. However, metals known collectively as ''nickel silver'' (Mexican silver, Indian silver, alpacca) are alloys of nickel, copper, and zinc that contain little to no silver at all. This type of inexpensive jewelry, with significant nickel content, can frequently cause hypersensitivity reactions, especially when perspiration provides a ''carrier'' for the nickel alloy (similar to an aqueous carrier in a patch test).[39,40]

Historically, dermal patch testing has been used most often in determining the presence or severity of a patient's metal sensitivity. Transdermal patch testing involves exposing the skin to an antigen (metal ion) bound to a carrier, such as petroleum jelly. After exposure of 48 to 96 hours, depending on ion concentration and specific testing kit instructions, the skin reaction is graded on a scale of 1 (mild or absent response) to 4 (severe red rash with weeping blisters).[20] The applicability of this mode of testing to the reaction of metals in synovial tissue is still debated.[17,20,23] As stated above, the primary cell responsible for mediating an immunologic response in the dermis is the Langerhans cell, whereas the dominant APC in the

periprosthetic tissues remains unknown. In addition, the short duration of exposure (48-96 hours) probably does not provide an accurate portrayal of the long-term exposure of a total joint implant.[17,20,35]

Perhaps a more accurate and applicable testing method involves an in vitro challenge. The lymphocyte transformation test has been developed to study the proliferation of lymphocytes, obtained from a peripheral blood sample, after contact with different metallic substances.[7,19,20,23] A variation on the lymphocyte transformation test, the memory lymphocyte immunostimulation assay,[45] as well as leukocyte migration inhibition testing,[19,20,42] have been developed as alternative in vitro options with equal sensitivity and specificity as existing testing strategies. However, given the questions regarding applicability, as well as the cost and need for specialized laboratories, large scale in vitro testing has, to date, been unpopular.[17,35]

In their 2012 meta-analysis, Granchi et al[17] determined that, given the available data, preoperative or postoperative screening for metal hypersensitivity in patients undergoing joint arthroplasty should not be recommended as a general screening tool for patients without a history of cutaneous metal hypersensitivity because no predictive value was found with a positive *or* negative result. This review included 22 studies in which metal sensitization was analyzed in patients undergoing total joint replacement. However, they noted that most authors *did* recommend some sort of preoperative testing, whether patch testing or the lymphocyte transformation test, in patients with a history of actual or suspected metal allergy.[1,17,35]

A poll in 2013 of 119 dermatologists who receive metal hypersensitivity referrals showed 54% of respondents favored dermal patch testing before implantation, whereas 38% forgo formal testing and recommend a titanium-only prosthesis based on concern from a history of cutaneous metal hypersensitivity alone.[38] A Cleveland Clinic dermatology group shared their experience with preoperative and postoperative testing for a variety of metal implants, including THA, total knee arthroplasty (TKA), total shoulder arthroplasty (TSA), and spinal hardware (among others). They recommend preoperative patch testing in patients with a clinical history of cutaneous metal hypersensitivity.[1] They reported no dermatologic symptoms after implantation of nonsensitizing metals (based on preoperative positive patch testing) and complete resolution of dermal symptoms after removal of the offending metal (based on postoperative positive patch tests). Furthermore, in 13 of 21 cases of positive preoperative patch testing, the surgeon chose an implant different from the implant of choice based on the positive result. Whether justified or not, this underscores the effect of preoperative patch testing on the surgeons' decision making and availability of implants with alternative metal compositions (Table II).

The literature consensus generally recommends patch testing for patients with a history of cutaneous metal hypersensitivity.[17] The authors of these recommendations concede that the data behind patch testing, including its positive and negative predictive values, are lacking. However, the test is simple and relatively benign; therefore, many advocate patch testing despite the dearth of concrete data. We, however, take a different strategy, due to the availability of titanium shoulder implants at comparable cost. We advocate the use of an implant system that does not contain nickel in any patient with a history that elicits concern for cutaneous metal hypersensitivity. In patients with a failed TSA, we recommend patch testing once infection and mechanical failure have been ruled out.

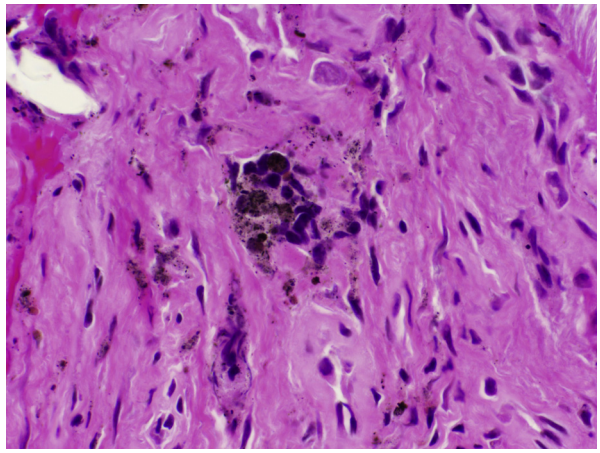

Figure 1 Histologic section shows abundant black metal particles in macrophages in tissue from resected failed reverse total shoulder arthroplasty (hematoxylin and eosin stain, original magnification ×600). Patient had obvious metallosis in his soft tissues and significant trunionosis of the implant.

Surgical management options

The glenohumeral articulation is a relatively non–weight-bearing surface; however, particulate debris still occurs in TSA, with translational motion being the predominate articulation.[22,32,49] Differences have been documented in the size, shape, and texture of particles generated by wear of shoulder components compared with those after THA.[46,49] In general, polyethylene particles in TSA are larger and more spherical than those found in THA.[49] Although no current, commercially available shoulder systems use MoM bearings, polyethylene and metallic particles have both been found in resected TSA implants.[26] The metallic particles, specifically, are felt to be generated at any location where metal parts interface, including Morse taper junctions, polyethylene locking mechanisms, and screw-implant interfaces in reverse shoulder baseplates.[8,10,37]

Day et al[10] recently presented their findings on fretting corrosion in shoulder arthroplasty implants at the 2014 American Academy of Orthopaedic Surgeons annual

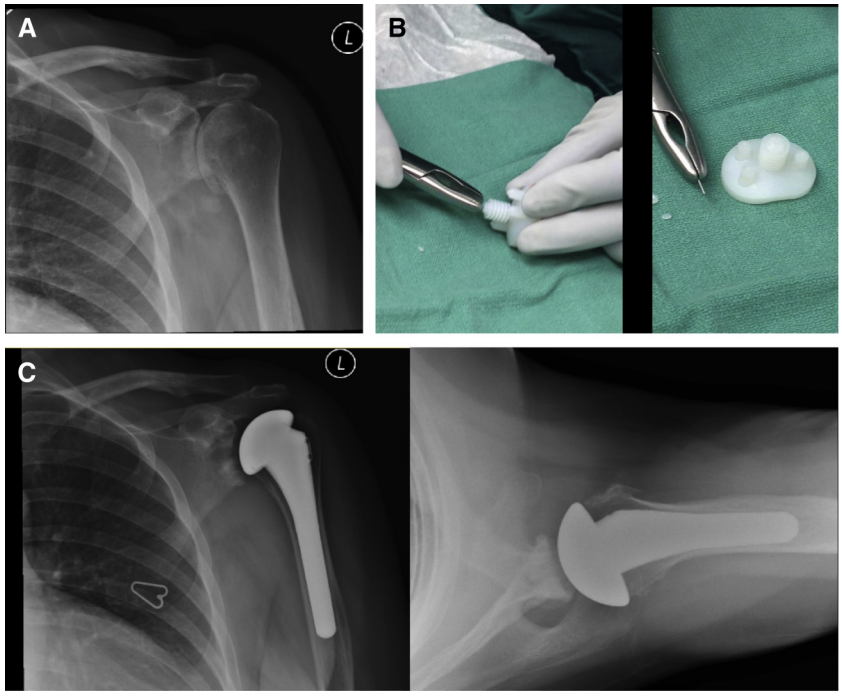

Figure 2 (**A**) A 68-year-old woman with end-stage osteoarthritis and a history of cutaneous sensitivity as well as a positive patch test to nickel. (**B**) Intraoperative photos demonstrate removal of the stainless steel marker with minimal disruption to the polyethylene glenoid component. (**C**) Postoperative views of an Aequalis titanium-zirconium-vanadium prosthesis (Tornier, Edina, MN, USA) with the glenoid stainless steel marker removed.

meeting. They reported moderate to severe fretting corrosion of the modular junctions in 23% of anatomic and 22% of reverse total shoulder implants. In shoulder arthroplasty, metallic debris could, in theory, predispose to both a macrophage-mediated osteolytic response as metal particles undergo so-called frustrated phagocytosis[9] as well as a DTH reaction as metallic particles generate metal ions that bind with host proteins (Fig. 1).[5,25,48]

The predominate bearing surface used in total joint arthroplasty in the United States, including hips, knees, and shoulders, is metal on polyethylene.[30,36] The current standard configuration for anatomic TSA is a metallic humeral stem and a polyethylene glenoid component. Metal-backed glenoid components have historically led to higher rates of glenoid failure,[13,33] although newer designs attempt to reverse that trend.[6] Even though most THA and TKA use metal-backed components, much of the data regarding metal hypersensitivity should be applicable in shoulder arthroplasty because the alloys used for the metallic portions of the prosthesis are similar. One major difference from a mechanical standpoint is the relative non–weight-bearing function of the glenohumeral joint, although we do know that metal ions are released via biocorrosion and weight bearing is not necessarily required for a significant ion burden.[8,10,20,24,32]

Given the uncertainty surrounding the possible link between metal hypersensitivity and loosening/failure of implants, many manufacturers have developed alternatives to the cobalt-chromium alloy. So-called hypoallergenic options have been proposed, including an oxidized zirconium femoral component with an all-polyethylene tibial component for TKA.[23] Various industrial coatings available are also available that theoretically insulate the sensitivity-inciting metal underneath a nonallergenic substance. Examples of such coatings include a thin adhesive chromium layer, 5 alternating intermediate layers out of chromium nitride-chromium carbonitride, and a final shielding layer of zirconium nitride.[29] Long-term data are unavailable on these prostheses, but short-term follow-up in patients with a history of metal sensitivity have been consistent with well-performing implants.[29] Further, long-term outcome data are needed to fully assess the performance of these alternative implant materials.

All-titanium implant options, where the potentially problematic nickel is not present, remain favored among orthopedic surgeons and dermatologists.[1,38,43] There have been case reports of presumed sensitivities to titanium implants[28,34]; however, most of the available data support a much lower incidence of adverse side effects to titanium alloy.[20,35] In the United States market, 2 companies have commercially available, Food and Drug Administration-approved, nickel-free titanium alloy components as standard, noncustom options for anatomic and reverse TSA (Figs. 2 and 3 and Table II). In an anatomic glenoid component, most manufacturers implant a stainless steel marker in the polyethylene for radiographic follow-up. This

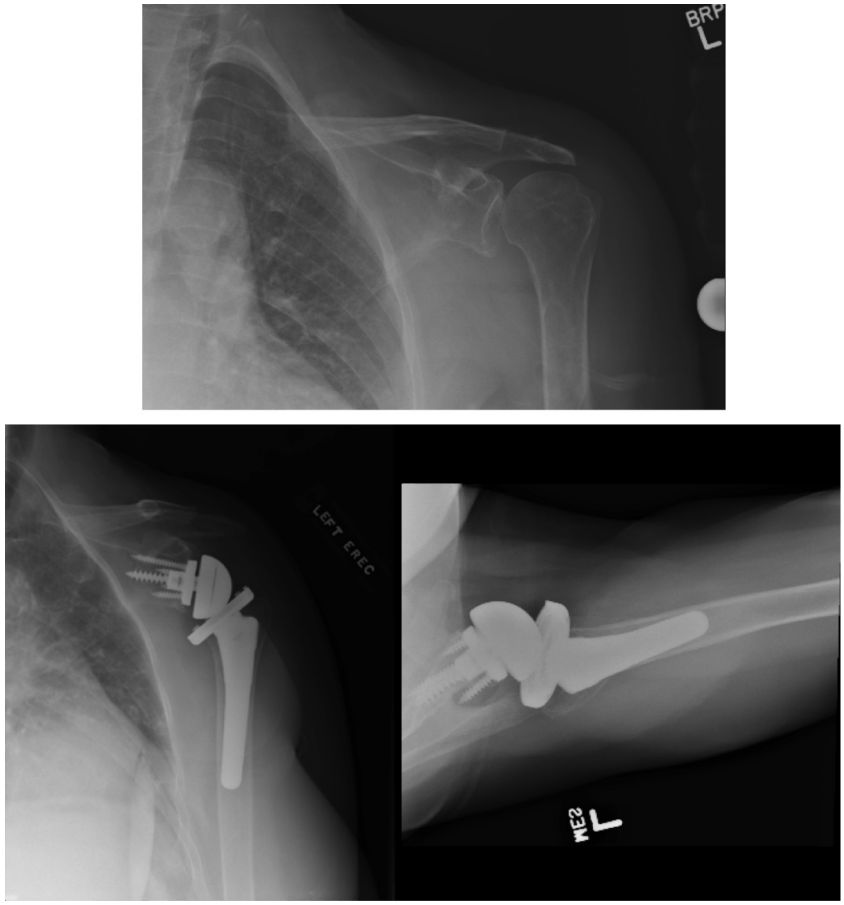

Figure 3 (**A**) A preoperative evaluation in a 65-year-old woman with end-stage osteoarthritis and a concomitant rotator cuff tear revealed a long history of sensitivity to nickel-containing jewelry. (**B**) Postoperative views with a Biomet Comprehensive titanium-aluminum-vanadium reverse total shoulder arthroplasty (Biomet Inc, Warsaw, IN, USA).

marker can be easily removed without significant damage to the polyethylene component (Fig. 2, *B*).

The authors' recommended practice guidelines

Preoperative evaluation before primary shoulder arthroplasty

- **History:** Screen for metal hypersensitivity by asking for any type of reaction to metals, including all types of jewelry (ie, earrings, bracelets, watches, etc).
- **Patch testing:** At the discretion of the surgeon. We do not use patch testing in this setting because we change our implant to a system that does not contain nickel based on a positive history alone.

Evaluation of a loose or painful shoulder arthroplasty

- **History:** Screening questions, as above.
- **Patch testing:** We recommend formal patch testing in this setting once infection and mechanical failure have been ruled out.

Conclusions

The in vivo effects of metal hypersensitivity remain a topic of much debate. At the core of this debate is the possible, though still hotly contested, role of metal hypersensitivity in poorly functioning or failing implants. Given this uncertainty, as well as the multitude of case reports that implicate metallic implants as a source of systemic allergic reactions,[2,14,28,34] we recommend careful evaluation of suspected metal hypersensitivities in all patients undergoing shoulder arthroplasty. As discussed above, there is no conclusive evidence supporting the positive or negative predictive value of dermal patch testing preoperatively, and there is also no consensus on the best preoperative testing modality. There are, however, multiple studies that suggest an *association* (but not direct causality) between metal hypersensitivity and early implant failure as well as documented dermal manifestations after implantation in patients with metal sensitivities. In the absence of reliable evidence-based recommendations, we do not recommend routine screening via patch testing or formal

allergist consultation in patients without this history. Furthermore, titanium-alloy implants should be considered in patients with a history of known or suspected metal hypersensitivity.

Disclaimer

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