REVIEWS

Hypersensitivity Reactions to Implanted Metal Devices: Facts and Fictions

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■ **Abstract**

The use of metals in the medical field has become increasingly prevalent over the past few decades. Patients find themselves being exposed to metals in a variety of ways, ranging from external exposure to instruments such as the stainless steel in surgical blades to internal exposure via medical devices being implanted in their bodies. There has been growing interest in the possibility of developing hypersensitivity reactions to constituent metals in medical implant devices, both in cutaneous and systemic forms. Hypersensitivity reactions to metals are uncommon, but they are reported and require appropriate evaluation and management, particularly if they are symptomatic. In view of the lack of consensus in the field on the appropriate steps to evaluate and manage patients with suspected metal hypersensitivity reactions, this review aims to analyze current evidence on hypersensitivity reactions to metallic implants in orthopedic surgery, endovascular surgery, obstetrics and gynecology, and dental surgery.

Key words: Metal hypersensitivity. Metallic implants.

■ **Resumen**

El empleo de metales dentro de la medicina ha ido aumentando de forma progresiva en las últimas décadas. Los pacientes se exponen a metales de diferentes formas desde fuentes externas, como instrumental quirúrgico como el presente en las hojas de acero de los bisturíes, hasta implantes metálicos. Como consecuencia de ello se está produciendo un interés creciente por la posibilidad de desarrollar reacciones de hipersensibilidad a metales presentes en los materiales y objetos implantados, tanto en forma de reacciones cutáneas como sistémicas. Las reacciones de hipersensibilidad a metales no son frecuentes, pero pueden desarrollarse, y por ello, requieren de un diagnóstico y tratamiento adecuado, especialmente en aquellos pacientes que desarrollen síntomas. No existe un consenso en el proceso diagnóstico ni en el tratamiento de estas reacciones en los pacientes con sospecha de alergia a metales. Esta revisión tiene por objeto actualizar la evidencia existente sobre las reacciones de hipersensibilidad a implantes metálicos en cirugía ortopédica, cirugía endovascular, cirugía obstétrica y ginecológica (OB-GYN) así como la dental.

Palabras clave: Hipersensibilidad a metales. Implantes metálicos.

Introduction

The use of metals in medicine has become increasingly prevalent over the past few decades. Patients find themselves exposed to metals in a variety of ways, ranging from external exposure to instruments such as the stainless steel in surgical blades to internal exposure via medical devices implanted in their bodies. There has been growing interest in hypersensitivity reactions—both cutaneous and systemic—to constituent metals in implanted medical devices. Although uncommon, hypersensitivity reactions to metals do occur and require appropriate evaluation and management, particularly if they are symptomatic. Given the lack of consensus among clinicians on the appropriate steps to evaluate and manage patients with suspected metal hypersensitivity reactions, this review aims to explore in depth the existing body of evidence pertaining to hypersensitivity reactions to metallic implants in orthopedic surgery, endovascular surgery, obstetrics and gynecology, and dental surgery.

The Rising Potential Impact of Metal Hypersensitivity

In the United States, the number of total knee replacements performed annually has doubled over the last decade, with more than 620 000 procedures carried out in 2009 [1] and an estimated 5.2 million total knee replacements performed from 2000 to 2010 [2]; these numbers are likely to double by 2020 [3]. A similar trend is noted for total hip replacements: the number of procedures among patients aged 45 and over more than doubled from 2000 to 2010, with 310 800 procedures being performed in 2010 [4]. The total incidence of total shoulder arthroplasty has also increased steadily, from 10 000 to 27 000 in 2008 [5]. In addition to orthopedic implants, the numerous medical devices that also have metal constituents include dental implants, intracoronary stents, prosthetic valves, endovascular prostheses, and selected gynecologic devices.

The association between metal implants and metal sensitivity is well documented, although, unfortunately, reactions are relatively unpredictable, poorly understood, and highly debated [6-8]. Dermal hypersensitivity to metal is common and can affect up to 15% of the population [9]. The insertion of metallic implants has been linked to hypersensitivity reactions, generally type IV delayed-type hypersensitivity reactions [9], which can manifest as cutaneous eczematous eruptions, as device failure, and as a range of adverse reactions, including chronic inflammation, pain, loosening of joint prostheses, and restenosis of cardiac stents [10]. In some cases, metallosis (metallic staining of the surrounding tissue), excessive periprosthetic fibrosis, and muscular necrosis have also been reported [11-13].

The link between metal hypersensitivity and metal implants has been established in a multitude of cohort studies. In 1966, the link between eczematous dermatitis and metallic orthopedic implants was first reported by Foussereau and Laugier [14], who observed that nickel was associated with hypersensitivity responses. One of the first few case reports was published in the Journal of the American Medical Association

in 1975: Barranco et al [15] reported the case of a 20-year-old woman with extensive eczematous dermatitis on the chest and back after stainless steel screws were implanted to treat chronic patellar dislocation. Extensive therapy with topical corticosteroids failed to alleviate the symptoms, but the eczema subsided the day after removal of the screws and disappeared after 72 hours. A more recent case report discussed a case of systemic dermatitis after placement of a cobalt-chromium-molybdenum implant in total knee arthroplasty (TKA); thanks to a revision TKA with a zirconium-niobium implant, pruritus resolved 3 days and eczema 2 months after surgery [16]. Apart from orthopedic implants, there are numerous case reports linking adverse immune reactions to metallic implants used in cardiovascular [17-19], plastic [20], and dental surgery [21-23]. There are more case reports concerning the use of stainless steel and cobalt alloy implants than titanium alloy implants [9].

Numerous cohort studies have examined the association between metal hypersensitivity and implant failure. In 2001, Hallab et al [9] looked at 15 studies carried out in the 1970s and 1980s and found a weighted mean prevalence of hypersensitivity to nickel, cobalt, or chromium of 25% in patients with well-functioning hip arthroplasties, as compared with a prevalence of 60% in patients with a failed or poorly functioning hip implant. In fact, the prevalence of metal hypersensitivity in the latter group was nearly 4-fold greater than in the general population. In 2006, Granchi et al [24] performed a retrospective case-control study of 223 patients and reported that in contrast to a median survival of total hip arthroplasty (THA) implants of 120 months in patients who had no reaction to patch testing, the median survival for patients with positive patch test results was only 78 months. In 2012, the same group performed a systematic review and meta-analysis of peer-reviewed literature that focused on metal sensitivity testing in patients undergoing total joint replacement. They found that the probability of developing a metal allergy was higher after surgery (OR, 1.52; 95%CI, 1.06-2.31) and that the risk was even higher when failed implants were compared with stable total joint replacements (OR, 2.76; 95%CI, 1.14-6.70) [25]. A few recent prospective studies have also suggested an increase in cases of metal allergy following THA, even in patients with well-functioning prostheses [26-28].

Therefore, a positive correlation between metal-induced hypersensitivity reaction and metallic implant failure is well-established in the literature, and it is clear that each is significantly associated with the other. However, none of the authors draw robust conclusions on the direction of causation: it remains unknown whether implants fail or function poorly owing to pre-existing metal hypersensitivity or whether secondary sensitization is the result of excessive metal release from failing implants [29].

In view of the aging population and increasingly frequent use of metallic devices, clarifying the association between metal hypersensitivity reactions and device failure not only has colossal repercussions in terms of health care costs, but it also holds immense potential for avoiding unnecessary morbidity [29]. The paucity of robust evidence to guide clinical practice in this area also raises possible legal issues. Physicians may expose themselves to unwarranted medical malpractice suits when patients allege inadequate preoperative allergy

assessment. This situation becomes even more problematic given the noticeable lack of established guidelines on standards of assessment and treatment, particularly in patients with self-reported metal allergies before surgery [30].

Orthopedic Implants

Orthopedic implants often contain nickel, cobalt, chromium, and/or titanium [31]. Stainless steel, which contains a large percentage of nickel, is often used for screws while cobalt-chromium alloy, which has approximately 1% nickel content, is often used in total joint arthroplasty [9,32]. Metal hypersensitivity has long been studied as a potential cause of complications after total joint arthroplasty, ever since the first case of metal-related dermatitis was first reported in 1966 [33-37]. Cutaneous manifestations of suspected metal hypersensitivity reactions can include localized and generalized eruptions in the form of erythema, urticaria, and vasculitis, and such manifestations can be observed with static implants, dynamic joint prostheses, and, occasionally, in the implants used in TKA [16,38-43].

Orthopedic hip implants underwent different stages of development, with the first generation of orthopedic hip bearings introduced in the 1960s and early 1970s being metal-on-metal (MoM), usually with cobalt-chromium alloys. The first-generation implants included several designs, including ring MoM press fit prostheses [44]. These bearings were associated with high rates of metal release and sensitization, and elevated levels of cobalt, nickel, and chromium were found in blood, hair, and urine samples, as compared with a lack of similar increase in patients with prostheses in which metal articulated with polyethylene [34,45-47].

There is conflicting evidence on the association between metal hypersensitivity in first-generation MoM hip arthroplasties and loosening of metallic implants causing failure of total joint arthroplasties [44]. In a study involving 50 patients, the prevalence of metal sensitivity in patients with unexplained loosening of implants was 73.7%, which is significantly higher than 14.8% in those with stable implants [47]. Other small studies support this association [42,48]. On the other hand, Brown et al [49] studied patients (n=20) with sterile, loose MoM McKee-Farrar hip replacements and found that none had positive patch test results and that the biopsy specimen from the surrounding tissue in the 17 patients who had revision surgery showed no histological evidence of metal hypersensitivity [49]. In view of the uncertainty of the possible association with metal hypersensitivity and implant failure, as well as other design-related mechanical shortcomings, MoM bearings fell out of favor and were replaced with Charnley metal-on-plastic (MoP) prostheses [50].

It is arguable that MoP prostheses fared better than MoM prostheses in terms of metal hypersensitivity. A prospective study showed that there was no evidence of induction of metal hypersensitivity after total hip replacement with MoP articulations [51]. Metal allergy also appeared to be an uncommon cause of prosthesis failure, and skin reactions and joint loosening have been shown to be uncommon in patients known to be nickel-allergic before surgery [52]. Positive patch test results to acrylates, cement, and cement components were also infrequent or shown to be no different between patients with loosened or stable total knee arthroplasty or controls with no implants [2,47,52-54].

The pathophysiology of immune reactions to MoM and MoP prostheses also differs and likely has an impact on the varying clinical outcomes of the implants. MoP implants generally produce a higher volume of wear particles than MoM implants, but the latter generate a larger number of particles, as metal particles are an order of magnitude smaller [55-59]. The adaptive immune system reacts differently to MoM and MoP implants: unlike MoM implants, a specific cell-mediated response to ultrahigh molecular weight polyethylene (UHMWP) does not appear to play a major role in MoP implant loosening. In MoM implants, cobalt-chromium particles generate metal ions that act as haptens and combine with large carrier protein molecules to elicit immune responses [9,60-62]. Pseudotumours are also strongly associated with MoM arthroplasties [63,64], although the term pseudotumour has also been used to describe the rare development of granulomatous soft-tissue mass in MoP arthroplasties [65-73]. The major histopathological feature of the MoP pseudotumors is a marked macrophage response to UHMWP wear particles, which contrasts with the significantly lymphocytic infiltrate often seen in MoM pseudotumours [63,69-72,74,75]. The outcome of revision surgery in patients with pseudotumours is often poor [64], and Grammatopoulos et al [76] suggest that the persistence of this lymphoid infiltrate in periprosthetic tissues may be responsible for the poor outcomes observed.

MoP implants were not without problems: periprosthetic bone resorption and aseptic loosening were common major problems causing implant failure [47]. Second-generation MoM hip replacements were introduced in the 1980s to tackle this problem and have a lower volumetric wear rate, high fracture toughness, and reduced risk of postoperative instability owing to the use of larger femoral heads [77]. However, it remains unclear whether these replacements are associated with metal allergy and loosening of implants. Athanasou et al [78] note that reports of an adverse local tissue response to deposition of cobalt-chromium particles in periprosthetic tissues in modern third-generation MoM implants are similar to those from studies that analyzed first-generation MoM implants, arguing that insufficient importance was assigned to these findings in the earlier studies.

The existing literature has yielded conflicting results, and the degree to which metal sensitivity impacts on implant viability is highly contested. A large case-control study with 356 cases and 712 controls found that the risk of surgical revision of THA was not increased in patients with metal allergies and that the risk of metal allergy was not increased after THA [79]. However, some studies support the opposite conclusion, although their cohorts are smaller. A retrospective series of 165 patients found that patients with early osteolytic changes had a significantly higher rate of patch test positivity for cobalt than controls [80]. Studies by Antony et al [81] and Milavec-Puretic et al [82] also found a higher rate of metal allergy in patients with joint loosening and prosthetic failure and patients undergoing revision surgery for a failed implant, respectively. The literature review by Hallab et al [9] in 2001

revealed that the prevalence of metal allergy was ~25% among patients with a well-functioning arthroplastic hip implant and 60% among patients with a failed or poorly functioning implant [9].

Many studies, including case reports, that look at histopathological samples of periprosthetic tissues also support the link between metal hypersensitivity, wear particles, and implant failure [63,83-88]. Korovessis et al [89] looked at histological samples of periprosthetic tissues from 11 patients who had undergone revision arthroplasty because of aseptic loosening or technical failure and found metallosis and extensive lymphocytic and plasma cell infiltration around the metal debris. The group concluded that their findings support the possibility of an association between metal hypersensitivity and osteolysis and aseptic loosening in hips with MoM implants [89]. As mentioned earlier, pseudotumors are strongly associated with second-generation MoM implants [63,64,66,67,90,91]. The presence of acute, lymphocyte-dominated vasculitis-associated lesions (ALVALs), which are perivascular lymphocytic infiltrates comprising mainly T cells, strongly suggests a hypersensitivity reaction; these lesions are often found in patients with failed MoM implants and are more common in women under the age of 40 years [76,92-94].

Unsurprisingly, there is no consensus between studies on TKA. On the one hand, some studies support a relationship between pre-existing metal allergy, metal hypersensitivity reactions to TKA, and implant failure. In a prospective study of 94 patients with total knee arthroplasty, positive patch test results to metals were significantly more common in patients with a loose prosthesis (59%) than in stable patients (48%) or controls with no implants (20%) [95]. The same study showed that implant failure was 4 times more likely in patients with a medical history of metal allergy before receiving a knee implant [95]. Another study showed a significant association between the preoperative positive lymphocyte stimulation test result for chromium and the subsequent development of implant-related eczema [96].

On the other hand, metal hypersensitivity after TKA is quite rare and is often only a diagnosis of exclusion, after ruling out other much more common causes of pain and swelling such as infection, instability, component loosening, malrotation, referred pain, or chronic regional pain syndrome [97]. There are also studies that strongly dispute the link between metal hypersensitivity and implant failure. A recent matched cohort study by Bravo et al [98] of 127 patients with 161 TKAs and 161 control knee arthroplasties showed that patients with a positive patch test result did not have higher complication, reoperation, or revision rates than patients with a negative patch test result and matched controls. The authors did not find any statistically significant difference in postoperative pain between patients with positive and negative skin patch results and controls. An older study of 50 patients who underwent metal hinge arthroplasty of the knee showed no correlation between positive patch test reactions and loosening of the prosthesis [99]. A recent review of the literature by Middleton and Toms [100] arrived at the conclusion that although a relationship is present, they could not find any evidence of implant failure due to allergy. However, patient-reported allergy is found to be associated with decreased functional outcomes after TKA and decreased mental health scores after THA [101].

The number of total shoulder arthroplasties performed in the United States increased steadily from 10 000 in 2002 to 27 000 in 2008 [5]. Although numerous studies on THAs and TKAs have been performed, there are no prospective or retrospective studies that examine the link between metal hypersensitivity and aseptic loosening of total shoulder arthroplasty [31].

Bone cement components (methyl methacrylate, N, N-dimethyl-p-toluidine, and benzoyl peroxide with added antibiotics [mainly gentamicin or tobramycin]) can also cause hypersensitivity reactions [102]. While there are small-group studies that report hypersensitivity reactions to these individual components [103,104], the extent to which the individual components are directly responsible for hypersensitivity-induced implant failure is uncertain.

Intravascular Devices

Intravascular devices such as coronary stents, perforated foramen occluders, pacemakers, and implantable cardioverter defibrillators contain several metals and may cause hypersensitivity reactions.

Percutaneous transluminal coronary angioplasty and stent placement are becoming more prevalent, with bare metal stents and drug-eluting stents (DES) being commonly used. Bare metal stents are often made with several alloys, including stainless steel, and metallic ions are most likely the potential allergens in coronary stents [105]. DES may also contain alloys such as stainless steel and cobalt-chromium, but other allergens include the polymer coating the stent. Svedman et al [106] showed that metal can be released from coronary stents in vitro, and it has long been postulated that hypersensitivity to the metallic components of the stent may lead to in-stent restenosis (ISR).

Current literature on the link between pre-existing metal allergies, metal hypersensitivity reactions, and ISR has yielded conflicting results. Hillen et al [107] and Norgaz et al [108] reached the conclusion that pre-existing metal allergy should not be considered a risk factor for developing ISR, although they acknowledged that the small number of patients limited the study. Thyssen et al [109] performed an individual linkage study of 149 patients and found that nickel and/or chromium allergy in dermatitis patients does not appear to increase the overall risk of ISR after percutaneous coronary intervention. Honari et al [105] reached the same conclusion after an extensive review of the literature in 2008, namely, that studies performed until then often involve a limited number of patients and known risk factors (eg, stent length, reference diameter, patient characteristics including diabetes, and smoking) may confound the results. However, a recent meta-analysis of 9 studies by Gong et al [110] in 2013 (total of 1223 patients) arrived at the opposite conclusion, namely, having a pre-existing metal allergy increases the risk of ISR, with an odds ratio of 2.65. The study also found that the odds ratio for Asian patients was higher than for European patients (3.71 vs 2.25), suggesting that the former group may be more susceptible to ISR.

With regards to DES in particular, Honari et al [105] noted that the existing data "suggest spectrums of hypersensitivity responses to DES," which include excessive inflammation, stent malposition, aneurysm formation, and late in-stent thrombosis. It is worth noting that hypersensitivity reactions to DES may be driven by factors other than the metal components, ie, the polymer. First-generation DES were linked to a higher risk of late stent thrombosis than bare metal stents, and although the pathophysiology underlying this phenomenon was never clearly elucidated, the stent polymer was thought to be a contributing cause [111]. This has resulted in the development of newer generations of DES that contain biocompatible or biodegradable polymers, such as the Nobori stent [111].

Gold-coated stents were initially developed based on the belief that gold is an inert metal and would hence be less allergenic than alloys [10]. However, subsequent studies revealed that exposure to the gold in cardiac stents increases the risk of ISR. Kastrati et al [112] conducted a randomized trial to compare the risk of ISR with gold-coated versus uncoated steel stents and found that gold-coated stents were associated with an increased risk of restenosis during the first year after stenting. The study by Svedman et al [113] showed that this risk increases, particularly if the patient has a pre-existing gold allergy.

Transcatheter devices are also used for the repair of patent foramen ovale and atrial septal defects, with the most widely used occluders being the Amplatzer series (AGA Medical Corporation). The Amplatzer occluder is made of nitinol (approximately 45% nickel) [10], and on rare occasions, it may cause allergic reactions, as evidenced in sporadic case reports. A recent case report discusses a patient with severe progressive generalized exanthema 3 days after implantation of the Amplatzer device [114], while earlier case reports discussed patients presenting with systemic allergic reactions (such as fever and dyspnea) with no apparent rash, although they their patch test results were positive [115-117]. In all these cases, the patients' symptoms resolved either with the removal of the device or with the use of corticosteroids. A recent case series analyzed Atriasept II (Cardia), which contains less metallic material for treatment of patent foramen ovale, in 4 patients with known nickel allergy and reported no allergic manifestations or complications [118].

Titanium casing for pacemakers was developed in the 1970s. Pacemakers are frequently made of titanium because of its biocompatibility, but they also contain other metals such as nickel and silicone [105]. Implantable cardioverter defibrillators (ICDs) were introduced in the 1980s and approved by the United States Food and Drug Administration (FDA) in 1985 [105]. Allergic reactions to pacemakers and ICDs primarily involve localized pain or dermatitis that presents within 2 days to 24 months after implantation, with occasional reports of generalized pruritus that resolved with the removal of the pacemaker [18,119,120]. Other measures to manage hypersensitivity reactions include control of local dermatitis with topical corticosteroids, replacement of the device with one that does not contain the suspected allergen, such as customized silicone or gold-coated pacemakers [17,121-123], and wrapping the device in a PTFE sheet [124-128].

Obstetrics-Gynecology

Gynecologic devices may contain metals such as copper, nickel, and titanium, which could lead to systemic hypersensitivity reactions. Intrauterine contraceptive devices (IUD) that contain copper are used for reversible contraception in approximately 5% of British women and 10% of Danish women [129]. Copper IUDs, such as the Paragard 380A (Duramed Pharmaceuticals), are relatively pure and contain polyethylene, barium sulfate, and 99.9% pure cooper wire [130]. There are at least 5 cases in which patients with copper-containing IUDs reported having systemic allergic contact dermatitis that was confirmed using patch tests; the symptoms resolved upon removal of the copper-containing IUD in these cases [131-135].

Permanent contraceptive devices such as the Essure device (Bayer Corp) and the Filshie clip (Cooper Surgical) may also cause metal hypersensitivity, as the former contains nickel and the latter contains titanium. The Essure devices are implanted transvaginally and expanded in the fallopian tubes to induce fibrosis and tubal occlusion, resulting in permanent contraception. These devices contain nitinol (55% titanium/45% nickel) in the outer coils, with an SAE 316L stainless steel inner coil. Nickel allergy is a contraindication to placement, likely owing to release of nickel from the nitinol alloy, which puts the user at risk of systemic allergic contact dermatitis [136]. On September 24, 2015, the FDA reconvened its Obstetrics and Gynecology Devices Panel to evaluate the safety and effectiveness of the Essure device in response to complaints submitted by users to the Manufacturer and User Facility Device Experience (MAUDE) database, some of which pertained to possible nickel allergy [137]. Following the advisory committee meeting, the FDA made recommendations such as ordering the manufacturer to conduct a postmarketing surveillance study and to include proper labeling that warns users about the risks [138].

Dental

There are a huge range of potential metallic allergens in dental implants, orthodontic devices, and restorations, including—but not limited to—gold, mercury-containing amalgam, nitinol/nickel, titanium, and palladium. Dental devices also contain nonmetallic allergens such as acrylates, epoxies, and flavoring components, but these are beyond the scope of this paper. Hypersensitivity reactions can occur in response to the metals used, and the most common is allergic contact dermatitis. There are numerous case reports that establish the link between dental metallic implants and allergic contact dermatitis, with early cases dating as far back as 1966 in which generalized dermatitis resolved completely after removal of dentures made from chromium-nickel alloy [14] or chromium-cobalt alloy [139,140]. Allergic reactions to gold in dental prostheses have been well documented since the 1980s [141]. More recent literature has also discussed allergic reactions in response to dental implants using nickel [142-145], titanium [141,146], and palladium [147].

Allergic contact dermatitis caused by dental implants can manifest differently in different patients. Contact allergies more

rarely affect the oral mucosa than the skin [148], and a study of 206 patients by Raap et al [149] revealed that clinically relevant contact allergies to dental metals are infrequent. The most common presentation is a lichenoid reaction characterized by oral lichenoid lesions (OLLs), which is a type IV hypersensitivity reaction [150]. The lesions are often located close to the implant and may be reticular, atrophic, erosive, or plaque-like in form [10]. Dental amalgams containing mercury and gold have long been shown to have an association with lichenoid contact reactions [151,152], although some studies and case reports link OLLs to other metals such as copper [153], chromate, thimerosal (mercurial) [151], nickel [154,155], and palladium [155]. Of note, the onset of allergic contact dermatitis seems to require prolonged intimate contact between the oral mucosa and the eliciting agent over a period of years; in addition, the mean age of patients with OLL was 54.6 years in one study [156,157]. Other possible signs of oral allergy include stomatitis, erythema, labial edema, purpuric patches on the palate, oral ulcers, gingivitis, angular cheilitis, and perioral eczematous eruptions [141].

Pathophysiology of Metal Hypersensitivity Reactions

Metal sensitization in nonsensitized individuals may result from a hypersensitivity response to metal ions released from metallic implants. The occurrence is evidenced by findings of elevated levels of a range of immune cells and markers found in peri-implant tissue at various time intervals after implantation, including $CD3^+$ and $CD4^+$ T lymphocytes, $CD11c^+$ macrophages/dendritic cells, and cells with abundant expression of MHC class II (human leukocyte antigen-DR) (dendritic cells) [158-160]. In addition, significant levels of metal ions can be found in various parts of the body, including capsular and periprosthetic tissues, distant organs (liver, spleen, lymph nodes), and in the urine and serum of patients undergoing total hip arthroscopy [161-166].

Metal ions can be released via 3 possible mechanisms: mechanical wear, physiochemical corrosion when the implant comes into contact with biological fluids such as sweat and blood, and cellular-gated mechanisms, where it is debatable whether mature osteoclasts can corrode the metal surface [9,24,167]. Cadosch et al [161] demonstrated that osteoclast precursors can grow and differentiate on stainless steel, aluminum, and chromium in vitro and can directly corrode the metal surface and release metal ions.

The types of metallic ions that are released are dependent on the metallic composition of the implants: stainless steel devices release iron, chromium, molybdenum, and nickel ions, while titanium devices release titanium (IV), vanadium, and aluminum ions [167]. Amongst the different alloys, standard SAE 316L stainless steel releases the most nickel ions [105]. Exposure to metal ions triggers various immune reactions both locally and remotely.

Both local and systemic immune reactivity to metal ions are likely to be driven by adaptive immunity via type IV reactions (delayed-type), with cells that are necessary for the development of T cell–mediated type IV hypersensitivity

that often affects perivascular tissue next to stainless steel or titanium implants [168,169]. The typical pathological features of a type IV hypersensitivity reaction are a heavy perivascular lymphocytic infiltrate, a macrophage response, and granuloma formation with tissue necrosis [78].

Histologically, pseudotumor-like periprosthetic tissue reactions and ALVALs can be seen around implants. ALVALs are the result of a pronounced perivascular lymphocytic (and plasma cell) reaction commonly found in periprosthetic tissues in response to the deposition of cobalt-chromium wear particles from MoM implants [63,84,170,171]. The formation of ALVALs is thought to be the result of a specific adaptive, cell-mediated type IV delayed hypersensitivity reaction to wear particles [172]. Pseudotumors are solid or cystic masses that communicate with the prosthesis and are strongly associated with MoM arthroplasties [63,65-69]. They show features of pronounced cell and tissue necrosis and a heavy macrophage response to wear particles and are often accompanied by an ALVAL infiltrate [63,65-67,173].

In the effector phase, metal ions that are released may activate the immune system by binding to endogenous proteins to form metal–protein complexes, which are recognized by T lymphocytes as antigens and elicit hypersensitivity reactions [9,160,174,175]. Nickel, however, may act as a superantigen and directly activate T-cell receptors [176]. Single titanium ions are not antigenic, as they are too small, but they are able to form complexes with proteins to form a hapten [175]. A recent study was able to demonstrate the strong and specific antigenicity of titanium ions released by biocorrosion, by showing that titanium-specific T lymphocytes are generated when human monocyte-derived dendritic cells are exposed to titanium ions [177]. However, there is still a need to investigate and analyze the extent to which other metals in metallic implants form immunogenic complexes or how they become antigenic and are presented to T lymphocytes.

Stimulated T cells release lymphokines, which attract and activate macrophages and other lymphoid cells [78]. Reactions surrounding the implant are probably T_H1-dominant, with research studies showing that there are increased levels of IFN-γ and IL-6 in metal allergic patients with joint arthroplasties [178,179]. Summer et al [180] found that there was predominant IFN-γ expression to nickel-allergic patients both without implants and with well-functioning implants, while there was predominant, significant IL-17 expression to nickel in patients with symptomatic joint implants.

Pseudotumors and ALVAL can be caused by wear particles or metal hypersensitivity. Although the extent of ALVAL correlates with the amount of wear particles in most cases, there are a few cases where a small number of pseudotumours had relatively low wear and a heavy ALVAL response and a few with high wear and a minimal ALVAL response. Campbell et al [65] proposed examining histological samples to differentiate between the 2 groups and using a 10-point histological score to rank the degree of ALVAL. The results showed that when tissues of patients with suspected high wear were compared with those of patients with suspected metal sensitivity, the former had a lower ALVAL score and fewer lymphocytes but more macrophages and metal particles. Athanasou [78] postulated that while

an increase in wear increases the frequency of ALVAL and pseudotumours in periprosthetic tissues, some reactions can be associated with low wear, likely owing to variability in the adaptive immune responses, and cited studies supporting this conclusion [181,182].

A similar type IV hypersensitivity reaction is seen in contact dermatitis in response to metal allergy, which occurs in 10%-15% of the population [9,62,78,172]. The most common cutaneous reactions associated with metallic implants typically present as dermatitis, eczema, and occasionally urticaria and vasculitis [9,183]. Cutaneous reactions may be localized, presenting as dermatitis overlying the site of the implant, or generalized, presenting as eczematous reactions. Although there are various diagnostic criteria for implant-induced cutaneous allergic reaction, the most recent criteria can be found in the Table [184]. A few prospective longitudinal studies assess the association between cutaneous allergic reactions and metal sensitivity. In one, it is suggested that up to 5% of all patients with total joint arthroplasty and up to 21% of patients with preoperative metal sensitivity may go on to develop cutaneous allergic reactions when they are re-exposed to the same metal [96].

The innate immune system is also involved and is likely to be the mechanism responsible for managing the metallic particles resulting from mechanical wear. This is mediated primarily by macrophages, which are part of the first-line defense against potential pathogens [185,186]. Wear particles released from implants are first coated with host proteins in blood and interstitial fluids before being presented to macrophages as a large complex [78,187-189]. Macrophages phagocytose various foreign particles, form foreign body giant cells, and release proinflammatory cytokines, including TNF-α, IL-6, and IL-1α/β [190-192]. Phagocytosis of biomaterial wear particles is influenced by factors including particle load, size, shape, and chemical composition [60,172]. Macrophages also release chemokines that mediate inflammatory cell migration and activation, such as MCP-1 (or CCL2) and CCL3 (MIP-1 α)

Table. Diagnostic Criteria for Postimplantation Metal Hypersensitivity Reactions [182]

Major
Eruption overlying the metal implant
Positive patch test reaction to a metal used in the implant
Complete recovery after removal of the offending implant
Onset of chronic dermatitis weeks to months after implantation

Minor
Dermatitis reaction is resistant to therapy
Morphology consistent with dermatitis (erythema, induration, papules, vesicles)
Systemic allergic dermatitis reaction
Histology consistent with allergic contact dermatitis
Positive in vitro test to metals, eg, the lymphocyte transformation test

[188,189,192-195]. Neutrophils react differently to metal ions: both titanium and vanadium ions stimulate neutrophils to produce superoxide anions [196], whereas nickel destroys neutrophil cell membranes at high concentrations [196]. A significant adverse effect of the innate immune system on biomaterial wear particles is osteolysis, which in turn leads to loosening of implant components and failure [78]. The mechanism of aseptic loosening is beyond the scope of this paper and will not be discussed.

Testing

The lack of an evidence-based consensus on metal allergy and implant failure is reflected in the lack of consensus on patient management. Given the uncertain extent to which a pre-existing metal allergy can and does cause implant loosening and failure, the primary question is whether it is necessary to perform screening before implantation. If so, which test should we use: patch testing, the leukocyte migration inhibition test, or self-reporting of metal allergy? In addition, how should we tailor management for people who test positive for metal allergy before implantation? Should we use "hypoallergenic implants" that surgeons may be less familiar with and may be more costly, or does it make no difference?

Which Test?

Testing for delayed hypersensitivity can be performed in vivo by patch or intradermal testing or in vitro with a lymphocyte transformation test (LTT) or leukocyte migration inhibition test.

The patch test offers a breadth of evaluation and ease of use and is more readily available than the LTT [197]. The intradermal test has limited use owing to the possibility of false-positive reactions and is rarely used in the evaluation of metal allergy [198-203]. The LTT measures the proliferation of lymphocytes from peripheral blood in the presence of a potential allergen after incubation for 7 days, and the result is compared with the proliferation of lymphocytes in the absence of an allergen and reported as a stimulation index. The leukocyte migration inhibition test measures mixed-population leukocyte migration activity; the presence of a sensitizing antigen slows migration down [9].

Dermatologists agree that patch testing reveals systemic delayed-type hypersensitivity to an allergen: 83% of American Contact Dermatitis Society members in a survey favored patch testing to evaluate metal hypersensitivity reactions. The survey also showed that 88% rarely use the LTT [198,204]. However, orthopedic surgeons are generally reluctant to accept the direct correlation between patch testing and the immune response to implants [44]. The relationship between cutaneous reactions and response to an implanted orthopedic device remains unclear [205]. Cutaneous exposure to an allergen is not the same as the constant exposure in the closed environment of a metallic implant, and it is entirely possible that the periprosthetic regions are only partially recreated through the patch test [206,207]. Macrophages and dendritic cells are the antigen-presenting cells in the closed environment of the joint, while Langerhans cells take on this role in the skin and have

greater antigen-presenting capability than macrophages in the blood [9,208]. Consequently, some authors believe that the LTT may have a better diagnostic value than patch testing [209,210].

Nonetheless, the LTT is unlikely to replace patch testing as the gold standard for numerous reasons. The LTT is not widely available or standardized. It is also more costly, may be subject to interlaboratory variability, and may give rise to false-positive reactions. In addition, the rapid decay of T cells means that samples must be processed quickly [211]. Therefore, patch testing appears to be the best available approach for potential metal hypersensitivity reactions, both before and after implantation, while the role of LTT in clinical practice remains unclear [204,211-213]. Schalock et al [184,211] recommended a protocol for patch testing using a baseline series and an adjunctive metal series based on implant type [214].

A possible use for LTT may arise when there is residual doubt about potential allergy after patch testing. In one study, 56 individuals with titanium implants had systemic symptoms but negative patch test results. The patients tested positive with LTT, and 54 out of 56 patients had complete resolution of symptoms when the implants were removed [215]. Alternatively, a combined approach using a battery of 3 in vitro assays to measure the different components of lymphocyte activation may improve the diagnosis of delayed hypersensitivity responses, including lymphocyte proliferation and enzyme-linked immunosorbent assays to assess migration inhibitory factor and lymphocyte migration inhibition [216]. However, more extensive studies are necessary to establish the validity and clinical applicability of these tests [167].

Is There a Need for Allergy Testing Before Implantation?

In general, the existing literature appears to agree that there is no need for widespread or routine patch testing prior to implantation. Opinions diverge when it comes to testing selected patients, which is unsurprising given that there is no consensus on the clear causal relationship between metal allergy and clinical outcomes.

Reed et al [217] suggested that preimplantation patch testing may be useful in evaluating cases of patients who have a reported history of metal sensitivity. This approach is similar to that suggested by Granchi et al [25], who performed a comprehensive systematic review on metal allergy and total joint replacement in 2012. Thyssen et al [197] took it a step further and recommended that clinicians refrain from carrying out routine patch testing prior to surgery, unless the patient reports having a history of clinical metal intolerance of a magnitude sufficient to cause concern to the patient or to the doctor. Even if the patch test results are positive, how management should be changed is unclear. A German consensus paper suggested that titanium implants should be used for all patients with a history of metal allergies [218]. A survey of patch testing among dermatologists from the American Contact Dermatitis Society and European Academy of Contact Dermatitis garnered mixed opinions: 54% felt that preoperative evaluation by patch testing was necessary in patients with a history of moderate or severe metal dermatitis, while 38% felt that using a titanium implant was adequate [198]. Schalock et al [211] recommended a

cautious and tailored approach to a positive patch test result: it is important to decide which implant will provide the best outcome in terms of functionality and durability, and the surgeon must choose the 'best' device for the patient.

Other authors adopt a firmer stance by proposing that no testing is needed at all, as the results of testing have no implications for clinical outcome and should therefore not alter management. Razak et al [219] performed a Delphi consensus study amongst joint arthroplasty experts and concluded that standard cobalt chromium/stainless steel implants should be used regardless of the patient's metal allergy status. In a matched cohort study performed over 5.3 years, 127 patients with 161 TKAs (56 patients had positive skin patch test results) were compared with 161 matched control TKAs with no history of metal allergy and no skin patch testing [98]. Most notably, patients with a positive patch test result did not have higher complication, reoperation, or revision rates than patients with a negative patch test result and matched controls, and there was no statistically significant difference in postoperative pain between patients with positive or negative patch test results and matched controls. The authors hence arrived at the conclusion that patch testing is of little practical value in predicting medium-term clinical outcomes following TKA and should not be strongly recommended to guide the surgeon's selection of implant type. Middleton and Toms [100] concluded that although there is an association between metal allergy and implant failure, there is no evidence of a causal relationship and hence no justification for using "hypoallergenic" implants, thus indirectly supporting the stance that there is no need for preimplantation testing.

This conclusion is in line with the approach taken in Sweden and is also supported by the results of earlier studies. In an editorial published in 2008, Bruze [220] pointed out the contrast between the approaches used in the United States and Sweden: in the former, patients with orthopedic implants seem to be evaluated more frequently for allergy, whereas in Sweden, "virtually no such patients are evaluated" [220]. Lachiewicz et al [97] believe that widespread screening of patients for metal allergies before TKA is unwarranted, and that metal hypersensitivity after TKA is rare and is a diagnosis of exclusion. Carlsson and Möller [221] followed 18 patients with preimplant-confirmed metal allergy for a mean of 6.3 years after implantation, and none of the individuals had systemic or cutaneous reactions. Webley et al [99] studied 50 patients with hinged arthroplasty of the knee in 1978 and found that while 32% (n=16) had positive patch test results to the metal constituents, there was no correlation with loosening of the prosthesis [99]. In 2007, Granchi et al [25] reported that while there is a higher frequency of patch testing in patients with TKA than in the normal population, no predictive value of TKA failure could be attributed to sensitization, as patch testing was similarly frequent in both patients with stable and patients with loose implants.

While there may be no clear guidance on the direct benefits of patch testing or LTTs prior to implantation, there may be merit in soliciting information from patients about possible metal allergies. Geisinger et al [217] noted that in addition to physical, mechanical, and biomedical issues, a patient's psychological status can strongly affect clinical

outcomes [222]. Granchi et al [25] reported that the presence of symptoms of metal allergy before implantation might be a risk factor for TKA failure, and Nam et al [101] found that patient-reported metal allergy was associated with decreased functional outcomes (University of California at Los Angeles Activity, Short Form 12 [SF-12], Modified Harris Hip Score, and Knee Society Score) after TKA and decreased mental health scores after THA. Earlier studies report similar findings, ie, multiple, patient-reported allergies may be a surrogate for mental health factors that negatively impact postoperative morbidity and functional and psychosocial outcomes [223-225]. Graves et al [226] followed 459 patients undergoing THA or TKA and found that patients who reported ≥4 allergies had less improvement in functional outcomes (using Western Ontario and McMaster Universities Arthritis Index function scores) than those who reported having <3 allergies. Given that one of the strongest predictors of patient satisfaction following TKA is meeting preoperative expectations [227], making efforts to establish patients' self-reported metal allergy status can contribute meaningfully to the tailoring of the management plan. Nam et al recommend that surgeons counsel patients with self-reported allergies on the reduced probability on achieving outcomes that are on par with those of patients who have no allergies. The study also suggests that in patients with a reported metal allergy, it may be helpful to consider using implants free of the allergenic metals to pre-emptively eliminate this as a potential source of pain.

Postimplantation

Patients with asymptomatic, well-functioning devices do not need to undergo testing for metal allergies. Management of patients with residual pain or other conditions after implantation is not as clear. The dilemma lies in the difficulty in ascertaining whether a patient has genuinely experienced metal hypersensitivity from patch testing alone and, more importantly, whether the patient will benefit from removal and replacement of the offending implant.

Granchi et al [25] performed a systematic review and meta-analysis in 2012 and found that it is generally thought that hypersensitivity testing should be performed in failed total joint replacements when the cause of loosening is unclear and the patient has an MoM implant. There are numerous more common causes of pain and implant loosening or failure, and these causes should be explored before considering metal hypersensitivity as a cause of pain or symptoms. Park et al [228] summarized the literature on the various causes of anterior knee pain that can cause the patient to be dissatisfied after TKA. These include infection, instability, component malalignment, crepitation and patellar clunk syndrome, patellofemoral symptoms, early aseptic loosening, complex regional pain syndrome, and hypersensitivity to metal or cement. The authors proposed a diagnostic algorithm for residual pain after TKA and stated that metal hypersensitivity should only be suspected if the patient had a normal physical examination, normal laboratory workup, and normal findings on radiographs, CT scans, or metal artifact reduction sequence MRI. The patient's condition should also have improved after intra-articular injection.

Schalock et al [184] recommend using a major and minor criterion to properly evaluate metal reactions (Table).

Paradoxically, a patient can sometimes only be diagnosed with metal allergy when the symptoms resolve upon replacement with an immunologically inert implant. In fact, Middleton et al [100] point out that diagnosis of implant-related allergy is almost impossible and requires the demonstration of abundant typical T lymphocytes in immunohistopathology, a positive patch test result to a specific implant-derived allergen, and improvement of symptoms upon replacement of the implant with an immunologically inert implant. Consequently, reaching a diagnosis of metal allergy is akin to putting the cart before the horse, as the patient would have to undergo implant removal regardless.

There is no consensus or clear guidance on the management of patients with unresolved pain following implantation. It remains unclear to what extent the symptoms could be attributed to metal allergy and how patients should be managed. More extensive and controlled studies are needed to elucidate a definitive and evidence-based diagnostic and management algorithm in this murky area.

Conclusion

A review of the existing literature reveals an ostensible lack of consensus on the evaluation and management of possible metal hypersensitivity reactions. This is in part due to the lack of strong evidence-based understanding of the relevance of these reactions to the viability of implants. More extensive and controlled research needs to be carried out to elucidate the exact relationship between metal hypersensitivity reactions and the survival of metallic implants before proper guidelines can be created to prevent or manage metal hypersensitivity reactions.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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