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REVIEW

Updates in Metal Allergy: A Review of New Pathways of Sensitization, Exposure, and Treatment

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Abstract

Purpose of Review Metal exposures are widespread, and ensuing allergic sensitization leads to secondary disease processes, especially contact dermatitis, with chronic implications. This review covers recently described mechanisms of sensitization, sources of exposure, and treatment options.

Recent Findings Sensitization to metals is similar to other allergic processes: it is triggered by innate responses, which then facilitate allergic priming. Early oral exposures may lead to tolerance, whereas initial cutaneous exposures by piercings start the pathway toward sensitization. Nickel 'allergy' may be ubiquitous because of multiple pathways of immune response. Although the most frequent reaction to metals is a type IV immune response, some metals, including platinum and sometimes nickel, can also trigger a type I IgE mediated response. Current treatment involves avoidance of exposure and suppression of the response, although inducing tolerance by early oral exposure may be the best method to avoid disease.

Summary Better understanding of the factors and contacts that drive metal sensitization will enable better management of the types and timing of exposure, which then may instead induce tolerance and prevent disease.

Keywords Metal sensitization · Allergy · Nickel · Platinum · Metal implants and biomedical devices · Innate immunity · Tolerance

Introduction

Metals are defined by their physical characteristics as a class of substances that are malleable, ductile (able to be drawn out into a wire or thread) and reflective, possessing high electrical and thermal conductivity. Although metals differ by their melting points, they generally have relatively high melting and boiling points, and as such, are usually solid at room temperature. Indeed, the majority of elements in the periodic table are classified as metals or metalloids. Given these characteristics of common, malleable, yet relatively hard solids, metals have been used since the Stone Age as tools and implements. The Bronze Age, dating from 5,000 to 1,200 BC developed the metal alloy of copper and tin, followed by the Iron Age from 1,200 to 500 BC. However, it was only in 1913, while attempting to solve the problem of corrosion in the British Army gun barrels, that the British metallurgist Harry Brearley created the first stainless steel by the addition of 12.8% chromium and 0.24% carbon to iron.

Today, metals are critical for the functioning of day-to-day life. Alloys, a mixture of at least one metal with a second metal or other element, are created to make them stronger, harder, lighter, or better in some characteristic. Common examples of alloys include bronze, brass (copper and zinc), pewter (tin, antimony and lead), dental amalgam (50% mercury plus silver, tin, copper, and trace amounts of zinc, indium, and palladium), Nitinol (nickel and titanium), and beryllium copper. Metals are often used in a salt formation, in which a metal replaces a hydrogen atom, and function as catalysts, in electronics, optics, electroplating etc. In a metal salt, the metal exists in a charged form, which makes

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it more reactive. The charged, dissociated metal is then able to act as a hapten or complete allergen in triggering immune responses and secondary disease.

Case

A 50-year-old male chemist has worked in platinum R & D for the past 10 years. His job is to develop a generic version of platinum chemotherapy to treat breast cancer. Specifically, he has spent the past five years developing and testing a chemical process to manufacture carboplatinum and oxaliplatin. In developing these compounds, the patient describes the initial process as follows: He starts by weighing out potassium tetrachloroplatinate, a dark orange-red powder, into a vessel on an open bench. He then would carry the vessel with the powder to a work area hood. There, the powder is dissolved in water, stirred and heated, and potassium iodide and ammonia are added. The resultant product is iodo cis-platinum in a gooey, yellow powdered form. The compound is washed with water and added as a slurry into a closed vessel to which other chemicals are added, and the solution is heated and stirred for 7–8 h in a covered system. The end product is cis-platinum in solution with a final volume of 8–10 mL. Several other chemicals, including powdered barium oxide, are then added to create a final product of white carboplatin in solution. The solution is then dehydrated to produce a final product of carboplatin in powder form.

The patient does use personal protective equipment in his job, including nitrile gloves, a lab coat, and a half face dual-cartridge respirator and goggles, but he is not always consistent with their use. When he handles potassium iodide, he wears a dust mask. However, after several years spent developing the process, he developed an itchy rash on his arms and chest that lasted for months. He subsequently developed eye swelling and watering, a runny nose, and round, raised, itchy hives that lasted for 2–3 h around his neck area. He did note that his rash appeared to be better at home and worse at work. He specifically describes a persistent skin rash between where his lab coat ends and the nitrile gloves begin, as well as a facial rash in the area between the goggles and his respirator.

Using both commercially available platinum patch test reagents as well as platinum powders from the workplace, the patient was patch tested to ammonium tetrachloroplatinate 0.25% in petrolatum, obtained from Allergeaze Smart Practice, Canada. Patch #3 was 0.25% iodocis-platin, and patch #5 contained 0.25%, potassium tetrachloroplatinate, both prepared and diluted by the patient in his lab. Patch #1 and 4 were control patches with petrolatum alone. The patient reacted strongly with a blistering vesicular rash to all platinum compounds after two days of exposure.

The day after placement of the platinum patches, the patient also developed rhinoconjunctivitis and wheezing. Spirometry showed a clinically significant bronchodilator response consistent with asthma triggered by the platinum patch tests. The patient was treated with a prednisone burst and taper, provided with an albuterol inhaler, topical nasal steroids and Lidex 0.05% external gel to be applied to the chest and patch test sites twice daily until the rash resolved. He was restricted from any further work with platinum powder or liquid.

His final diagnoses included both a type I and type IV sensitization response to platinum salts.

This case highlights the four major updates in metal allergens included in this review:

1. The importance of the route of exposure and the role of epithelial barrier dysfunction in eliciting metal sensitization and disease
2. Turning on innate immunity to drive metal sensitization
3. Sources of occupational and environmental metal exposures leading to disease
4. Treatment and the role of avoidance and tolerance in mitigating the immune response

The Importance of the Route of Exposure and the Role of Epithelial Barrier Dysfunction in Eliciting Metal Sensitization and Disease

As in many immune-mediated diseases, the route of exposure is critical in driving sensitization or tolerance to metal allergens. One of the most important studies of the specific type of exposures driving nickel allergy was performed in 2002 by CG Mortz and colleagues. They assessed the prevalence of nickel sensitization, detected by patch testing to several different nickel concentrations, in 1501 8th grade Danish schoolchildren. Questionnaire responses provided information on the presence of atopic dermatitis, inhalant allergy, and allergic contact dermatitis, as well as the prevalence of hand eczema, allergic contact dermatitis caused by metal contact, and the presence and timing of ear piercing and use of dental braces. Those without either exposure had a baseline rate of nickel sensitization of 2.9%. Those with dental braces only, or braces first and pierced ears second had similarly low rates of nickel sensitization, 2.7% and 1.7% respectively. Of those with only pierced ears, 12.2% were allergic to nickel, and those with pierced ears first or in the same year as braces had the highest rates of nickel sensitization of 20.4% to 22.2% [1]. Similar results were reported in a Swedish adolescent cohort, which identified risk factors for nickel allergy. A higher number of piercings, female sex, and vocational education were risk factors for

nickel sensitization; orthodontic appliances before piercing was protective [2, 3].

Based on these and other reports, the initial sensitization to metal occurs primarily through the skin, and disruption of the skin barrier is the critical first step in permitting sensitization. To understand the effects of metals on and beneath the skin barrier, it is important to first recognize the structure of the skin barrier.

Most skin barrier function resides in the highly stratified epidermis. The outermost horny layer of the epidermis, the stratum corneum, is about 15 cells thick, composed of flattened, nucleus-free cells known as corneocytes. The interior of the corneocytes contain keratins that are aggregated by Filaggrin monomers into cross-linked microfibrils. Corneocytes are enclosed in a resistant protein and lipid cell envelope, the cornified envelope, and connected by corneodesmosomes. Intercellular spaces are filled with stacks of hydrophobic and hydrophilic structures formed by intercellular lipids. These include ceramides, free fatty acids, and cholesterol, stored in lamellar granules, and also extending into the extracellular space between the stratum corneum and the stratum granulosum immediately below. The stratum granulosum, called the tight junction, is the second absorption barrier composed of keratinocytes and located between the cornified and noncornified epithelium. Tight junctions seal the intercellular spaces between the keratinocytes, but do exhibit some targeted loosening depending on cell type and physiological requirements [4]. With loosening of the tight junctions, dendritic processes from antigen presenting cells, including Langerhans cells and dendritic cells, are able to penetrate through the barrier and take up antigens. Physical and chemical agents, including water alone, can disrupt these multi-laminar membranes and create lacunae through which allergenic substances, including metals, can now pass.

Loss of skin barrier function is associated with higher rates of sensitization, both atopic, and to other agents. Inherited examples include Netherton's syndrome (loss of function in SPINK5) and peeling skin syndrome type B (mutations in the CDSN gene), both of which demonstrate elevated IgE levels, peripheral eosinophilia, and atopic sensitization. Filaggrin loss of function mutations are common in Northern European subjects, with a carrier frequency of 12%. The main function of Filaggrin is to aggregate keratin filaments leading to keratinocyte compaction and formation of the stratum corneum. Filaggrin is expressed in the stratum granulosum layers as a large precursor protein, profilaggrin, which is then dephosphorylated and cleaved into Filaggrin monomers that bind keratin and contribute to the stratum corneum barrier function. Filaggrin monomers are then further degraded into natural moisturizing factors (NMF) that maintain hydration of the upper stratum corneum and have anti-staphylococcal properties. Expression of Filaggrin is primarily localized to the cornified epithelium of the skin, with expression also in the oral mucosa, and nasal vestibule. Loss of function mutations are associated with early atopic dermatitis onset, disease severity, eczema herpeticum, atopic dermatitis related asthma, and greater allergen sensitization [4]. In Filaggrin deficient knockout mice, the animals demonstrate an ichthyosis phenotype, skin barrier defects, and accelerated percutaneous sensitization [5]. In humans, loss of function mutations in the Filaggrin gene have also been associated with allergic contact sensitization to nickel and a clinical phenotype of intolerance to fashion jewelry, demonstrating the importance of an intact skin barrier in preventing metal allergy [6].

Metals in the form of charged ions may permeate the skin, where they are able to bind to tissue proteins and form antigens. Small amounts of skin surface nickel, chromium and beryllium have been shown to dissolve under conditions of replicated human sweat, and become available to penetrate through the outer stratum corneum of the skin [7]. Using ex vivo human skin, 0.15 M metal salts, including nickel (II) sulfate hexahydrate, cobalt (II) chloride hexahydrate, and chromium (III) chloride hexahydrate, were incubated separately for 24 h before localization using mass spectrometry imaging [8]. Nickel mainly accumulated in the stratum corneum, with a smaller amount detected in the upper epidermis. Cobalt and chromium species penetrated considerably deeper into the epidermis. Both nickel nanoparticles and cobalt nanoparticles have been shown to penetrate human skin, with increased permeation in damaged skin [9, 10].

In general, uptake of all antigens, including metals, is facilitated when the skin barrier is damaged, and damage can occur with a variety of irritants. The most common irritants, especially in the occupational setting, are water, and detergents. Within the stratum corneum, water is bound by hygroscopic components within the corneocytes, keratins, and natural moisturizing factors originating from the enzymatic degradation of Filaggrin. Too little water results in a dry and scaly stratum corneum which is fragile and tends to crack and increase permeability. Too much water can cause the corneocytes to swell, with pockets of water in the intercellular regions and alterations in the rigid organization of the lipid bilayers that no longer exclude other agents.

Detergents, also known as surfactants, can also disrupt the epithelial barrier by emulsifying and separating the intercellular lipids, thus reducing their ability to exclude outside agents. The most common surfactant is sodium lauryl sulfate (SLS) == sodium dodecyl sulfate (SDS), found ubiquitously in toothpaste, shampoos, detergents, cleaning agents and beauty products. Treatment with detergents such as SLS decreases the amount of stratum corneum lipids, disordering the lamellar structure and secondarily the barrier function.

Both SLS and alcohols (frequently used as hand sanitizers) will decrease the levels of NMF. This may be the mechanism of skin dehydration in wet work occupations that involve frequent hand washing and disinfection.

Skin Barrier Damage Activates Innate Immunity that Secondarily Drives Metal Sensitization

Disruption of the skin barrier then allows skin resident Langerhans cells or dendritic cells to elongate their dendrites and capture skin-exposed antigens that normally would be excluded. In the epidermis, Langerhans cells form a dense network that covers the whole body, with a similar network of dermal dendritic cells in the dermis. Although their presence provides immunological defense, necrosis or damage to the epidermal barrier will release mediators and activate the innate immune system necessary to set in motion the adaptive response. Cell stress and tissue damage will cause the release of pro-inflammatory molecules, the damage associated molecular patterns (DAMPs) that are recognized by pattern recognition receptors (PRRs), such as TLRs primarily expressed on immune cells. For example, microbial products from a secondary infection will trigger TLR2, TLR3, TLR4, and TLR5. Tape stripping of normal human skin triggers the expression and release of TNF-α, CSCL8/IL18, IL-10, IFN-γ, and TFG-α, TSLP, and alarmins such as HSP70, HSP90, and IL-33 [4].

Of central importance is the finding that sensitization to contact allergens, including metals, depends on initial activation of the innate immune response. In the skin, activation of innate immunity occurs with damage or breaching of the skin barrier. Many metal ions are small and positively charged, and able to diffuse through the damaged skin barrier. Nickel is also able to penetrate the skin barrier due to its ability to bind to histidine, which is abundant and a degradation product of Filaggrin [11]. The small size and charge of metal haptens enable them to bind to tissue proteins, and transform from haptens to complete antigens recognized by skin APCs. Some metals are also able to activate innate immunity by direct binding and activation of TLR4: well demonstrated with nickel, but also for cobalt and palladium [12, 13]. Nickel and Chromium (VI) compounds also directly activate the NLRP3 inflammasome as the first step in an adaptive response [14, 15].

Nickel Specific Immunology

Nickel is the most common contact allergen in the world. This is in part due to its frequent use in many household and personal care products, and in part due to flexible pathways of immune activation. Several groups have identified common TCR chain usage in nickel specific T cells, including TRAV9-2, TRBV18 (Vβ17), TRBV19, and TRBV20-1 [16, 17]. In one study, the alpha and beta chain combination of TRAV41-TRBV18 accounted for 13.5% of the Ni^{2+} specific CD4 + population from a joint failure donor [18]. Nickel binding requirements appear flexible, and not limited to a single pathway. For example, a mimotope with a lysine in the p7 position mimics Ni^{2+} in the natural TCR ligand, and MHCII β-chain flexibility in the area around the peptide p7 position forms a common site for cation binding in metal allergies [19]. Use of the same DR52c/Ni2 + mimotope tetramer was able to identify Ni^{2+} reactive CD4 + T cells in patients with joint replacement failure [20]. Other studies indicate that Ni^{2+} can functionally bind to the TCR gene segment TRAV9-2, or to a histidine in the complementarity-determining region 3 (CDR3), the main antigen-binding region of the TCR α- or β-chain [21]. Other postulated pathways of Ni^{2+} recognition by T cells include a metal ion pre-loaded to the MHC-presented peptide, or Ni^{2+} ion binding to tyrosine 36 in the CDR1 of TRAV9-2 + TCR and histidine 81 in the MHC II β [16]. Ni^{2+} binding may also lead to structural conformation changes of the presented peptide, and create a metal-free neo antigen recognized by the TCR [21]. Preferential MHC II usage has been reported for HLA-DR52 and DR53 (DRB4*01) in Ni^{2+} sensitized joint failure patients. In these patients, we have found that different Ni^{2+} specific CD4 T cell clones may respond to different MHC, and cross-react with many, or few, other metal ions (unpublished data), demonstrating great flexibility in response that may explain the prevalence of nickel sensitization [22, 23].

Bringing the science back to the importance of the route of exposure, these findings explain the high rates of nickel 'allergy' in response to early skin piercings. In an otherwise metal naïve individual, the act of skin piercing compresses, abrades and damages the skin barrier, initiating innate protective responses along with presentation of a novel metal allergen. The stage is set for sensitization. In contrast, metal braces do not damage the oral epithelium, and release small amounts of metal allergens to a mucosal system already primed for tolerance.

Sources of Occupational and Environmental Metal Exposures Leading to Disease

Method and Route of Exposure

Several industries have significant metal exposure with varying pathological manifestations. More often, metals exhibit a typical type IV hypersensitivity with the generation of metal specific T cell responses. The clinical manifestations can range from mild dermatitis to severe

pulmonary disease as in the case of chronic beryllium disease. Type I hypersensitivity has been described with platinum salts, and rarely with nickel [24]. As discussed above, the route and method of exposure may influence the presentation of disease as well.

Nickel, Cobalt, and Chromium

Common metals involved in occupational exposure include nickel, cobalt, chromium, palladium, platinum, and beryllium. Nickel can be found in many tools and consumer products, placing many exposed professions at risk such as metalworkers, as well as hairdressers, retail clerks, caterers, and domestic cleaners. In one study, nickel was the culprit occupational allergen in up to 23% of cases of occupational dermatitis [25]. In addition, metalworkers were found to have much higher sensitization rates to nickel, cobalt, and chromium as compared to the general population, suggesting that frequent exposure contributes to disease [26]. The type of metalwork affects the pattern of sensitization, as metal cutters more frequently exhibit cobalt sensitization, compared to welders, electroplaters, locksmiths, and foundry operators who are more likely to demonstrate chromium sensitization [27]. Leather tanners also have been described to have a higher incidence of chromium sensitization.

Beryllium

Workers in aerospace, nuclear power, and production of ceramic materials are at risk of developing chronic beryllium disease (CBD), a severe granulomatous lung disease caused by significant exposure and sensitization to beryllium. The immunologic mechanism by which beryllium induces disease is in part associated with an allelic substitution of a Glu69 in the HLA-DPB1 gene, with the highest risk for CBD and severity of disease in those homozygous for the variant [28, 29]. Beryllium is able to induce posttranslational modification in a preexisting HLA-DP2-peptide complex that forms neo-antigens recognized as non-self [30]. The result is a chronic type IV hypersensitivity reaction, with disease triggered by inhaled and retained beryllium ions in the lung. The US Department of Labor worker programs cover Department of Energy workers exposed to beryllium. Sensitization is determined by a positive result in the beryllium lymphocyte proliferation assay [31].

Platinum

Platinum is a key ingredient in catalyst manufacturing and recycling industries, where workers exposed to platinum salts may develop respiratory symptoms indicative of sensitization, such as asthma and rhinitis. A study involving 153 workers revealed that 14.4% exhibited positive skin prick test reactions to platinum salts, underscoring the allergenic potential of these compounds in triggering type 1 allergic disease [32].

Interestingly, type IV reactions to platinum presenting as contact dermatitis are reported, but rare. Case reports describe an itchy dermatitis in contact with a platinum siloxane complex in elastic compression stockings, persistent irritation and prolonged wound healing in contact with the Eversense E3 continuous glucose monitor, contact stomatitis due to sensitization to palladium and platinum in dental alloys, and occupational allergic contact dermatitis to platinum and palladium in an analytical [33–36]. Sensitization was demonstrated in each case by positive patch testing, although the triggering extract differed in each case; platinum catalyst 1% in the first subject, ammonium tetrachloroplatinate (II) 0.25% pet in the next two subjects, and ammonium hexachloroplatinate (0.1% aq) in the last subject. Nonetheless, positive patch test reactions to platinum were reported to be rare in a consecutive series of 446 patients tested in a patch test clinic for contact dermatitis. Only two positive patch tests were reported to platinum, of which one was deemed not clinically relevant [37]. This may be due to the unselected spectrum of patients; sensitization to platinum should be tested in patients with known exposure and related dermatitis.

Platinum-Based Chemotherapy and Hypersensitivity Reactions

Platinum-containing chemotherapeutic agents, including cisplatin, carboplatin, and oxaliplatin, are cornerstone treatments for a number of malignancies, including testicular, ovarian, bladder, lymphoma, breast, head and neck, cervical, lung, and colorectal cancers. Although platinum based chemotherapeutic agents are well tolerated in most cases, more frequent exposure results in higher rates of acute, type 1, hypersensitivity reactions. One study suggested that upwards of 25% of patients receiving seven or more cycles of platinum chemotherapy experienced acute hypersensitivity reactions [38]. Platinum salts have been shown to be the cause of acute hypersensitivity reactions based on positive skin prick testing and intradermal tests to platinum salts [39]. However, other data suggests cross reactivity between platinum-based chemotherapeutics is not universal. For example, upwards of 45% of patients that are oxaliplatin sensitized are also sensitized to carboplatin, but able to tolerate cisplatin without a clinical reaction. This suggests that there are also platinum drug-specific epitopes that drive type 1 hypersensitivity reactions [40]. In the context of patients reactive to a number of platinum salts as well as patients with a single platinum specific skin test response, it is likely that several different platinum epitopes play a role in platinum-based chemotherapy hypersensitivity reactions.

In addition, there are of delayed, type IV, hypersensitivity reactions which can complicate treatment, with major risk factors described as the dose received, as well as a timeline > 13mos since the most recent usage [41].

Biomedical Devices

Prosthetic Joints

Allergic reactions to metals such as nickel, cobalt, and chromium are common conditions affecting between 3% of males and 17% of females in developed countries [42]. Over the last several years, a growing body of evidence has demonstrated that metal allergy may be a cause of prosthetic failure in patients with metal joint implants [43]. First generation replacements were formulated as metal-on-metal prosthetic implants, and Johnson & Johnson developed and released a metal on metal (MOM) hip replacement in 2003, implemented between 2004 in Australia and 2008 in the US [44]. These generated high levels of metal wear debris causing both metallosis (localized muscle necrosis from the toxicity of metal particles) and metal sensitization. The primary mechanism of metal sensitization is hypothesized to involve a type IV immune reaction to metal ions produced from small metal wear particles within the joint [45]. There is likely both local and systemic absorption of the metal ions, which activate dendritic cells, and trigger significant perivascular T cell activation and infiltration within and around the synovial capsule [46]. The process is similar to the pathophysiology of contact dermatitis to metals. In the case of MOM hips, by 2014, most of the devices were withdrawn from the market both though formal and silent recalls and based on their higher rates of failure and revision. The use of metal-on-plastic prosthetics and the development of new second-generation alloys proved to be more durable and resulted in less metal release and resultant sensitization [47].

Although metal allergies have been implicated in total joint replacement failure, it remains an understudied cause of joint failure overall. Symptoms that are more easily associated with metal allergy as a cause of joint complications include localized rash/eczema, swelling, and deep itching. Symptoms such as pain and limited range of motion are common to joint failure, but can also be caused by infection or mechanical issues, and are not specific to metal allergy as the culprit [48, 49]. In these cases, metal allergy should be considered as part of the differential diagnosis of failure. These studies also suggest that patients with metal allergy induced joint failure, when revised to a prosthetic implant without the sensitized metal, have improved functional outcomes.

Intravascular Stents

Since the utilization of intravascular stenting for vascular disease, early complications such as in-stent restenosis of bare metal stents made of stainless steel raised initial concerns regarding metal hypersensitivity as a cause. Early retrospective studies of patients with bare metal stents found higher rates of nickel and molybdenum sensitization in those with stent re-stenosis [50]. Later prospective studies demonstrated that the initial stenosis was not associated with metal hypersensitivity, but that 40% of patients with recurrent re-stenosis were sensitized to relevant metals [51]. More modern intravascular stents are commonly manufactured from an alloy of nickel and titanium (Nitinol) and are usually drug eluting. There is far less literature regarding the role of metal allergy affecting the efficacy of drug eluting stents. One study found no significant impact on metal hypersensitivity as a cause of stent re-stenosis with a sirolimus eluting stent [52]. The anti-inflammatory drugs that are released from these stents are postulated to suppress hypersensitivity reactions as well as other inflammatory responses that may contribute to stent re-stenosis.

Pacemakers/Pulse Generators

Implantable cardiac devices such as pacemakers or cardioverter-defibrillators have been developed for use in many cardiac dysrhythmias. In addition, implantable pulse generators for other organ systems, such as nerve stimulators and cochlear implants, also affect physiological function by releasing pulses of electrical activity. These devices have similar structures, including a case that houses the battery, leads, lead connector blocks, and electrode contacts. Specific elements of these products are coated with materials such as polyurethane, or silicone to prevent direct metal exposure. The case material is typically a pure titanium case, and lead connectors may be an alloy of cobalt, nickel, chromium, and molybdenum or a stainless-steel alloy of chromium, nickel, and manganese. Electrode contacts may also be stainless steel, gold, or a platinum-iridium alloy [53]. Several case series and one systematic review highlight sensitization patterns that have been detected to each of the included metals, as well as to their protective coatings. Most patients present with localized dermatitis at the site of the implant, or with device failure or malfunction [54, 55]. These same studies highlight possible solutions, such as the use of a gold-coated device, nickel-free device, or polytetrafluoroethylene (Teflon) coated device. The emergence of leadless pacemakers made of parylene-coated titanium utilizing Nitinol leads may reduce the amount of metal exposure leading to sensitization and failure. One

case report demonstrated that a patient sensitized to potassium dichromate, cobalt chloride, titanium, and nickel sulfate was able to tolerate a leadless pacemaker device when a gold-coated pacemaker was not available [56].

Dental Materials

The use of metals and non-metal materials in dentistry and oral surgery have long been implicated as the cause of persistent oral symptoms after dental intervention. Frequent symptoms include stomatitis, and lichenoid reactions of the oral mucosa, tongue, and lips, with more rare manifestations of facial dermatitis [57]. Although numerous dental products, including acrylates, propolis, and balsam of Peru fragrances, have been implicated in some of these reactions, nickel, palladium, and amalgam (a mixture of liquid elemental mercury, powdered silver, tin, copper, and zinc) remain the most frequent cause of clinical allergy after dental procedures [58]. The use of dental amalgam fillings have declined by nearly 21% since 2017, although they are still utilized with greater frequency in more socially vulnerable populations due to the inexpensive nature of the material. However, modern dental resin composites, which are increasingly being used as compared to amalgams, often are composed of acrylates that have been implicated in allergy [59]. Dental implants and maxillofacial hardware are composed of metals including titanium, zirconium, stainless steel, or cobalt, chromium, molybdenum alloyed with nickel [60]. Many of these, especially stainless steel and cobalt/chromium alloys, have been implicated as the cause of oral reactions following dental procedures.

Treatment and the Role of Avoidance and Tolerance in Mitigating the Immune Response

First-Line Treatments

When managing metal sensitization, best treatment approaches focus on identifying and avoiding contact with the offending allergen [61, 62].

In addition to avoidance of exposure, symptomatic treatment for suspected allergic contact dermatitis to metal includes adjunct medical treatments such as topical corticosteroids of escalating strength, with second line therapies including phototherapy, oral retinoids and systemic immunosuppression [62]. However, even with topical or systemic corticosteroids, persistent dermatitis can occur in more than 1 out of 3 individuals [63].

If there is evidence of implant or device failure associated with sensitization and systemic symptoms, a 21-day oral prednisone tapering course has been suggested, although there is little evidence that this would resolve the immune reaction [53, 64, 65]. There are mixed short-term benefits in using systemic corticosteroids to treat orthopedic implant failures, and even more evidence suggesting ineffectiveness in managing hypersensitivity reactions in cardiac implantable electronic devices [43, 55].

The role of biologics is also not well understood in the context of metal allergy, although there are scattered case reports of benefit. One patient with a TKA and nickel, cobalt and gold sensitization had contact dermatitis refractory to systemic steroids but responsive to dupilumab [66]. Another case described a patient with nickel allergy to their endovascular stents and vascular clips, responsive to dupilumab [67]. Importantly, these case reports describe use of biologics treating suspected allergic contact dermatitis to metal, but not other systemic symptoms attributed to metal allergy.

Removal from Exposure

Management approaches for potential or present contact dermatitis or implant failure need to be based on clinical history, testing results and the risk/benefit of possible outcomes [53].

In the context of failed metal joint prostheses, and prior to consideration of a metal hypersensitivity reaction, it is paramount to evaluate for a missed periprosthetic joint infection (PJI). This is another possible source of unexplained pain, and the current methods to exclude PJI are sometimes inadequate [68].

Prior to implant revision, there are a number of important features to consider.

- Does the patient has another implant of the same material which is doing well,
- Are there are obvious confounding mechanical issues,
- Are patch testing results equivocal,
- Are symptoms overall mild and tolerable to the patient,
- Are symptoms are improving with time, or
- Are there are medical comorbidities or underlying physical frailty where reoperation would do more harm than good [53].

If the suspicion for metal hypersensitivity remains despite these considerations, then a revision to a nonallergenic implant is recommended. There are conflicting data about resolution of symptoms with this approach [49, 53, 69–72].

Development of Tolerance

Given the burden of nickel allergy, public health initiatives attempted to combat the growing nickel allergy prevalence with large-scale avoidance measures. In 2001, the European

Union (EU) Nickel Directive was enacted to regulate consumer nickel exposure. Consumer items intended to be in direct and prolonged skin use were not allowed to release more than 0.5 µg/cm^2/week [73]. Although these large-scale efforts did have some success in decreasing nickel allergy, high prevalence of nickel allergy continued to persist in the EU. One possible explanation for this persistence of nickel allergy is the existence of prior nickel sensitization, and how local memory to nickel can be induced in skin even by low levels of nickel within regulatory limits [74].These findings were important in shifting the treatment paradigm towards the concept of tolerance.

Tolerance is a state of systemic unresponsiveness, and may be induced by exposure via the gastrointestinal tract, skin or via inhalation [75]. In food allergy, oral tolerance is attributed to induction of T regulatory cells, T cell anergy, and the interplay of macrophage and innate lymphoid cell regulation in the gut microbiota [75].

The mechanisms of nickel oral tolerance have only been partially elucidated but involve proliferation of T helper CD4 + cells leading to upregulation of T regulatory 1 cells and CD4 + CD25 + T cells [76].

Murine studies evaluating tolerance in nickel-sensitized mice demonstrated the development of anergic lymph node cells with persistent suppressor activity [77]. Further murine models suggested oral tolerance to nickel could be transferred by CD8 + cells in a dose dependent manner [78].

In humans, CD4 + CD25 + T cells derived from peripheral blood of healthy non-nickel allergic individuals were able to dose-dependently regulate primary and secondary nickel-specific T cell responses and were recruited in the skin after nickel application [79]. This finding was important in showing that human derived CD25 + Treg in non-nickel allergic individuals have the ability to control activation of both naive and effector nickel-specific T cells.

There is growing evidence that nickel exposure may lead to tolerance. Epidemiological studies have shown nickel allergy prevalence was lower in individuals who wore dental braces prior to ear-piercings compared to those who first underwent piercings [1]. Another study suggested Russian women exposed to drinking water containing nickel had a lower prevalence of nickel allergy than non-exposed Norwegian women did from a nearby geographical area [80].

Efforts at nickel desensitization, with daily oral nickel intake for weeks to months, may lead to the development of partial tolerance in patients with systemic nickel allergy syndrome [81, 82]. However, these protocols are not typically offered in the clinical setting and further placebo-controlled trials are needed to evaluate efficacy and safety.

A novel treatment approach for the management of allergic contact dermatitis focused on the development of a micro particle-based system called “TRI MPs” to promote tolerance to contact allergens by expanding Treg populations in vivo. Specifically, the sustained local release of TGF-β1, rapamycin, and IL-2 from TRI MPs injected near the site of cutaneous sensitization or challenge expanded allergen specific Treg populations and suppressed proinflammatory effector T cell populations in the skin [61]. This is a promising potential route of treatment although future studies are needed to determine whether TRI MPs can permanently reverse the allergen specific memory T cell response in previous sensitized subjects [61].

Alternative Treatment Approaches

The concept of systemic nickel allergy syndrome (SNAS) refers to patients with nickel allergic contact dermatitis who suffer from systemic (intestinal or cutaneous) symptoms after ingestion of nickel rich foods [83]. A prior placebo-controlled trial studying SNAS demonstrated oral administration of low nickel doses improved clinical conditions and reduced IL13, IL5 and IFNγ after 4 months [83].

The potential benefits of a low nickel diet in reducing nickel-induced systemic disease has been a long-term speculation [84, 85]. In a more recent study, a group of subjects with positive patch tests to nickel, cobalt, chromium or selenium were instructed to follow a low metal diet with the help of a dietician; these participants had reduction in SCORAD compared to control [86]. Of note, however, indices for oozing/crusting and urinary metal levels were reduced in both the control and intervention group. More studies are needed to better understand the impact of dietary modifications and metal allergy. Furthermore, the decision to pursue stringent low nickel diets must be weighed against the considerable risk of malnutrition [76].

A recent study identified Semaphorin 3 A as a potential therapeutic target, since it is upregulated in keratinocytes upon nickel exposure, and subsequently promotes Th1 cytokine responses driving nickel reactions [87]. Further research is necessary to investigate clinical applications.

Conclusions

The spectrum of metal allergens in disease is a rapidly evolving field, as more and diverse metals are integrated into an expanding array of personal and medical uses. Solutions to metal sensitization need a deeper understanding of immune pathogenesis, with interventions more efficiently targeted to suppress the early, necessary innate response. We need better identification of the metal components used in devices, and their potential contact with the immune system, to design appropriate diagnostic strategies. Although not discussed in this review, the issue of the best method of diagnosing metal allergies, by patch testing or LPT, has not been resolved. Lastly, the role of tolerance induction

to common metals may be a better treatment option rather than reducing or removal from exposure in the prevention of metal allergies. These are all important research priorities for the future. In order to design solutions to metal allergies, we have to first understand their mechanism.

Key References

- Mortz CG et al. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Acta Derm Venereol. 2002;(5):359–64.

  This study demonstrates that risk for, and rates of nickel sensitization, are driven by the site of the initial exposure. Oral exposure through dental braces reduces risk, whereas dermal/percutaneous exposure increases the risk, and the effect of the initial exposure is dominant.

- Pacheco KA and Thyssen JP. Contact Dermatitis From Biomedical Devices, Implants, and Metals-Trouble From Within. J Allergy Clin Immunol Pract. 2024;12(9):2280–2295.

  This impressive review explores the reported skin and local internal reactions to orthopedic implants as well as reactions to smaller categories of medical appliances including cardiac devices and vascular stents, neuromodulation devices, diabetic appliances, Nuss bar surgery for pectus excavatum, and dental and spinal implants.

- Wennervaldt M et al. Subclinical immune responses to nickel in sensitized individuals-a dose–response study. Contact Dermatitis. 2024;91(1):1–10.

  This study reinforces the limitations of avoidance alone as an effective public health approach to metal allergy. Wennervaldt, M., et al. presents evidence of immune activation in response to even low-dose nickel exposure in skin with local memory, even in the absence of a clinical reaction. These findings underscore the shifting treatment paradigm towards the concept of tolerance.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing interests The authors declare no competing interests.

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