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REVIEW

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The contribution of metal allergy to the failure of metal alloy implants, with special reference to titanium: Current knowledge and controversies

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Abstract

After almost three-quarters of a century during which contact dermatologists have often struggled to comprehend the relationship between metal allergy and failure of metal-alloy containing implant, it is possible to say that a relationship does exist, particularly for cobalt and chromium, but also for nickel. There is still debate as to whether allergy develops as a consequent of failure but thenceforth contributes to it, or whether sensitisation starts first and induces failure secondarily—opinion probably favours the first. Metal-on-polypropylene articulations were associated with few metal allergic problems but now are less favoured by orthopaedists due to plastic wear products causing osteolysis and pseudotumour formation through local inflammation. New metal alloys are regularly being introduced such that interested dermatologists need to stay on top of the situation. The jury is still out as to whether the recent favouring of titanium-containing alloys will confirm them to be more inert allergenically. Case reports do show some clinical reactions to titanium-containing implants and patch test series have inferred sometimes quite a high background rate of allergy, but interpretation must be tempered by the awareness that titanium salts on patch testing have a tendency to cause irritant reactions. Blood monitoring of metal ion values is now recommended in certain situations after joint replacement and increasing levels may be an indication that allergy with joint failure can develop, in which case patch testing is indicated, and suggested series are available. Predictive patch testing, whilst generally not recommended in the past, has been introduced into some protocols often by non-dermatologists, such that it is now needed for temporo-mandibular joint and Nuss bar insertion, and it can be anticipated that this may become more commonplace in the future. One of the major current deficits for patch testers is standardised guidance on which preparation or preparations to use for suspected titanium allergy. One suggestion is 0.5% titanium sulphate in petrolatum, though experience in at least one centre suggests the use of a battery of titanium salts might be desirable.

KEYWORDS
implant, joint replacement, metal allergy, patch testing, titanium

1 | INTRODUCTION

Joint replacement surgery is common—recent data from the National Joint Registry for England, Wales and Northern Ireland (NJR) show that the number of primary hip replacements has been climbing, with 98 649 procedures done in the year of 2019—over double from the year 2006. Similarly, primary knee replacements have doubled to 106 572 over the same period.[1] The implants are usually made of alloys such as stainless steel, vitallium (cobalt 65%, chromium 30%, molybdenum 5%) and cobalt-chromium—other metals employed include aluminium, nickel, vanadium, titanium, zirconium and iron.[2] Since the early days of the procedure, insertion of metallic orthopaedic implants have been shown to sometimes result in cutaneous complications such as localised dermatitis, urticaria, bullous reactions and vasculitic eruptions and, uncommonly, systemic allergic dermatitis reactions.[3–5] Pseudotumour formation and implant loosening are important non-cutaneous complications.[4,6] Metal hypersensitivity in the context of modern joint replacement surgery is believed to be uncommon but it is recorded in association with total hip arthroplasty (THA) and total knee arthroplasty (TKA).[7] The estimated prevalence of cutaneous allergies to nickel, cobalt and chromium in the general population—unrelated to arthroplasty—is respectively around 10%–13% (female), 2%, and 1% based on patch testing and blood analysis.[8]

Greater numbers of people, extending to the ninth decade or even older, are undergoing arthroplasties with ever-evolving implants.[1] Our aim in this paper is a timely re-evaluation of the role for metal hypersensitivity in the failure of modern replacement joints with, additionally, an examination of the potential of titanium (Ti)—increasingly employed in implants—to cause allergic problems. Selective searches, extending back to the 1960s up to 2023, were performed using PubMed and Google Scholar. No review protocol was used. This is not a systematic review. Not all relevant articles have been referenced in the interests of space since the issues being addressed span over 60 years. However, representative views have been presented. Conflicting views have been presented where relevant. First, to give background, we briefly review the history of joint replacement and metal allergies.

2 | EARLY 1960s IMPLANTS AND THEIR SUCCESSORS

The first generation metal-on-metal (MoM) prosthesis of the 1960 and 1970s were often cobalt–chromium alloys, and were associated with complications such as dislocation and sciatic nerve damage in the short term, and mechanical failures in the longer term.[9] Some studies showed a high incidence of metal sensitivity (13%–38%), amongst patients with first generation MoM prostheses.[10–12] This was thought to have been due to the MoM articulations shedding wear particles, producing high concentrations in the local tissue and blood leading, in some cases, to the development of cell-mediated allergy. Occasional reactions to methyl methacrylate used in bone cement were also reported.[13]

Dermatological reactions, such as localised to generalised eczematous responses, have also been noted in patients who underwent MoM joint replacement in and after the 1970s.[14] In one study, 19 out of 50 patients tested patch test positive to metals—two to nickel only, eight to cobalt, six to both cobalt and nickel, one to both nickel and vanadium and two to chromium.[11] Thirteen out of the 50 patients had an erythematous or eczematous rash adjacent to the joint replacement site after the operation (the onset varied from 1 week to 24 months after operation). In patients who had unexplained joint loosening, 74% were patch test positive to metals.[11]

Compared to their predecessor, metal-on-polyethylene (MoP) prostheses, introduced from the 1970s, were not generally felt to be associated with the development of metal allergy though one study seemed to indicate that up to 18% of patients could develop metal allergies.[9,15] With MoP prostheses, the problem was mainly one of polyethylene wear products, which were associated with local inflammation and peri-prosthetic osteolysis, aseptic loosening, implant failure and pseudotumour formation.[16]

3 | SECOND-GENERATION METAL-ON-METAL PROSTHESES

With the aim to reduce polyethylene wear, second-generation MoM prostheses were introduced in the 1980s.[9,17] Although these MoM prostheses had higher wear particles than MoP prostheses with the same usage, the granulomatous inflammatory reaction and foreign-body giant cell build-up were less pronounced.[17] A concern with the reintroduction of MoM bearings was the possibility of metal hypersensitivity, as seen with first-generation MoM arthroplasties, and potentially associated with joint failure of various types.[9,11,14] Nonetheless, the use of second-generation MoM articulations proceeded, with attention focusing on possible metal allergies. Joint effusions, early osteolysis and implant failure, though uncommon, were seemingly more prevalent in patients with metal hypersensitivities.[6,18,19] Histology of periprosthetic tissues from such patients revealed both T and B lymphocytic infiltrates, as well as fibrin exudation, macrophages and eosinophilic granulocytes, suggesting lymphocyte-dominated immunological responses.[6,12] The term aseptic lymphocytic vasculitis-associated lesions (ALVAL) was introduced to describe this. The clinical correlation of painful soft tissue reactions in the absence of loosening or infection was thought to denote a chronic inflammatory response to metallic wear particles.[20]

4 | HYPERSENSITIVITY TESTING

Epicutaneous patch testing is generally considered the gold standard to diagnose cell-mediated (type IV) hypersensitivity to metals.[21] Patch testing is widely available, though it requires expert interpretation.[22] It has a sensitivity of 77% and a specificity of 71%.[23] However, some have raised concerns that the epicutaneous route utilises a different immunological pathway, utilising epidermal Langerhans cells, than that

which may pertain at joint level, where macrophages and tissue dendritic cells might mediate the antigen presentation.[22,24] Additionally, patch test interpretation can be difficult, and may be associated with both false positives and false negatives. Hence some researchers have sought in vitro tests as alternatives in an attempt to overcome such concerns. Of these, the best known is the lymphocyte transformation test (LTT), based on measuring the proliferation of lymphocytes in response to the addition of a metal salt in the presence of appropriate antigen-presenting cells.[25] LTT may have a higher sensitivity, estimated at between 55% and 95%, than patch testing,[26] and can also deliver objective quantitative results. Since LTT utilises peripheral blood lymphocytes, it can be argued that it is more appropriate for detection of internal immunological sensitivity, and it has the added benefit, if properly validated, of scale in terms of patients to be assessed, though it is applicable to a smaller number of allergens than is patch testing.[27,28]

5 | RELEVANCE OF METAL ALLERGY TO JOINT FAILURE

Several studies suggest metal hypersensitivity to be a contributing factor to adverse outcomes in patients with total joint replacements. Two reviews identified raised rates of metal allergy identified by patch test or in vitro test in patients with failing prostheses, compared to a control population.[28,29] A systemic review and meta-analysis of literature focusing on metal sensitivity in patients undergoing total joint replacement compared the prevalence of hypersensitivity reactions using pooled data of 1208 patients awaiting surgery and 1190 with existing replacements. The probability of having a metal allergy was higher in patients with a joint replacement, even if the risk was not so remarkable (OR: 1.52; 95% CI: 1.06–2.31; $p = 0.02$).[29] The probability of having a metal allergy was more than doubled in patients who had a failed replacement than in those with a stable replacement (OR: 2.76; 95% CI: 1.14–6.70; $p = 0.02$).[29] A prospective analysis of LTT compared the situation in 40 patients when awaiting hip implants (titanium, nickel, cobalt and chromium were tested) with their results 3 years after surgery and found that 18% developed new sensitivity to metals (patch tests were apparently negative).[30] Twelve percent still showed positive LTTs 6 months later.

Sometimes the local histological findings in MoM failure are compatible with metal allergy and blood metal ion levels are elevated but in vitro tests are negative, in which case local metal ion toxicity might be implicated.[31] Some researchers have suggested that sequestration of lymphocytes in peri-prosthetic tissue might explain negative LTTs by reducing the number of circulating sensitised lymphocytes, though this seems an unlikely explanation.[32]

Based on clinical studies, Schalock and Thyssen in 2013 devised a set of criteria for the acceptance of the involvement of metal hypersensitivity in implant failure, with major and minor criteria.[33] Their major criteria included: chronic dermatitis starting weeks to months after implant insertion, eruption overlying implant, positive patch test to a relevant metal, recovery after removal. Minor criteria were treatment-resistant dermatitis, consistent dermatitic morphology, systemic dermatitis reaction, consistent histology and positive LTT.

6 | ALLERGENICITY OF METALS, AND BLOOD LEVELS OF METAL IONS AFTER MoM INSERTION

Some researchers see the allergenicity of certain metals as being due to their haptenic ability to allow recognition by antigen-presenting cells, though the actual mechanism by which such cells recognise metal ions remains unclear.[34,35] In normally functioning MoM hips, there is some systemic release of metal—serum levels of cobalt, titanium and chromium have been found to be increased (the latter two on average threefold and fivefold higher, respectively) from 3 months to 3 years after insertion.[36,37] Indeed the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) has issued guidance on monitoring blood levels of metals in patients who have received MoM arthroplasties, based on this concern and the observation that rising blood levels of metals are associated with an increased chance of prosthesis failure.[38]

7 | TITANIUM HYPERSENSITIVITY

There is now a considerable body of evidence in the form of case and series reports (Table 1) to support the contention that cell-mediated hypersensitivity to titanium is a reality, though tests to confirm clinical suspicion have proven a stumbling block. Titanium has been introduced for use in human replacement joints based on its biocompatibility and corrosion resistance, in part due to the bioinert layer of TiO_2 that forms on the surface of a prosthesis using a titanium-containing alloy. Despite this, in vitro and in vivo studies have proven that this oxide layer can be compromised, for example by local mechanical trauma, with release of titanium-ions and particles. Proteins such as albumin, α-globulin, transferrin, fibrinogen and amino acids have a strong affinity for metal ions, and since these elements are capable of forming metallo-organic complexes, they significantly increase the corrosion rate of Ti alloys.[39] Although once considered to be bio-inert compared to say cobalt and chromium, it is now recognised that released Ti ions from implants can trigger hypersensitivity reactions.[40,41] Histologic and immunohistochemical evidence around problematic titanium-containing dental implants[42,43] and knee replacements[44] are compatible with allergic reactions, and Ti ions have been detected at between 100 and 300 parts per million (ppm) in tissues both locally and in regional lymph nodes, accompanied by black discoloration.[40] Local tissue from five subjects with failed titanium-containing hips showed particulate titanium together with macrophages and T lymphocytes with an absence of B cells, taken by researchers to suggest sensitisation to Ti.[45] In vitro murine studies showed TiO_2 nanoparticles (NP) to promote Th2-biased immune

TABLE 1 Reports of clinical reactions to implants implicating possible titanium allergy.

Author	Type	Study summary	Tests for allergy to titanium or other metals
Tanwar et al.[75]	Case report	A 56-year-old male showing allergic symptoms after 1 week of dental (Ti) implant placement with no perioral or facial signs, but eczema was shown on the distant body parts, and complete remission was attained after removing the dental implant.	Not performed.
Towers and Kurtom[76]	Case report	A 67-year-old female with an unreported nickel reaction clinically developed severe debilitating anorexia and fatigue 1-month post operatively, secondary to thoracic spinal fixation. Over a 2-year period, weight loss reached approximately 25 kg with loss of muscle mass and subcutaneous tissue surrounding the spinal implants. The screws and rods were removed to avoid skin erosion. Upon hardware removal, the patient had rapid weight gain, improved stamina and generalised sense of well-being. She also had a clavicular plate placed 6 weeks post spine fusion. She developed a skin rash over the clavicular plate site 9 months post operatively and it was removed.	Not performed
Peters et al.[53]	Case report	Patient had four cardiac pacemakers implanted and removed due to localised symptoms of pruritus, redness and swelling of the skin overlying the pacemaker that developed within 3 weeks to 17 months after insertion. These reactions were interpreted as contact sensitivity to the pure titanium encasing of the pacemaker.	Patch test positive—tested with a thin square of titanium metal applied with artificial sweat.
Hosoki et al.[77]	Case report	A 69-year-old male, with no history of metal hypersensitivity, had undergone an uneventful dental implantation in 2008. In 2010, he had fractured a lower limb and underwent open reduction with titanium screws. Six months later, generalised nummular eczema developed. The titanium screws were removed a year later; however, the eczema was only reduced by 50%. All metal prostheses except the implant screw and abutment were removed, and the eczema reaction was reduced to 30%, but still remained. The entire removal of the titanium implant screw and abutment in 2014 led to a full recovery.	Patch test had positive reaction to cobalt, tin, palladium, indium, iridium, copper and titanium.
Lim et al.[78]	Case report	A 70-year-old woman developed contact stomatitis after treatment with titanium nitride implant abutment. Symptoms improved after the removal of titanium abutments.	Patch test positive to Ti nitride.
Ishii et al.[79]	Case report	A 52-year-old man with Down's syndrome was implanted with a cardiac pacemaker for advanced atrioventricular block. He developed eczema and partial exposure of the generator 1 year after implantation. After reimplantation of a pacemaker wrapped with a polytetrafluoroethylene sheet, the dermatitis did not recur.	Patch test was positive for the metal of the generator (purity 99.9% titanium) after 72 h.
Hofmann et al.[80]	Case report	A 27-year-old non-atopic female developed progressive painful oedema of the right inguinal area 2 weeks after hernia repair with a mesh anchored by pure Ti clips. She had a history of a pruritic inflammation in the perianal region after a haemorrhoidopexy using Ti staples at the age of 26, with symptom relief after the staples had fallen off. One-week post removal of surgical clips, the patient reported complete remission of symptoms. Histology showed a granulomatous reaction adjacent to the clips.	Patch test with TiO_2 and Ti clip, positive reactions to both on Day 3 reading. Patch test was repeated 3 years later, with negative results.
Buonomo et al.[81]	Case report	A female developed a well-demarcated, erythematous plaque over the left breast 13 months after reconstructive breast surgery with the placement of a temporary tissue expander (TTE). The port of the TTE contained Ti. Dermatitis resolved after removal of the tissue expander.	Patch test was positive for a few metals, including Ti.
van Opstal and Verheyden[82]	Case report	A 46-year-old woman with persistent dermatitis following total knee arthroplasty revision with an oxidised zirconium femoral component and titanium-containing tibial baseplate. She developed persistent dermatitis 3-month post-surgery. After revision with a customised tibial component, and removal of any Ti components, symptoms resolved completely.	Patch tests were negative.

TABLE 1 (Continued)

Author	Type	Study summary	Tests for allergy to titanium or other metals
Heitmiller et al.[66]	Part of case series	A 53-year-old African-American female had lumbar metal implants (Ti alloy) placed for degenerative disc disease. Three months after her procedure, she experienced worsening lower back pain, bilateral leg pain and paraesthesia, as well as erythema, warmth and tenderness overlying the midline surgical scar. The spinal implant was removed and replaced with bone morphogenic protein. Pathology of the tissue samples was consistent with ALVAL. Following implant removal, the patient experienced resolution of her symptoms. The patient later disclosed a history of suspected metal allergy after a failed left foot bunionectomy, requiring removal of titanium screws used during the procedure.	Initial patch test with extended metal series was not tolerated due to an asthmatic reaction and facial angioedema within 24 h of patch test placement. Limited patch tests to nickel and titanium were subsequently performed. Positive to nickel and negative to Ti at Day 3 reading. Prick tests were positive to both nickel and Ti.
Thomas et al.[41]	Case report	Localised eczema and poor bone healing was observed in a 35-year-old male patient following a titanium implant for a hand fracture. After removal of the titanium material, the healed and the eczema cleared.	Patch tests negative to titanium, nickel, chromium and cobalt. LTT showed a positive reaction to titanium. Post removal, LTT was negative to Ti
Egusa et al.[83]	Case report	A 50-year-old Japanese woman with no history of atopy, developed persistent facial eczema post Ti dental implant. Symptoms completely resolved post removal of the Ti materials.	Positive LTT to titanium.
Ko et al.[84]	Case report	A 33-year-old woman developed cervical eczema 9 months after titanium dental restoration. The eczema resolved after removal of the titanium.	Lymphocyte stimulation test to Ti prior to restoration was negative, but post restoration showed a positive reaction to Ti.
Müller and Valentine-Thon[85]	Cohort study	Fifty-six patients who had developed clinical symptoms after receiving titanium-based dental or endoprosthetic implants were reviewed. Following removal of the implants in 54 patients (2 refused removal), all 54 showed clinical improvement.	Fifty-four patients were patch tested, all with negative results. Fifty-six were tested with LTT to titanium: 21 were positive, 16 were ambiguous and 19 negative. In 15 who had a LTT repeated later, the test was negative.

responses and release histamine locally.[46] Titanium alloys can contain trace quantities of more allergenic metals such as nickel and cobalt, seemingly in sufficient amounts to initiate an allergic reaction in someone sensitised to the metals.[47,48] However, this does not explain the positive LTTs or patch tests to titanium salts shown in a number of studies (Table 1). There is an accumulating body of evidence to support the concept of titanium allergy developing in some patients following implantation of a titanium-containing prosthesis and for a potential role of this in clinical complications including joint failure.

Patch testing has always proved to be difficult with titanium salts, largely thought to be due to the inability of even nanoparticles of TiO_2 to penetrate the epidermis.[49–52] However, upping the concentration seemed to solve the problem in one instance. Patch tests were negative in five patients with failed titanium-containing hips, using titanium salicylate, titanium tannate, titanium dioxide and titanium peroxide, each at 1%, 2% and 5% in white soft paraffin, but when tested with Metanium ointment (Thornton & Rose Ltd, UK) containing 20% titanium dioxide, 5% titanium peroxide, 3% titanium salicylate and 0.1% titanium tannate in a silicone-paraffin base, two returned positive.[45] A thin square of titanium metal applied with artificial sweat proved positive (++) in another instance of a patient who developed pruritus with erythema, and swelling 17 months after insertion of a titanium-containing cardiac pacemaker.[53]

Some researchers have found that increasing the number of titanium-containing salts used in patch testing has increased the yield of positive results. In a general patch test clinic setting, using patch test preparation of the oxide, isopropoxide, oxalate hydrate, lactate and citrate of titanium, 5.7% patients (26 out of 458) tested positive to at least one titanium salt.[54] Clinical relevance was found in 16 of the 26 (62%), which would seem to suggest that true allergic responses had been observed.[54] Of the 248 patients in this study, who were thought to have potential titanium allergy, 22 (9%) showed positive tests. Amongst the 163 patients suspected of having other metal allergies, 2 showed positive reactions (1.2%) and in the control group of 47 patients with no Ti implants or history of Ti allergy, 2 had positive reactions (4.3%). The authors, de Graaf et al., concluded that the number of positive Ti reactions in the formal group was not statistically different from that in the control group ($p = 0.39$)[54]; however, the control group was limited by a small sample size and referral bias. A key finding was that the frequency of Ti sensitivity in this large group of patients was 5.7%. This frequency was higher than that found in a study by Sicilia et al., who found an allergic positive rate of 0.6%[55] amongst 1500 dental implant patients, and that observed in a study by Lhotka et al., in which it was 2%.[56] However, in these two studies, only TiO_2 patch tests were used, which could explain the difference in sensitisation occurrence as compared to the findings by de Graaf et al.

Titanium allergy appears to be uncommon though a standardised approach to its diagnosis by patch testing has yet to be defined. Some reports suggest that titanium allergy can contribute to joint failure, though it seems too early to state the extent of this.

8 | TOXIC EFFECTS OF METAL IONS AND IMPLANT FAILURE

Metal ions released from arthroplasties undoubtedly can cause toxic effects, including local inflammation and osteolysis—quite apart from the induction of allergy—that contribute to joint failure. Electrochemical corrosion of metal alloys whilst in contact with bodily fluids causes release of metal ions.[57] The resultant inflammatory response is proportional to the particulate load. Metal particles are pro-inflammatory and generation of wear particles can cause osteoclast activation via macrophage ingestion.[58] Pro-inflammatory cells trigger an immune response that could cause soft-tissue inflammation with subsequent periprosthetic tissue damage.[24,59] Periprosthetic osteolytic lesions have been identified and are suggested by studies to involve titanium ion-induced expression of chemokines, resulting in precursor osteoclasts recruitment to the periprosthetic region, and cytokines released by the pro-inflammatory cells, promoting osteoclast differentiation and activation.[60–62]

9 | CURRENT TRENDS IN IMPLANT MATERIALS

In some procedures, for example certain fracture fixations, non-biodegradable materials such as plates, screws and pins, are removed by a second surgery after sufficient tissue healing. In an attempt to obviate the necessity of a second operation, a new class of biodegradable metals has emerged as an alternative to traditional fixation implants. These biodegradable materials are expected to degrade completely in vivo, being replaced by newly formed bone.[63] The three main types of biodegradable alloys are based on magnesium (Mg), iron (Fe) and zinc (Zn).[64] Amongst them, Mg-based alloys have been most extensively studied in vitro and clinically. Fe-based alloys still need more long-term clinical trials. One drawback of Fe-based alloys is the slow degradation in the physiological environment. Zn-based alloys, in the initial development stages, have a degradation rate mid-way between Mg-based and Fe-based alloys. Some alloys based on non-toxic or low toxicity elements including Zn, zirconium (Zr), calcium (Ca), strontium (Sr) and tin (Sn) are being considered for orthopaedic use, for example combination of Mg–Zn, Mg–Zr, Mg–Ca, Mg–Sr and Mg–Sn alloys.[63] Allergic problems with these metals are anticipated to be uncommon.

Other than metals, two types of orthopaedic ceramic, the bio-inert and the bio-active, are under development. Bioinert ceramic materials are said to possess excellent wear resistance, high compressive strength, inherent chemical inertness, and biocompatibility and elicit minimal response from the living tissues because they undergo little physical or chemical alteration inside the human body.[65] Bioinert ceramic materials are commonly used as articular components in total joint replacements but generally have not been applied to fracture fixation applications mainly due to their poor ductility. Amongst the various types of bioinert ceramics, Al_2O_3 (alumina), ZrO_2 (zirconia) and silicon nitride (Si_3N_4) have been

investigated. Bioactive ceramic materials can bond directly with surrounding living bone tissues.[65] These ceramic materials are applied as coatings on metal bone implants rather than load-bearing components due to the low mechanical strength. As an example, hydroxyapatite with a porous structure allows bone tissues to grow inside the pores leading to a better integration between the implants and adjacent tissues. Allergic problems are not anticipated with these elemental salts.

10 | DISCUSSION

The increased usage of titanium alloys in prostheses of a variety of joints has brought with it the primary question of the extent to which allergy to this metal might occur and the secondary question of, if allergy is present, to what extent might it be contributing to joint failure?[39,40] The jury is still out on the first of these, largely because standardisation of patch testing or of in vitro testing has not been universally agreed upon, and until that matter is settled, a view on the second issue must be held in abeyance.[54] Nonetheless, on the question of titanium, we have sufficient data to make preliminary inference that, although allergy to this metal appears to be infrequent, it is worth considering when there are clinical pointers, even though demonstration by patch testing may be difficult.[66]

As regards other metals such as cobalt and chromium, there is a sufficient body of evidence to identify, especially in MoM prostheses, that sensitisation may occur and that this may be linked with joint failure. In the 1960s, it seems likely that metallic wear products from failing MoM prostheses lead to metal allergy, although some might argue the reverse—that allergy led to joint failure.[9,14] Wear products with the second-generation MoM articulations are much less, though the rise in blood levels of metallic ions demonstrates that this occurs.[20] Since blood levels rise greater and faster in the failing prosthesis, the same question arises.[37] It seems possible that mechanical factors initially induce increased wear products with induction of cell-mediated allergy as a secondary event, which through increasing local inflammation contributes even more to failure of the articulation in a vicious circle. The possibility of a direct toxic effect of metallic ions in some instances also needs to be considered.[32]

Routine pre-operational 'predictive' patch testing or LTT is not generally recommended, the exceptions being the stipulation by maxillo-facial surgeons for this prior to the insertion of replacement temporo-mandibular joints[67] and, according to guidelines of the American Contact Dermatitis Society, prior to the Nuss procedure for correction of pectus excavatum using either a stainless steel or a titanium alloy bar.[68] However, it would not be surprising if more institutions were to recommend predictive patch testing, considering the medico-legal milieu of many societies, despite the drawbacks of the procedure—principally on interpretation, plus false negatives and false positives, but also persistent patch test reaction, for example if gold salts are tested. Nonetheless, for patients with failing metal articulated prostheses, especially if blood levels of metal ions are elevated, patch testing or LTT are indicated (guided by clinical history) to inform clinicians of how to best to manage the case.[27]

Schalock and colleagues in 2011 went some way towards suggesting which allergens might be appropriate for testing, though for titanium they recommended two salts, titanium (VI) chloride 0.1% pet and titanium oxide (likely TiO_2) 0.1% in petrolatum.[25] However, in the extensive study of de Graaf and colleagues, titanium chloride was not considered and titanium dioxide was seen as not adequate, as it gave fewer positives compared to the oxalate hydrate, isopropoxide, citrate and lactate salts of titanium—the use of which would seem to be the patch test materials of choice if titanium cell-mediated allergy is being considered.[54] However, further series of the size of de Graaf and his Amsterdam colleagues (they tested 458 subjects) are awaited to see if their level of a 5.7% allergic reaction to one or more of a series of titanium salts in a general patch test population can be replicated. It is desirable to see some standardisation of approach to patch testing to titanium, though a 7 day or even later reading seems to be a sensible measure.[54] Indeed, this has been recommended when patch testing in this context for other metals, as it has been shown that an extra reading at Day 7 or later can increase the allergic positives on patch testing by around 14%, especially in patients aged 50 years or older.[69] An irritant patch test reaction to titanium salts is recognised, and common if tested at 1% concentration.[70] This is unsurprising considering that studies on ex vivo biopsies and reconstructed skin models have shown several titanium salts to be cytotoxic.[71–73] Even lower concentrations of titanium salts may cause irritant patch test reaction—reported at 6% for both 0.5% and 0.1% titanium sulphate, and 14% for 0.1% titanium chloride.[74] Bearing this in mind, 0.5% titanium sulphate in petrolatum may be the most appropriate single testing agent, though this view has yet to gain widespread acceptance.[74] Clearly, standardisation guidance on appropriate titanium preparations and their concentrations for patch testing is required, especially for comparative studies.

In conclusion, orthopaedic use of metal alloys is a continually evolving field and one in which contact dermatologists with an interest in metals need to keep informed. It is clear that MoP prostheses are pretty much free of any association with metal allergies though they suffer from the local toxic effects of polypropylene wear products causing inflammation and osteolysis. Early MoM joints had a strong association with metal allergies, most likely operating as a vicious circle effect. Recent research shows that second generation MoM articulation can also be associated with metal allergy, which contributes to joint failure, though mechanical forces and the rise in local and systemic levels of metallic ions may be the initiating factor in the development of hypersensitivity. Some years' experience is now available with titanium alloys in implants, sufficient to say that allergic problems appear to be rare but seem to be in play in certain circumstances, though evaluation is currently suboptimal. Further work is needed here and also in the developing fields of newer permanent metallic alloys using less common metals. It is yet to be seen whether the exciting future field of biodegradable metallic alloys will impinge upon the world of metal allergy.

AUTHOR CONTRIBUTIONS

Chenghao Huang: Investigation; methodology; writing – original draft; writing – review and editing; visualization; project administration; formal analysis; resources. **Shu Yu Vanessa Chiang:** Investigation; methodology; writing – original draft; writing – review and editing; visualization; project administration; formal analysis; resources. **David J. Gawkrodger:** Conceptualization; methodology; investigation; writing – review and editing; visualization; validation; project administration; formal analysis; supervision; resources.

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