

Understanding immune-mediated titanium allergy to in situ orthopaedic implants: a narrative review of the current literature

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Abstract

Introduction: Clinical recognition of potential immune-mediated allergic responses to implanted metal devices is increasing. For orthopaedic implants, while ‘pure’ compounds are used in specific circumstances, the majority of components are alloys – a combination of two or more distinct metals. Titanium is found commonly in many orthopaedic devices and is often championed as a ‘hypoallergenic’ option or inclusion. In the absence of a relevant previously published summary on the topic, this paper explores the current state-of-understanding of titanium allergy and proposes a patient management algorithm whereby such immune reactions are clinically-suggested.

Methods: A structured, systematic literature review was performed following PRISMA search principles to provide a contemporary summary-of-understanding in this area and to highlight clinical and knowledge deficiencies.

Results: Thirty-five topic-related articles were identified, the majority reflecting small case series’ or proof-of-concept studies. The general standard of scientific evidence available was poor. Justification for arthroplasty utilization of titanium as a ‘hypoallergenic’ option is largely extrapolated from non-orthopaedic domains.

Conclusions: Both ionic and conjugated titanium particles released from implant surfaces have the potential to trigger innate immune responses and true allergy. There exists no simple, high-sensitivity, screening test for titanium allergy. Conventional skin-patch testing is unreliable due to poor dermal penetration. Given established lymphocyte and macrophage activation pathways for allergy responses, in vitro methods using both cell-types show diagnostic promise. Surgical biopsy analysis from host-implant interfaces remains the contemporary ‘gold-standard’, however this represents an invasive, costly and highly-specialized approach not readily available in most settings. Further research to establish reliable/accessible diagnostic methods are indicated.

Introduction

True, clinically significant, immune-mediated hypersensitivity reactions (Table 1) to implanted medical components have historically been considered likely a rare or ‘uncommon’ event.¹ In the circumstance where genuine concerns for metal allergy exist – or there has been a positive reaction to pre-operative basic skin (patch) testing – hypoallergenic options are often recommended. In the domain of orthopaedic surgery, titanium implants and titanium-based alloys are often used for this purpose in an attempt to

minimize subsequent deleterious risk. However, in its pure or composite form, titanium is not an entirely biochemically inert material and poses its own independent potential risk for immune reactivity. There has been increasing awareness recently of the potential for metal-related pathology^{1,2} and patient-specific/genomic drivers for phenotypical diversity of reactivity expression.^{3,4} The findings of a recent large international collaborative study suggested that previously underappreciated reactions may offer a possible explanation for at least a proportion of reported patient-dissatisfaction with otherwise unremarkable in situ joint replacements as well as being

Table 1 Hypersensitivity reaction classifications

	Mediator	Physiological Function	Examples
Type I	IgE	Response against parasites via mast cells and basophil activation	Asthma Anaphylaxis
Type II	IgG/IgM	Cytotoxic – targets antigens expressed on infected cells	Heparin-induced thrombocytopenia
Type III	Immune complex	Accumulation of antigen–antibody complex formation	Systemic lupus erythematosus
Type IV	Cell-mediated	Four subtype activations: macrophages, eosinophils, cytotoxic CD8+ cells, neutrophils	Contact dermatitis Behcet's disease

a potential contributor to early component revision rates.⁵ There are few authoritative documents that exist to guide surgeons in investigating patients deemed to be of increased risk of such pathologies.^{1,6} In the absence of an available summary publication on the topic – the current review aimed to explore the contemporary state-of-understanding of true allergy to titanium materials and to consider currently available diagnostic testing methods (including accepted ‘gold standards’) and their respective efficacies. Based on the findings of this review, we aimed to also propose an assessment and investigation pathway for the clinician faced with a patient presenting genuine concern for such immune-mediate reactivity to titanium.

Search strategy and selection criteria

To ensure a relevant, accurate and representative synopsis of the current state-of-understanding of immune-mediated allergy to implanted titanium-containing metal implants, a structured and systematic search and retrieval of publications was performed according to the accepted preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The search results are depicted in Figure 1. Three databases: (i) Cochrane; (ii) EMBASE; and (iii) Medline were searched from inception until 9 November 2022. Search results were limited in the first instance to articles available in the English language with available abstracts. The following MESH terms were used: [(titanium)] AND [(orthopaedic*) OR (implant)] AND [(allergy) OR (immuno*) OR (hypersensitivity)]. Titles and abstracts of identified records were screened to exclude obviously irrelevant studies. Articles that described in vivo, in vitro or topical applications of titanium compounds, and/or specifically immunologic testing of such materials were reviewed. No limitations were placed on age, gender, date, type of study, or length of follow-up. Articles were excluded if they did not specifically discuss or report titanium-based allergic reactions/reactivity, or if no full-text in English language was available. The bibliographies of relevant papers were manually reviewed to identify further studies, with additional data sourced from international joint registries.

Initially, 233 articles were identified during preliminary database searching. After exclusion of duplicates, articles which did not match the search intent (i.e., papers not specifically exploring content related to titanium implant hypersensitivities) and articles not available in full text form, 35 full text papers were manually reviewed. At the end of the review process, 14 articles were

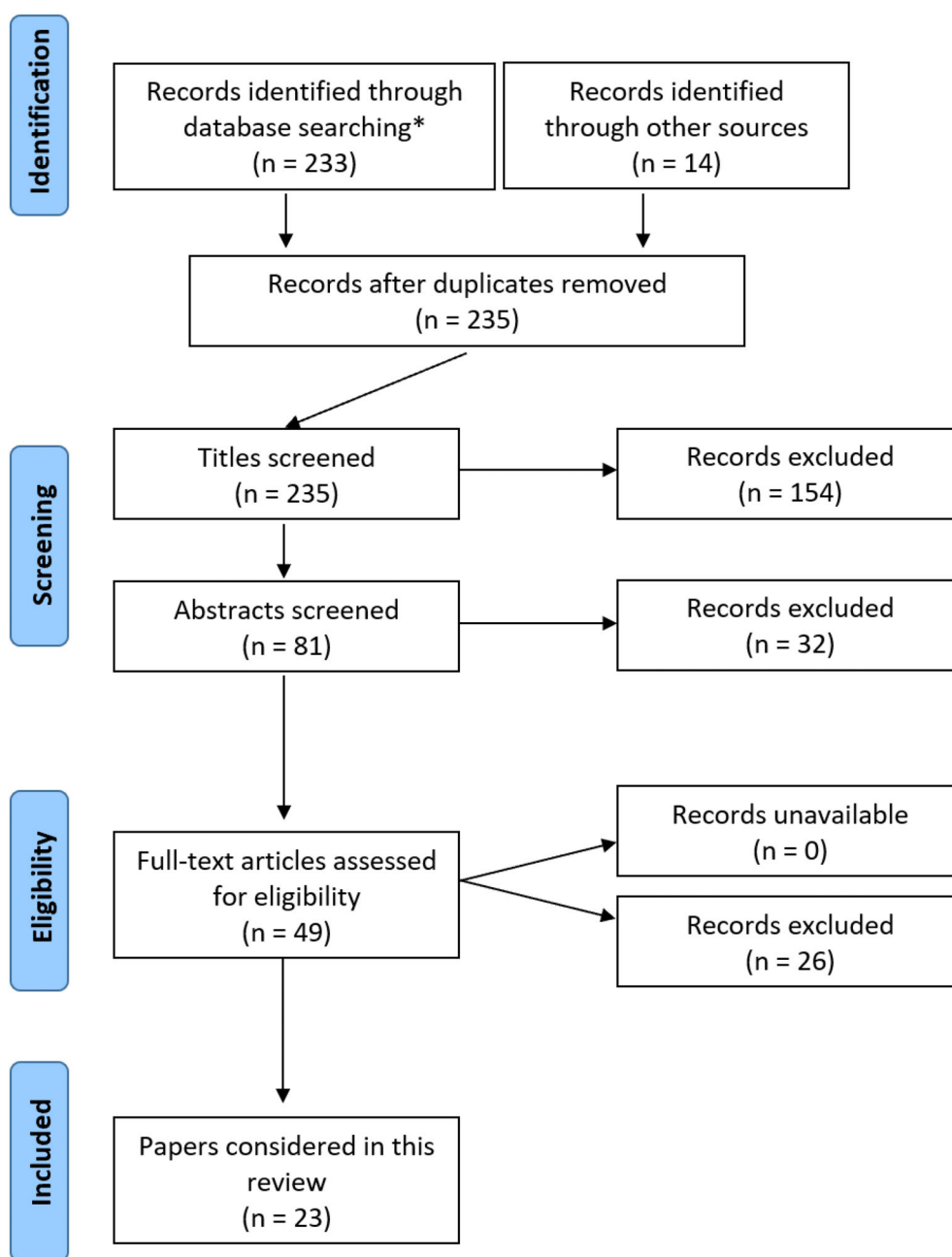
deemed appropriate for inclusion (Table 2). The initial methodology was the inclusion of prospective RCTs that involved diagnostic testing of titanium hypersensitivity in arthroplasties. As a relatively new topic in the field, it was identified that there existed a lack of quantitative research within the domain thus preventing formal ‘meta-analysis’, *per se*. With the preserved intent of providing a contemporary synopsis of the topic, a structured review of the identified literature was performed in keeping with meta-synthesis principles. The inclusion criteria were broadened to include papers that compared different diagnostic methods of titanium allergies, papers that involved alternative implants (including dental implants) and prior review papers that had considered titanium allergies. Other papers included were papers comparing diagnostic tests of alternative metals in specifically orthopaedic implants. A summary of key findings of the included papers are shown in Table 3.

Titanium hypersensitivity reactions

Hypersensitivity reactions to metallic joint replacement components are a significant potential contributor to implant failure.⁵ While at present ‘pure’ titanium devices are uncommon in arthroplasty surgery, extrapolation of extensive parallel work in the field of dental implants has demonstrated significant local reactions around such metals which remain a recognized contributor to morbidity and failure.^{7,8} The reality that titanium is used extensively in contemporary orthopaedics as either a compositive alloy or as a dedicated surface coating highlights the broad potential for similar provoked peri-implant allergic reactions and has prompted consideration of titanium allergy as a contributory mode of failure.

Hypersensitivity reactions are typically categorized into four different types as summarized in Table 1. Titanium allergy likely represents a type IV hypersensitivity whereby a sensitized T helper cell will activate macrophages and neutrophils involved in the reaction. A summary pathway is demonstrated in Figure 2. Despite the widespread use of titanium in orthopaedic trauma and arthroplasty implants,⁹ there is little robust evidence to define its immune reactivity nor actually support the widespread claims of its hypoallergenic status. The published literature provides very few reports of specific metal hypersensitivity to implanted titanium with the majority of works limited to descriptions of skin (patch) testing findings to titanium, rather than in vitro testing of pure titanium isolates and TiO₂ themselves.^{6,10,11} Pure or even high-grade titanium (i.e., >95% pure) allergies have previously been suggested to be ‘rare’, largely on account of the metal’s high reactivity with local

Fig. 1. PRISMA search summary.
 *Wed Nov 09 12:42:102022 **Search:**
 [(titanium)] AND [(orthopaedic*) OR
 (implant)] AND [(allergy) OR (immuno*)
 OR (hypersensitivity)] AND (English
 \[Language]).



oxygen species leading to the surface formation of titanium dioxide.¹² The resultant conjugate has been suggested to be largely (but not entirely) biologically inert in tissue conditions. For orthopaedic surgery, approximately one-third of all utilized metal-based implants contain some measure of titanium, with the majority of the remaining implant types principally being either cobalt-chrome or stainless steel based. However, almost all metal-based oral dental implants are reported to contain titanium.^{13,14} On this basis, much can be inferred regarding in vivo reactivity based on the longstanding experience from dental care. While precious little work has confidently elucidated the aetiological pathophysiology, it has been reported that not-insignificant levels of non-infective peri-implantitis routinely occur,¹⁵ with incidences as high as 56% in some series.¹⁶

The accepted common pathway of most immune-mediated allergic reactions is the local recruitment and activation of key pro-inflammatory mediators.^{17,18} Manifesting as the fundamental stigmata of inflammation, the common signs of hypervascularity, swelling, pain (and/or pain sensitization) are often seen in the peri-implant environment. The pathophysiological consequences may also be seen at a systemic level with activated cytokines transported via serum, lymph, and other body fluids to remote anatomic sites with consequences dependent upon the body region/system involved (e.g., synchronous or metachronous joint pain, skin reactions/dermatitis, myocarditis, hypertension etc.).^{17,19,20} In the context of allergic reaction to orthopaedic joint replacement components, the frequency and magnitude of these remote or 'secondary' reactions remains a poorly investigated and understood phenomenon.

Table 2 Key article inclusion table

Author (year)	Study type and reasoning for inclusion
Albrektsson (2018)	Review article, titanium implant-specific, periodontic osteolysis.
Bravo (2016)	Cohort study, metal hypersensitivity of TKA comparing patch test and post-op pain scores. Discussed role for metal allergy skin patch testing.
Desai (2019)	Cohort study, metal hypersensitivity of TKA comparing patch test and post-op pain scores. Discussed role for metal allergy skin patch testing.
Høl (2018)	Novel diagnostic concept utilizing in vitro flow cytometry specific to titanium antigens. The potential role for future diagnostic testing?
Fage (2016)	Review article, titanium specific. Summarizes literature base describing skin patch test's viability for titanium/titanium salts.
Hotchkiss (2016)	Novel study describing titanium surface characteristics relating to macrophage and cytokine activation and chemoattraction. Also, discusses in vitro testing options specific to titanium.
Kręcis (2012)	Prospective cohort study which includes skin patch tests comparing pre-op vs. post-op reactivity to several common orthopaedic implant metals, including titanium.
Ma (2014)	Novel study describing titanium implant surface characteristics relating to macrophage and cytokine activation and chemoattraction.
Matar (2021)	Review article describing metal allergy in TKA primary and revision (all metals) Discusses potential role for titanium allergy and summarizes generic contemporary metal allergy testing methods.
Müller-Heupt (2022)	Systematic review reporting metal hypersensitivity and available diagnostic testing in titanium-containing dental implants.
Ozden (2021)	Prospective comparative study describing the efficacy of skin patch test of ingredients in toothpaste. Discusses specifically the limited clinical utility of titanium Skin patch testing.
Podlipec (2021)	Novel study/case report of patient with likely titanium implant allergy undergoing revision surgery. Discusses potential diagnostic tests for titanium hypersensitivity/allergy.
Smeets (2014)	Review article of peri-implantitis and inflammatory/allergic drivers. Discusses impact of titanium-based tools and implants.
Wang (2018)	Novel study describing titanium surface characteristics relating to fibroblast and macrophage activation and in vitro testing options for suspected titanium allergy.

Patch testing

A composite of provided symptom history, patient-reported 'reactions' to previous metal exposures, and transdermal (i.e., skin) patch testing have formed the historical basis of most allergy diagnosis.⁶ Robust evidence does exist to support the reliability and predictive value of such testing – when performed correctly by an appropriately qualified individual – in the context of specific metals.²¹ Several common (non-titanium) alloy components of orthopaedic implants are known to show consistent reactivity during formal skin contact testing including nickel, cobalt, and

chromium – the recent publication by Desai *et al.*¹⁰ reported community reaction prevalence rates in the order of 8.58%, 6.43%, and 11.58% for these three metals, respectively. A subjective 'positive' reaction to any of these metals has often been deemed enough to consider a patient 'allergic'. In patients with titanium-containing alloys, patch testing of 'other' metals within the alloy prior to specific investigations of titanium is therefore indicated and may represent a simpler and more cost-effective starting point.

Patch testing has many appeals in the mainstream clinical setting through considerations including ease of performance, minimal invasiveness, and relatively low cost. A 'positive' result (suggestive of allergy) is classically defined through a morphologic criterion recommended by the International Contact Dermatitis Research Group. A reaction will typically involve erythema, infiltration, and papules in varying severity.²² In many circumstances however it can be difficult to clinically distinguish local (i.e., direct contact) irritative reactions from true immune driven allergy. However, in the specific setting of implanted orthopaedic devices and/or arthroplasty components there exists little (if any) evidence to support correlative value between such skin level testing and deep in situ immune-mediated allergy or meaningful clinical outcomes.¹¹ In this vein, it is important to consider that mucosa, skin, and deep tissues (including in periarticular locations) behave differently to direct immune challenges largely due to the extent of local expression of Langerhans cells and other cellular immune subtypes. Well-performed previous dental research has demonstrated the phenotypic importance of this with individuals known to have strong skin reactivity to nickel-containing compounds tolerating implanted orthodontic implants without clinical manifestation of pathology secondary to far lower local concentrations of Langerhans cells in oral mucosa.²³ It has been suggested that in the order of 5–12 times the antigen concentration may be required in the oral cavity setting to see induction of similar severity reactions to those seen from basic skin contact.^{23,24} Skin patch testing in the context of suspected titanium allergy is not clinically supported due to the fundamental lack of penetration of titanium dioxide through the intact skin barrier to permit lymphocyte activation. However, patch testing of non-titanium metals within the alloy prior to efforts centred around dedicated titanium allergy testing likely remains a relatively inexpensive and resource efficient method to assist in the diagnostic dilemma of metal hypersensitivity.

Current research

Beyond concerns regarding the basic utility of metal antigen skin patch testing as an accurate surrogate for true titanium allergy, previous research has highlighted fundamental barriers to the effective use of such methods for titanium assessment. As discussed previously, surface titanium in its pure form in contact with biological materials will rapidly transform to a dioxide conjugate (TiO₂). These nanoparticles (i.e., titanium salts) have low biologic solubility²⁵ and pass through the intact skin barrier poorly, with demonstrated lack of penetration through epidermal and subjacent viable skin layers^{12,26} otherwise necessary to permit exposure to deeper-seated key immune cells (i.e., and effectively trigger an intrinsic immune reaction). While arguably of value for other metals, these

Table 3 Key inclusion article – key findings summary

Author (year)	Relevant findings
Albrektsson (2018)	Utilization of inconsistent clinical definitions of peri-implantitis likely leading to prevalence rate variability. 10-year follow-up oral peri-implantitis rates: 1–2% 10-year follow-up all implants peri-implantitis rates: 28–56%
Bravo (2016)	Matched case–control study reporting the medium term follow up data contrasting clinical outcomes with Positive Skin Patch Test (SPT+) versus Negative Skin Patch Test (SPT-) for patients undergoing primary knee arthroplasty. Cases matched by age, gender, BMI, ASA, implant type/manufacture. 5-year survivorship free of revision: 98.1% SPT+; 100% SPT- vs. 97.6% SPT+, 99.0% SPT- control group. No statistical difference was demonstrated in post-op pain between cohorts.
Desai (2019)	Longitudinal Study following patients post-primary TKAs: Patch test >3 months post-op, and after clinical and radiological evaluation. A significant difference in loss-of-function and patient dissatisfaction associated with positive skin patch test compared to negative controls, 0.03 and 0.01 respectively. No statistically significant differences were identified regarding pain, swelling and local skin rashes ($P>0.05$). 12% of the cohort were symptomatic, yet 16% had positive skin patch test results. Reason for disparity is unclear. The paper recommended pre-op patch testing of cobalt, chromium and nickel.
Hol (2018)	In vitro flow cytometry immunogenic responses to soluble ionic Ti and insoluble TiO ₂ , measuring CD-69 and HLA-DR expression and 24 cytokines measured. Statistically significant between-group response differences. Cytokines with increased expression were macrophage and monocyte-type CD-69 and HLA-DR increased expression only with ionic Ti; nil difference for TiO ₂ .
Fage (2016)	Described contemporary evidence base exploring TiO ₂ dermal penetration: 9 studies demonstrate penetration to the stratum corneum layer with an additional 3 studies demonstrating Ti penetration only to the epidermis. These well-controlled results suggest limited (if any) clinically meaningful penetration of titanium oxides through an intact skin layer. MELISA and LTT specificity: ranges from 17% to 79% (i.e., widely variable).
Hotchkiss (2016)	Titanium discs with different surface roughness values/wettability and measured effects on naive macrophages, as measured by local cytokine release. Wettability characteristics had the greatest effect on provoked interleukin release. Increased surface roughness (hydrophilicity) was most strongly associated with increases in both pro- and anti-inflammatory protein production. M2-activated (anti-inflammatory) macrophage production.
Kręcis (2012)	Prospective cohort study, skin patch tests comparing subject reactivity from the pre-op state versus 24 months post-implantation. Despite a quantitative increase in the incidence of positive test results (pre-op SPT+: 21.7%; post-op SPT+: 25%) this did not achieve statistical significance. Authors speculate trend towards increase may reflect a sensitizing phenomenon. Cobalt and chromium can be allergenic – $P = 0.05$ and $P = 0.02$, respectively. Nil positive TiO ₂ patch tests.
Ma (2014)	Demonstrated the effect of titanium surface characteristics on chemoattractant and signalling macrophage differentiation and cytokine pathways. Anodization of nanostructured TiO ₂ surface at 5 and 20 V (NT5 and NT20). Non-human biologic study. NT20 surface configuration demonstrated greater macrophage infiltration while NT5 demonstrated greater proportion of M2-activated macrophage production
Matar (2021)	Titanium nitride (TiN) coating: Three studies demonstrate nil difference between TiN-coated and non-coated implants at 5- and 10-year follow-up. Two other studies demonstrated lower 5-year survivorship rates in TiN-coated implants compared to ceramic implants. TiN implant: satisfactory 5- and 10-year survivorship rates at 97.2% and 95.1% respectively
Müller-Heupt (2022)	Systematic review, titanium hypersensitivity diagnostic tests in dental implants. Patients with a known history of intolerance to titanium composites. Skin patch test to titanium: Positive reactions ranged from 0% to 25.7%. MELISA/LTT to titanium: 37.5% positive reaction, 28.6% questionable reaction, 33.9% negative reaction. Overall inconsistent reliability and validity. Study demonstrates innate immune response from macrophages towards nanoparticles, as opposed to adaptive immune response.
Ozden (2021)	Prospective comparative study patch test of ingredients in toothpaste Titanium dioxide SPT+: Patient 5.6%, control 8.5%, P -value 0.606 (no statistical difference). Study concluded intra-oral patch testing may yield better results. Oral mucosal surfaces and intrinsic immunologic responses may not mirror that seen in the peri-articular / synovial cavity environment.
Podlipec (2021)	Novel study/case report of patient with titanium alloy revision surgery Micro-spectroscopy, HIM, SEM-EDS and micro-PIXE demonstrate the effects of wear debris on surrounding tissue and inflammatory responses with lysosome and provoked hydroxyapatite-like formation.
Smeets (2014)	Review article of peri-implantitis – presents quantitative data with regard to biologic reactivity in the immediate per-implant space. <i>S. aureus</i> has shown to have a high affinity to titanium-containing surfaces which may predispose to indolent septic peri-implantitis. (80% PPV and 90% NPV). Smooth surfaces have greater local peri-implant inflammatory responses. Titanium implants with air polishing had 39–46% increased re-osseointegration.
Wang (2018)	Novel study, titanium surface characteristics relating to macrophage differentiation and polarization. Greater gene expression surrounding 'sand-blasted surfaces with large grit followed by acid-etching' (SLA) surfaces, when compared to smooth surface and control cohorts. Minimal observable differences between smooth and control surfaces.

specific transport considerations largely render transcutaneous exposure/diagnostic testing methods for titanium unviable. These concepts are demonstrated in Figure 2, showcasing the ineffective nature of patch testing. A number of recent investigations – including a

prospective clinical trial – have confirmed the limited utility of skin patch testing for titanium allergy.^{12,27,28} Anecdotal clinical evidence and the contemporary medical literature (largely case report based) do however continue to suggest titanium allergy as a 'real' phenomenon,

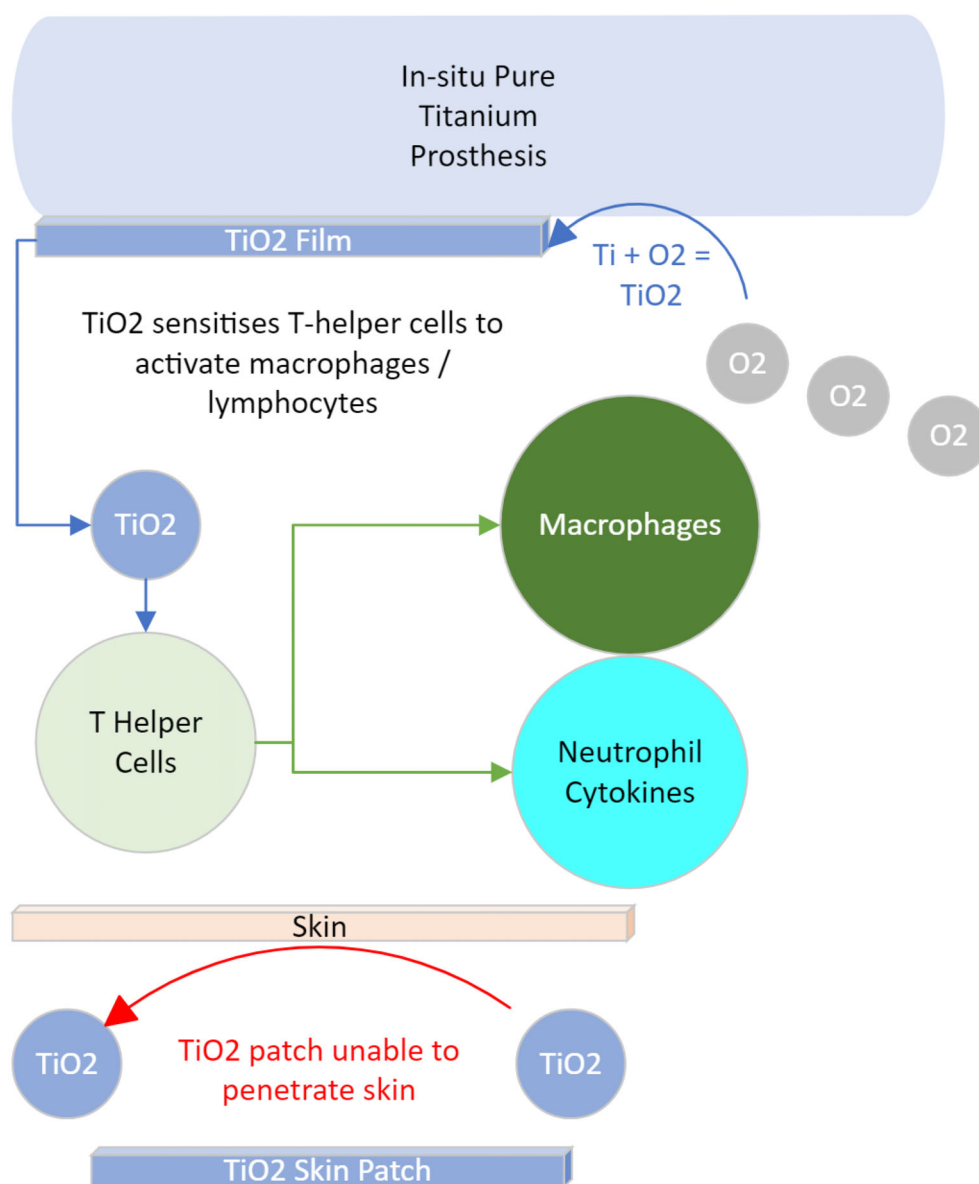


Fig. 2. Titanium hypersensitivity pathway.

albeit with definitive diagnosis hampered by the lack of an accepted 'gold standard' testing method. Basic skin patch testing continues to be widely employed,²⁹ although physiologic principles would suggest such processes likely carry a high false negative rate. Given the common use of titanium as part of metal alloys, it has been often shown that suspected 'allergy' was indeed due to reactivity to other alloy constituents.^{12,30}

Given the unreliable nature of skin patch testing – with poor acknowledged diagnostic specificity – there has been recent research interest surrounding alternative (i.e., 'better') diagnostic studies to more confidently allow the determination of true titanium-related allergies and/or hypersensitivities. Flow cytometry determining lymphocyte stimulation index is an advanced diagnostic tool which has been utilized to quantify metal hypersensitivity. The recent hypersensitivity testing study by Hol *et al.*,²⁵ compared both isolated titanium ions and titanium dioxide nanoparticles in an in vitro setting by exposing collected peripheral blood mononuclear

cells to these respective antigens. Their well-performed study was able to show a far greater reactivity response to the ionic form. Recruited test subjects were selected based on suspected metal allergies with six subjects testing positive for nickel. Twelve of the 20 participants had in situ titanium-based (i.e., 'hypoallergenic') implants. All 20 patients had a positive flow cytometry response to the ionic form of titanium. This work (and that of later authors) proposed an immune activation pathway for this result via increased expression of both macrophage and monocyte-type cytokines confirming that immune-mediated reactions to titanium are indeed likely equivalent to type IV hypersensitivity reactions.^{12,25} The significance of macrophage contributions to this pathway in the context of in situ joint replacement components is consistent with previous findings whereby purposeful mediation of macrophage activity led to improvements in the interface osseointegration of titanium implants.^{31–33} However, despite this seemingly clear patho-aetiological association, there remains little published evidence to

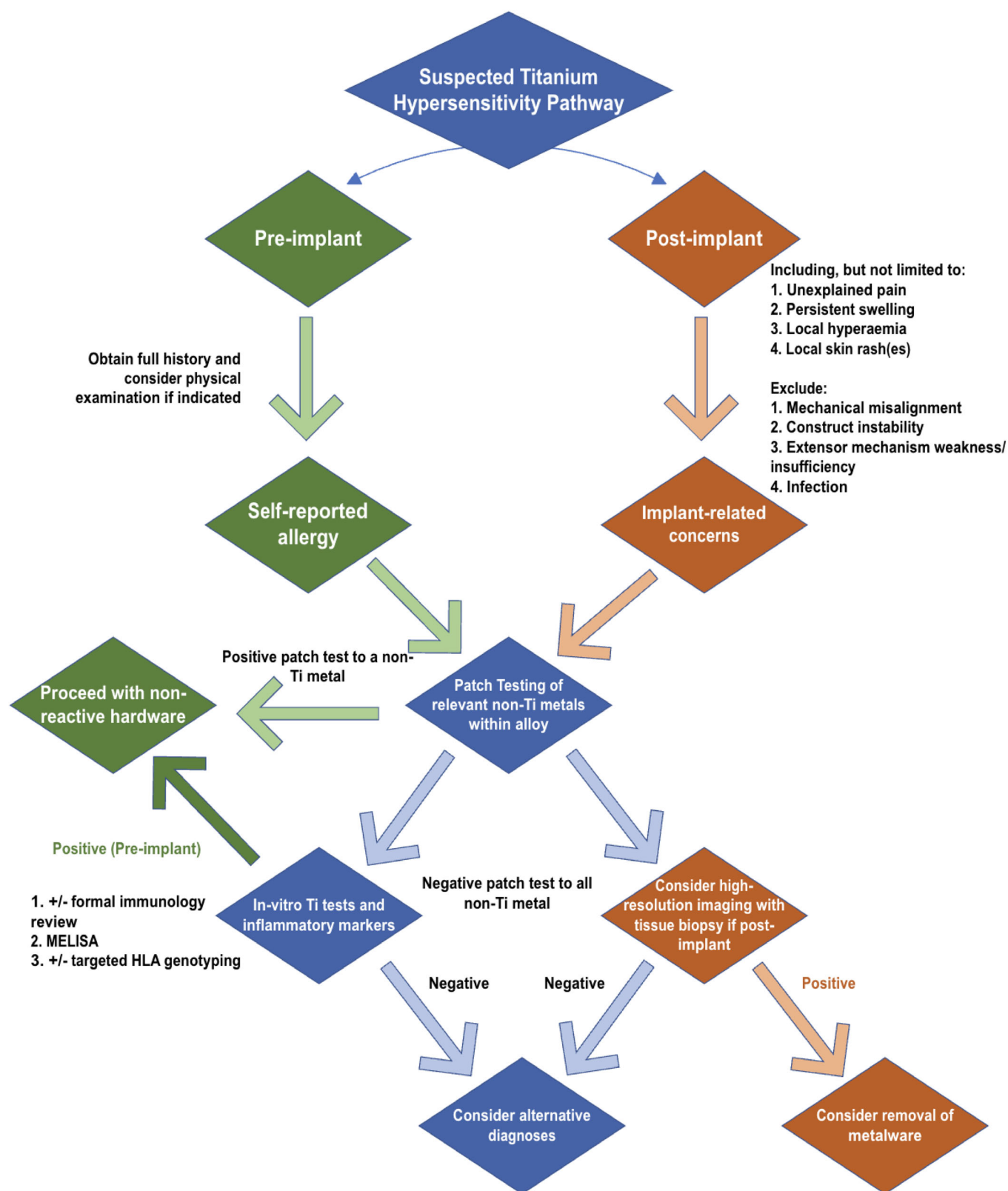


Fig. 3. Titanium hypersensitivity patient management algorithm. * in the context of an intact skin barrier, the poor fundamental penetration of titanium dioxide through skin grossly limits the utility of dedicated patch testing for suspected titanium allergy. However, evidence does exist to support such testing for other metals commonly included in the alloys of joint replacement components, such as nickel, cobalt and chromium. We recommend consideration for skin patch testing for these three metals which are recognized confounders of titanium allergy suspicions. Data adapted from Chen (2024)³⁹.

suggest the specific role of macrophage activation testing in specific relation to titanium allergy – and the subsequent correlation with clinical allergy – has been explored. This presents an exciting opportunity for future research to explore the diagnostic utility of such testing.

Other newer/more novel testing approaches for metal allergy assessment have generated some clinical enthusiasm and include in vitro blood-specimen based investigations such as lymphocyte transformation testing (LTT) and memory lymphocyte immunostimulant assay (MELISA).⁷ Although seemingly highly accurate and effective in other contexts, MELISA testing specifically for potential titanium hypersensitivities has been shown to have low and inconsistent diagnostic specificity, in the order of 17% to 79%.^{12,26} Recent reviews of the testing capacity and reliability of both MELISA and LTT, however, concluded that the internal validity of previous work was limited by both study designs lacking direct (healthy) comparative controls and equally due to limitations in the described testing approaches to allow allergen-sensitized T-lymphocytes to incorporate TiO₂ as a trigger hapten. The authors of these contemporary reviews sensibly cautioned that although in vitro blood tests are an exciting a conceivably useful future testing option that – under current utility considerations – results garnered should be interpreted alongside screening inflammatory markers and clinical findings and not employed as an independent diagnostic standard.

Testing with in situ implants

In the setting of in situ joint replacements (particularly of the hip and knee) there seems a plausible association between the volume of liberated ionic and/or particulate metal debris and subsequent immune-triggered local reactions. To a critical point, larger amounts of antigen exposure to biological environments increase the likelihood of sensitization and immune reaction.¹⁴ Metallic foreign materials are released from articulating components in situ from a number of recognized pathways including direct bearing wear, chemical/galvanic corrosion (including non-articulating ‘back side wear’) and through surface fretting.^{34,35} Once released from components, pure titanium, and titanium-based alloys rapidly oxidize following exposure to the biological environment. This considered, no robust causal relationship has been established between either simple contact exposure and accelerated component wear and increased rates of secondary immune sensitization (i.e., current understanding remains that physical wear may not be a critical element of allergy development).

As with many peri-prosthetic considerations, the true diagnostic gold standard for immune-mediated reactivity remains formal histopathological analysis of surgical biopsy specimens carefully collected from the host-implant interface tissues. The obvious limitations to such testing includes the invasive nature, the appropriateness and representativeness of the sampling technique itself, the morbidity associated with such specimen collection, the risk of damaging the in situ implant(s) and/or key local structures, and the need for appropriate surgical and pathology expertise. While many proposed diagnostic/grading systems have been proposed for such tissue analysis, the histologic classification systems previously

reported by Campbell *et al.*³⁶ and later by Kurmis *et al.*³⁷ have shown utility in specific arthroplasty contexts.

The recent work of Podlipec *et al.*³⁶ reported on the histopathological findings of periprosthetic tissue specimens associated with the chronic inflammatory response induced by wear debris around titanium-based (alloy) implants.³⁶ They employed a series of ultra-high-resolution (multi-modal) imaging techniques. Initial helium ion microscopy (HIM) showed consistent tissue arrangement in the form of hydroxyapatite-like layers with wear debris packed in the local cellular/tissue planes.³⁸ Subsequent micro-particle-induced x-ray emission (micro-PIXE) showed higher elemental sensitivity, with homogenous and widespread titanium debris throughout the tissue sample and confirmed selective metal leaching which correlated well with the observed elevations in serum titanium concentrations.³⁸ This novel study concluded that on a microscopic inflammatory level – micron-sized titanium debris resulted in direct oxidative tissue stress and resultant lipopigment accumulation within lysosomes which drove macroscopic induction of a hydroxyapatite-like layer causing focal inflammation.

This encouraging preliminary evidence suggests that HIM and micro-PIXE may be invaluable tools in definitively diagnosing true titanium-related hypersensitivity/immune reactions. These exciting early results will undoubtedly encourage future targeted research in this field and may facilitate better physiologic understanding and higher diagnostic accuracy related to implant-associated immune-mediated reactions to titanium. Such work will permit the determination of the wider external validity of the index findings and will frame the diagnostic potential of this testing approach on a greater scale. However, at present, both advanced testing techniques are associated with considerable per-patient expense and have limited general accessibility. In most regions, such diagnostic methods are only available in select highly-specialized facilities/tertiary (quaternary) centres and access is unlikely for the majority of community-based orthopaedic surgeons.

Discussion

Surprisingly to us, despite the widely-accepted role of titanium-based, coated, or pure implants in mainstream orthopaedic and arthroplasty use, there actually exists very little solid contextual evidence to support this. Such applications have fundamentally been underpinned by in vitro analyses and/or that of general immunology fields (largely reliant upon skin patch testing data). As we have described, the utility of the latter approach may be considered questionable at best, and likely grossly flawed.

General medical and indeed specialist arthroplasty groups increasingly recognize immune-mediated, metal allergies as a real entity there is a pressing need for accurate and reliable means of screening clinically ‘at risk’ patients.³⁹ As this paper has shown, little evidence exists to suggest titanium as an independent (i.e., separate from other common alloy constituents), potential immune-triggering, allergen has been comprehensively considered. Equally, ‘all metals are NOT equal’ (from a histo-immunologic perspective), and therefore accepted allergy testing methods for other metals (i.e., nickel, chromium, cobalt, etc.) may not be reliable or appropriate. Further focussed research is indicated to initially

establish an accepted 'gold standard' testing method which can be made readily available, generates a consistent, accurate and reliable result, and can be used to confidently inform clinical decision-making in the patient care setting. Such investigations should consider titanium in its pure form, but perhaps more importantly in its ionic compound form – thus mimicking the exposure antigen most likely dominant in the *in vivo* biological state.

While current evidence would suggest that surgical biopsy specimens obtained from the implant-host interface likely yield the best diagnostic result, combined HIM and micro-PIXE analysis is an expensive and expertise-dependent high-end approach that requires highly specialized testing resources and is certainly not available in the mainstream setting. Equally, the high-cost nature of such testing, and the need for invasive surgical specimen collection from precise locations around in situ implants may render it a prohibitive consideration in most environments. Under current and foreseeable conditions, *in vitro* analyses of simple peripheral blood specimens appear to represent the most practical and feasible options. It remains unclear whether activated lymphocyte (T cells) or macrophage colonies will prove the best pathway forward and well-performed head-to-head comparative studies will shed light on this. The value of minimally-invasive peripheral blood screening will lie in both pre-implantation screening (i.e., to determine the risk profile of a patient being considered for joint replacement surgery – this result may inform prosthesis selection to minimize allergic risk) and in post-implantation testing for patients with symptomatic and/or underperforming in situ constructs for whom other potential differential diagnoses have been reasonably excluded. In the latter case, the result may be used to inform the difficult conversations with patients regarding revision surgery or symptomatic retention.

We acknowledge several limitations to our current review. Firstly, while it had been our intent to complete a formal meta-analysis of the available literature, it quickly became clear that the limited body of evidence in this novel field would preclude this. Nonetheless, with the intent of providing the most up-to-date contemporary summary of the current knowledge base we have attempted to complete our review following transparent meta-synthetic principles.

Based on our comprehensive review, we propose the patient investigation and management pathway as shown in Figure 3. We acknowledge the lack of a true current 'gold standard' testing approach and the absence of international authoritative guidelines in this area. Based on the best available contemporary evidence we suggest the pathway to be a sensibly conservative approach for the arthroplasty surgeon charged with the task of managing the individual patient in front of them for whom a potential immune-mediated allergy to titanium is a clinical consideration. Undoubtedly, with time, this pathway will evolve and change as new credible evidence comes to light. We have incorporated separate starting positions for without or with an in-situ joint replacement (i.e., pre- and post-implant) to allow prompting for consideration of potentially confounding considerations unique to each setting. At later stages, the pathways converge into a common investigation sieve. Based on the current knowledge in this area, we advocate for reliable screening of 'other' metals known to be potential triggers for allergic reactions (such as nickel, cobalt and chromium) as well as a suite of targeted screening blood tests. Skin patch testing for the same common metals is likely still a valuable next step, again as a

positive result in this regard may provide a tangible explanation for symptoms or concerns held. Thereafter, *in vitro* activation testing as per local conventions and availability (i.e., T cell or macrophage) may add another layer of information to aid diagnostic determination. In the situation whereby the patient does have an in situ joint replacement of concern, there may be a role for invasive local tissue sampling (i.e., arthroscopic interface biopsy) for formal histopathologic analysis. The morbidity and inherent risks of such a process (i.e., iatrogenic periprosthetic infection seeding) must be balanced against the potential benefit in this case.

Conclusions

Despite titanium being widely championed as a 'hypoallergenic' option for orthopaedic implants – including joint replacement prostheses – this review highlights that the evidence underpinning such assumptions is poor. Surface wear or corrosion from in situ titanium-containing implants forms a local TiO₂ film under biologic conditions which may directly trigger immune-mediated hypersensitivity reaction. Such responses involve the coordinated recruitment of several important cell lineages, although T cells (lymphocytes) and activated macrophages play key pathogenic roles. Skin patch testing has arguably no screening value in the diagnosis of titanium allergy given the lack of penetration through skin. Two patient groups are likely to benefit from the ability to diagnose titanium allergy – those being considered for joint replacement and those with an aseptic in situ joint which remains symptomatic. Based on the findings of our review, we have proposed investigative/diagnostic approaches for both groups. While formal histopathologic assessment of solid tissue surgical specimens taken from around joint replacements likely remains the true 'gold standard', the invasiveness and associated morbidity provide impetus for the identification of alternatives. There exists an opportunity for further, high-quality, research in this area, as current testing approaches are further refined and targeted immunogenetic screening becomes more widely available.

Author contributions

Arnold Chen: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Andrew P. Kurmis:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing.

Conflicts of interest

None declared.

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