Arthroplasty Today 28 (2024) 101462

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original Research

Existing and Novel Assessment Methods for Metal Sensitivity in Elective Lower-Limb Arthroplasty—A Scoping Review

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ARTICLE INFO

Article history:
Received 20 November 2023
Received in revised form
13 May 2024
Accepted 9 June 2024
Available online xxx

Keywords:
Metal sensitivity
Arthroplasty

ABSTRACT

Background: Metal sensitivity is a possible cause for revision in elective lower-limb arthroplasty. This scoping review aims to identify and evaluate all existing and novel assessment methods for metal sensitivity in elective lower-limb arthroplasty.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, and Google Scholar databases were searched for studies published between January 1, 2000, and September 1, 2023. Studies evaluating one or more metal sensitivity assessment method preoperatively, perioperatively, or postoperatively were included. Studies were grouped based on the assessment methods reported and summarized based on the study design, outcome measure, results, and comments on the method's validity.

Results: A total of 1220 results were screened, with 39 results (15 retrospective cohort studies, 11 prospective cohort studies, 6 case reports, 5 randomized controlled trials, and 2 case control studies) included, identifying 12 assessment methods. The most used one was patch testing, featuring in 17 studies (43.6%). Lymphocyte transformation assay/testing featured in 12 studies (30.8%). Plasma/serum concentration of metal ions featured in 6 studies (15.4%). Patient history and serum cytokine testing featured in 7 (17.9%) and 4 (10.3%) studies each. Generalized serum inflammatory markers featured in 3 studies (7.7%). The remaining 6 methods each featured in one or 2 studies. Evidence of the reliability of most metrics was limited.

Conclusions: Several assessment methods were identified. However, evidence of any methods reliably predicting and diagnosing the occurrence of metal sensitivity was limited. There is a need for improved metrics of metal hypersensitivity.

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Introduction

Metal hypersensitivity refers to the immune-mediated allergic reaction to metals exhibited by some humans in response to metal-containing stimuli. This most commonly presents as a localized allergic reaction to jewelry and metal components found on clothing [1]. This localized allergic reaction to metal, contact dermatitis, is relatively common and widespread globally. It is estimated to affect 10%-15% of the population, with a slight predominance in women [2,3]. Its incidence is projected to rise in the coming years [4]. The most common causative metal is nickel, although beryllium, cobalt, chromium, tantalum, titanium, and vanadium have also caused documented hypersensitivity reactions [5]. While often a relatively innocuous allergy, metal hypersensitivity becomes problematic in individuals undergoing procedures that require the permanent implantation or fixation of metal within the body, as commonly occurs with dental procedures and arthroplasty surgery. In such instances, metal sensitivity and allergy can contribute to complications in management and impaired clinical outcomes [6].

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https://doi.org/10.1016/j.artd.2024.101462
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Metal sensitivity, in the case of contact dermatitis, is caused by a type I hypersensitivity "immediate" reaction, where overactive IgE-mediated antibodies cause mast cell degranulation resulting in histamine release [7]. However, when within the body, metal implants can solicit a range of immune hypersensitivity reactions. Following implantation, metal implants interact with biological tissues, resulting in wear and corrosion [8]. Metal particulate that is released through wear may then ionize and interact with proteins to form complexes that behave as antigens, capable of eliciting an immune response from circulating lymphocytes at the site of implantation [5]. These complexes, known as haptens, may trigger several types of hypersensitivity reaction in susceptible individuals, including a type I hypersensitivity reaction; a type II reaction, whereby IgG and IgM antibodies activate the complement system; a type III reaction, caused by immune complex formation resulting in the formation of polymorphonuclear leukocytes; and most commonly, a type IV "delayed" reaction, whereby macrophages are released in response to inflammatory cytokines [7].

While there is consensus that type IV hypersensitivity is the most common reaction underlying metal hypersensitivity, knowledge of the cells involved in metal-protein complex formation is less well understood, with several mechanisms posited, and may in part explain the limitations in current metrics of accurately predicting and diagnosing metal hypersensitivity reactions [2,9,10]. The impact of metal hypersensitivity on outcomes following metal implantation, particularly in dentistry and arthroplasty surgery, is a topic of controversy and paucity in the present literature. Prior research has implicated metal hypersensitivity as a cause of implant failure in revision total hip and knee arthroplasty [11,12]; however, at present, metal hypersensitivity as a cause of implant failure is frequently a diagnosis of exclusion, which may account for a major proportion of implant revisions due to pain.

Given its increasing incidence and the documented deleterious impact metal hypersensitivity can confer in invasive medical procedures, the ability to recognize metal hypersensitivity in patients before and after arthroplasty surgery is increasingly important. Novel prostheses have shown promise as hypoallergenic alternatives to common metallic implants, with utility in patients susceptible to metal hypersensitivity; however, at present, such implants are in their experimental infancy [2,9]. An understanding of how to reliably assess for hypersensitivity, both preoperatively and postoperatively, is presently limited, with methods used varying widely across countries and institutions. There is, therefore, a need for a contemporary review to evaluate the present literature to identify the most common and novel assessment methods for metal hypersensitivity being used in present clinical practice, to improve the management of this challenging and poorly understood patient cohort. This scoping review aims to address this gap in the present literature and provide an overview of novel assessment methods for metal sensitivity most widely used in lower-limb arthroplasty surgery.

The aim of this study is to identify and evaluate all existing and novel assessment methods for metal sensitivity in use for elective lower-limb arthroplasty

Methods

Search strategy and study selection

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for scoping reviews guide [13]. Briefly, a search of the Cochrane Central Register of Controlled Trials (CENTRAL 2023), Ovid Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, and Google Scholar online databases was conducted in September 2023. A range of databases were chosen to maximize the number of included studies. Three separate searches of each database were conducted using the following search phrases: (1) All text: "metal sensitivity test", (2) All text: "metal hypersensitivity testing", (3) "Assessment methods for metal sensitivity". These search terms were intended to be broad to maximize the number of studies included. The results of the 3 searches were then pooled, to maximize the scope of this literature search.

Studies were eligible for inclusion if they were published between January 1, 2000, and September 1, 2023; written in English; original primary research evaluating one or more metal sensitivity assessment methods for elective lower-limb arthroplasty, with the full text available; and focusing solely on human subjects. Studies were excluded if they were published outside of the date window of interest, not written in English, non-primary research (narrative reviews and systematic reviews were excluded), not focusing solely on human subjects, study protocols or those with the full-text unavailable, or not focused on metal sensitivity assessment methods for elective lower-limb arthroplasty. The detailed search strategy can be found in this study's appendix (Appendix).

Data extraction

The titles and abstracts from the results of each database search were closely inspected and evaluated against the stated inclusion criteria. Eligible studies were then assessed, and all pertinent data were extracted in a narrative review summarizing evidence from each study. Studies were separated based on the metal sensitivity assessment method mentioned or evaluated.

Results

Results of database search

Studies identified

A total of 1220 studies were identified from searching CENTRAL, MEDLINE, PubMed, and Google Scholar databases. They were then assessed against our inclusion criteria, with 39 results included in the narrative synthesis (Fig. 1). A range of study types were identified, ranging from case reports (n = 6), retrospective (n = 15) and prospective (n = 11) observational cohort studies, randomized controlled trials (n = 5), and case-control (n = 2) studies. Some studies evaluated more than one sensitivity testing method.

Assessment methods identified

This search identified 12 distinct assessment methods for metal sensitivity (Appendix Tables 1-13, Appendix). The most widely used assessment method was patch testing, featuring in 17 (43.6%) of included studies. Lymphocyte transformation assay/testing was the second most widely used assessment method, featuring in 12 (30.8%) of all included studies. Plasma/serum concentration of metal ions featured in 6 studies (15.4%), while a patient history and serum cytokine testing featured in 7 (17.9%) and 4 (10.3%) studies each. Generalized serum inflammatory markers featured in 3 studies (7.7%), and the remaining 6 methods each featured in one or 2 studies.

Narrative synthesis was used to provide summary of each assessment method identified, with the number of studies using that testing method, the range of publication dates, evidence types, and any strengths or limitations of that testing method (Table 1).

Patch testing

Patch testing was the most widely used metal sensitivity assessment method identified in the literature, featuring in 17

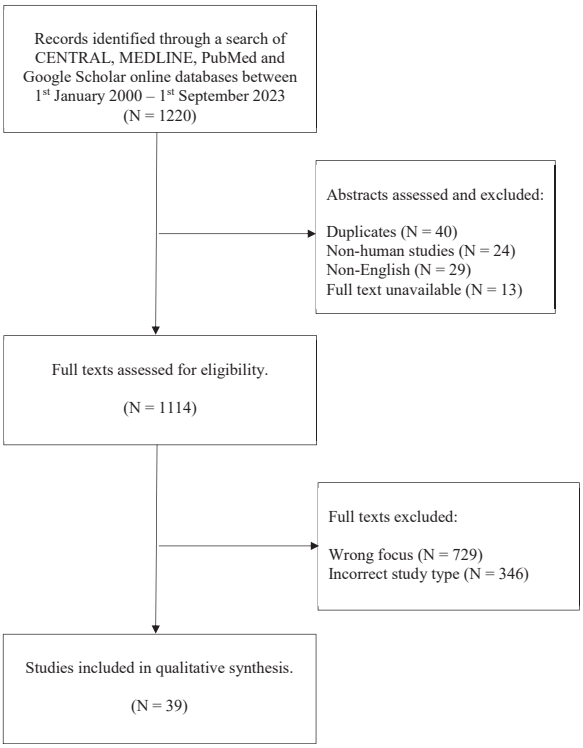

Figure 1. PRISMA flow diagram of study selection.

(43.6%) studies. Of these, 2 (11.7%) were randomized controlled trials, 6 (35.2%) were prospective cohort studies, 5 (29.4%) were retrospective cohort studies, 3 (17.6%) were case reports, and one (5.9%) was a case-control study. All were published between 2010 and 2023, making most evidence highly contemporary [4,14–29].

There was limited evidence of studies directly evaluating the efficacy of patch testing as an assessment method for metal sensitivity, although the studies that did mention its efficacy emphasized its limitations. For instance, Keller et al commentated that: "The sensitivity and specificity of patch testing, in general, are limited when evaluating patients with metallic joint replacements." [21]. Similarly, Bracey et al found that results of patch testing differed to those of lymphocyte-based testing methods, with each test given conflicting findings on the presence of metal sensitivity in some patients [16].

Lymphocyte transformation assay/testing

Lymphocyte transformation assay/testing was the second most widely featured testing method used in the literature, featuring in 12 (30.8%) studies. Of these, 2 studies (16.7%) were randomized controlled trials, 5 studies (41.7%) were retrospective cohort analyses, 4 (33.3%) were retrospective cohort analyses, and one (8.3%) was a case-control study. Of these 12 studies, 2 (16.7%) were published between 2000 and 2010, with the remainder (83.3%) published between 2010 and 2023 [14,16,24,26,27,30–35]. The conclusions of articles evaluating lymphocyte transformation testing/assay (LTT) were conflicting, with some researchers, such as Bracey et al, Malahias et al, and Keeling et al emphasizing the limitations of LTT as an assessment method [16,31,35]. By contrast, some researchers, such as Vermes et al, concluded it may have some utility as an assessment method for implant-related sensitivity [26], while some researchers suggested the test confers little certainty of a sensitivity diagnosis [16].

Urinary excretion of metal ions

Urinary excretion of metal ions as an assessment method for metal sensitivity was presented in one study (2.6%), a randomized controlled trial, published in 2014 [14]. The study provided promising results on the utility of urinary ion levels as a metric of metal hypersensitivity, finding a direct relationship between concentration of urine nickel and level ingested [14].

Patient history/self-report of allergy

Seven studies (17.8%) evaluated the utility of patient self-reporting of allergy/patient history as a measure of metal sensitivity. One was a randomized controlled trial, while the remainder were retrospective cohort studies. All were published between 2010 and 2023. There was limited evidence of any of these studies evaluating the utility of patient self-reporting allergy as a metric of metal sensitivity [14,18,36–40].

Plasma ion concentration

Six studies (15.4%) evaluated the use of plasma ion concentrations as a marker of metal sensitivity. Of these, 2 (33.3%) were randomized controlled trials, 2 (33.3%) were prospective observational cohort studies, one was a retrospective observational cohort study, and one was a case report. In a similar fashion to other testing modalities, the results from these studies were conflicting [15,27,41–44]. Despite one study finding a statistically significant difference in levels of plasma ion concentration in patients with metal hypersensitivity compared with non-sensitive patients [41], no studies commented on the method as having any strong predictive or diagnostic value for metal hypersensitivity.

Serum cytokines

The presence of serum cytokines as a marker of metal sensitivity was an assessment method evaluated by 4 studies (10.3%): one randomized controlled trial, one was a case-control study, one prospective, and one retrospective observational cohort analysis [26,45–47]. Of these, all were published between 2010 and 2023. The results of these studies were broadly concordant, that patients with metal sensitivity demonstrated increased levels of inflammatory cytokines [26,45–47].

Generalized serum inflammatory markers

The utility of testing generalized serum inflammatory markers (complete blood count, C-reactive protein, erythrocyte sedimentation rate, white blood count) as markers of metal sensitivity was presented in 3 studies (7.7%): one case-control study and 2 case reports, all of which were published between 2020 and 2023 [24,34,48]. One study did not comment on the utility of such markers to assess for metal sensitivity, although 2 commented on it as a limited metric.

Lymphocyte Proliferation Testing

Lymphocyte proliferation testing (LPT) was evaluated in one retrospective cohort study, from 2022. This study determined that LPT was weakly sensitive to nickel and cobalt, but minimally sensitive to nickel, and weakly sensitive to titanium, but strongly sensitive to chromium and cobalt, further commenting that concordance between LPT and LTT was weak and concluded that this testing metric is of limited value in determining metal sensitivity [15].

Memory Lymphocyte Immunostimulation Assay

The use of Memory Lymphocyte Immunostimulation Assay (MELISA), a novel assessment method, was evaluated in 2 studies (5.1%): one a case-control study from 2022, and one case report from 2021. Both highlighted the clinical utility of MELISA as a testing method for metal sensitivity, although the sample size of

Table 1
Metal sensitivity assessment methods identified from literature search.

Assessment method	Number of studies	Years published	Evidence type	Strengths mentioned	Limitations mentioned
Patch testing	17	2013-2022	Case report—RCT	N/A	The sensitivity and specificity of patch testing, in general, are limited when evaluating patients with metallic joint replacements.
Lymphocyte transformation assay/ testing	12	2001-2022	Retrospective observational cohort—RCT	Leukocyte triple assay technique might be a useful tool to test implant material-related sensitivity	A positive LTT may not indicate that an immune reaction is the cause of pain and stiffness post-TKA.
Urinary excretion of metal ions	1	2014	RCT	N/A	N/A
Patient history/self-report of allergy	7	2014-2023	Retrospective cohort study—RCT	N/A	N/A
Plasma ion concentration	6	2013-2018	Case report—RCT	N/A	Sensitization after TKA was rare and had no influence on clinical results. TKA with coated implant and standard TKA demonstrated no plasma metal ion elevation
Serum cytokines	4	2013-2022	Retrospective Observational Cohort - RCT	The study indicates that CD8+ CD45RO + CLA + T lymphocytes and T lymphocytes with a type 2 cytokine profile are involved in SCD elicited by nickel.	There was similar clinical outcome 5 y after standard and surface-coated TKR. In peripheral blood there was an increased pro-inflammatory status, i.e., significant elevation of IL-8 and the anti-inflammatory IL-10, after standard uncoated prosthesis. Any long-term effects of these cytokine changes are unknown.
Generalized serum inflammatory markers	3	2020-2022	Case control study—case report	N/A	A method to better distinguish postoperative hypersensitivity from infection is paramount so that patients suffering from hypersensitivity can be appropriately treated.
Lymphocyte proliferation testing	1	2022	Retrospective cohort study	N/A	SPT and LPT showed weak agreement for nickel and minimal agreement for cobalt. SPT and LTT showed minimal agreement for nickel; weak agreement for titanium, bone cement, vanadium, and zirconium; but strong agreement for chromium and cobalt. LPT and LTT agreement was weak.
Memory Lymphocyte Immunostimulation Assay (MELISA)	2	2021-2022	Case report—case control study	N/A	N/A
Ultrasound testing	1	2017	Prospective cohort study	N/A	Ultrasound findings of an abnormal straight or convex ligament may be suggestive of early ALTR and warrant streaming of patients to a more frequent surveillance program.
Periprosthetic tissue sampling	1	2021	Prospective cohort study	N/A	Periprosthetic TKA tissue reactions were indistinguishable between LTT-positive and LTT-negative patients. LTT does not predict the periprosthetic tissue response.
Perivascular lymphocytic infiltration (PVLI)	1	2021	Retrospective observational cohort analysis	N/A	Large-scale histological analysis in TKAs at aseptic revision surgery was not associated with worse clinical outcomes or rates of re-revision

studies evaluating this testing methodology (n = 2) limits the generalizability of these findings [46,49].

Ultrasound testing

Another uncommon assessment method documented in the literature was the use of ultrasound to assess for adverse local tissue reactions that occur due to metal hypersensitivity to orthopedic prostheses. One prospective cohort study, from 2017, evaluated the use of this assessment method, concluding that: "Ultrasound findings of an abnormal straight or convex ligament may be suggestive of an early Adverse Local Tissue Reaction" [50]. However, due to the limited sample size of studies evaluating this testing method, the generalizability of these findings is limited [50].

Periprosthetic tissue sampling

Periprosthetic tissue sampling as a method of comparing patient sensitivity to conventional vs hypoallergenic total knee arthroplasty prostheses was a novel assessment method evaluated by one 2021 prospective cohort study that compared tissue samples in LTT-positive and LTT-negative patients, determining that tissue samples were indistinguishable, concluding that periprosthetic tissue sampling is superior to LTT testing in the diagnosis of metal sensitivity [51].

Perivascular lymphocytic infiltration

Another novel assessment method evaluated by one retrospective observational cohort analysis from 2021 was assessing for the presence of perivascular lymphocytic infiltration (PVLI) in revision knee arthroplasty patients, as a marker of metal sensitivity; however, it determined that PVLI found on large-scale histological analysis in TKAs at aseptic revision surgery was not associated with worse clinical outcomes or rates of re-revision [52].

Discussion

This scoping review sought to identify all existing and novel assessment methods for metal sensitivity in use in elective lower-limb arthroplasty, identifying 12 distinct assessment methods from 39 studies, most of which were highly contemporary. The most widely used assessment method was patch testing, featuring in 17 (43.6%) of the included studies, while lymphocyte transformation assay/testing was the second most widely used, featured in 12 (30.8%) of all included studies. Plasma/serum concentration of metal ions featured in 6 studies (15.4%), and patient history and serum cytokine testing featured in 7 (17.9%) and 4 (10.3%) studies, respectively. Generalized serum inflammatory markers featured in 3 studies (7.7%). The remaining 6 methods each featured in one or 2 studies. Despite a range of testing methodologies being identified, the evidence of researchers assessing the validity of each testing method was limited, with limited concordance among researchers of the reliability and clinical utility of any sensitivity method.

Patch testing was the most widely used and well-validated assessment method for metal sensitivity, featuring in 17 studies. Despite its widespread use, there was major divergence among researchers on the clinical utility of patch testing as an accurate predictor of metal sensitivity, without consistent testing results for different metals. The limitations of patch testing as a testing method for metal sensitivity are documented in the literature, particularly in the context of diagnosing metal sensitivity in arthroplasty. In their 2012 systematic review, Granchi et al concluded that: "Hypersensitivity testing was not able to discriminate between stable and failed total joint replacements, as its predictive value was not statistically proven" [53]. Despite its documented limitations in diagnosing metal sensitivity, there are several advantages to patch testing that may in part explain its widespread use. Owing to its design, patch testing allows for many allergens to be tested at once and is a cheap and cost-effective method of screening patients for a range of common allergens, which is particularly of value in the management of contact dermatitis, which has a range of causative allergens [54].

LTT also featured in a number of studies (12). A limited number of studies actually evaluated the utility of LTT as a measure of metal sensitivity; however, among those that did, the attitudes of researchers to its clinical utility were mixed, although one prospective cohort analysis by Vermes et al compared the results of LTT to patch testing in hip arthroplasty patients with suspected metal sensitivity, determining it to be more sensitive in diagnosing metal sensitivity [26]. That said, it is challenging to conclusively comment on the utility of LTT as a testing method, as most studies were retrospective cohort analyses, involving very small sample sizes (often less than 20 patients). LPT, a similar testing methodology, showed conflicting results and variable reliability based on the metal assessed, while MELISA testing, another variation of LTT, showed utility, but only in one study, with the other evaluating its use being a case report. There are downsides to lymphocyte-based testing methods which may in part explain why their use is not more widespread, particularly LTT and LPT. Both LTT and LPT involve a complex process of incubation, centrifugation, and suspension in specialized filter plates, a time-consuming process which requires skilled technicians [54]. Both investigations are also costly. While figures may differ, LTT testing may cost more than $150 per LTT and over $300 per LPT test depending on test type and manufacturer [55,56].

The use of urinary metal ion levels and plasma ion levels as metrics of metal sensitivity featured in one and 6 studies, respectively, with both testing methods demonstrating some promise in diagnosing metal sensitivity in arthroplasty [14,15,27,41–44]. Urinalysis is a cheap and widely used testing method, frequently used as a diagnostic tool in other specialties, although it is unclear why so few studies have evaluated its use in diagnosing metal sensitivity in arthroplasty [57]. Similarly, metal ion analysis of blood serum has shown some promise and likely merits further investigation as a diagnostic tool in metal sensitivity. The use of other blood markers, particularly generalized inflammatory markers, and serum cytokines as measures of metal sensitivity was evaluated by 3 studies and 4 studies, respectively, [24,26,34,45–48]. The studies evaluating these assessment methods were generally concordant that patients with metal sensitivity exhibited increased levels of inflammatory markers and serum cytokines, although the specificity of such measures is limited, meaning that while they may indicate an allergic reaction is underway, their ability to accurately predict sensitivity before implantation and to exclude other causes of complication is limited.

In addition to the assessment methods listed earlier, several novel assessment methods for metal sensitivity were identified from the literature. The presence of PVLI around revision knee arthroplasty prostheses as a marker of metal sensitivity yielded poor results. Researchers determined that "PVLI found on large-scale histological analysis in TKAs at aseptic revision surgery was not associated with worse clinical outcomes or rates of re-revision" [52]. Given these limitations, the applicability of such novel and discipline-specific assessment methods for metal sensitivity is confined to experimental infancy.

Another novel assessment method is the use of human leukocyte antigen (HLA) genotype testing as a predictor of metal sensitivity, currently under investigation by Langton et al [58]. Different individuals confer different HLA alleles, which have been implicated by some researchers in the development of metal sensitivity following arthroplasty surgery. In their recent single-center observational cohort study, Langton et al demonstrated that

variations in HLA genotype influence the susceptibility of individuals to developing metal sensitivity after implantation of cobalt chromium hip prostheses, offering the prospect that predictive testing may be available in the future to identify patients at risk of metal sensitivity [58]. These novel findings show some promise and offer a potentially predictive test that may be used before arthroplasty surgery to prevent the occurrence of metal sensitivity, although at present are confined to experimentation, and merit further investigation.

This scoping review has several strengths. Several databases were searched, leading to a range of contemporary studies being identified and a range of different existing and novel metal sensitivity testing metrics. It has also identified the major limitations in most existing metrics of metal sensitivity, most of which are unreliable. Evidence suggesting the utility of some metrics was retrospective and limited in scope, highlighting the need for randomized controlled trials comparing testing metrics for patients with suspected metal sensitivity undergoing arthroplasty surgery. There are, however, several limitations to this scoping review. Seminal research by Langton et al [58], who have identified the use of HLA antigens as a prognostic marker of metal sensitivity, was not identified in using the present search strategy. That said, a range of studies were identified from several databases and allowed for a relatively comprehensive overview of the present literature and the limitations in current metrics of diagnosing metal sensitivity in patients undergoing elective lower-limb arthroplasty.

Conclusions

This scoping review has identified 12 distinct existing and novel assessment methods for analyzing metal sensitivity in patients undergoing elective lower-limb arthroplasty, with patch testing being the most commonly used one. Despite a range of assessment methods being identified from a range of contemporary studies, most of which were published between 2010 and 2023, evidence of assessment methods reliably and accurately predicting and diagnosing the occurrence of metal sensitivity in arthroplasty is presently limited, with the most promising research highlighting the clinical utility of some metrics such as being small in size, often retrospective, and of limited scope. There is a need for improved metrics of metal hypersensitivity in arthroplasty surgery that are able to reliably predict its occurrence before procedures are undertaken to prevent the complications associated with this challenging and poorly understood diagnosis.

Funding

Professor Pandit is a National Institute for Health Research (NIHR) Senior Investigator. This study/research is funded by the NIHR Leeds Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. No other funding was received for this project.

Conflicts of interest

HP receives institutional grants from NIHR, Charnley Trust, AO Foundation, Vs Arthritis, Zimmer Biomet, Depuy Synthes, B Braun, and Invibio; receives consulting fees from Medacta International, Smith and Nephew, Paradigm Pharmaceuticals, Allay Therapeutics, Teleflex, Zimmer Biomet, Depuy Synthes, Microport, MATOrtho, and Invibio; receives support for attending meetings and/or travel from Zimmer Biomet, Medacta International, and Invibio; and has 2 patents planned, issued, or pending linked to his work at the University of Leeds, related to sensors. These declarations do not affect or pertain to this work. The other authors declare no conflicts to disclose.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2024.101462.

CRediT authorship contribution statement

Alexander Abouharb: Writing – original draft, Methodology, Formal analysis. **Prince Josiah Sajanthan Joseph:** Writing – original draft, Methodology, Formal analysis. **Hemant Pandit:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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