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■ SYSTEMATIC REVIEW

Metal allergy in primary and revision total knee arthroplasty

A SCOPING REVIEW AND EVIDENCE-BASED PRACTICAL APPROACH

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Aims

Metal allergy in knee arthroplasty patients is a controversial topic. We aimed to conduct a scoping review to clarify the management of metal allergy in primary and revision total knee arthroplasty (TKA).

Methods

Studies were identified by searching electronic databases: Cochrane Central Register of Controlled Trials, Ovid MEDLINE, and Embase, from their inception to November 2020, for studies evaluating TKA patients with metal hypersensitivity/allergy. All studies reporting on diagnosing or managing metal hypersensitivity in TKA were included. Data were extracted and summarized based on study design, study population, interventions and outcomes. A practical guide is then formulated based on the available evidence.

Results

We included 38 heterogeneous studies (two randomized controlled trials, six comparative studies, 19 case series, and 11 case reports). The evidence indicates that metal hypersensitivity is a rare complication with some histopathological features leading to pain and dissatisfaction with no reliable screening tests preoperatively. Hypoallergenic implants are viable alternatives for patients with self-reported/confirmed metal hypersensitivity if declared preoperatively; however, concerns remain over their long-term outcomes with ceramic implants outperforming titanium nitride-coated implants and informed consent is paramount. For patients presenting with painful TKA, metal hypersensitivity is a diagnosis of exclusion where patch skin testing, lymphocyte transformation test, and synovial biopsies are useful adjuncts before revision surgery is undertaken to hypoallergenic implants with shared decision-making and informed consent.

Conclusion

Using the limited available evidence in the literature, we provide a practical approach to metal hypersensitivity in TKA patients. Future national/registry-based studies are needed to identify the scale of metal hypersensitivity, agreed diagnostic criteria, and management strategies.

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Introduction

The demand for primary total knee arthroplasty (TKA) continues to rise worldwide. In the USA, the projected increase in demand is estimated to rise 182% by 2030 and 401% by 2040.^{1,2} In its 17th annual report (2020), the UK National Joint Registry (NJR) recorded over 1.3 million TKAs, with an estimated revision TKA (rTKA) rate of 4.82% at 15 years. The

majority of revisions are due to aseptic loosening, infection, and instability.² However, 10,051 rTKAs were recorded for the indication of unexplained pain, accounting for 0.56% of revisions at 15 years. It is conceivable that unexplained pain may be a consequence of metal hypersensitivity.

Several metal alloys (cobalt, chromium, nickel, titanium) are used in TKA implants

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Table I The international expanded classification of the synovial-like interface membrane (SLIM).

SLIM type	Description
I	Wear-induced synovitis
II	Infection-induced synovitis
III	Mixed synovitis
IV	Indifferent (not wear-induced, not infection-induced) synovitis
V	Prosthesis-associated arthrofibrosis
VI	Adverse local tissue reactions to implant materials (allergy/hypersensitivity)
VII	Local osseous pathologies

with the aim of providing long-term durability with optimal biocompatibility. However, should the metal alloys induce toxic reactions or inappropriate activation of the innate or adaptive immune system the implant may fail.³⁻⁵ The interaction between foreign materials and biological tissues is a complex process between metals, bone metabolism, and the immune system.^{6,7} Allergic reactions to implant materials as the cause of implant failure is a contentious topic. In the literature there are varying views, with some authors questioning the existence of this pathological entity as a cause for failed TKA.^{8,9} In the general population, the prevalence of nickel allergy is estimated at 13%, cobalt allergy at 2%, and chromium at 1%.^{10,11}

From a histopathological point of view, implant-associated pathologies involving the synovial-like interface membrane (SLIM) is categorized in accordance with the consensus classification of joint implant related pathologies¹²⁻¹⁴ (Table I). SLIM type VI describes adverse local tissue reactions in implant materials, including allergy and hypersensitivity. The SLIM-VI category also encompasses adverse implant reactions, otherwise known as aseptic lymphocyte-dominated vasculitis-associated lesion (AVAL). Although it is clinically important to differentiate between particle toxicity (as seen in metal-on-metal bearings) and hypersensitivity or allergy, there is currently limited knowledge of the mechanisms and reactions to allow for a distinct characterisation of both.¹⁵ Nonetheless, a number of cases have been reported exhibiting a high number of mast cells and eosinophils with or without formation of perivascular lymphocytic germinal centres, which represent a reaction to toxic wear with allergic/hypersensitivity components.^{16,17}

The aim of this study was to review the literature systematically and evaluate the evidence on managing patients with metal hypersensitivity/allergy in TKA practice formulating a practical approach to inform clinical practice.

Methods

Following the PRISMA for scoping reviews guide,¹⁸ we carried out the electronic searches in April 2020 and

updated in November 2020. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2020, issue 1), Ovid MEDLINE (including epub ahead of print, in-process, and other non-indexed citations, Ovid MEDLINE Daily, Ovid MEDLINE and versions; 1946 to 20 April 2020), and Embase; 1980 to 20 April 2020). We limited our searches to the English language literature. The following search strategy was used [(metal*).ti,ab, exp METALS/ae (allerg* OR hypersensitivity* OR "contact dermatitis").ti,ab exp *HYPERSENSITIVITY/ exp *"DERMATITIS, contact"/((knee) AND (arthroplasty OR (total ADJ2 arthroplasty*))).ti,ab exp *"ARTHROPLASTY, Arthroplasty, KNEE"/(review).ti].

We examined the titles and abstracts of articles identified in the search as potentially relevant studies. We obtained the full-texts of studies that fulfilled our inclusion criteria, and those that were unclear from perusal of the abstracts. We excluded reviews of the literature. Studies that met our inclusion criteria were assessed and data extracted in a narrative review summarising the evidence.

Statistical analysis. Results are expressed descriptively in numbers and percentages. SPSS 16.0 software (SPSS, USA) was used for descriptive statistical analysis.

Results

The electronic searches produced 530 records; a further four records were identified from reference lists of some included studies (Figure 1). After removing duplicates and screening abstracts, 122 studies were assessed for eligibility and 38 studies met the inclusion criteria and were included in the review including two randomized controlled trials (RCTs), six comparative studies, 19 case series, and 11 case reports (Tables II–V).

There were considerable variations and heterogeneity in patients' populations, interventions, outcome measures, and nomenclature (metal hypersensitivity/metal allergy) across the included studies. Therefore, quantitative analyses could not be performed. Instead, a narrative review is presented with broad categories of the studies, including: a) studies of patients with no prior history of metal hypersensitivities/allergy but later became symptomatic following TKA; b) studies of patients with known metal allergy following TKA; c) studies of revision TKA for symptomatic patients; and d) case reports of symptomatic patients with TKA.

Patients with no prior history of metal hypersensitivities/allergy. There were eight studies in this group (one RCT and seven case series) with a total of 1,501 patients. Lons et al,¹⁹ in their interesting prospective study of 90 TKA patients, measured the metallic ion levels (Cr, CO, and Ti) preoperatively and at one-year follow-up. They found significant increase exceeding normal values (Cr 0.45 µg/l to 1.27 µg/l, CO 0.22 µg/l to 1.41 µg/l, and Ti 2.94 µg/l to 4.08 µg/l; $p < 0.0001$). However, no TKA-related

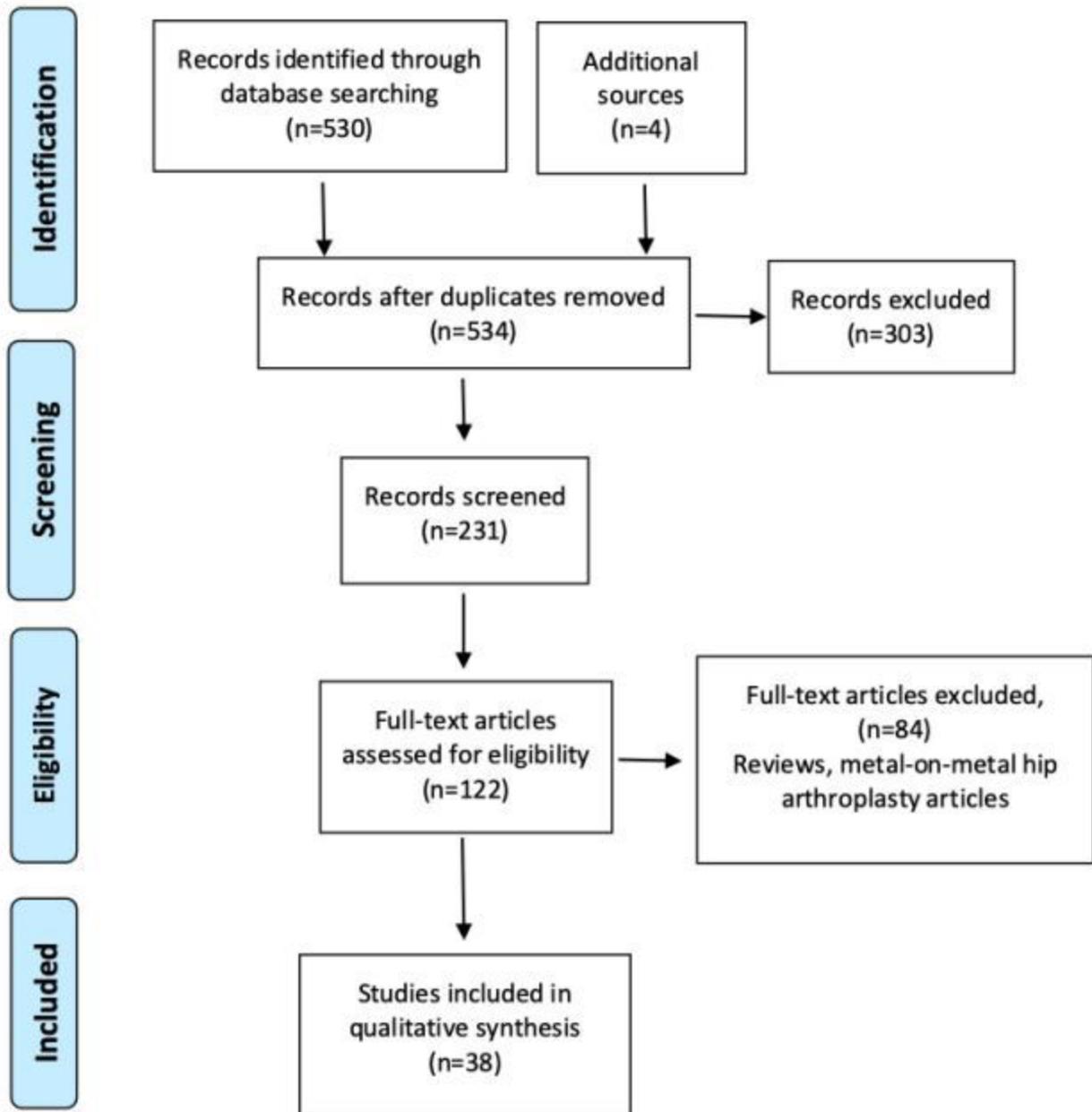


Fig. 1

PRISMA flow diagram of literature review.

complications were associated with the increased metallic ion levels.

In their RCT, Lützner et al²⁰ randomized 120 patients to either coated or uncoated implant TKA with Columbus Knee System (Aesculap, Germany). A standard uncoated implant was made of CoCrMo alloy with less than 1.0% nickel. In the coated version, a thin adhesive chromium layer, five alternating intermediate layers out of chromium nitride-chromium carbonitride (CrN-CrCN), and a final shielding layer of zirconium nitride (ZrN) was added. They compared hypersensitivity patch testing (Cr, Co,

Mb, Ni) and plasma ions concentration preoperatively and one-year postoperatively, with no significant differences between the two groups and no plasma metal ion elevation in either group compared to baseline.

Bloemke et al²¹ studied the rate self-reported cutaneous, metal allergy, or sensitivities in patients undergoing primary TKA (n = 194) with 14% prevalence. On the other hand, Nam et al,²² in a large cohort (n = 589), found the self-reported metal allergy at 4.1%; however, patient satisfaction and outcome scores were significantly reduced in this group.

Table II. Studies of patients with no prior history of metal hypersensitivities/allergies.

Study	Design/Intervention	Outcome measures	Results/comments
Lons 2017 ¹⁹	Case series: 90 patients undergoing same implant TKA	Ions levels (Cr, Co, Ti), ROM, OKS, satisfaction scores at one year	Significant blood elevation of Cr, Co, and Ti levels one year postoperatively exceeding normal values
Lützner 2013 ²⁰	RCT: 120 patients undergoing coated vs uncoated implant TKA	Cr, Co, Mb, Ni hypersensitivity patch testing, and plasma ion concentrations pre- and one year postoperatively	No significant differences between the groups
Bloemke 2015 ²¹	Case series: 194 patients undergoing TKA (single surgeon)	Rate of self-reported cutaneous metal allergy	Prevalence of self-reported cutaneous metal allergy, or sensitivity, was 14%
Nam 2016 ²²	Case-series: 589 patients undergoing primary TKA	Preoperative Incidence of patient-reported metal allergy, UCLA, SF-12, and KSS	Incidence of patient-reported metal allergy was 4.1%; 97.8% of metal allergy patients were female. Postoperative KSS, satisfaction, and expectation scores were all decreased in the metal allergy cohort ($p < 0.001$)
Kręcisz 2012 ²³	Case series: 60 patients undergoing primary TKA	Pre- and postoperative patch testing	Preoperative: symptoms of "metal dermatitis" found in 21.7%, allergy to metals confirmed by patch testing in 84.6% of the subjects with a history of metal dermatitis. Postoperative (48/60): 10.4% complained of implant intolerance, and 4.2% of the examined persons reported skin lesions
Desai 2019 ²⁴	Case series: 233 patients undergoing primary TKA	Prevalence of metal hypersensitivity at three months postop using CREDISOL kit patch test	15.87% had patch test positive (Cr 11.58%, Ni 8.58%, Co 6.43%). 12.01% were symptomatic (patient dissatisfaction significantly associated with metal hypersensitivity)
Niki 2005 ²⁵	Case series: 92 patients undergoing 108 primary TKA	Preop modified lymphocyte stimulation test (mLST to Ni, Co, Cr, and Fe)	24/92 (26%) displayed positive preoperative responses to at least one metal. Five patients displayed implant related eczema and were mLST-positive preop; two underwent revision TKA with resolution of symptoms and mLST changed from positive to negative
Zeng 2014 ²⁶	Case series: patients undergoing TKA/THA (29 TKA)	Patch testing preop, pre- and postoperative VAS pain, lymphocyte transforming test	No relationship between metal allergy and post-surgery pain

Co, cobalt; Cr, chromium; Fe, iron; KSS, Knee Society Score; Mb, molybdenum; Ni, nickel; OKS, Oxford Knee Score; RCT, randomized controlled trial; ROM, range of motion; SF-12, short form-12; THA, total hip arthroplasty; Ti, titanium; TKA, total knee arthroplasty; UCLA, University of California at Los Angeles scale; VAS, visual analogue scale.

Skin patch testing detects metal hypersensitivity by placing patches that contain a specific allergen on the skin and observing the development of dermatitis following placement and removal of the patch at 48 hours, and then after 72 to 96 hours or more, causing a type 4 reaction to allergens on the skin.⁵⁶ Kręcisz et al²³ reported positive tests in 60 of their patients (21.7%) undergoing primary TKA; however, by two years, 48/60 patients were assessed, with 10.4% complaining of implant intolerance and had positive tests. Desai et al²⁴ also reported on their 233 patients undergoing primary TKA, with 15.87% positive tests at three months postoperatively with 12% symptomatic patients; patient dissatisfaction was significantly associated with metal hypersensitivity.

Lymphocyte transformation testing (LTT) detects metal hypersensitivity by measuring lymphocytes in peripheral blood that are produced in the span of seven days following allergen exposure. The ratio of lymphocyte proliferation after allergen challenge to proliferation without allergen is expressed as a stimulation index.⁵⁷ LTT is thought to have particular benefit in indeterminate or negative patch test results in a patient strongly suspected of having metal hypersensitivity.⁵⁸ Niki et al²⁵ reported on their preoperative LTT in 92 patients (108 primary TKAs)

and found 26% of patients displaying positive response to at least one metal (Ni, Co, Cr, and Fe). Five patients displayed implant related eczema and had tested positive, and two underwent revision TKA with resolution of symptoms subsequently tested negative. On the other hand, Zeng et al²⁶ prospectively tested 96 arthroplasty patients (29 TKAs) using both patch testing and LTT. Overall metal allergy, at least one metal, was 51.1%. In TKA patients, 11 had metal allergy. They found no relationship between metal allergy and post-surgery pain in either total hip or knee patients.

Patients with known history of metal hypersensitivities (PWKHHM). Nine studies were included in this group (one RCT, four case control comparative studies, and five case series). Postler et al²⁷ randomized 122 patients with known metal hypersensitivities to either standard or titanium-niobium-nitride (TiNbN)-coated implants of the same system. They reported increased chromium ion levels in the standard group; however, there were no differences in the levels of other ions or knee function/patient outcomes.²⁷ Similarly, Schmidt et al²⁸ found no differences in early functional outcomes of complications comparing 168 PWKHHM versus 858 sex-matched cohort of patients without metal sensitivities. Bravo et al²⁹

Table III. Studies of patients with known history of metal hypersensitivities (PWKMHM).

Study	Design/intervention	Outcome measures	Results/comments
Postler 2018 ²⁷	RCT: Coated versus standard TKA in PWKMHM at three years follow-up (n = 122)	Metal ion concentrations, knee function and PROMS	No difference in PROMS or knee function. No difference in metal ion levels (Co, Mo, Ni). Higher elevation of chromium levels (1.30 µg/l standard vs 0.75 µg/l coated; p = 0.012)
Schmidt 2019 ²⁸	Case control: 168 PWKMHM (89% received Ni-free implants, 11% received CoCrNi implants) versus sex-matched control cohort 858 TKA patients	KSS, stiffness, knee flexion, and WOMAC	No differences between the groups except for WOMAC subscore for pain 89.1 PWKMHM versus 85.2 (p = 0.030). No differences were found between nickel-free and CoCr
Bravo 2016 ²⁹	Case control: 127 PWKMHM underwent 161 TKA (56 PT+) versus 161 matched controls	Complications, revision rates, survivorship at 5.3 years follow-up	No differences between the two groups; a PT+ for metals was of little practical value in predicting the mid-term outcome after TKA
Walker 2019 ³⁰	Case series: 82 PWKMHM standard CoCr UKA	Functional outcome, signs of hypersensitivity, and survivorship at minimum 1.5 years	No local or systemic symptoms of hypersensitivity to metal were observed
Thomas 2015 ⁸	Case control: 20 PWKMHM versus control specimens from five complicated TKA without metal sensitization versus 12 OA patients before arthroplasty versus eight PT patients without arthroplasty	PT, LTT, histopathological analysis, real-time-PCR-based periprosthetic inflammatory mediator analysis (IFN γ , TNF α , IL1- β , IL-2, IL-6, IL-8, IL-10, IL17, and TGF β)	Lymphocytic infiltrates were seen and fibrotic (SLIM type IV membrane) tissue response was most frequent in the metal sensitive patients as well as marked periprosthetic IFN γ expression. Combined use of allergy diagnostics with histopathology and periprosthetic cytokine assessment allow better diagnostic strategies
Carossino 2016 ³¹	Comparative diagnostic: G1- 8 PWKMHM hypoallergenic TKA vs. 22 patients with painful TKA suspected of metal allergy versus nine healthy volunteers with no metal implants	PT versus LTT, cytokine production, metal debris endocytosis, and cytoskeletal rearrangement at one year	G1 no complications, good outcomes. G2: 11/22 (positive LTT or positive LTT plus PT): revision arthroplasty using hypoallergenic implants with good function and no complications. 11/22 (negative LTT, different responses to PT): were considered as not allergic to metals; eight treated conservatively, three revision with hypoallergenic implants with resolution of symptoms. Combined use of PT, LTT, and cytokine detection increases diagnostic accuracy
Granchi 2008 ³²	Case series: 94 (20 patients a/w TKA, 27 well-functioning TKA, and 47 loose TKA)	Frequency of sensitisation using patch testing	Frequency of positive skin reactions to metals increased significantly after TKA, either stable or loosened: no implant 20%; stable TKA 48.1%; loose TKA 59.6%, p = 0.001). TKA failure was four-fold more likely in patients who had symptoms of metal hypersensitivity before TKA
Caicedo 2017 ³³	Case series: 2,613 patients (2,053 TKA) with idiopathic joint pain referred for metal-sensitivity testing	Sex-associated rates and levels of metal sensitization. Lymphocyte stimulation index	Females demonstrated a significantly higher rate and severity of metal sensitization compared with males. Implant-related level of pain was also significantly higher among females (p < 0.0001)
Innocenti 2014 ³⁴	Case series: 24 PWKMHM hypoallergenic TKA	Clinical outcomes, VAS, KSS, and complications	No patient reported any reaction related to hypersensitivity or complications after TKA
Rossi 2020 ³⁵	Case series: 72 PWKMHM hypoallergenic TKA	Survivorship, OKS, EQ-5D, VAS, and Forgotten Joint Score at ten years	Survivorship: 97.2% at five years and 95.1% at ten years. OKS 42.1, EQ-5D 0.80, EQ-VAS 80.1, and Forgotten Joint Score 71.2

Co, cobalt; EQ-5D, EuroQol five dimension; KSS, Knee Society Score; LTT, lymphocyte transformation test; Mo, molybdenum; Ni, nickel; OA, osteoarthritis; PROMS, patient-reported outcome measures; PT, patch testing; RCT, randomized controlled trial; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

also reported no differences at 5.3 years follow-up comparing 127 PWKMHM (161 knees) with matched controls with no metal allergies. Walker et al³⁰ reported no local or systemic symptoms of hypersensitivity to metal in their 82 PWKMHM who had standard CoCr unicompartmental knees at minimum 1.5 years follow-up.

However, Thomas et al,⁸ Carossino et al,³¹ and Granchi et al³² found histopathological evidence of SLIM type VI, an increase in cytokine detection diagnostic accuracy, and a significant increase in frequency of positive

skin reactions to metals after TKAs. Additionally, greater changes were identified within these parameters in failed PWKMHM. Furthermore, in their large series of 2,053 TKAs with idiopathic joint pain referred for metal-sensitivity testing, Caicedo et al³³ found that females had a significantly higher rate and severity of metal sensitization compared with males, and that implant-related level of pain was also significantly higher among females (p < 0.0001).³³ Innocenti et al³⁴ reported satisfactory clinical and radiological outcomes of hypoallergenic

Table IV. Summary of studies for patients who underwent revision total knee arthroplasty (rTKA) for metal allergy.

Study	Design/intervention	Outcome measures	Result/comments
Zondervan 2019 ³⁶	Case series: 39 patients underwent rTKA to hypoallergenic components at one-year follow-up	Functional, pain, and satisfaction assessment, lymphocyte, and LTT score	Patients had satisfactory outcome following revision (improved pain scores, walking function, and ROM)
Sasseville 2019 ³⁷	Case-series: 39 patients (painful TKAs and contact dermatitis) underwent rTKA	Clinical outcomes, functional assessments, and role of PT, LLT	No statistically significant differences in outcome of revision surgery between patients with positive versus negative PT or LTT
Yang 2019 ³⁸	Case series: 27 patients with positive LLT underwent rTKA at ~two years follow-up	Histopathologic analysis, ALVAL score, KSS, and ROM	63% cases showed fibrosis, lymphocytic infiltration with ALVAL score 3.1 ± 1.9 (maximum 10). No correlation between ALVAL score and LTT testing. Improved outcome scores post-revision
Guenther 2016 ³⁹	Case series: 14 patients with metal allergy underwent rTKA ~two years follow-up	Clinical outcomes, and HSS score	12/14 (85.7%) had improved outcomes; two patients had persistent skin reactions with itching and local redness
Thakur 2013 ⁴⁰	Case series: five patients with metal allergy underwent rTKA	Intraoperative histopathology analysis, and clinical outcomes	All had thickened synovium with either a predominantly lymphocytic or histiocytic monocellular response, all improved clinically
Dietrich 2009 ⁴¹	Case-series: four patients metal allergy underwent rTKA	Clinical outcomes	All patients had resolution of symptoms
Lionberger 2018 ⁴²	Comparative: 19 Ni-sensitized versus 13 non-sensitized patients at time of rTKA (ceramic coated implants)	Cell counts of synovium CD4+ and CD8+ cell lines, functional outcomes, ROM, and LLT	Ratio of CD4+/CD8+ T-lymphocytes was 1.28 in nickel-sensitive patients versus 0.76 in the control ($p = 0.009$). No difference in functional or clinical outcomes after revision
Thomas 2012 ⁴³	Comparative: ten patients with metal allergy versus five patients without undergoing rTKA	Peri-implant histology, cytokine expression, and microbiological analysis, and WOMAC	Metal allergy pts: scattered, partly dense T-lymphocytes, and predominant IFN-gamma expression
Münch 2015 ⁴⁴	Registry study: 327 patients with metal allergy (+ PT) who have/have not undergone rTKA	Risk of rTKA in patients with confirmed metal allergy	Prevalence of metal allergy was comparable in patients with and without revision surgery. However, in patients with two or more episodes of revision surgery, the prevalence of cobalt and chromium allergy was markedly higher

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesion; Co, cobalt; Cr, chromium; HSS, Hospital for Special Knee Surgery; KSS, Knee Society Score; LTT, lymphocyte transformation test; Mb, molybdenum; Ni, nickel; PT, patch testing; ROM, range of motion; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table V. Summary of case reports,

Study	Patient description	Intervention	Outcome/comments
Thomsen 2011 ⁴⁵	Chromium allergy and painful TKA (negative LTT)	Hypoallergenic rTKA	Resolution of symptoms
Van Opstal 2011 ⁴⁶	Persistent dermatitis following TKA	Hypoallergenic rTKA	Resolution of symptoms
Gao 2011 ⁴⁷	Chromium induced dermatitis following TKA	Hypoallergenic rTKA	Resolution of symptoms
Bergschmidt 2012 ⁴⁸	Metal hypersensitivity painful TKA	Hypoallergenic rTKA	Resolution of symptoms
Post 2013 ⁴⁹	Whole-body dermatitis following TKA, hair loss (positive PT but negative LTT)	Hypoallergenic rTKA	Resolution of symptoms
Gupta 2015 ⁵⁰	Painful TKA history of metal hypersensitivity	Hypoallergenic rTKA	Resolution of symptoms
Kenan 2016 ⁵¹	Pseudotumor over 13 years (positive PT to cement)	Hypoallergenic rTKA	Resolution of symptoms
Stathopoulos 2017 ⁵²	Pruritus and metal taste after TKA (positive PT nickel, cobalt, and cement)	Hypoallergenic rTKA	Resolution of symptoms
Apostolopoulos 2018 ⁵³	Painful unicompartmental knee (positive PT nickel)	Hypoallergenic rTKA	Resolution of symptoms
Peat 2018 ⁵⁴	Erythematous rash around the incision site and trunk (positive PT vanadium and palladium)	Topical steroids	Cutaneous symptoms shown partial response to topical steroids
Dass 2019 ⁵⁵	Diffuse pruritic rash with fatigue three months post-TKA	Biopsy, positive PT gold, nickel, cobalt, and thimerosal	Treated successfully with oral Omalizumab

LTT, lymphocyte transformation test; PT, patch testing; rTKA, revision total knee arthroplasty; TKA, total knee arthroplasty.

implants (zirconium femur, all-polytibia) in their series of 24 patients at ~6.6 years follow-up. Finally, Rossi et al³⁵ reported on their long-term outcomes using Nex Gen LPS Titanium knee (Zimmer Biomet, USA), coupled with the Prolong highly crosslinked polyethylene-bearing in

72 patients with confirmed metal allergy. They reported satisfactory clinical outcomes and survivorship data (any cause revision 97.2% at five years and 95.1% at ten years). **Symptomatic patients who underwent revision TKA for metal allergy.** Six case series with 128 patients reported on

Table VI. Examples of hypoallergenic knee implants.

Manufacturer	TKA system	Tibial component	Femoral component
B Braun & Aesculap	Columbus AS implant system	Zirconia nitride coating of standard implant	Zirconia nitride coating of standard implant
Biomet	Vanguard	Titanium niobium nitride coating of standard implant	Titanium niobium nitride coating of standard implant
Corin	AMC	Partial TiN coating (custom-made)	Partial TiN coating (custom-made)
DePuy	PFC Sigma	Complete TiN coating (custom-made)/ or all-poly tibial component	Complete TiN coating (custom-made)
	LCS complete	Complete TiN coating of standard implant	Complete TiN coating of standard implant
Implant cast	ACS	Complete TiN coating of standard implant	Complete TiN coating of standard implant
Smith & Nephew	Genesis II	Titanium tibial component/ or all-poly tibial component	Oxinium oxidized zirconium implants
Stryker	Triathlon	Complete TiN coating of standard implant/or all-poly tibial component	Complete TiN coating of standard implant
Stanmore	Smiles-hinged prosthesis	Complete TiN coated implant (custom-made)	Complete TiN coated implant (custom-made)
Zimmer	Nexgen	Titanium component/ TiN coating or all-poly tibial component	Titanium component or TiN coating

TiN, titanium-nitride.

their findings in patients with painful TKA and metal allergy, infection, and other causes of pain excluded, who underwent rTKA with hypoallergenic components and reported overall improvements in clinical outcomes and patients' symptoms at short term follow-up.³⁶⁻⁴¹ Interestingly, there were no differences in outcomes between patients with positive or negative patch testing/LTT.³⁷ Histologically, intraoperative specimens showed fibrosis and lymphocytic infiltration, but no correlation with LTT testing,³⁸ and thickened synovium with either a predominantly lymphocytic or histiocytic monocellular response was also reported.⁴⁰

Lionberger et al⁴² in their comparative study of 19 Ni-sensitized versus 13 non-sensitized patients at time of rTKA to ceramically coated implants found higher synovial CD4+/CD8+ cell counts T lymphocytes (1.28 vs 0.76; $p = 0.009$). Thomas et al⁴³ also performed peri-implant histological studies at time of rTKA (ten patients with metal allergy vs five without) and found scattered, partly dense T-lymphocytes and predominant IFN-gamma expression.

Finally, in their interesting study from the Danish joint registry, Münch et al⁴⁴ used both rTKA registry as well as the Danish national database for contact allergy patch testing. They identified 327 patients who had both rTKA and a positive patch test. Only patients who had \geq two rTKA were found to have higher prevalence of cobalt and chromium allergy.

Case reports. There were nine case reports of patients with symptomatic TKAs and metal allergies revised to hypoallergenic rTKA components with resolution of symptoms.⁴⁵⁻⁵³ Two further cases reported on pharmacological treatments with topical steroids⁵⁴ and oral omalizumab (recombinant, monoclonal antibody against human immunoglobulin IgE).⁵⁵

Discussion

In this study, we present a comprehensive review of the literature on metal allergy in knee arthroplasty patients in 38 studies. Although significant differences in study designs, interventions, and outcome measures are noted, some practical conclusions can be drawn. Metal allergy or hypersensitivity to metal alloys does appear to be a contributing factor to symptomatic patients with painful TKAs once a thorough and systematic assessment of the painful knee is completed, with common causes excluded such as infection, instability, and component malpositioning.⁵⁹ This is supported by histopathological studies of synovial/peri-implant samples at time of revision surgery and reported resolution of symptoms with hypoallergenic components at short-term follow-up. Nevertheless, there is conflicting evidence on the diagnostic criteria and the diagnostic value of commonly used tests, such as the skin patch test and even the lymphocyte transformation test.

Patients who self-report metal allergy prior to primary TKA seem to benefit from hypoallergenic components at short-term follow-up. It is unclear whether these implants will have similar long-term survivorship to standard implants made of conventional alloys. However, if patients develop metal allergy following their primary TKA, the evidence presented supports revision surgery with hypoallergenic components with satisfactory short- to medium-term outcomes.

Metal allergy as a cause of failure in patients with TKA is of low prevalence. However, the UK joint registry recorded 10,051 rTKAs for the indication of unexplained pain accounting for 0.56% risk of revision at 15 years.² This indicate that other causes of revisions have been excluded (aseptic loosening, infection, dislocation/subluxation, lysis, instability, polyethylene wear, component dissociation, malalignment, periprosthetic fracture, implant fracture, stiffness, progressive arthritis, and other which

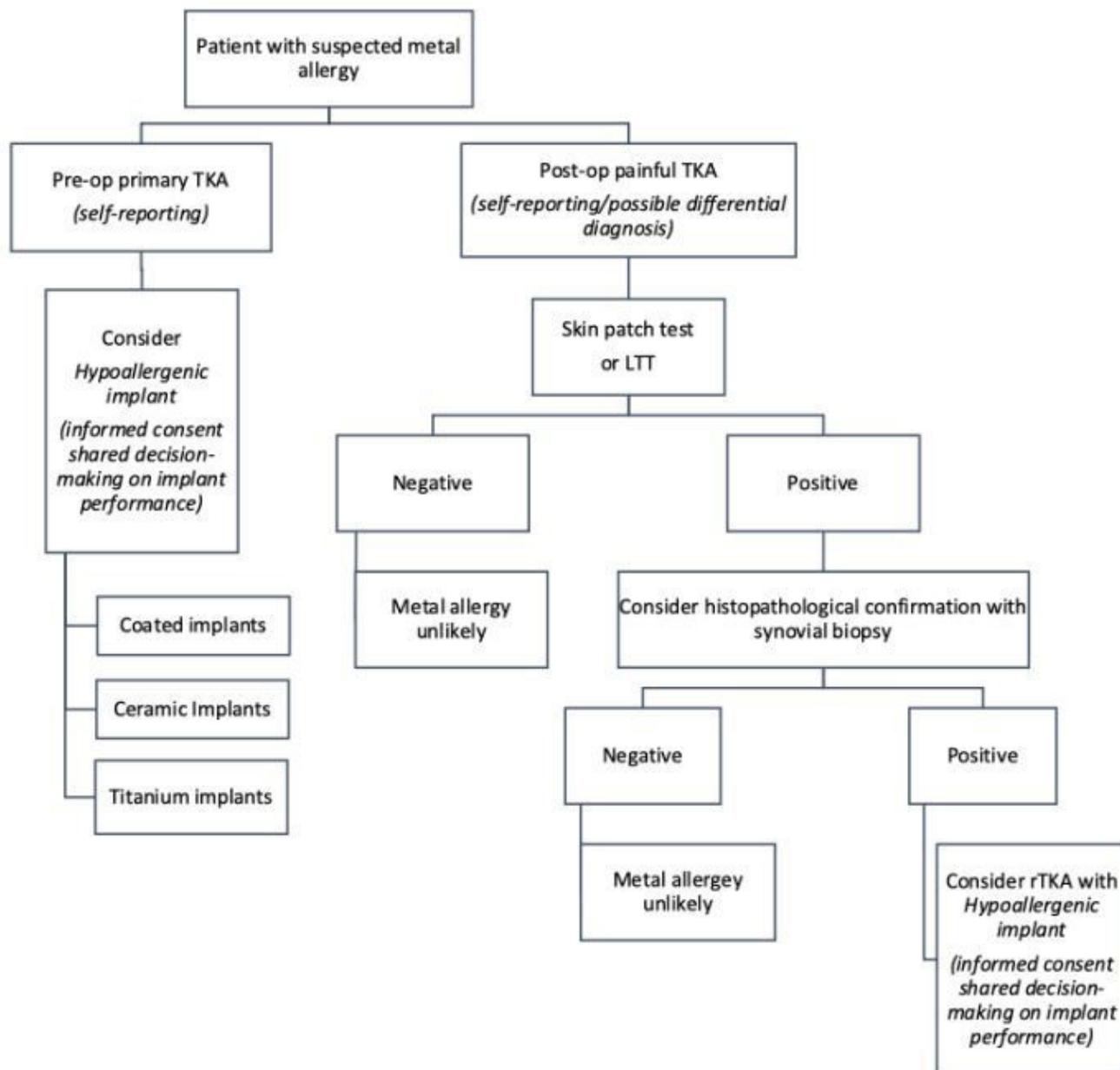


Fig. 2

Suggested clinical algorithm based on the evidence reviewed.

includes incorrect sizes or wrong side implant). Therefore, it is conceivable that a number of rTKA performed for unexplained pain could be attributed to metal allergy.

Hypoallergenic implants most manufactures include a hypoallergenic implant in their knee systems (Table VI). These can be divided into three types: coated implants, ceramic implants, and titanium implants. Some knee systems also have the option of all-polyethylene tibial component.

Coated implants. Most manufacturers use this method of producing hypoallergenic implants by adding a

coated layer on their cobalt-chromium standard implants. Titanium-nitride (TiN) coating is the most commonly used (Table VI); others include zirconia nitride and titanium niobium nitride. TiN coating of CoCrMo alloy was initially introduced in an attempt to enhance the mechanical properties and biocompatibility of these implants as it increases hardness with higher resistance to adhesive wear.⁶⁰ However, there is conflicting evidence in the literature on its effects on implant performance and clinical outcomes. In their series of 305 mobile bearing TiN coated TKAs (ACS; Implantcast, Germany) implanted in young active patients, Mohammed et al⁶¹ reported 95.1% (95% CI 92.4 to 97.8)

estimated ten-year survivorship with revision for any cause as an end point. Similarly, Breugem et al⁶² reported on their results (1,031 TKAs) using same implant in their routine practice for all patients with a mean follow-up of 46 months (1 to 92) and overall implant survival was 97.7% and 95.1% for any cause revision. In their RCT comparing mobile bearing TiN-coated cementless ACS with a cementless mobile-bearing Low Contact Stress (LCS Complete; DePuy, USA) in 101 patients, there were no differences at five-year follow-up in clinical outcomes or revision rate.⁶³

On the other hand, Song et al⁶⁴ recently reported higher failure rates (7% tibial component aseptic loosening) in a matched cohort of 200 TKAs (mobile vs fixed-bearing TiN coated cementless ACS) with five-year survivorship of 91.3% versus 98.9%. Lionberger et al⁶⁵ also reported a high failure rate using the TiN-coated cemented implant (Vega Aesculap, Germany) with aseptic failure requiring a reoperation rate of 6% at an average of 7.7 months was observed over a cohort of 249 TKAs. Of the revised failures, 12 (37%) were tibial, eight (23%) were femoral, and 14 (40%) were combined tibial. In their retrieval analysis of 28 coated knee prostheses (TiN, TiNbN, and ZrN on TiAl6V4 and CoCr28Mo6) from nine different manufacturers, Herbst et al⁶⁶ analyzed coating designs on preserved regions (substrate, layer thickness and roughness, mechanical properties, adhesive strength, and friction performance against polyethylene) and found an incidence of 79% discoloration, 21% coating delamination, pitting damage leading to corrosion underneath the coating layers.

Ceramic implants. Zirconia (Oxinium), oxidized zirconium, biologically inert with similar physical properties to titanium is used as a hybrid material to produce knee arthroplasty femoral implants with titanium tibial base plate.⁶⁷ In addition to its theoretical improved wear profile, it is void of nickel and used in patients with metal allergy. In their study from the Australian joint registry, Vertullo et al⁶⁸ reported 12-year outcomes of cruciate-retaining TKAs with an Oxinium femoral component and those with the same prosthetic design but with a CoCr femoral component (11,608 CoCr vs 5,969 Oxinium). They found higher overall risk of revision with Oxinium knees at 12 years 4.8% versus 7.7%; the main difference between the two groups was seen in older patients (aged ≥ 75 years).

Titanium implants. Few studies have reported on titanium implants. As previously mentioned, Rossi et al³⁵ reported their satisfactory outcomes at ten years follow-up using Titanium Ti-6Al-4V alloy (nitrided Ti6Al-4V) where the surface hardening process is a thermal nitriding process that creates a nitrogen-enriched zone on the surface of titanium alloy prostheses. This nitrogen reacts with the titanium within the prosthesis surface zone to form titanium nitride, which imparts its inherent hardness and abrasion resistance.

Evidence-based approach. Based on the evidence provided, although limited, a clinical algorithm may be employed to help managing patients with suspected metal hypersensitivity (Figure 2). At time of primary TKA, there is no strong evidence for the use of preoperative screening methods (patch test/LTT) for all patients. Patients who do self-report metal hypersensitivity may benefit from the use of hypoallergenic implants, although concerns exist on the longevity and clinical performance with ceramic implants outperforming coated implants. Informed consent, shared decision-making, and documented discussions on the pros and cons of such approach are advised.

For patients presenting with a painful TKA and suspected metal hypersensitivity, as a diagnosis of exclusion, skin patch testing/LTT are reasonable screening tests, which can be used as adjuncts, followed by synovial biopsies for histopathological studies and features of adverse local tissue reactions to implant materials (SLIM). This can act as a confirmatory step before revision surgery is considered to hypoallergenic implants with appropriate informed consent, shared decision-making, and documented discussions on the pros and cons of such undertaking.

However, this is not a universally accepted view, despite the evidence presented. The existence of metal allergy in TKA is questioned and refuted by many. In their review of the literature, Middleton et al⁶⁹ concluded that metal hypersensitivity as an allergic process cannot justify a revision in TKA, and that there were no basis for the use of unproven hypoallergenic components.

Finally, future national/registry-based studies are needed to better inform clinical practice and identify the true scale of metal hypersensitivity in TKA practice. Clear diagnostic criteria and long-term clinical performance data on hypoallergenic implants, both in primary and revision settings, are needed.



Take home message

- Patients who self-report metal hypersensitivity may benefit from the use of hypoallergenic implants although concerns exist on the longevity and clinical performance with ceramic implants outperforming coated implants.
- Patients who present with a painful total knee arthroplasty and suspected metal hypersensitivity, as a diagnosis of exclusion, skin patch/lymphocyte transformation testing are reasonable screening tests followed by synovial biopsies for histopathological studies, and features of adverse local tissue reactions to implant materials. This can act as a confirmatory step before revision surgery is considered to hypoallergenic implants with appropriate informed consent.

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