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Systematic Review

Hypoallergenic Knee Implant Usage and Clinical Outcomes: Are They Safe and Effective?

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ABSTRACT

Background: One of the most debated topics in modern total knee arthroplasty (TKA) is the impact of metal hypersensitivity (MH) as a potential cause of prosthesis failure. Implanting hypoallergenic prostheses to avoid potential problems in suspected cases of MH is one treatment option that can be used in such cases. However, their long-term clinical safety and efficacy are not well proven.
Methods: All literature relevant to modern hypoallergenic implants were reviewed and summarized to provide a comprehensive synopsis. In addition, a detailed literature search was performed on PUBMED, MEDLINE, and Google Scholar to identify all the clinical studies reporting outcomes for hypoallergenic knee implants. Our search was confined to those studies published as full manuscripts in the English language from July 2018 to July 2023.
Results: To minimize the risk of MH, new implant variants have been developed which are either under clinical evaluation or in routine clinical use. These include conventional metal implants with protective coatings (mono- or multilayer) and metal-free implants. However, there is insufficient clinical data to confirm the rationale and effectiveness of using these "hypoallergenic" TKA implants.
Conclusions: Published studies and arthroplasty registry data analyses indicate no significant differences between hypoallergenic and standard TKAs with overall good survival rates. In the future, further high-quality studies are needed to better understand the complexity of this subject.

Introduction

Total knee arthroplasty (TKA) is a commonly performed surgical intervention, and TKA numbers are projected to increase exponentially over the coming decades [1]. Despite its popularity, it is estimated that up to 20% of patients are not satisfied with the outcome of their TKA [2]. Allergic reaction to orthopaedic implant metals is a possible cause, but establishing this association is tricky due to the difficulty in testing for and diagnosing allergic responses [3]. Metal hypersensitivity (MH) is a diagnosis of exclusion once the usual reasons for TKA failure, such as aseptic loosening and infection, have been ruled out [4,5]. Currently, the majority of the studies cite patch testing (PT) and lymphocyte transformation testing (LTT) as the standard methods for screening and diagnosis of MH [5]. However, there is a lack of agreement over the clinical utility of PT and LTT patients with TKA [6]. This is in part due to the disconnect between dermal response to metal (type I) and deep tissue response to metal (type IV).

To avoid complications and to expand the durability of the implants used for patients with confirmed or suspected metal hypersensitivities, one treatment option depends on the use of "hypoallergenic" prostheses, of which there are 2 groups. The first group is composed of the commonly used base (substrate) metals (cobalt, chromium) coated with a protective ceramic layer, such as zirconium oxide (ZrO_2), zirconium nitride (ZrN), or titanium nitride (TiN), with different numbers of layers and associated thicknesses of the coating [7]. The second group consists of metal-free implants that are either fully ceramic (alumina or zirconium) or made from

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biocompatible high-performance polymers, such as polyether-ether-ketone (PEEK). The femoral components of either group can be implanted in a construct with an all-polyethylene (PE) or a metal-backed tibial component [8].

Owing to the limited evidence and lack of comparative studies, the safety and effectiveness of hypoallergenic knee implants in primary TKA in patients with suspected or proven MH remain controversial, and there is a wide variation in practice. This article analyzes the up-to-date literature with a focus on the following concerns: 1) Is there a correlation between any preoperative diagnostic tests and clinical outcomes in patients with suspected or proven MH? 2) Which hypoallergenic implants are currently available on the market? 3) Is the use of hypoallergenic implants associated with fewer complications in patients with suspected or proven MH? 4) What are the short, medium, and long-term clinical outcomes of hypoallergenic implants?

Prevalence of metal hypersensitivity

Several metal alloys (cobalt, chromium, nickel, and titanium) are used in TKA implants. The frequency of cutaneous allergies to nickel, cobalt, and chromium in the general population, not related to arthroplasty, has been estimated to be 13%, 2%, and 1%, respectively, based on PT and blood analysis [9]. The prevalence of cutaneous MH in the general population is estimated to be 10%-15% [10], while the reported prevalence in patients with metallic implants is varied. Bloemke et al. [11] studied the rate of self-reported cutaneous, metal allergy, or sensitivities in patients undergoing primary TKA ($n = 194$) with 14% prevalence. On the other hand, Nam et al., in a large cohort ($n = 589$), found the self-reported metal allergy at 4.1% [12].

Krecisz et al. reported positive tests in 60 of their patients (21.7%) undergoing primary TKA; by 2 years, 48 out of 60 patients were assessed, with 10.4% complaining of implant intolerance and having positive tests [13]. Peacock et al. [6] conducted a systematic review to assess the nickel-sensitizing potential of TKA and explore the relationship between hypersensitivity and clinical outcomes. Authors concluded that the current literature does not support the concept that patients undergoing TKA with no prior history of nickel hypersensitivity are at an increased risk of developing hypersensitivity. There is conflicting evidence that patients with established nickel hypersensitivity are more likely to experience dermatological or orthopaedic complications such as persistent pain, implant loosening, or failure. Indeed, psychological distress related to the fear of using a metal TKA in patients with a history of metal sensitivity may play a significant role in their perception of on-going symptoms post-TKA.

Symptoms and diagnostic tests of metal hypersensitivity

Patients with MH may present with various signs and symptoms. As a surgeon, one should be aware of the manifestation of a cutaneous allergy to metal, which may be mentioned by a patient preoperatively. In a patient with a TKA, there are 2 main distinctions in the signs and symptoms to consider in the assessment for MH: those related to the joint itself and any changes related to the skin. The more challenging symptoms to deal with are those attributed to the knee joint itself. Patients may present with knee synovitis or effusion. The synovitis may present as pain at rest, swelling, decreased range of motion (ROM), stiffness, and recurrent joint effusions [14,15]. The symptoms are often vague, and nonspecific dissatisfactions are often encountered [16]. In addition, there have been several reports of skin changes following TKA in the dermatological literature. A typical rash can be characterized as erythematous, pruritic, papular, and a scaly rash may result in exudate [3,6].

MH has been assumed to be a diagnosis of exclusion given the lack of objective diagnostic tests with sufficient sensitivity and validity [17]. While a variety of diagnostic tests exist, skin PT and LTT remain the most common testing modalities. Other less commonly used tests include the lymphocyte proliferation test and the memory lymphocyte immunostimulation assay [18–21].

The following articles highlight the conflict between different metal allergy and hypersensitivity testing modalities, which questions their utility and reliability for clinical decision-making. Yang et al. [19] reported 27 primary, well-fixed, aseptic TKA cases in which the patient had persistent pain or stiffness, and determined on the basis of positive LTT, underwent revision TKA due to a suspected metal allergy. The level of MH in patients with a positive LTT finding for chromium or cobalt did not correlate significantly with the aseptic lymphocyte-dominated vasculitis-associated lesion score, ROM, or clinical or functional Knee Society Score. The authors concluded that LTT results were unreliable for the diagnosis of TKA failure due to an immune reaction. In summary, a positive LTT may not demonstrate that an immune reaction is the reason for pain and stiffness post-TKA. Bravo et al. [22] reviewed 127 patients who underwent 161 TKAs after skin PT with 56 of them having had metal allergies diagnosed through PT. PT-positive patients did not have higher complications, revision rates, or reoperation compared with PT-negative patients. In addition, within the PT-positive patients, those implanted with hypoallergenic knee prostheses had outcomes that were no different from patients who were treated with nonhypoallergenic knee prostheses. Thomas et al. [23] analyzed the results of PT, LTT, and histology tests in 25 TKA patients with unexplained complications following the use of cobalt chromium molybdenum alloy (CoCrMo) implants. They included patients with proven metal sensitization: 9 patients only had positive reactions to LTT tests with negative PT reactions; 11 patients only had positive reactions to PT tests with negative LTT reactions; and 5 patients had positive reactions to both PT and LTT tests. Bracey et al. [24] reviewed 28 primary and 20 revision TKA patients receiving hypoallergenic implants for MH diagnosed through PT, LTT, or lymphocyte proliferation testing. PT and LTT showed strong agreement for chromium and cobalt but showed weak agreement for titanium, bone cement, vanadium, and zirconium, with minimal agreement for nickel.

In summary, currently, there is conflicting evidence on the diagnostic value and the diagnostic criteria of commonly used tests, such as PT and the LTT. Many patients who have had a positive PT or LTT test for MH have good clinical results following TKA, and a poor functional result is not necessarily the result of metal allergy or hypersensitivity as suggested by current testing modalities. In general, it has been shown that PT or LTT do not have any prognostic utility in TKA clinical outcomes [22].

Treatment and alternative hypoallergenic implants

If the patient only experiences cutaneous reactions to metals, including localized or generalized cutaneous erythema, dermatitis, and eczema, without affecting joint mobility and stability and without signs of prosthetic loosening, topical steroid therapy is considered effective [25]. However, when severe synovitis reaction occurs, often accompanied by stiffness and the signs of prosthetic loosening, NSAIDs or physical therapy can be tried, but they are of limited value and should only be used for a short duration [14]. Definitive resolution of symptoms in such cases usually requires revision TKA, where the primary prosthesis is removed and a hypoallergenic prosthesis is implanted. Thakur et al. [26] reviewed 5 patients with metal allergy, who developed severe synovitis and

Table 1
Examples of hypoallergenic knee implants.

Manufacturer	TKA system	Femoral component	Tibial component
BBraun Aesculap	Columbus AS implant system	Zirconium nitride coating of standard implant	Zirconium 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 Synthes	PFC Sigma	Complete TiN coating (custom-made)	Complete TiN coating (custom-made) or all-poly tibial component
	LCS complete	Complete TiN coating of standard implant	Complete TiN coating of standard implant
Implantcast	ACS	Complete TiN coating of standard implant	Complete TiN coating of standard implant
Smith & Nephew	Genesis II	Oxinium oxidized zirconium implants	Titanium tibial component or all-poly tibial component
Stryker	Triathlon	Complete TiN coating of standard implant	Complete TiN coating of standard implant or all-poly tibial component
Stanmore	Smiles-hinged prosthesis	Complete TiN coated implant (custom-made)	Complete TiN coated implant (custom-made)
Zimmer	Nexgen	Titanium component or TiN coating	Titanium component/TiN coating or all-poly tibial component
Lima	Multigen Plus	Ceramic	Biolox Delta

Please note that this list is not necessarily complete, and indeed, not all implants are available in all countries.

persistent pain after TKA using a cobalt-chromium (CoCr) component. None of the knees demonstrated evidence of any infection; they had appropriate ligamentous balance, were well aligned, and had all components noted to be well fixed at the time of revision surgery. After revision to an oxinium-oxidized zirconium femoral component and a titanium metal-backed tibial component, functional outcome and pain scores improved in all patients. In recent years, some case reports have similarly demonstrated that patients who have had a failure of TKA as a result of suspected metal allergy and who have then undergone a revision TKA with hypoallergenic prostheses have demonstrated satisfactory outcomes [27–30]. At the same time, some researchers have also summarized the management plan for MH reactions, hoping to provide guidance for clinical practice [3,5,17,31–33].

A variety of hypoallergenic knee implants are available on the market. These can be grouped into 2 main types: (1) conventional cobalt-chromium knee prostheses that have been coated with a hypoallergenic material such as zirconium nitride (ZrN), zirconium oxide (ZrO_2), or titanium nitride (TiN), and (2) implants made from a hypoallergenic material other than cobalt, chromium, or nickel [8].

Currently, there are different coating technologies for hypoallergenic TKA implants in use. The coating of metallic prostheses was first conceived as a potential solution for patients with allergic reactions to cobalt, chromium, or nickel. Historically, single-layer coatings, also called monolayer coatings, were the first to be used in clinical practice. Monolayers are available in clinical practice in 2 versions: coatings composed of titanium niobium nitride (TiNbN) and titanium nitride (TiN). TiNbN and TiN monolayer coatings have been in clinical application for joint replacement since the early 1990s. They are applied by means of physical vapor deposition on traditional orthopaedic implant materials such as CoCrMo or titanium alloy (Ti6Al4V). As for multilayer coatings, these are typically represented by a zirconium nitride coating made up of 7 layers and have been in clinical application since 2006 [31]. This type of prosthesis is composed of zirconium nitride (ZrN) as the surface coating, with chromium carbon nitride and chromium nitride (CrN) as transition layers, and finally chromium (Cr) as a bonding layer that combines with the base (substrate) material of the implant.

Besides coated implants, another option is for the entire implant to be made from a hypoallergenic material other than cobalt-chromium-nickel. For example, femoral components made from pure ceramic, titanium alloys, and PEEK would be implanted in construct with an all-PE tibial component. PEEK is a thermoplastic polymer featuring a chemical structure composed of aromatic rings linked by ether and ketone groups. Widely utilized in high-demand applications, PEEK boasts excellent mechanical properties, chemical resistance, and thermal stability [17]. Its biocompatibility gives utility in medical implant manufacture, commonly spinal cages, dental components, and more recently, total knee replacement prostheses. Its strength and weight make it a viable alternative to metals while eliminating the potential for metal ion release. Oxidized zirconium, also known as zirconia (Oxinium, Smith & Nephew, London, UK), is biologically inert with physical characteristics similar to titanium and is applied as a hybrid material in the manufacture of TKA femoral components. These are typically used in construct with a PE insert and titanium tibial base plate. Matar et al. [18] summarized the most used hypoallergenic implants currently available on the market. These are outlined in Table 1 below.

Clinical studies and registry data on hypoallergenic implants

Hypoallergenic prosthetic implants are designed to help surgeons treat patients with MH presenting with symptomatic end-stage knee osteoarthritis. In theory, these offer several benefits over traditional implants beyond the obvious advantage of reducing the risk of premature implant failure associated with MH. Some manufacturers claim that hypoallergenic implants are made from materials that resist bacterial growth and thereby reduce infection risk [34,35]. Moreover, they also believe that hypoallergenic implants may reduce complications related to metal prostheses such as aseptic loosening because hypoallergenic materials present better compatibility with the human body. However, the theoretical advantages of these so-called “hypersensitivity-friendly” implants need to be confirmed in clinical practice. Furthermore, future clinical research should seek to define the indications for the use of hypoallergenic TKA implants to ensure that the higher manufacturing costs associated with these implants can be justified clinically.

Clinical studies

All literature relevant to modern hypoallergenic implants was reviewed and summarized to provide a comprehensive synopsis. In addition, a detailed literature search was performed on PUBMED, MEDLINE, and Google Scholar to identify all the clinical studies reporting outcomes for hypoallergenic knee implants. Our search was confined to those studies published as full manuscripts in the English language from July 2018 to July 2023.

Table 2
Clinical studies of hypoallergenic primary knee implants in recent 5 years.

First author and year of publication	Methodology of clinical study	Type of implant	Number of hypoallergenic implants	Length of follow-up (years)	Survival (%)	Number of revisions (all reasons)	Primary objectives and results
Thienpont 2023 [36]	Retrospective study	Titanium Niobium Nitride-coated (TiNbN) Vanguard PS TiNbN Femur	53	6.5	96.5%	3	The use of titanium niobium nitride-coated implants for primary knee osteoarthritis in self-reported metal hypersensitivity patients shows similar outcomes and survivorship rates as conventional chrome cobalt TKA, with no revisions for allergy at medium-term follow-up.
Siljander et al. 2023 [37]	Retrospective cohort study	5 Zimmer Biomet Persona Ti-Nidium and 238 Smith and Nephew Oxinium (Oxidized Zirconium)	243	1	98%	4	In this retrospective cohort study, there was no difference in revision rates or clinical outcomes in patients who had a nickel allergy undergoing primary TKA with CoCr or nickel-free implants. Further studies are needed to determine if nickel allergy is an independent risk factor for worse TKA outcomes in general.
Lützner et al. 2023 [31]	Randomized-controlled trial	Multilayer coating system (Advanced Surface, AS)	44	10	98.3%	1	There were no problems with the new multilayer coating system. The new coating system demonstrated equally good patient-reported outcomes as the standard TKA. Excellent implant survival was observed in both groups
Lodge et al. 2023 [38]	Retrospective study	Columbus AS ceramic coating	659	5	97.9%	14	There was no significant difference in implant survivorship using any component revision as the endpoint between the CoCrMo implants and the ceramic-coated implants. At midterm follow-up, there was no benefit in terms of implant survivorship in using a ceramic coating.
Deroche et al. 2023 [39]	Retrospective study	TiN-coated (Score AS) CS mobile bearing prostheses (Amplitude, Valence 26000, France)	14	5	92.9%	1	TiN-coated TKA with mobile bearing resulted in satisfactory clinical outcomes, and a low revision rate, and there was no complication related to the coated implant. The use of TiN-coated prostheses in cases of confirmed or suspected metal allergy provides satisfactory short-term clinic outcomes.
Louwerens et al. 2021 [40]	Randomized-controlled trial	TiN-coated cementless MB rotating platform total knee prosthesis (CCI, Implantcast Gmbh, Buxtehude, Germany)	51	10	94%	n/a	TiN-coated cementless TKA provides comparable good long-term results, similar to uncoated cementless CoCrMo TKA.
Law et al. 2020 [41]	Retrospective study	Titanium Vanguard (Zimmer Biomet, Warsaw, IN)	451	4.6	98.9%	5	These early results are encouraging for the use of alternative metal titanium alloy implants in metal-sensitive patients undergoing primary TKA. At 4.6 y of mean follow-up, patients had substantial improvement in the range of motion and clinical outcomes with a low frequency of revision.
Rossi et al. 2020 [42]	Case Series report	NexGen LPS Tivanium total knee replacement (Zimmer Biomet Warsaw, IN)	72	10	97.2% at 5 y; 95.1% at 10 y	3	This nitrided Ti-6Al-4V titanium alloy fixed-bearing total knee replacement with a highly crosslinked polyethylene-bearing showed interesting results and survival rates in patients with metal allergy at mid- to long-term follow-up.
Peña 2020 [43]	Retrospective study	Oxinium-cemented PS Genesis II (Smith & Nephew, Memphis, TN)	76	n/a	n/a	n/a	Patients who underwent hypoallergic TKA had lower scores on the quality of life (QoL) and functional capacity scales than patients who received conventional Cr-Co implants. Additionally, patients with psychological distress had worse results on the questionnaires, and those with a metal allergy had even lower scores; the differences were statistically significant.
Hauer et al. 2020 [44]	Retrospective study	TiN-coated un-cemented Advanced Coated System (Implantcast, Buxtehude, Germany)	260	10	n/a	n/a	This study suggests that TiN coating does not provide improved clinical outcomes in this patient cohort after a long-term follow-up. Interestingly, sensitivity to weather changes were more correlated with un-cemented TiN coating implants.
Schmidt et al. 2019 [45]	Retrospective study	Ni-free im plant (Oxinium; Smith & Nephew, Memphis, TN)	150	2.6	n/a	n/a	No differences were found between nickel-free and cobalt-chrome SRMA (self-reported metal allergy) groups. Patients with SRMA and those without demonstrated similar early functional outcomes. Patients with SRMA who received standard cobalt-chrome implants had no significant difference in functional outcomes compared with patients with nickel-free implants.
Thomas et al. 2018 [46]	Retrospective study	Multilayer zirconium nitride-coated system (Advanced Surface, AS)	97	5.7	98%	n/a	The study revealed differences in the cytokine patterns between patients with coated and uncoated implants but with similar clinical and radiological outcomes after the 5-y follow-up.

Clinical outcomes and survivorship of hypoallergenic primary implants

This section summarizes the literature published in the past 55 years on clinical outcomes and survivorship of hypoallergenic primary implants (Table 2). Although significant differences in type of implant, outcome measures, and methodology of clinical study are noted, some meaningful conclusions can be drawn.

Methods to reliably diagnose MH against TKA implant materials are still not fully understood. Short-to-medium-term [36,37,41,45,46] and even long-term clinical results [38,39,44,47] of hypoallergenic implants are satisfactory, and implant survival is comparable to traditional prostheses (Table 2). No significant differences between standard TKA and the hypoallergenic implants were found in terms of implant survival, adverse effects, and patient-reported outcome measures (PROMs). Lützner et al. [31], reported on a randomized-controlled trial initiated to compare the standard knee implant with a new multilayer hypoallergenic coating system in TKA. The authors reported that a total of 120 patients were randomized to receive either a standard or coated TKA of the same knee system (Columbus CR-DD, BBraun Aesculap, Tuttlingen, Germany). Eighty-five patients (41 with standard TKA and 44 with coated TKA) completed the follow-up. The 2 groups were well-matched with regards to the preoperative and perioperative data, such as age, sex, body mass index, comorbidities, and operative time. The results demonstrated that most patients had serum metal ion levels below the limit of detection. The detection limit of the method was 0.5 μg/L for cobalt, chromium, and molybdenum and 1.0 μg/L for nickel. Both groups showed equally good improvement in PROMs post-TKA. In 2023, Siljander et al. [37] reported on 282 patients who had preoperative nickel allergy. In this retrospective study, patients were divided into 2 cohorts: those receiving Oxinium (n = 243) or standard CoCr (n = 39) implants. Revision rates and clinical outcome scores were assessed. There was no significant difference in the revision rate between the 2 groups. Survivorship free of revision was 98% in the nickel-free implant cohort and 94% in the standard implant cohort. As for comparing clinical outcome scores between the 2 groups, there was no difference in preoperative, 6-week, or 1-year Patient-Reported Outcomes Measurement Information System, Knee Osteoarthritis Outcome Score Joint Replacement, Veterans RAND 12-item scores, visual analog scale, and Lower Extremity Activity Scale between cohorts.

Some patients may also be allergic to cobalt, chromium, and bone cement at the same time. Cementless fixation of hypoallergenic implants is thought to be advantageous in such cases. In 2021, Louwerens et al. [40] reported that at 10-year follow-up, treatment with both an uncoated CoCrMo and a TiN-coated cementless primary TKA implant results in a good functional outcome with low revision rates.

Ceramic or PEEK implants could solve the problem of exposure to cobalt, chromium, and nickel [10]. Bergschmidt et al. [48] reported on a total of 109 ceramic TKAs (MULTIGEN PLUS, Lima Corporate S.p.A, Italy) implanted at 7 centers in 3 European countries, and there was one case of traumatic prosthesis fracture in this case series. Mean Hospital for Special Surgery Knee Score and Western Ontario and McMaster Universities Arthritis Index (WOMAC) increased significantly from 55.1 ± 11.5 (21-83) and 48.1 ± 16.6 (3-90) preoperatively to 85.6 ± 9.6 (49-98) and 73.3 ± 20.4 (17-100) at 60 months. Mean MOS Short Form showed significant improvements in patients' quality of life (49.1 ± 17.6 [12-96] preoperatively vs 67.7 ± 23.1 [12-100] at 60 months). Nonprogressive radiolucent lines (<1 mm) were observed around the femoral component in 4 cases. Neither implant migration nor loosening were registered. Kaplan-Meier survivorship was 96.0% at 60 months (92.1%-100%, confidence interval 95%). It should be noted that ceramic tibial components do not yet have clearance for clinical use, but ceramic femoral components can be used in construct with an all-PE tibial component.

Preclinical testing and computational simulation have yielded positive results for PEEK total knee replacement femoral components, with respect to wear [49,50], strength [51] and stress shielding [52], indicating the potential of the PEEK material in this application. Well-designed clinical studies are needed to establish its safety and efficacy.

In summary, the hypoallergenic TKAs, including coated implants and ceramic implants, have demonstrated equally good results when compared to the standard metal prostheses with excellent survival rate in both groups. However, there are some limitations to these studies. Firstly, most of the studies were retrospective and contained a small sample size. Secondly, the heterogeneity of the hypoallergenic primary prostheses makes conclusions and comparisons very hard. Thirdly, there are potential confounding variables such as prosthesis design, the type of PE insert (cruciate-retaining or posterior-stabilized), the type of cement, whether patellar resurfacing was conducted, and the alignment strategy implemented (mechanical or kinematic). Fourthly, if the performance of the primary TKA implant is the outcome of interest, standard and hypoallergenic implants should be tested in similar populations. However, it is difficult in clinical practice to randomize patients with MH.

Clinical outcomes and survivorship of hypoallergenic revision implants

In this section, we discuss the literature published in the past 55 years on reported clinical outcomes and survivorship of hypoallergenic revision implants (Table 3).

Few studies are available that provide details of hypoallergenic revision implants, and even fewer cover the use of these implants in patients with MH with sufficient sample size and medium-to-long-term follow-up results.

As illustrated in Table 3, most studies [20,29,30,53–55] reported on their findings in patients with metal allergies and painful TKA. In these revision cases, infection, loosening, and other reasons for pain were excluded, and patients subsequently underwent revision TKA (rTKA) with hypoallergenic implants. Overall improvements in patients' symptoms and clinical outcomes at short-to-medium-term follow-up were reported. In 2019, Zondervan et al. [54] conducted a retrospective review of patients who underwent a rTKA after metal allergy testing over a 3-year period. Based on the results of metal allergy testing, patients either underwent rTKA with a conventional metal or hypoallergenic component. Following revision, patients returned to the clinic for assessments of pain, function, and satisfaction at intervals of 6 weeks, 5 months, and 12 months. Zondervan et al. [54] reported that patients presenting with a positive metal LTT and a painful knee arthroplasty have improved ROM, pain scores, and walking function following revision with a hypoallergenic implant. In 2022, Whiteside et al. [29] reported on 5 documented metal allergic patients (5 knees), which were revised with custom-made ceramic femoral components, and an additional 23 patients (23 knees) met inclusion criteria but underwent different treatment because the hypoallergenic implant was unavailable. The results of this study indicate that patients who manifest clinical symptoms of metal allergy before or after TKA can be treated effectively with a hypoallergenic implant (Magnesia-stabilized Zirconia implant systems), and those who had a rTKA with ceramic-coated implant systems experienced a similar

Table 3
Clinical studies of hypoallergenic revision knee implants in recent 5 years.

First author and year of publication	Methodology of clinical study	Type of implant	Number of hypoallergenic implants	Length of follow-up (years)	Survival (%)	Number of revisions (all reasons)	Primary objective and results
Whiteside 2022 [29]	Prospective study	Custom porous-coated ceramic femoral components (Magnesia-stabilized Zirconia)	5	5	n/a	n/a	This series showing resolution of metal sensitivity symptoms and signs with revision using ceramic-coated implants offers more support to the notion that the metal sensitivity syndrome is caused by the CoCr femoral component and suggests that it can be alleviated by a revision with a ceramic femoral surface in carefully selected cases
Bulaïd et al. 2022 [30]	Retrospective study	Multilayer coating AS Solution range (B. Braun, Aesculap, Tuttlingen, Germany)	30	3.8	93.0%	n/a	There was significant functional improvement after rTKA for MHS. There were no short-term complications related to the zirconium nitrate coating. However, studies with longer follow-up will be needed for confirmation.
Bracey et al. 2022 [24]	Retrospective study	The hypoallergenic implants included a mixture of titanium components, titanium nitride-coated implants, all-polyethylene tibial components, and oxinium oxidized zirconium implants.	28 primary TKA 20 revision TKA	1	n/a	n/a	Metal allergy tests produce conflicting results. Hypersensitivity patients may experience inferior clinical outcomes even with hypoallergenic implants. Clinician awareness may influence the choice of testing and improve preoperative counseling of this patient population.
Pahlavan et al. 2021 [53]	Case Series report	Custom cementless revision implants: Biomet Vanguard custom titanium alloy 7 DePuy PFC Sigma TC3 custom porous coated 1	8	3.7	n/a	1	Cementless revision implants in this series provided a good result at the latest follow-up. But revision surgery may not totally relieve the presenting symptoms. Additional investigation into both the diagnosis and pathophysiology of bone cement hypersensitivity is necessary to further elucidate its role in TKA failure.
Yang et al., 2019 [19]	Retrospective study	Titanium custom Biomet implants (Vanguard Super-Stabilized Knee [SSK])	27	2	n/a	n/a	The current cohort of patients improved after revision to hypoallergenic implants. While this improvement could be interpreted as resolution of an immune response to the initial CoCrNi-containing implant, the histopathology did not support that position.
Zondervan et al. 2019 [54]	Retrospective study	n/a	39	1	n/a	n/a	Patients presenting with a painful knee arthroplasty and positive metal LTT have improved pain scores, walking function, and range of motion following revision to a hypoallergenic component.
Lionberger et al. 2018 [55]	Prospective study	Multilayer zirconium nitride-coated revision system (Advanced Surface, AS)	32	2.5	n/a	1	There was a significantly increased level of CD4+ reactivity in patients with positive LTT testing compared to the control group. Clinical, functional, and range of motion improvements were similar between the groups. Over 70% of patients in the sensitive group who have been treated with AS technology reported a subjective improvement after the revision.

improvement in their clinical outcomes. Those who had a revision with standard CoCr femoral components or were not revised continued to display severe symptoms and failed to improve.

In 2022, Bracey et al. [24] conducted a retrospective study and reported that patients undergoing rTKA for metal allergy had worse clinical outcomes with significantly worse improvements. Middleton et al. [56] indicated that MH as an allergic process needs clarification but cannot justify a revision TKA. They believe that there is no basis to guide the surgeon to use unproven hypoallergenic implants in revision TKA.

Registry data

In the UK National Joint Registry [57], Genesis II Oxinium (OxZr) has a cumulative revision rate of 3.43% at 5 years, 5.96% at 10 years, and 7.39% at 15 years compared to the standard CoCr implants (2.01% at 5 years, 2.97% at 10 years, and 3.42% at 15 years). However, the Genesis II Oxinium implant has a remarkably lower patient median age (59 years) at the time of undergoing primary TKA when compared to the standard CoCr implant (71 years).

In the Australian Orthopaedic Association National Joint Replacement Registry [58], there are 67,634 procedures with an alternate surface (AS) femoral component. AS femoral components, which can be made of a ceramicized metal or have a zirconia or titanium nitride coating, had a cumulative revision rate of 4.3% at 5 years, 6.5% at 10 years, 9.0% at 15 years, and 10.9% at 20 years compared to the standard CoCr implants (3.1% at 5 years, 4.5% at 10 years, 6.1% at 15 years, and 7.8% at 20 years). Femoral components with an alternate bearing surface (ie, not cobalt chrome) have a higher rate of revision, but there is variation in the revision rate depending on the type of material used on the AS. Zirconia-based AS femoral components had a lower rate of revision (1.0% at 1 year, 2.2% at 3 years, and 2.4% at 5 years) compared to those with a TiN surface (1.4% at 1 year, 3.8% at 3 years, and 4.7% at 5 years) and compared to ceramicized metal (1.2% at 1 year, 3.2% at 3 years, and 4.4% at 5 years). TiN AS components had a higher rate of revision compared to ceramicized metal components.

The manufacturer and material of the hypoallergenic implants used in the subset of patients who underwent revision TKA were not recorded in the registry data. Clear diagnostic criteria and medium-to-long-term follow-up data on hypoallergenic implants, used both in primary and revision TKA, are needed. We believe this is still an evolving field, and our understanding will improve with time.

Conclusions

MH remains poorly addressed in the current literature given the relatively low incidence, vague clinical manifestations, and definitive diagnostic difficulty. MH from an implant should be considered a diagnosis of exclusion with traditional modes of failure (aseptic loosening, infection, or instability) first investigated and excluded. The 2 most commonly used tests are PT and LTT for testing for MH, but there is no gold standard test for MH that can reliably confirm a causal association between hypersensitivity to metal and pain related to the implant itself.

Once a diagnosis of MH is made and the surgeon embarks on surgical treatment, a thorough risk-benefit discussion should be carried out between the surgeon and the patient. The limited evidence available suggests that there are no significant differences between standard CoCr TKA and hypoallergenic implants in primary or revision TKA in terms of survival ratios, adverse effects, and PROMs. Thus, hypoallergenic implants appear to be safe and could thus be used as an alternative. However, there is currently a lack of long-term follow-up data with a large enough sample size. Additionally, when considering the higher cost of hypoallergenic implants, a cost-benefit comparison with conventional TKA implants should be conducted. In order to find the possible adverse effects of MH and the possible advantages of hypoallergenic implants compared to standard TKA implants, long-term, prospective multicenter clinical investigations are needed to further evaluate the results in the future.

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Conflicts of interest

V. Ram is a paid consultant for Invibio. H. Pandit is a paid consultant for Medacta International, Zimmer Biomet, Microport, Invibio, Allay Therapeutics, Paradigm Pharmaceuticals, Teleflex, and MATOrtho and receives research support from Medacta International, Zimmer Biomet, Invibio, and Depuy Synthes. All other authors declare no potential conflicts of interest.

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CRediT authorship contribution statement

Feng Xie: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Shuya Sheng:** Writing – review & editing, Data curation. **Venkatesh Ram:** Supervision, Investigation, Data curation. **Hemant Pandit:** Writing – review & editing, Supervision, Conceptualization.

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