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Comparison of hypoallergenic knee arthroplasties in patients with metal hypersensitivity versus standard arthroplasties in non-hypersensitivity patients: A scoping review

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ABSTRACT

Background: Metal hypersensitivity in Total Knee Arthroplasty (TKA) continues to intrigue surgeons and researchers, with significant limitation of allergy tests due to the absence of clear cut-offs for a definitive diagnosis and their limited diffusion worldwide. We analyzed the literature to compare clinical outcomes in patients with metal hypersensitivity undergoing hypoallergenic knee arthroplasties and subjects without metal allergy undergoing standard knee arthroplasties.

Methods: This review adhered to PRISMA guidelines. A comprehensive search of MEDLINE, EMBASE, and Cochrane databases was conducted from inception to October 1st, 2023. Eligibility criteria included studies comparing clinical outcomes of hypoallergenic and standard knee arthroplasties in patients with and without metal hypersensitivity, respectively. Two independent reviewers screened studies, extracted data, and assessed risk of bias using the ROBINS-I tool. The primary outcome measure was the Knee Society Score (KSS). A random-effects model meta-analysis was performed to account for heterogeneity, with results expressed as standardized mean differences (SMD) with 95 % confidence intervals.

Results: From an initial 1846 studies identified, six met the inclusion criteria after rigorous screening. The quantitative included 409 knee replacements from three studies, comprising 95 hypersensitive patients who received hypoallergenic TKA and 314 non-allergic patients who underwent standard CoCr implant procedures. Risk of bias assessment revealedmoderate risk or lower across all included studies. Analysis of the KSS yielded an overall effect size (SMD) of −0.18 (95 % CI: −0.54 to 0.18), slightly favoring standard knee arthroplasties. Moderate heterogeneity was observed ($I^2 = 53$ %, $\tau = 0.0526$). The qualitative analysis included three studies. Significantly lower improvements were found in KSS, WOMAC, SF-12, and Euro-QoL-5D L-VAS among metal-sensitive patients. The third one reported no significant clinical differences between groups.

Conclusion: The scoping analysis showed similar clinical outcome after hypoallergenic TKA in patients with metal hypersensitivity compared to standard knee implants in patients without metal allergy.

1. Introduction

Metal hypersensitivity in Total Knee Arthroplasty (TKA) is a rare clinical phenomenon that continues to intrigue surgeons and researchers, resisting comprehensive explanation.[1–4]

Prosthetic implants can release metal particles or ions that may function as haptens or adjuvants in the body.[5–9] These metal components can trigger a type IV delayed hypersensitivity reaction, which is orchestrated by T-lymphocytes.[10–14] This immune response leads to a cascade of events, resulting in the substantial production of self-sustaining pro-inflammatory and bone-resorbing osteoclastogenic cytokines.[6,13,15,16] Ultimately, this immunological process can manifest as symptoms associated with metal sensitivity.

The mismatch between patients' self-reported metal skin allergies and actual allergic reactions confirmed through diagnostic tests casts doubt on the dependability of using medical histories alone for clinical decisions.[17,18] A variety of diagnostic methods are currently used to detect metal hypersensitivity in patients scheduled for knee replacement

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surgery such as skin patch testing (PT), lymphocyte transformation tests (LTT), serum-specific IgE assays, Memory Lymphocyte Immunostimulation Assay (MELISA), and confocal microscopy are among the commonly employed modalities.[19–21] These diagnostic tools, however, come with notable limitations. A key challenge is the lack of clearly defined thresholds for conclusively diagnosing metal hypersensitivity.[19–21] Rather than providing straightforward positive or negative results, these tests often produce outcomes along a continuous spectrum. This variability makes it difficult for clinicians to interpret results definitively and complicates the decision-making process.[19–21] Additionally, many of these advanced testing methods are not widely available worldwide, further limiting their practical application in clinical settings.

While diagnostic tests may indicate an immune response to metal components in some patients, this doesn't necessarily mean all these individuals will develop noticeable symptoms or experience adverse effects.[11,22–25] Skin patch testing (PT) is known for its high sensitivity in detecting metal allergies.[19–21,23] As a result, a positive PT result doesn't reliably predict whether a patient will develop a localized or systemic hypersensitivity reaction to their implant.

The literature on the relationship between metal hypersensitivity and clinical outcomes presents conflicting findings.[3,24–27]

The development of hypoallergenic components for knee arthroplasty has emerged as a potential solution to address concerns about metal hypersensitivity.[7,28–30] These innovative prostheses are specifically designed to reduce the release of metal ions and minimize direct contact between metal surfaces and the synovial membrane. No significant differences were found regarding post-operative complications, clinical scores, or metal blood concentrations after surgery between ceramic-coated knee prostheses compared with standard implants in primary TKA among non-allergic patients.[7,18,31,32] Research has demonstrated positive mid-to long-term results for oxidized zirconium implants, both in patients with confirmed metal sensitivity and in younger, more physically demanding individuals.[33–38]

This scoping review aims to synthesize data from multiple studies, addressing the statistical limitations of small sample sizes, to compare clinical outcomes between patients with metal hypersensitivity receiving hypoallergenic knee implants and those without metal allergies undergoing standard knee arthroplasties.

2. Materials and methods

This scoping review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[39] The electronic databases MEDLINE, EMBASE, and Cochrane database were reviewed for studies. Examined for relevant studies, only published articles in English were considered from the beginning up to October 1st, 2023. The following search terms were employed in combination to identify studies.: arthroplasty, replacement, knee, prosthesis, surgery, hypersensitivity, delayed, metal, nickel, allergy, hypersensitive, reaction.

2.1. Eligibility criteria

The reference lists of chosen articles were examined to find additional relevant studies that may have been missed during the initial database search. The PICOS-based eligibility criteria were subsequently applied to further refine the selection of articles for inclusion in the scoping meta-analysis (Table 1). Exclusion criteria included in vitro studies, case reports, case series with less than 10 cases, expert opinions, prior systematic reviews, letters to the editor, and otherwise included studies whose full text was not obtained. The aim of the current study was to analyze the literature to compare clinical outcomes in patients with metal hyper-sensitivity undergoing hypoallergenic knee arthroplasties and subjects without metal allergy undergoing standard knee arthroplasties.

Table 1
A table showing the PICO question for the included studies.

Table 1 PICO question of the included studies	
P	Patients with metal hypersensitivity undergoing primary knee arthroplasties
I	Hypoallergenic knee arthroplasties
C	Patients without metal-proven or self-reported metal allergy undergoing knee arthroplasties with conventional uncoated CoCr knee implants
O	Clinical outcomes
S	Cohort studies, case-control studies

2.2. Study selection

Duplicate publications were first removed using Zotero software (Zotero, Roy Rosenzweig Center for History and New Media, 2016). References were screened by two independent orthopedic residents for titles and abstract. Two independent clinicians then screened titles and abstracts of the remaining references. Full texts of potentially eligible studies were obtained and reviewed. The citations of selected articles were also examined for additional relevant literature. In cases of disagreement between reviewers about including or excluding a reference, a senior author was designated to make the final decision.

2.3. Data extraction

Two independent reviewers extracted and documented the following key information from each included study: the study design, sample size, average follow-up duration, implant type, clinical outcome scoring methods, and a concise narrative summary of the results.

2.4. Quality assessment

The risk of bias in each selected cohort study was evaluated by two authors (MI and CC) using the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.[40]

2.5. Statistical analysis

A pooled analysis was conducted to compare the most frequently reported and clinically relevant outcomes between allergic and non-allergic groups. For continuous outcomes, differences were expressed as weighted mean differences ± standard deviation (SD). All statistical analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021). To ensure consistent analysis, only the Knee Society Score (KSS) was considered across studies. Standardized mean differences were adjusted for small-sample bias using Hedges' g. Heterogeneity among studies was evaluated using the chi-squared statistic, with $P < 0.10$ considered significant. A random-effects model was used for significant heterogeneity; otherwise, a fixed-effects model was applied. Statistical significance was set at $p < 0.05$.

3. Results

The initial search across four databases yielded 1846 studies. After removing 131 duplicates, 1715 papers were screened by title and abstract. This screening identified 20 articles closely related to the research topic. Following a thorough full-text review, 14 articles were excluded for not meeting the inclusion criteria. The final selection resulted in six original articles that fully met both the inclusion and exclusion criteria. The study selection process, following the PRISMA 2020 guidelines, is illustrated in Fig. 1[39] After initial screening of titles and abstracts, six articles underwent full-text evaluation for qualitative analysis (Table 2). Following detailed assessment, four of these were excluded from the quantitative analysis for specific reasons detailed later. The studies by Bracey et al.[41] and Pellengahr et al.[42] were excluded from the quantitative analysis due to insufficient statistical data. Specifically, these

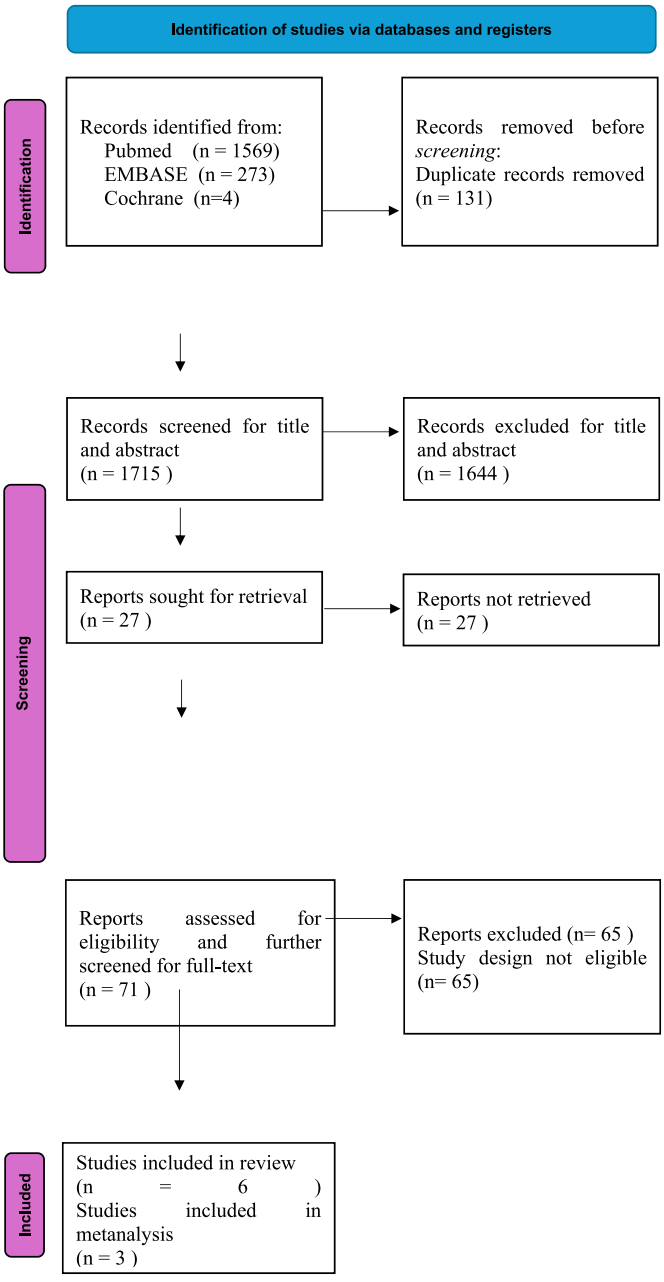

Fig. 1. Research flowchart of the screening process for the studies included in the qualitative analysis and in the quantitative analysis according to PRISMA.

studies did not report standard deviations, confidence intervals, or minimum and maximum ranges for their results, making them unsuitable for inclusion in the meta-analysis. The study by Peña et al.[43] was excluded from the quantitative analysis because it used a different outcome scoring system compared to the other studies, making it incompatible for meta-analysis. The remaining three articles were included in the meta-analysis.[32,44,45]

Deroche et al.[32] and Thienpont[45] selected patients for their hypoallergenic cohorts based on strong evidence of metal allergy from patient history or positive skin prick testing (SPT).

In contrast, D'Ambrosi et al.[44] enrolled patients based solely on SPT.

3.1. Risk of bias

The quality and risk of bias for the studies included in the meta-analysis were assessed using the ROBIN-I tool (Fig. 2). Deroche et al.[32] and D'ambrosi[44] provided strong evidence in their non-randomized studies, but their findings were not fully comparable to well-conducted randomized trials. They were assessed as having a moderate risk of bias overall. Thienpont[45] study showed some significant issues, resulting in an overall judgment of serious risk of bias. Despite this, it was still included in the meta-analysis. Fig. 3 presents the unweighted summary plot of the ROBINS-I assessment for these studies.

3.2. Metanalysis

The meta-analysis encompassed 409 knee replacements from three studies, comprising 95 hypersensitive patients who received hypoallergenic TKA and 314 non-allergic patients who underwent standard CoCr implant procedures. The analysis of the KSS yielded an overall effect size (SMD) of −0.18, with a 95 % Confidence Interval ranging from −0.54 to 0.18 (Fig. 4). A random-effects model was employed to account for potential heterogeneity, which was assessed with an I^2 value of 53 % and a tau of 0.0526. The negative SMD suggests marginally lower mean clinical outcomes in the hypoallergenic group compared to the standard group. The I^2 value indicates moderate heterogeneity among the studies analyzed.

4. Discussion

This scoping analysis revealed comparable clinical outcomes between patients with metal hypersensitivity who received hypoallergenic total knee arthroplasty (TKA) and those without metal allergy who underwent standard knee implant procedures. The meta-analysis demonstrated moderate heterogeneity, as indicated by an I^2 value of 53 %. This level of heterogeneity suggests moderate variability in effect sizes across the included studies. To account for this variability, a random-effects model was employed in the meta-analysis. This approach assumes that the true effect size may differ between studies, acknowledging that the observed differences may be due to factors beyond simple sampling error.

Such this result can be justified by numerous reasons. All the included cohort studies were not randomized, and the study designs were different. D'Ambrosi et al.[44] reported a prospective cohort study, but Deroche et al.[32] and Thienpont[45] reported a cohort study in a retrospective fashion. Another source of heterogeneity may result from differences between the baseline characteristics of the population of the included studies. While D'Ambrosi[44] et al. and Thienpont[45] provided for the demographic characteristics of the individuals, Deroche et al.[32] failed to produce such informations. Finally, D'Ambrosi et al.[44] conducted the study evaluating TiNbN unicompartimental arthroplasties and CoCr UKAs (not TKAs) potentially introducing some level of heterogeneity in the current metanalysis.

Bracey et al.'s study[41] found no preoperative differences between the metal-sensitive and non-sensitive groups. However, postoperatively, the metal-sensitive group showed less improvement across all measures, with a significantly smaller increase in Knee Society Score (36.1 vs 53.8, $p = 0.03$). These contrasting results might be attributed to the variety of testing methods used (patch testing, lymphocyte transformation test, and lymphocyte proliferation test) and the limited sample size. The authors also noted that the surgeons' infrequent use of hypoallergenic implants could potentially negatively impact clinical outcomes, and this factor could not be ruled out in their analysis.

Peña et al.[43] revealed that patients who underwent hypoallergenic total knee arthroplasty (TKA) achieved lower scores on several outcome measures - WOMAC, SF-12, and Euro-QoL-5D L-VAS - compared to those who received conventional chromium-cobalt implants. The authors acknowledged a significant limitation in their study design: the procedures were performed by different surgeons. This variation in surgical expertise and technique could have introduced potential bias to the results, making it challenging to determine whether the observed differences were solely due to the implant type or influenced by individual

Table 2
Summary information of the studies included in the qualitative and quantitative synthesis.

Study	Design	Level of evidence	N. of knees	Mean FU (months)	Hypersensitivity assessment	Type of implant	Outcomes	Inclusion/ exclusion for metanalysis	Description of main results
Deroche E, 2023[19]	Retrospective matched cohort	3	14 allergic knees vs 34 non-allergic knees	67 ± 6 vs 39 ± 2	Strong evidence of anamnestic metal allergy or SPT	TiN-coated vs CoCrMo mobile-bearing CS	KSS	Included	No clinical statistical difference
D'Ambrosi R, 2021[20]	Prospective cohort	3	43 allergic kneesvs 200 non-allergic knees	69.79 ± 17.49 vs 67.13 ± 16.20	SPT	UKA TiNbN vs UKA CoCr	Oxford Knee Score (OKS), Knee Society Score (KSS)	Inlcuded	No clinical statistical difference
Bracey DN, 2022[16]	Retrospective matched cohort	3	18 allergic knees vs 18 non-allergic knees	>12	SPT, LTT, LPT, MELISA	TiNi coated TKA or OxZi TKA vs CoCr	ROM, KSS, and Veterans RAND 12 score	Excluded because do not provides enough data	Hypoallergenic TKA have lower PROMs scores
Pellengahr C, 2003[17]	Retrospective matched cohort	3	35 allergic knees vs 36 non-allergic knees	29 vs 30	Epicutaneous testing	Natural Knee prosthesis vs Genesis-I prostheses	KSS, HSS, ROM	Excluded because do not provides enough data	No clinical statistical difference
Thienpont E. 2015[21]	Retrospective matched cohort	3	38 allergic knees vs 80 non-allergic knees	24 ± 10	Strong evidence of anamnestic nickel, chrome or cobalt allergy	TiNbN TKA vs CoCr TKA	KSS, KOOS FJS-12	Included	No clinical statistical difference
Peña P, 2020[18]	Retrospective matched cohort	3	76 allergic knees vs 168 non-allergic knees	34.48 ± 11.56 vs 27.49 ± 8.666	SPT	OxZi TKA vs CoCr TKA	WOMAC, SF-12, Euro-QoL-5D L-VAS	Excluded because do not provides comparable scoring system data	Hypoallergenic TKA have lower PROMs scores

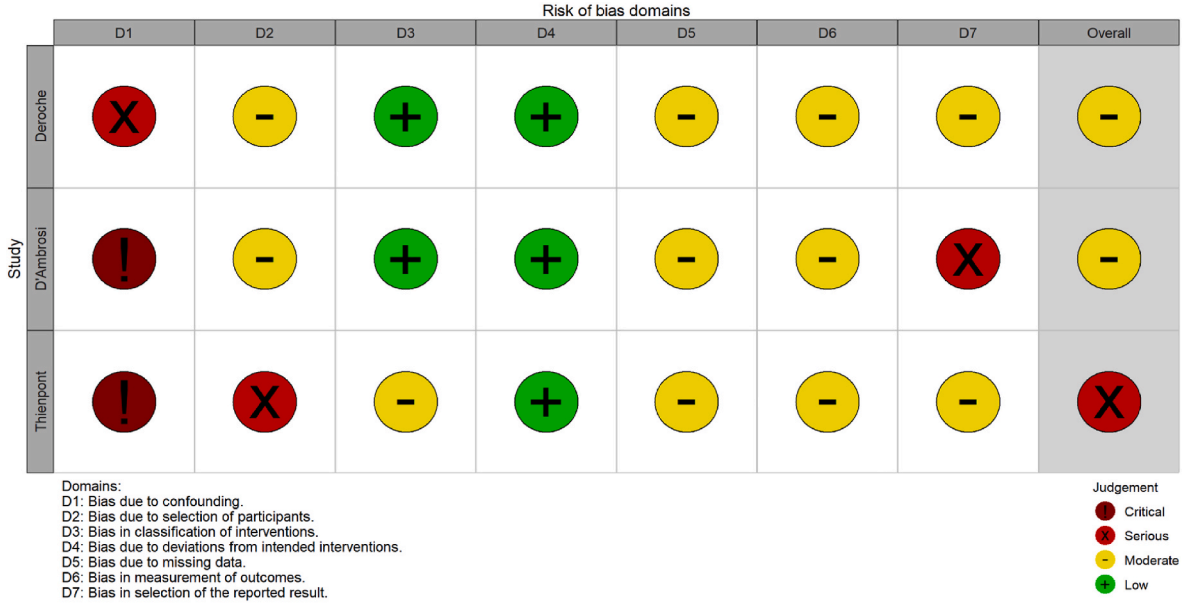

Fig. 2. Risk-of-bias assessment with ROBINS-I tool shown as traffic lights chart.

surgeon factors.

Pellengahr et al.[42] found no statistically significant clinical differences between the hypersensitive and control groups. However, the study had potential limitations. The authors noted a possible undisclosed conflict of interest, likely stemming from the exploratory nature of their research on Natural Knee prostheses. While the study provides valuable information, these limitations should be considered when interpreting its findings in the context of comparing hypoallergenic and standard knee implants.

These results collectively paint a complex picture of the clinical outcomes for hypoallergenic versus standard knee implants in patients with and without metal hypersensitivity. In conclusion, while the overall analysis suggests comparable outcomes between hypoallergenic and standard implants, the individual study results and noted limitations indicate that this conclusion should be interpreted cautiously. The findings underscore the need for larger, well-designed randomized

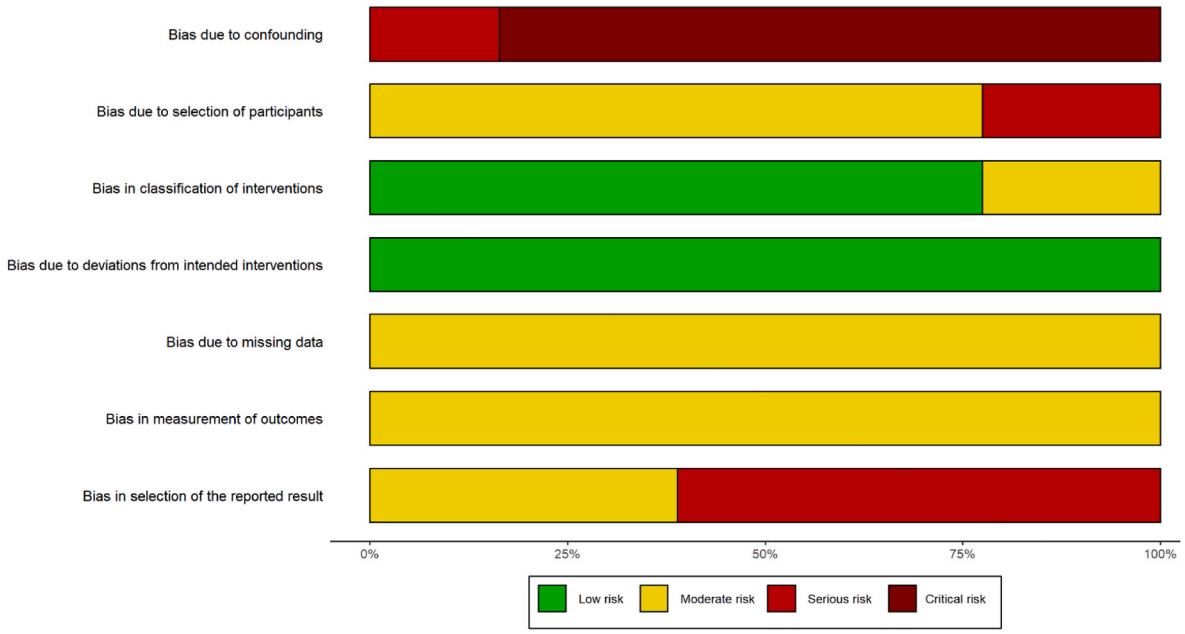

Fig. 3. Risk-of-bias assessment with ROBINS-I tool shown summary plot.

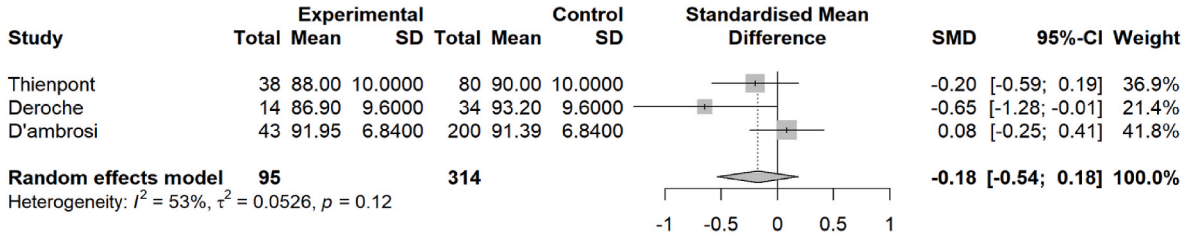

Fig. 4. Forest plot of the KSS knee score.

controlled trials that account for potential confounding factors and use standardized outcome measures to provide more definitive evidence on the efficacy of hypoallergenic implants in patients with metal hypersensitivity.

This is the first systematic review in the literature to compare clinical outcomes between two groups: patients with metal hypersensitivity who received hypoallergenic knee arthroplasty and those without metal allergy who underwent standard knee replacement.

Siljlander et al.[46] conducted a retrospective study comparing outcomes in patients with preoperative nickel allergy who received either nickel-free or cobalt-chromium (CoCr) implants. The study included 243 patients with nickel-free implants and 39 with CoCr implants. Results showed no significant differences in clinical outcomes, scores, or revision rates between the two groups. Both cohorts demonstrated substantial improvements in clinical measures during the first-year post-surgery and displayed satisfactory implant survival rates in early follow-up evaluations. This research suggests that the choice between nickel-free and CoCr implants may not significantly impact short-term outcomes in patients with nickel allergy.

A recent meta-analysis by Banci et al.[7] compared ceramic-coated and uncoated implants in primary total knee arthroplasty (TKA). The study found no significant differences in survival rates between the two implant types over short to medium-term follow-up periods. Additionally, clinical outcomes measured by Knee Society Score (KSS) and Oxford Knee Score (OKS), complication rates, and blood concentrations of cobalt and chromium at one-year post-surgery were similar for both groups. This analysis supports the hypothesis that ceramic-coated implants do not result in inferior outcomes compared to conventional uncoated CoCr implants in primary TKA.

This study has several limitations, the primary one being the scarcity of high-level studies directly comparing outcomes of allergenic and non-allergenic implants in both sensitive and non-sensitive patients. The limited literature on this specific topic resulted in a restricted number of available studies and an overall pooled implant count insufficient for definitive conclusions in this meta-analysis. Furthermore, the quality of the selected studies introduces potential confounding biases. Another notable limitation is the variation in metal hypersensitivity assessment methods across studies, which could contribute to differing outcomes. Consequently, the overall level of evidence in this systematic review remains low, significantly impacting the reliability of any conclusions. However, these limitations also demonstrate that hypersensitivity in knee replacement is a complex issue that cannot be ignored and warrants further investigation.

5. Conclusions

While hypoallergenic knee implants appear to offer comparable short to medium-term outcomes to standard implants, the complex nature of metal hypersensitivity in TKA necessitates continued investigation. Clinicians should consider individual patient factors, including confirmed metal hypersensitivity, when selecting implants, while remaining aware of the current limitations in our understanding of this challenging clinical issue.

Statements and declarations

The authors certify that all investigations were conducted in conformity with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. All patients have given their informed consent for participation and there is no financial interest to report.

Competing interests

The authors did not receive support from any organization for the submitted work. The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Registration and protocol

This research was not registered. The review protocol was not prepared. PICOS: P=Patients with metal hypersensitivity undergoing primary knee arthroplasties, I=Hypoallergenic knee arthroplasties, C=Patients without metal-proven or self-reported metal allergy undergoing knee arthroplasties with conventional uncoated CoCr knee implants, O=Clinical outcomes, S = ; cohort studies, case-control studies.

CRediT authorship contribution statement

Christian Carulli: Conceptualization, screening process, quality assessment, Writing – review & editing, Supervision. **Filippo Leggieri:** screening process, data extraction, writing. **Domenico Rodà:** screening process, writing. **Fabrizio Matassi:** Writing – review & editing, Each author has read and approved the final version of the manuscript and has agreed to be personally accountable for their own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature, All authors involved meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors. **Roberto Civinini:** Conceptualization, Supervision. **Matteo Innocenti:** data extraction, quality assessment, writing.

Declaration of competing interest

The authors declare the have no conflict of interest.

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