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Nickel hypersensitivity and skin patch testing in total hip replacement surgery: a systematic review

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- Approximately 60,000 cemented femoral stems are implanted in the UK each year with the majority being manufactured from stainless steel containing 10–15% nickel. Nickel hypersensitivity has been reported in up to 13% of the general population and there is a concern that nickel hypersensitivity might adversely affect the outcome of total hip replacement (THR). We reviewed the current literature on the potential link between nickel hypersensitivity and THR complications, and the usefulness of patch testing.
- We conducted a literature search in PubMed, MEDLINE and EMBASE databases. The level of evidence and the quality of the selected studies were assessed using the Oxford Centre for Evidence-Based Medicine Criteria and the Methodological Index for Non-Randomised Studies tool, respectively.
- Twenty-six studies met the inclusion criteria, reporting on 1852 patients who underwent primary or revision THR. All studies detailed skin patch testing and recorded prevalence of nickel hypersensitivity from 1.5% to 33.3%. Five studies reported a rise in Nickel hypersensitivity following THR, while four reported a decreased prevalence post-operatively. Eight studies concluded that metal hypersensitivity could have developed following THR, while seven studies did not support a link between metal hypersensitivity and THR complications. Four of the studies recommended routine patch testing pre-operatively, but three others concluded that routine patch testing was not indicated.
- We have not identified a link between nickel hypersensitivity and THR complications, and the role of patch testing remains unclear. Further large-scale studies would be required to investigate this relationship and to clarify the role of patch testing in facilitating implant selection.

Keywords: nickel hypersensitivity; patch testing; THA; THR; total hip arthroplasty; total hip replacement

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Introduction

Total hip replacement (THR) is a frequently performed surgical procedure and in England, Wales and Northern Ireland with more than 90,000 hip replacements performed in 2019.[1] Metallic implants used in orthopaedic surgery are made of stainless steel, cobalt-chromium-molybdenum, titanium, zirconium and aluminium alloys, which contain a variety of metallic elements including chromium, nickel, manganese, molybdenum, cobalt, iron, titanium vanadium and zirconium.[2] The potential effects of pre-existing or developing hypersensitivity to these metals have been raised as a concern in orthopaedic surgery over the last half-century.[3]

Metal hypersensitivity is a type IV (or delayed-type) hypersensitivity reaction, which occurs when the body develops an immunological reaction to the metallic constituents of an implant. It has been estimated that cutaneous allergies to common metals such as nickel, cobalt and chromium occur in 13%, 2% and 1% of the general population respectively.[4] Since these metals are commonly used in THR implants, it has been suggested that patients who are hypersensitive to them may develop a hypersensitivity reaction post-operatively.[5] Metal hypersensitivity reactions in orthopaedic patients have been reported to present with localized pain, swelling, redness, warmth, itching and burning, as well as implant loosening that may mimic suspected infection.[6] Metal hypersensitivity is considered to be a diagnosis of exclusion when the other causes of implant failure have been ruled out.[5] Despite the lack of an established standard for diagnosing metal hypersensitivity, investigations such as skin patch and lymphocyte transformation testing have been advocated.[5]

Nickel is the fifth most common element on Earth and is widely used in everyday items including jewellery, clothing fasteners, kitchenware and coins, as well as in the steel and military-related industries. Nickel is a moderate sensitizer and in 1925 was demonstrated to be the aetiological

Table 1. Search strategy

	Keywords
1	**exp total hip replacement/or exp hip replacement/**
2	hip prosthesis/
3	(THR or "total hip replacement" or THA or "total hip arthroplast*" or "hip surger*" or "hip prosthes*" or "total hip prosthes*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4	hip surgery/
5	1 or 2 or 3 or 4
6	Nickel hypersensitivity/
7	("Nickel allerg*" or Nickel or "Nickel hypersensitiv*" or "Nickel reaction*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8	6 or 7
9	5 and 8

factor in the development of dermatitis in workers from the electroplating industry.[2] Subsequent studies investigated the role of nickel hypersensitivity in a variety of occupations, with a Swedish study demonstrating an increased prevalence in cleaners.[7] A high prevalence of nickel dermatitis was found in cooks with the increased use of stainless steel kitchenware[8] and in Britain in the late 20th century it was reported that hairdressers, cleaners and cooks with diagnosed occupational contact dermatitis usually had an established nickel hypersensitivity.[8] In Finland, nickel was implicated in 6.9% of occupational contact dermatitis cases, involving occupations such as machine and metal product assemblers, electrical equipment assemblers, footwear workers, industrial tailors, hairdressers and beauticians.[9]

The proportion of nickel in stainless steel is considerably higher than in cobalt-chrome (13–15%[10] against 1%[11]). In the UK, the femoral component of approximately two-thirds of all hip replacements is secured with bone cement. Almost all of these 60,000 stems are manufactured from stainless steel.[1] Over time, all metallic alloys corrode, particularly at junctions and when in contact with biological fluids. Therefore, it may be hypothesized that patients who are already sensitive to nickel could be more likely to experience a peri-articular reaction compared to those with no history of metal sensitivities. If this hypothesis was confirmed, patch testing, prior to orthopaedic device implantation, would be a useful tool to identify patients with nickel hypersensitivity.[12] It would then allow appropriate consideration for using a low or non-nickel containing implant.

We have reviewed the current literature and collated the evidence concerning the relationship between nickel hypersensitivity in patients with total hip replacement and any associated complications, along with the usefulness of patch testing in identifying nickel hypersensitivity. We have assessed the potential link between nickel hypersensitivity and THR complications as well as the usefulness of patch testing.

Methods

Search strategy and study selection

Systematic electronic literature searches were conducted in PubMed, Ovid and Healthcare Database Advanced Search (HDAS) searching EMBASE and Medline databases (until 13 April 2021). Combinations of medical subject heading (MeSH) terms and keywords were used to identify relevant papers with a high level of sensitivity. Table 1 shows the search string applied in the search. Further manual searches of the reference lists of the papers and searching the grey literature supplemented the systematic electronic search. Papers were screened initially by title and abstract. Two independent reviewers screened the selected studies and the results of the search strategy were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool.

Eligibility criteria

The inclusion criteria were: (1) clinical studies on testing nickel hypersensitivity with patch testing in patients with THR; (2) published in English or with translation freely available; (3) full text of studies available. Exclusion criteria included (1) case reports; (2) review studies; (3) cadaver studies and (4) no reported outcome.

Data extraction/analysis

The level of evidence (LE) was assessed based on previously published criteria from the Oxford Centre for Evidence-Based Medicine[13] and the methodological quality was assessed using the Methodological Index for Non-Randomised Studies (MINORS) tool.[14] The following information was obtained from each study:

I. Study characteristics (e.g. author, geographical area, study design)
II. Patient characteristics (e.g. number of patients included, and number of hip joints operated on, age, gender)
III. Implant characteristics (e.g. type of implant, bearing)
IV. Details on patch testing (patch substances used; time point at which patch test was performed)
V. Prevalence of nickel hypersensitivity (before and/or after surgery)
VI. Clinical results (e.g. complications, stable or failed implant, adverse reaction to metal debris, systemic adverse reactions)
VII. Main conclusions and recommendations

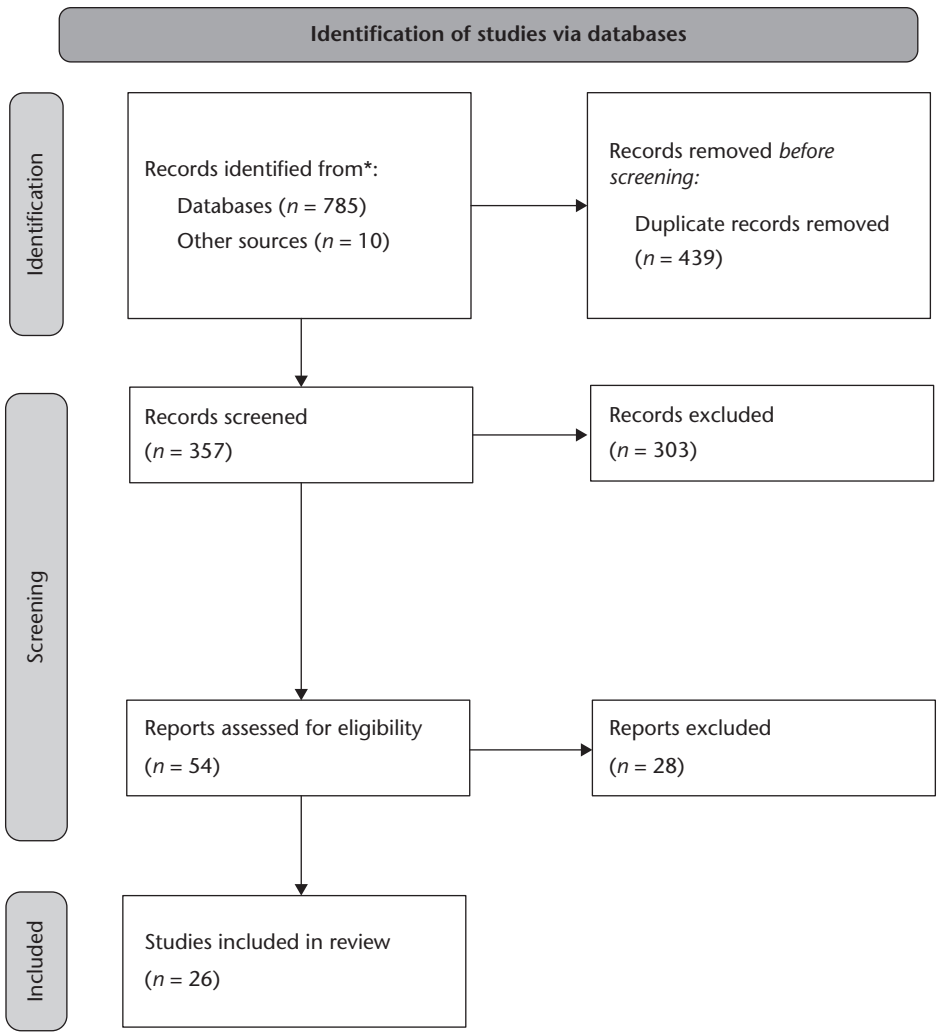

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) study selection flow diagram.

Results

Search results

Our initial literature search using the MeSH terms detailed in Table 1 identified 795 studies, and after the duplicates were removed 439 remained. The abstracts of these papers were screened. Twenty-six clinical studies met the inclusion criteria for this review (Fig. 1).

Quality assessment

All studies were of small to medium size and focused on metal and/or nickel sensitivity in patients who underwent total hip arthroplasty. Seven of the studies[18,20,24,26–28,39] had a cohort study design with LE of III, while the other 19 were case-series[16,21,25,29–34,37,40] or case-control led[15,17,19,22,23,35,36,38] with LE of IV. The average MINORS score was 12.2 (Table 2).

Cohort characteristics

Across all of the studies there were 3466 participants with an average age of 63.5 years (range 48–71) and average female proportion of 65.7% (range 24–89%). A total of 1852 primary and revision hip arthroplasties were performed, either prior to the conducted studies or as part of them. The rest of the participants either comprised control groups or underwent a different procedure, such as total knee replacement (TKR), or open reduction and internal fixation (ORIF). A detailed description of the study populations is shown in Table 3.

Implant characteristics

The implant type and type of bearing was documented in 15 studies,[15–17,19–23,26,27,30–33,39] with only the implant type being recorded in four studies[18,24,35,36] and only the type of bearing in a further four.[25,37,38,40] In the three remaining

Table 2. Study characteristics with level of evidence (LE) and Methodological Index for Non-Randomised Studies (MINORS) score

Author	Year	Study design	Country	Number of patients	Age (mean)	LE	MINORS score
Benson et al[15]	1975	Case-control	UK	105	67	IV	13
Brown et al[16]	1977	Case-series	US	20	62	IV	9
Carlsson et al[17]	1980	Case-control	Sweden	274	64	IV	14
Carlsson and Möller[18]	1989	Cohort study	Sweden	18	NR	III	13
Christiansen et al[19]	2019	Case-control	Denmark	20	65	IV	19
Deutman et al[20]	1977	Cohort study	Netherlands	212	NR	III	14
Elves et al[21]	1975	Case-series	UK	50	NR	IV	9
Frigerio et al[22]	2011	Case-control	Italy	100	68	IV	10
Granchi et al[23]	2005	Case-control	Italy	223	63	IV	13
Guenther et al[24]	2016	Cohort study	Germany	17	58	III	20
Gustafson et al[25]	2014	Case-series	Denmark	54	64	IV	11
Hallab et al[26]	2013	Cohort study	US	58	64	III	18
Hjorth et al[27]	2015	Cohort study	Denmark	41	52	III	14
Kręcisz et al[28]	2012	Cohort study	Poland	60	62	III	13
Lodi et al[29]	1995	Case-series	Italy	64	66	IV	9
Milavec-Puretić et al[30]	1998	Case-series	Croatia	40	60	IV	10
Nater et al[31]	1976	Case-series	Netherlands	66	70	IV	10
Pazzaglia et al[32]	1983	Case-series	Italy	40	69	IV	7
Rooker and Wilkinson[33]	1980	Case-series	UK	67	NR	IV	10
Shanmugham et al[34]	2020	Case-series	India	54	NR	IV	12
Thomas et al[35]	2013	Case-control	Germany	368	63	IV	13
Thomas et al[36]	2015	Case-control	Germany	250	65	IV	13
Thomas et al[37]	2009	Case-series	Germany	16	68	IV	12
Thyssen et al[38]	2009	Case-control	Denmark	1068	NR	IV	19
Waterman and Schrik[39]	1985	Cohort study	Netherlands	85	71	III	10
Zeng et al[40]	2014	Case-series	China	96	48	IV	9

Note. NR, not recorded.

studies[28,29,34] there was no clear documentation of either the type of implant used or the bearing. A breakdown of the type of implants used and the bearing from each study is shown in Table 3.

Patch testing

All 26 studies used patch testing to identify metal hypersensitivity. The substances applied in the patch testing along with the exact concentration of each substance were listed in 20 studies (Table 4). Thirteen of the studies[15,17,18,21–23,25,27–30,34,38] used 5% nickel sulphate, four [20,31,33,39] used 2.5% nickel sulphate, and the remaining three used nickel sulphate in concentrations of 1%,[19] 2%[16] and 3%.[32] In the other six studies[24,26,35–37,40] the strength of the nickel sulphate used was not documented.

In ten studies[17,18,20,22,28,31,33,34,36,39] the participants were patch tested both before and after their operation, and in 14 studies[15,16,19,21,23–27,29,30,32,35,37] participants were patch tested only after the primary arthroplasty took place. In three studies with patients undergoing revision THR, the timing of patch testing was not documented in relation to the revision procedure.[19,30,37] Additionally, in one study six patients had patch testing after the revision; however, for the remaining patients it was not documented when patch testing was performed.[16] In the study by Thyssen et al, patch testing was performed prior to THR in 292 cases (82%) and in 64 cases (18%) after THR was performed.[38] In one study patch testing was performed prior to primary THR.[40]

The reported time until patch testing was performed post-operatively ranged from three months to 18 years (Table 5).

Prevalence of nickel sensitivity

The prevalence of nickel sensitivity in each study ranged from 1.5% to 33.3%, and two studies[16,32] reported no positive reaction to nickel amongst the participants tested. Two studies[18,24] had selected only participants with a known hypersensitivity to nickel and subsequently reported nickel hypersensitivity on patch testing of 76.5%[24] and 83.3%[18] (Table 5, highlighted in pink).

Ten studies[17,18,20,22,28,31,33,34,36,39] compared the pre-operative and post-operative prevalence of nickel hypersensitivity in the same groups of patients and in five of these[17,28,31,34,39] it was reported there was an increase in the number of patients testing positive for nickel hypersensitivity post-operatively. Kręcisz et al concluded that the increase in nickel hypersensitivity prevalence was minimal (from 20% pre-operatively to 20.8% post-operatively), but it was noted that three patients had developed a new hypersensitivity to nickel following surgery.[28]

Four studies[18,20,33,36] noted a decrease in the number of patients hypersensitive to nickel after the operation. One study[22] did not report the results of patch tests post-operatively.

Table 3. Summary of the included studies with breakdown of number of hip replacements, total number of participants in each study, average age, proportion of female participants, the description of each study population, and the type of implant and bearing used

Study	Number of hip replacements (number of participants)	Average age	Proportion of females	Population	Type of implant	Bearing
Benson et al 1975[15]	91 joints (105 participants)	67.0 (range NR)	67%	72 patients with THR	39 patients – Charnley prosthesis 32 patients – McKee 1 patient – Stanmore	40 patients – MOP 32 patients – MOM
				33 control group – awaiting THR		
Brown et al 1977[16]	23 joints (20 participants)	62.0 (range 29–80)	80%	20 patients with THR and sterile loosening of implant	20 patients – McKee-Farrar (2 patients with previous Vitallium Austin Moore and 1 with a previous Vitallium Cup)	20 patients – MOM
Carlsson et al 1980[17]	134 joints (134 participants)	61.0 (±8)	59%	Group I - retrospective sample of 134 patients with THR	89 patients – stainless steel (Charnley) 45 patients – CoCr	89 patients – MOP
	112 joints (112 participants)	65.0 (±9)	65%	Group II – prospective sample of 112 patients awaiting THR	Stainless steel or Cobalt-chromium	–
	(28 participants)	66.0 (±12)	57%	Group III – prospective sample of 28 patients awaiting operation	–	–
Carlsson and Möller 1989[18]	5 joints (18 participants)	NR	NR	5 patients with THR	14 patients – CrNi 3 patients – CrCoNi 1 patient – CoNi	–
				13 patients with other orthopaedic implants		
Christiansen et al 2019[19]	6 joints (6 participants)	60.8 (range NR)	33%	Aseptic loosening patients for revision THR	3 patients – CoCrMo/TiAlV 2 patients – CoCrMo/FeCrNiMn 1 patient – CoCrMo	5 patients – MOP 1 patient – MOM
	6 joints (6 participants)	73.0 (range NR)	33%	THR revision for any other reason than aseptic loosening	2 patients – CoCrMo/TiAlVa 1 patient – TiAlVa/Ceramic 3 patients – CoCrMo/FeCrNiMn	5 patients – MOP 1 patient – COP
	8 joints (6 participants)	62.0 (range NR)	38%	Control group received primary THR	NR	NR
Deutman et al 1977[20]	(212 participants)	NR	82%	173 patients with no previous operations	–	–
				17 patients with other metallic implants but no THR	–	–
				16 patients to be re-operated	15 patients – McKee-Farrar 1 patient – Muller	15 patients – MOM 1 patient – MOP
				6 patients with stable THR contralaterally	6 patients – McKee-Farrar	6 patients – MOM
	66 joints (66 participants)	69.5 (range NR)	83%	66 patients from the previous study who did not have pre-operative sensitivity and underwent THR	All patients – Stanmore	All patients – MOP
Elves et al 1975[21]	61 joints (50 participants)	NR	NR	40 participants previous THR	36 patients – Stanmore 4 patients – special femoral prosthesis	36 patients – MOM
				10 participants with various orthopaedic implants investigated for failure	5 patients – McKee-Farrar (MOM) 5 patients – hip, knee, elbow prosthesis	5 patients – MOM
Frigerio et al 2011[22]	48 joints (100 participants)	68.0 (range 51–84)	73%	48 patients awaiting THR	24 patients – CoCrMo/TiAlVa 14 patients – TiAlVa 10 patients – CoCrMo	22 patients – COP 12 patients – MOM 7 patients – MOP 7 patients – COC

(continued)

Table 3. (continued)

Study	Number of hip replacements (number of participants)	Average age	Proportion of females	Population	Type of implant	Bearing
				52 patients awaiting TKR	33 patients – CoCrMo/TiAlV 10 patents – CoCrMo 9 patients – TIAlVa	–
Granchi et al 2005[23]	(66 participants)	59.6 (range 24–82)	74%	Patients awaiting THR	–	–
	53 joints (53 participants)	65.0 (range 35–81)	73%	Patients with stable THR	27 patients – TiAlVa 24 patients – CoCrMo/TiAlVa 2 patients – CoCrMo	47 patients – COC 5 patients – MOP 1 patient – MOM
	104 joints (104 participants)	64.7 (range 32–83)	75%	Patients with loosening of THR	31 patients - CoCrMo 25 patients – TiAlVa 22 patients – CoCrMo/TiAlVa 26 patients – unknown	48 patients – COC 39 patients – MOP 2 patients – MOM 15 patients – COP
Guenther et al 2016[24]	(34914 participants)	NR	NR	Historic database patients with primary and revision hip and knee arthroplasty	NR	NR
	3 joints (17 participants)	58.2 (±9.8)	100%	THR revision for likely allergic reaction	1 patient – Allofit (Zimmer) pure titanium	NR
Gustafson et al 2014[25]	54 joints (54 participants)	64.0 (range 56–70)	64%	44 patients with THR followed up	NR	25 patients – MOP/ COP implants 19 patients – MOM implants
Hallab et al 2013[26]	26 joints (58 participants)	NR	NR for Group 1&2	Group 1 (n = 21) awaiting THR	38 patients – Conserve plus	38 patients – MOM implants
		NR		Group 2 (n = 17) with THR		
		63.5 (range 44–74)	Group 3: 50%	Group 3 (n = 20) controls with no implant	–	–
Hjorth et al 2015[27]	49 joints (41 participants)	52.0 (range 26–68)	24%	Patients with THR	All patients: head (CoCrMo) and stem (TiAlVa)	MOM implants
Kręcizs et al 2012[28]	(60 participants)	61.7 (range NR)	72%	39 patients awaiting THR	–	–
				21 patients awaiting TKR		
	NR number of hip joints (48 participants)	NR	75%	Patients post TJR	NR	NR
Lodi et al 1995[29]	66 joints (66 participants)	65.9 (range 37–88)	80%	Patients with THR (13 cases with known aseptic mobilization)	NR	NR
	(41 participants)	61.4 (range 32–82)	71%	Control group – 41 patients awaiting THR	–	–
Milavec-Puretić et al 1998[30]	40 joints (40 participants)	Males: 58.7 (range 35–75) Females: 59.6 (range 29–76)	55%	40 patients undergoing revision THR	25 patients – CoCrMo 2 patients – Stainless steel 3 patients – CoNiCrMo (for 10 patients – 2nd revision of the same joint)	27 patients – MOP 1 patient – MOM
Nater et al 1976[31]	66 joints (66 participants)	69.5 (range NR)	89%	66 patients awaiting THR and followed up 6 to 12 months after	All patients – Stanmore	MOP
Pazzaglia et el 1983[32]	20 joints (20 participants)	68.8 (range 60–82)	NR	20 patients with THR	All patients – Charnley implants	MOP
				Control group – 20 patients without implant	–	–
Rooker et al 1980[33]	67 joints (69 participants)	NR	52%	67 patients awaiting THR	66 patients – Charnley implants 1 patient – Titanium implant	66 patients – MOP
				54 patients followed up after		
Shanmugham et al 2020[34]	(54 participants)	NR	NR	54 participants awaiting hip/knee or shoulder replacement	–	–

(continued)

Table 3. (continued)

Study	Number of hip replacements (number of participants)	Average age	Proportion of females	Population	Type of implant	Bearing
	(30 participants)	55.0 (±13.7)	47%	30 participants (out of 54) post hip/knee or shoulder replacement	NR	NR
Thomas et al 2013[35]	(68 participants)	Patients with eczema, but no CMI: 52.4 (range 18–75) Patients with eczema and CMI: 61.6 (range 44–75)	62%	Patients with eczema but without implants	–	–
	53 joints (100 participants)	72.4 (range 29–96)	75%	53 patients with symptom-free THR	CoCrMo	NR
				47 patients with symptom-free TKR	CoCrMo	–
	13 joints (200 participants)	64.4 (range 37–84)	65%	13 patients with symptoms/complications of THR	CoCrMo	NR
				187 patients with symptoms/complications of TKR	CoCrMo	–
Thomas et al 2015[36]	61 joints (250 participants)	64.8 (range 37–84)	66%	61 patients with THR (primary and revision) and suspected of having allergic reactions	CoCrMo	NR
				189 patients with TKR	CoCrMo	–
Thomas et al 2009[37]	16 joints (16 participants)	Average age NR (range 52–83)	50%	Patients awaiting THR revision due to pain, osteolysis, dislocation, loosening	NR	MOM implants
Thyssen et al 2009[38]	356 joints (1068 participants)	NR	67% in THR group	356 patients with previous patch test and THR (primary and revision)	NR	83 patients – MOP 25 patients – COP/COC 4 patients – MOM 244 patients – NR
				712 control patients from patch database	–	–
Waterman and Schrik 1985[39]	95 joints (85 participants)	71.0 (range 26–90)	88%	Patients awaiting THR and followed up post operation	78 patients – Stanmore alluvium 9 patients – Stanmore titanium 2 patients – Monk 3 patients – Freeman double cup 1 patient – Freeman cup-neck 2 patients – Waldemar Link	MOP bearing in all participants
Zeng et al 2014[40]	120 joints (94 participants)	48.3 (range 22–76)	48%	67 patients awaiting THR and follow up after surgery	NR	46 patients – COC 13 patients – COP 5 patients – MOP 3 patients – NR
				29 patients awaiting TKR	25 patients – Gemini MKII PS 4 patients – NR	–

Notes. Al, aluminium; CMI, cutaneous metal intolerance reactions; Co, cobalt; COC, ceramic-on-ceramic; COP, ceramic-on-plastic; Cr, chromium; Fe, iron; Mn, manganese; Mo, molybdenum; MOM, metal-on-metal; MOP, metal-on-plastic; Ni, nickel; NR, not recorded; THR, total hip replacement; Ti, titanium; TJR, total joint replacement; TKR, total knee replacement; Va, vanadium.

Study recommendations

Eight studies[20–22,24,28,31,34,39] concluded that orthopaedic implants could trigger metal hypersensitivity in patients, but that the relationship between the hypersensitivity and subsequent implant failure or loosening remained unknown.[21,28] Three studies reported a relationship between metal hypersensitivity and prosthesis loosening,[15] higher patch test reactivity in arthroplasty patients experiencing complications,[35] and a correlation between metal hypersensitivity and post-surgical thigh pain.[40]

Seven of the studies[16,18,19,29,30,33,38] concluded that they did not support a possible relationship between metal

Table 4. Patch test composition for each study

Author	Patch test composition
Benson et al[15]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 2%, barium sulphate 10%, benzoyl peroxidase 5%, formaldehyde 2%, hydroquinone 0.2%, monomer methyl methacrylate 1%, polymer 10%
Brown et al[16]	**Nickel sulphate 2%**, potassium dichromate 0.5%, cobalt chloride 1%, cobalt sulphate 2%, monomer methyl methacrylate 10%
Carlsson et al[17]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%
Carlsson and Möller[18]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%
Christiansen et al[19]	**Nickel sulphate 1%**, potassium dichromate 0.05%, cobalt chloride 0.02%, methyl methacrylate (2 wt.%), aluminium chloride (0.72, 0.38, 0.039 wt.%), ammonium molybdate (0.12, 0.013, 0.04 wt.%), ammonium titanium lactate, ammonium titanium peroxo-citrate (0.32, 0.16, 0.08, 0.04 wt.%), ferrous chloride (2 wt.%), gentamycin sulphate (20 wt.%), manganese chloride (0.24, 0.08, 0.06, 0.0057 wt.%), potassium titanium oxide oxalate (2.4, 1.2, 0.6 wt.%), solution Ti (0.16, 0.08, 0.04 wt.%), titanium dioxide (0.24 wt.%), titanium oxalate hydrate (0.32, 0.16, 0.08, 0.04 wt.%), vanadium chloride (0.24,0.12, 0.013, 0.04 wt.%), vanadium oxide sulphate hydrate (0.36, 0.18, 0.06, 0.02 wt.%)
Deutman et al[20]	**Nickel sulphate 2.5%**, potassium dichromate 0.5%, cobalt chloride 1%
Elves et al[21]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 2%
Frigerio et al[22]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, copper sulphate 2%, molybdenum 5%, palladium 2%, silver nitrate 1%, tin 50%, titanium 10%, vanadium 5%
Grachi et al[23]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, aluminium chloride 1%, chromium trichloride 2%, ferric chloride 2%, manganese chloride 2%, molybdenum chloride 2%, titanium dioxide 2%, vanadium trichloride 2%
Guenther et al[24]	NR
Gustafson et al[25]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, aluminium chloride 2%, ferric chloride 2%, manganese chloride 2%, molybdenum chloride 2.5%, titanium dioxide 10%, vanadium chloride 1%, zirconium chloride 1%
Hallab et al[26]	Nickel, cobalt, chromium
Hjorth et al[27]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, aluminium chloride 2%, ferric chloride 2%, manganese chloride 2%, molybdenum chloride 2.5%, titanium dioxide 10%, vanadium chloride 1%, zirconium chloride 1%
Kręcisz et al[28]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, aluminium 100%, ammonium molybdate tetrahydrate 1%, copper sulphate 2%, molybdenum 5%, palladium chloride 2%, vanadium 5%, vanadium chloride 1%, titanium oxide 10%
Lodi et al[29]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, aluminium chloride 1%, chromic chloride 2%, dimethyl phthalate 5%, epoxy resin 1%, ethylene glycol 5%, ferric chloride 2%, methyl methacrylate 5%, molybdenum chloride 2%, molybdenum chloride 5%, manganous chloride 2%, manganous chloride 5%, polyethylene glycol, titanium chloride 1%, titanium dioxide 5%, vanadium trichloride 2%, vanadium trichloride 5%
Milavec-Puretić et al[30]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, acrylate, balsam of Peru 25%, dibutyl phthalate 5%, formaldehyde 1%, metal rust, prostheses scrapings, titanium
Nater et al[31]	**Nickel sulphate 2.5%**, potassium dichromate 0.5%, cobalt chloride 1%
Pazzaglia et al[32]	**Nickel sulphate 3%**, potassium dichromate 0.5%, ferrous chloride 2%, manganous chloride 2%
Rooker et al[33]	**Nickel sulphate 2.5%**, potassium dichromate 0.5%, cobalt chloride 1%, benzoyl peroxide 5%, dimethyl-p-toluidine 2%, hydroquinone 1%, methyl methacrylate 5%
Shanmugham et al[34]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%, benzoyl peroxide 1%, gentamicin sulphate 20%, hydroquinone 1%, methyl methacrylate 2%, N, N-Dimethyl-4-toluidine 5%, titanium dioxide 10%, vanadium 5%
Thomas et al[35]	Nickel, chromium, cobalt
Thomas et al[36]	29 allergens, routine supplemental series and bone cement component series
Thomas et al[37]	Nickel, chromium, cobalt, manganous chloride 0.5%, sodium molybdate 2%, titanium dioxide 0.1%
Thyssen et al[38]	**Nickel sulphate 5%**, potassium dichromate 0.5%, cobalt chloride 1%
Waterman and Schrik[39]	**Nickel sulphate 2.5%**, potassium dichromate 0.5%, cobalt chloride 1%, ammonium molybdate 1%, ammonium vanadate 1%, benzoyl peroxide 1%, hydroquinone 1%, methyl methacrylate 10%, methyl methacrylate 25%, titanium dioxide 5%
Zeng et al[40]	Nickel, cobalt, chromium, aluminium, copper, iron, manganese, molybdenum, tin, titanium, vanadium, zirconium

Notes. NR, not recorded.

hypersensitivity and THR complications, implant loosening or the need for revision. Two of these studies[18,33] and one further study[32] concluded that the release of metal ions did not result in increased hypersensitivity.

Gustafson et al reported that, despite metal ion concentrations being higher in patients with metal-on-metal bearings, compared to those with metal-on-plastic articulations, there was no difference in the prevalence of metal hypersensitivity between the two groups[25] with Hjorth et al reporting no association between the formation of pseudotumours and serum metal-ion levels, metal patch test reactivity or atopic dermatitis in patients with metal-on-metal bearings.[27] Two studies investigated lymphocyte-mediated hyperactivity to metals rather than patch test reactions, but the clinical implications of such hyperactivity in patients with THR remained unknown.[26,37] One study concluded that it was doubtful that metal hypersensitivity was triggered by THR.[17] Granchi et al reported that it had not been possible to establish a cause–effect relationship between sensitization and THR complications but, reported a shorter THR lifespan in patients with a positive result to patch testing.[23] One study did not comment on the possibility of sensitization or any potential relationship between metal hypersensitivity and THR complications.[36]

Twelve studies concluded that patch testing was a valuable tool,[16,20,22–25,28,31,34–36,40] one of which recommended that it should be mandatory,[28] with three further studies recommending its targeted use.[24,25,34] Five of these studies concluded that patch testing was a valuable diagnostic tool in the detection of metal hypersensitivity,[16,35,40] even when the testing was delayed[36] and that testing might have an application in identifying sensitization to implants on a larger scale.[23] Four studies[20,22,28,31] recommended routine patch testing for all patients pre-operatively, one

Table 5. Nickel hypersensitivity prevalence across all studies and timing of patch testing. Two studies, highlighted in red, recruited patients with established nickel hypersensitivity as per inclusion criteria

Author	Total number of participants	Timing of patch testing	Prevalence of Nickel sensitivity		
			Population	Number of participants	%
Benson et al[15]	105 patients	Post-operatively (after 4.2–5.2 years)	Participants with THR (MOM bearing) (n = 33)	3	9.1
			Participants with THR (MOP bearing) (n = 39)	1	2.6
			Control group (n = 33)	3	9.1
Brown et al[16]	20 patients	NR when performed	Participants with THR with sterile loosening (MOM bearing) (n = 20)	0	0.0
Carlsson et al[17]	134 patients	Post-operatively (after 42–71 months)	Participants with THR (MOP bearing) (n = 134)	7	5.2
	112 patients	Pre-operatively (3 months)	Before THR	9	8.0
		Post-operatively (after 3-12 months)	After THR	10*	8.9
	28 patients	–	Control group (no implant)	4	14.3
Christiansen et al[19]	6 patients	NR when performed	Participants with THR and aseptic loosing	0	0.0
	6 patients	NR when performed	Participants with THR for revision	0	0.0
	8 patients	Post-operatively	Control group (Primary THR)	1	12.5
Deutman et al[20]	212 patients	Pre-operatively	Before THR	11	5.2
	66 patients	Post-operatively (after 6 months)	After THR	3*	4.5
Elves et al[21]	50 patients	Post-operatively (between 1–10 years)	Participants with THR (n = 45) and any other orthopaedic implant	9	18.0
Frigerio et al[22]	100 patients	Pre-operatively	Before operation (either THR or TKR)	21**	21.0
	72 patients	Post-operatively (after 1 year)	After operation	NR	NR
Granchi et al[23]	66 patients	Pre-operatively	Before operation	NR	22.7
	53 patients	Post-operatively (after 1 year)	Participants with THR (stable):	NR	
			TiAlV		33.3
			CoCrMo/TiAlV		25.9
	104 patients	Post-operatively (after 1 year)	Participants with loosening of THR:	NR	
			CoCrMo		12.9
			TiAlV		27.3
			CoCrMo/TiAlV		8.0
			Unknown		15.4
Gustafson et al[25]	54 patients	Post-operatively (after 5 years)	Participants with THR (MOM bearing) (n = 19)	4	21.1
			Participants with THR (MOP/COP bearing) (n=25)	7	28.0
Hallab et al[26]	16 patients	Post-operatively (after 4 years)	MOM resurfacing implant group	1	6.3
Hjorth et al[27]	40 patients	Post-operatively (after 5–7 years)	Patients with THR (MOM bearing)	2	5.0
Kręcisz et al[28]	60 patients	Pre-operatively	Before THR (n = 39) and TKR (n = 21)	12**	20.0
	48 patients	Post-operatively (after 24 months)	After hip or knee arthroplasty	10*, **	20.8
Lodi et al[29]	66 patients	Post-operatively (after 3–18 years)	Participants with THR	1	1.5
	41 patients	–	Control group	0	0.0
Milavec-Puretić et al[30]	40 patients	Post-operatively (after 7.6 years)	Awaiting revision THR	5	12.5
Nater et al[31]	66 patients	Pre-operatively	Before THR	0	0
	66 patients	Post-operatively (after 6–12 months)	After THR	3*	4.5
Pazzaglia et al[32]	16 patients	Post-operatively (after 10–13 years)	Participants with THR (MOP bearing)	0	0.0
	20 patients	–	Control group	NR	NR
Rooker and Wilkinson[33]	69 patients	Pre-operatively	Before THR	3	4.3
		Post-operatively (after 3–19 months)	After THR (n = 54)	1*	1.9
Shanmugham et al[34]	54 participants	Pre-operatively	Before hip/knee or shoulder replacement	3	5.6
	30 participants	Post-operatively	After hip/knee or shoulder replacement	3*,**	10

(continued)

Table 5. (continued)

Author	Total number of participants	Timing of patch testing	Prevalence of Nickel sensitivity		
			Population	Number of participants	%
Thomas et al[35]	68 patients	–	Without implant	13	19.1
	100 patients	Post-operatively	Participants with THR (stable)	9**	9.0
	200 patients	Post-operatively	Participants with THR (with complications)	35**	17.5
Thomas et al[36]	48 patients	NR	From historic database	13**	27.1
	250 patients	Post-operatively	Participants with THR and likely allergic reaction ($n = 61$) and with TKR and allergic reaction ($n = 189$)	32*,**	12.8
Thomas et al[37]	16 patients	NR when performed	Awaiting revision THR	4	25.0
Thyssen et al[38]	356 'cases'	In 292 cases (82%) pre-operatively In 64 cases (18%) post-operatively	Participants with THR	36	10.1
	712 patients	NR	Control group	70	9.8
Waterman et al[39]	85 patients	Pre-operatively (67 days on average)	Before THR	6	7.1
		Post-operatively (after 4-30 months)	After THR	8*	9.4
Zeng et al[40]	96 patients	Pre-operatively	Before THR ($n = 67$)	NR**	15.5
Carlsson and Möller[18]	*18 patients*	*From previous studies*	*All selected patients were allergic to nickel as per inclusion criteria*	*18*	*100*
		Post-operatively (after 10.4 years on average)		*15*,***	*83.3*
Guenther et al[24]	*34914 patients*	*NR*	*Primary and revision hip and knee arthroplasty from historic database*	*849*	*2.4*
	17 patients	*Post-operatively (after 2 years on average)*	*Revision hip and knee arthroplasty in patients with known Nickel allergy*	*13***	*76.5*

Notes. Al, aluminium; Co, cobalt; COC, ceramic-on-ceramic; COP, ceramic-on-plastic; Cr, chromium; Mo, molybdenum; MOM, metal-on-metal; MOP, metal-on-plastic; NR, not recorded; THR, total hip replacement; Ti, titanium; TKR, total knee replacement; V, vanadium.

*Change in nickel hypersensitivity prevalence when compared to baseline.

**No information about the breakdown number per type of prosthesis.

of which suggested that testing should be obligatory.[28] Three studies recommended considering the clinical relevance of patch tests[25] and only to perform this investigation when there was a known history of hypersensitivity reactions.[24,34]

Three studies reported that routine patch testing was not required[33,39] or that it was unrealistic.[17] One study concluded that patch testing was a poor diagnostic tool and might not be sufficient to accurately demonstrate an adaptive immune response.[26]

Ten of the studies did not comment on the usefulness of patch testing in identifying nickel hypersensitivities (Table 6).[15,18,19,21,27,29,30,32,37,38]

Discussion

The topic of nickel hypersensitivity and its implication in total hip arthroplasty remains controversial. We have reviewed the current literature addressing the relationship between nickel hypersensitivity in patients with total hip replacements and post-operative complications, implant loosening and revision and also studies on the value of skin patch testing. Although there have been several previous studies that have examined the relationship between metal hypersensitivity and THR complications, this is the first to also evaluate the application of patch testing in THR patients allergic to nickel and any reported complications which can be attributed to nickel hypersensitivity.

Eight of the studies supported the concept that the use of implants may result in metal hypersensitization.[20,21,22,24,28,31,34,39] Five studies[17,28,31,34,39] reported increased nickel sensitivity post-operatively and in three of those none of the patients experienced any complications of THR.[31,34,39] Kręcizs et al reported that three patients developed a positive reaction to nickel post-operatively and experienced periodical skin lesions, pain, swelling and erythema[28] whilst Carlsson et al reported that, in a retrospective cohort, more positive patch tests were observed in patients with THR complications compared to uneventful ones.[17]

Despite the hypothetical link between THR complications and hypersensitivity, several studies reported that it was difficult to establish whether the hypersensitivity was a cause or a consequence.[21,23,33] Several studies recommended further studies on a larger scale to establish the relationship between sensitization and THR,[21] between increased metal hypersensitivity and THR failure[26] and between post-surgical pain and metal hypersensitivy.[40]

Table 6. Study recommendations on the utility of patch testing in metal hypersensitivity in patients with total hip replacement

Studies	Conclusion on the role of patch testing in metal hypersensitivity
Brown et al[16] Granchi et al[23] Thomas et al[35] Thomas et al[36] Zeng et al[40]	Patch testing a valuable diagnostic tool
Deutman et al[20] Frigerio et al[22] Kręcisz et al[28] Nater et al[31]	Recommend routine patch testing ** Kręcisz et al[28] concluded patch testing should be mandatory*
Guenther et al[24] Gustafson et al[25] Shanmugham et al[34]	Consider clinical relevance and perform patch testing only in patients with a history of allergic reactions
Carlsson et al[17] Rooker et al[33] Waterman et al[39]	Did not recommend routine patch testing
Hallab et al[26]	Poor diagnostic tool
Benson et al[15] Carlsson and Möller[18] Christiansen et al[19] Elves et al[21] Hjorth et al[27] Lodi et al[29] Milavec-Puretić et al[30] Pazzaglia et al[32] Thomas et al[37] Thyssen et al[38]	Did not comment on the utility of patch testing

Seven of the studies did not support a link between nickel hypersensitivity and THR complications[16,18,19,29,30,33,38] and Carlsson et al, reporting on patients with known nickel hypersensitivity who were exposed to a nickel implant for an average of six years, reported the development of no orthopaedic complications.[18]

Patch testing

The systematic review confirmed that there was no consensus on the routine use of patch testing, but the studies were generally consistent in the chemical constituents that were used for the patch testing, although there was a wide range in the timing of administration. Some studies suggested that patch testing was a reliable, gold standard tool in establishing nickel hypersensitivity[16,23,35,36,40] and that it should even be mandatory,[28] but a similar number recommended that patch testing was not routinely required.[17,33,39]

A study by Thomas et al evaluated the usefulness of late reading of the patch testing. It reported an overall positive reaction to nickel in 32 patients (12.8%). Eleven of those positive reactions (34.4%) were recorded following a late reading of the patch test at day 6.[36] Reed et al, evaluating the usefulness of patch testing in the guidance of implant choice, concluded that patch testing might be helpful prior to operation, but had limited value post-operatively.[41] Furthermore, Hallab et al reported that patch testing was a poor diagnostic tool and suggested that there was no correlation with ion levels or measures of hypersensitivity and that there was no correlation with potential adaptive immune response in the deep tissue.[26]

There is evidence that patch tests have high sensitivity and specificity to detect hypersensitivity, but the immunologic response which occurs is triggered by the intradermal Langerhans cells, whereas the metal hypersensitivity reaction in the joint space is mediated by different mechanisms involving macrophages and lymphocytes.[5] Christiansen et al reported that there was a positive correlation between failure of joint arthroplasty and metal hypersensitivity, investigated by in vitro assay on peripheral blood lymphocytes, and that the findings were suggestive that prosthesis failure could be attributed to a cell-mediated immunity to metals.[42]

It is not therefore clear whether patch testing can accurately predict outcomes and complications following THR.[5] Lhotka et al reported a possible relationship between nickel hypersensitivity and reactions to metallic skin clips used for wound closure, but none of the studies included in this review specifically commented on this issue.[43]

Nickel hypersensitivity prevalence

It has been reported that the prevalence of nickel sensitivity in the general population is approximately 13%,[4] but the prevalence of nickel hypersensitivity following patch testing in the studies reviewed was reported to range from 1.5% to 33.3%. This discrepancy can be explained by the number of participants in each study, the inclusion and exclusion criteria, as well as the lack of uniform reporting of the nickel hypersensitivity. Eight of the studies supported the concept that THR triggers metal hypersensitivity in patients,[20,21,22,24,28,31,34,39] but in four there was a decrease in nickel hypersensitivity prevalence post-surgery.[18,20,33,36] Possible explanations could be false positive results pre-operatively, or false negative results following surgery, or development of immunological tolerance.[33]

Nineteen of the studies included patients who underwent primary THR.[15,17,18,20–23,25–29,31–35,39,40] The nickel hypersensitivity prevalence ranged from 0.0–33.3% across 18 of those studies, while in one study the prevalence was 83.3% as per inclusion criteria.[18] Five studies looked at patients awaiting revision THR.[16,19,24,30,37] Four of those studies reported nickel hypersensitivity prevalence of 0.0% to 25.0%, whereas in one study patients undergoing revision THR had known nickel hypersensitivity and the prevalence was 76.5%.[24] The study by Thyssen et al looked at both primary and revision cases and reported nickel reaction in 11% of the patients with primary THR, 10% in patients undergoing one revision, and 0% in patients undergoing two or three revisions.[38]

One study investigated metal hypersensitivity in patients with both primary and revision THR; however, it did not comment on the prevalence of each group separately.[36] Given the wide range of participants included in each study and the reported nickel hypersensitivity prevalence, it is impossible to compare the sensitivity rates between the two groups.

Implant type and bearing

A variety of implants and types of bearing were featured in the studies reviewed, but only 15 of the 26 studies[15–17,19–23,26,27,30–33,39] clearly reported the details of the implant used as well as the bearing or a breakdown of number of patients. Three of the studies[28,29,34] reported neither and this made it impossible to compare the nickel hypersensitivity prevalence between patient groups with different implant types or bearings.

Davies et al investigated peri-prosthetic tissue samples from metal-on-metal (MOM) and metal-on-plastic (MOP) THR and compared them to control samples from patients undergoing primary hip replacement. They observed a distinct and different pattern and type of inflammation between the samples, reporting that MOM tissue samples had a more prominent ulcerated appearance with extensive lymphocytic infiltration, while MOP tissue samples were less ulcerated with no plasma cell or lymphocytic infiltration.[44] A study by Brien et al reported that loosening of titanium-alloy implants led to disproportionally high levels of titanium and vanadium in synovial fluid and surrounding tissues when compared to cobalt, chromium and nickel levels released from loosened cobalt-chromium or stainless steel implants.[45] Although they raised concerns about the metallosis that could occur, it was unclear what effect this had on the eventual outcome of the THR.[45]

Limitations

There are several limitations in this systematic review, which include the low level of evidence of the studies, the limited number of patients involved in some of them, the methodological variability of the studies and the inadequate reporting of the results of certain studies. While the participant groups appeared similar across all of the studies, it was not possible to directly compare the prevalence of nickel hypersensitivity due to the lack of uniform reporting of the number of participants with positive patch tests in the THR and the control groups.

Several of the articles compared groups of patients undergoing not only hip but also knee[22,28,36,40] and shoulder[34] arthroplasties. However, the results of the patch testing of those patients were not stratified by the operation undergone, but only as a cohort.[18,22,24,28,34–36,40] Eleven of the studies were published in the last 10 years[19,22,24–28,34–36,40] but the review also included studies dating back to 1975, with 12 of the papers being published in 1997 or earlier.[15–18,20,21,29–33,39] Despite these limitations, it was still possible to draw some conclusions.

Conclusion

Nickel hypersensitivity is a common phenomenon in the general population. However, it remains unclear whether nickel hypersensitivity causes complications such as persistent pain, loosening of implants or increases the need for revision after THR. It is also unclear whether nickel hypersensitivity is a cause or an effect. The role of patch testing in establishing nickel hypersensitivity remains controversial, and the selection of an implant for patients with established nickel hypersensitivity should be made after discussion with the patient and at the surgeon's discretion. Further large-scale, appropriately designed studies would be required to establish the relationship between nickel hypersensitivity and THR complications as well as to guide the selection of the most appropriate implant for such patients.

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