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. 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. 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.

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. 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. 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. Metal hypersensitivity is considered to be a diagnosis of exclusion when the other causes of implant failure have been ruled out. Despite the lack of an established standard for diagnosing metal hypersensitivity, investigations such as skin patch and lymphocyte transformation testing have been advocated.

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...
factor in the development of dermatitis in workers from the electroplating industry. Subsequent studies investigated the role of nickel hypersensitivity in a variety of occupations, with a Swedish study demonstrating an increased prevalence in cleaners. A high prevalence of nickel dermatitis was found in cooks with the increased use of stainless steel kitchenware 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. 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.

The proportion of nickel in stainless steel is considerably higher than in cobalt-chrome (13–15% against 1%). 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. 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. 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 and the methodological quality was assessed using the Methodological Index for Non-Randomised Studies (MINORS) tool. 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

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**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 arthroplasty" or "hip sureg" 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 |
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 had a cohort study design with LE of III, while the other 19 were case-series or case-control led 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, with only the implant type being recorded in four studies and only the type of bearing in a further four. In the three remaining
studies 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 used 5% nickel sulphate, four used 2.5% nickel sulphate, and the remaining three used nickel sulphate in concentrations of 1%, 16% and 3%. In the other six studies the strength of the nickel sulphate used was not documented.

In ten studies the participants were patch tested both before and after their operation, and in 14 studies 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. 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.

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. In one study patch testing was performed prior to primary THR.

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 reported no positive reaction to nickel amongst the participants tested. Two studies had selected only participants with a known hypersensitivity to nickel and subsequently reported nickel hypersensitivity on patch testing of 76.5% and 83.3% (Table 5, highlighted in pink).

Ten studies compared the pre-operative and post-operative prevalence of nickel hypersensitivity in the same groups of patients and in five of these 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.

Four studies noted a decrease in the number of patients hypersensitive to nickel after the operation. One study did not report the results of patch tests post-operatively.

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

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

Note. NR, not recorded.
### 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 197515    | 91 joints (105 participants)                         | 67.0 (range NR) | 67%                   | 72 patients with THR                 | 39 patients – Charnley prosthesis    | 40 patients – MOP |
|                        |                                                     |             |                       |                                      | 32 patients – McKee                    | 32 patients – MOM |
|                        |                                                     |             |                       |                                      | 1 patient – Stanmore                  |               |
|                        |                                                     |             |                       |                                      | 33 control group – awaiting THR      |               |
| Brown et al 197716     | 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 Vitalium Austin Moore and 1 with a previous Vitalium Cup) | 20 patients – MOM |
|                        |                                                     |             |                       |                                      | Stainless steel or Cobalt-chromium   |               |
| Carlsson et al 198017  | 134 joints (134 participants)                       | 61.0 (±8)   | 59%                   | Group I - retrospective sample of 134 patients with THR | 89 patients – stainless steel (Charnley) | 89 patients – MOP |
|                        | 112 joints (112 participants)                       | 65.0 (±9)   | 65%                   | Group II – prospective sample of 112 patients awaiting THR | 45 patients – CoCr                     |               |
|                        | (28 participants)                                   | 66.0 (±12)  | 57%                   | Group III – prospective sample of 28 patients awaiting operation | –                                   |               |
|                        |                                                     |             |                       |                                      | –                                     |               |
| Carlsson and Möller 198918 | 5 joints (18 participants)                         | NR          | NR                    | 5 patients with THR                  | 14 patients – CrNi                    |               |
|                        |                                                     |             |                       |                                      | 3 patients – CrCoNi                   |               |
|                        |                                                     |             |                       |                                      | 1 patient – CoNi                      |               |
| Christiansen et al 201919 | 6 joints (6 participants)                           | 60.8 (range NR) | 33%                   | 13 patients with other orthopaedic implants Aseptic loosening patients for revision THR | 3 patients – CoCrMo/ TiAlV            | 5 patients – MOP |
|                        |                                                     |             |                       |                                      | 2 patients – CoCrMo/ FeCrNiMn        | 1 patient – MOM |
|                        |                                                     |             |                       |                                      | 1 patient – CoCrMo                    |               |
|                        |                                                     |             |                       |                                      | 2 patients – CoCrMo/ TiAlVa           | 5 patients – MOP |
|                        |                                                     |             |                       |                                      | 1 patient – TiAlVa/ Ceramic           | 1 patient – COP |
|                        |                                                     |             |                       |                                      | 3 patients – CoCrMo/ FeCrNiMn        |               |
|                        |                                                     |             |                       |                                      | All patients – Stanmore               |               |
|                        |                                                     |             |                       |                                      | All patients – MOP                    |               |
| Deutman et al 197720   | 8 joints (6 participants)                            | 62.0 (range NR) | 38%                   | Control group received primary THR   | NR                                   | NR            |
|                        | (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         |               |
|                        |                                                     |             |                       |                                      | 6 patients with stable THR contralaterally |               |
|                        |                                                     |             |                       |                                      | 66 patients from the previous study who did not have pre-operative sensitivity and underwent THR |               |
|                        |                                                     |             |                       |                                      | 15 patients – McKee-Farrar            | 15 patients – MOP |
|                        |                                                     |             |                       |                                      | 1 patient – Muller                    | 1 patient – MOP |
|                        |                                                     |             |                       |                                      | 6 patients – McKee-Farrar             | 6 patients – MOM |
|                        |                                                     |             |                       |                                      | All patients –                      |               |
|                        |                                                     |             |                       |                                      | Stanmore                              |               |
|                        |                                                     |             |                       |                                      | All patients – MOP                    |               |
| Elves et al 197521     | 61 joints (50 participants)                          | NR          | NR                    | 40 participants previous THR         | 36 patients – Stanmore                | 36 patients – MOM |
|                        |                                                     |             |                       |                                      | 4 patients – special femoral prosthesis |               |
|                        |                                                     |             |                       |                                      | 10 participants with various orthopaedic implants investigated for failure | 5 patients – McKee-Farrar (MOM)      | 5 patients – MOM |
|                        |                                                     |             |                       |                                      | 5 patients – McKee-Farrar             |               |
|                        |                                                     |             |                       |                                      | 5 patients – hip, knee, elbow prostheses |               |
|                        |                                                     |             |                       |                                      | 10 patients – CoCrMo                   |               |
| Frigerio et al 201122  | 48 joints (100 participants)                         | 68.0 (range 51–84) | 73%                   | 48 patients awaiting THR             | 24 patients – CoCrMo/TiAlVa           | 22 patients – COP |
|                        |                                                     |             |                       |                                      | 14 patients – TiAlVa                  | 12 patients – MOM |
|                        |                                                     |             |                       |                                      | 10 patients – CoCrMo                   | 7 patients – MOP |
|                        |                                                     |             |                       |                                      |                                   | 7 patients – COC |

(continued)
| Study                          | Number of hip replacements (number of participants) | Average age | Proportion of females | Population Type of implant | Bearing                  |
|-------------------------------|---------------------------------------------------|-------------|-----------------------|---------------------------|--------------------------|
| Granchi et al 2005<sup>23</sup> | 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  | –                        |
|                               | 104 joints (104 participants)                      | 64.7 (range 32–83) | 75%                   | Patients with loosening of THR | –                        |
| Guenther et al 2016<sup>24</sup> | (34914 participants)                               | NR          | NR                    | Historic database patients with primary and revision hip and knee arthroplasty THR revision for likely allergic reaction | NR                       |
|                               | 3 joints (17 participants)                         | 58.2 (±9.8) | 100%                  | 1 patient – Allofit (Zimmer) pure titanium | NR                       |
| Gustafson et al 2014<sup>25</sup> | 54 joints (54 participants)                        | 64.0 (range 56–70) | 64%                   | 44 patients with THR followed up | NR                       |
| Hallab et al 2013<sup>26</sup> | 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 3: (n = 20) controls with no implant | Group 2 (n = 17) with THR | –                        |
| Hjorth et al 2015<sup>27</sup> | 49 joints (41 participants)                        | 61.7 (range NR) | 72%                   | 39 patients awaiting THR | –                        |
| Kreččis et al 2012<sup>28</sup> | (60 participants)                                  | NR          | 75%                   | 21 patients awaiting THR Patients post TJR | NR                       |
| Lodi et al 1995<sup>29</sup>  | 66 joints (66 participants)                        | 65.9 (range 37–88) | 80%                   | Patients with THR (13 cases with known aseptic mobilization) | NR                       |
|                               | (41 participants)                                  | 61.4 (range 32–82) | 55%                   | Control group – 41 patients awaiting THR | –                        |
| Milavec-Puretić et al 1998<sup>30</sup> | 40 joints (40 participants)                        | NR          | 75%                   | 40 patients undergoing revision THR | –                        |
|                               |                                                   | 69.5 (range NR) | 89%                   | 66 patients awaiting THR and followed up 6 to 12 months after | –                        |
| Nater et al 1976<sup>31</sup>  | 66 joints (66 participants)                        | 69.5 (range NR) | 89%                   | All patients – Stanmore | MOP                      |
| Pazzaglia et al 1983<sup>32</sup> | 20 joints (20 participants)                        | 68.6 (range 60–82) | NR                    | All patients – Charnley implants | –                        |
| Rooker et al 1980<sup>33</sup>  | 67 joints (69 participants)                        | NR          | 52%                   | Control group – 20 patients without implant | –                        |
| Shanmugham et al 2020<sup>34</sup> | (54 participants)                                 | NR          | NR                    | 54 patients followed up after 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 |
|------------------------------------|----------------------------------------------------|-------------|-----------------------|------------------------------------------------------|-----------------|---------|
| Thomas et al 2013^15               | (30 participants)                                  | 55.0 (±13.7) | 47%                   | 30 participants (out of 54) post hip/knee or shoulder replacement | NR              | NR      |
|                                    | (68 participants)                                  | Patients with eczema, but no CMI: 52.4 (range 18–75) | 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      |
|                                    | 13 joints (200 participants)                       | 64.4 (range 37–84) | 65%                   | 47 patients with symptom-free TKR                     | CoCrMo          | –       |
| Thomas et al 2015^16               | 61 joints (250 participants)                       | 64.8 (range 37–84) | 66%                   | 13 patients with symptoms/complications of THR        | CoCrMo          | NR      |
|                                    | 13 joints (200 participants)                       | 64.4 (range 37–84) | 66%                   | 187 patients with symptoms/complications of TKR       | CoCrMo          | –       |
| Thomas et al 2009^17               | 16 joints (16 participants)                        | Average age NR (range 52–83) | 50%                   | Patients awaiting THR revision due to pain, osteolysis, dislocation, loosening | CoCrMo | NR      |
|                                    | 16 joints (16 participants)                        | NR           | 50%                   | 189 patients with TKR                                 | CoCrMo          | MOM implants |
| Thyssen et al 2009^18              | 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 |
|                                    | 95 joints (85 participants)                        | 71.0 (range 26–90) | 88%                   | 712 control patients from patch database               | –               | MOP bearing in all participants |
|                                    | 120 joints (94 participants)                       | 48.3 (range 22–76) | 48%                   | Patients awaiting THR and followed up post operation  | 78 patients – Stanmore allulium 9 patients – Stanmore titanium 2 patients – Monk 3 patients – Freeman double cup 1 patient – Freeman cup-neck 2 patients – Waldemar Link 46 patients – MOP, 13 patients – COP, 3 patients – MOP, 3 patients – NR | 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. 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. Four studies concluded that they did not support a possible relationship between metal hypersensitivity and prosthesis loosening,^31,34,39,40
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 5\%, potassium dichromate 0.5\%, cobalt chloride 1\%, barium sulphate 2\%, monomer methyl methacrylate 10\%                              |
| Carlson et al\(^{17}\)  | Nickel sulphate 5\%, potassium dichromate 0.5\%, cobalt chloride 1%                                                                                   |
| Carlson 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.%), aluminum chloride (0.72, 0.36, 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 (2.4, 1.2, 0.6 wt.%), solution Ti (0.16, 0.08, 0.04 wt.%), titanium dioxide (0.24 wt.%), titanium oxide 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.%). |
| Deuteman 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%                                                                                   |
| Grachi et al\(^{23}\)   | 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\%          |
| Guenther et al\(^{24}\) | Nickel sulphate 5\%, potassium dichromate 0.5\%, cobalt chloride 1\%, aluminium chloride 1\%, chromium trichloride 2\%, ferric chloride 2\%, manganese chloride 2\%, molybdenum chloride 2.5\%, titanium dioxide 2\%, vanadium trichloride 2\% |
| Gustafson et al\(^{25}\) | Nickel sulphate 5\%, potassium dichromate 0.5\%, cobalt chloride 1\%, aluminium chloride 1\%, chromium trichloride 2\%, ferric chloride 2\%, manganese chloride 2\%, molybdenum chloride 2.5\%, 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 2.5\%, titanium dioxide 10\%, vanadium chloride 1\%, zirconium chloride 1\%          |
| Krečić 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\%          |
| Lodí et al\(^{29}\)     | Nickel sulphate 5\%, potassium dichromate 0.5\%, cobalt chloride 1\%, aluminium chloride 1\%, chronic chloride 2\%, dimethyl phthalate 5\%, epoxy resin 1\%, ethylene glycol 3\%, ferric chloride 2\%, methyl methacrylate 5\%, molybdenum chloride 2\%, molybdenum chloride 5\%, manganese chloride 1\%, manganese chloride 2\%, manganese 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\%, manganese chloride 2\%                                                              |
| Roeker et al\(^{33}\)   | Nickel sulphate 2.5\%, potassium dichromate 0.5\%, cobalt chloride 1\%, benzoyl peroxidase 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                                                                           |
| Thyssen et al\(^{37}\)  | Nickel sulphate 5\%, potassium dichromate 0.5\%, cobalt chloride 1\%                                                                                   |
| Waterman and Schrik\(^{19}\) | 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\(^{38}\)     | Nickel, cobalt, 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\(^{16,20,22–25,28,31,34–36}\) of which one of 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 al15   | 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 al16    | 20 patients                 | NR when performed       | Participants with THR with sterile loosening (MOM bearing) (n = 20) | 0 | 0.0  |
| Carlsson et al17 | 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  |
| Christiansen et al19 | 28 patients             | NR when performed       | Control group (no implant) | 4 | 14.3 |
|                  |                             |                         | Participants with THR and aseptic loosing | 0 | 0.0  |
| Deutman et al20  | 212 patients                | Pre-operatively | Before THR | 11 | 5.2  |
|                  | 66 patients                 | Post-operatively (after 6 months) | After THR | 3* | 4.5  |
| Elves et al21    | 50 patients                 | Post-operatively (between 1–10 years) | Participants with THR (n = 45) and any other orthopaedic implant | 9 | 18.0 |
| Frigerio et al22 | 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 al23  | 104 patients                | Post-operatively (after 1 year) | Before operation | NR | NR   |
|                  |                             |                         | Participants with THR (stable): | NR |   |
| Gustafson et al25| 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 al26   | 16 patients                 | Post-operatively (after 4 years) | MOM resurfacing implant group | 1 | 6.3  |
| Hjorth et al27   | 40 patients                 | Post-operatively (after 5–7 years) | Patients with THR (MOM bearing) | 2 | 5.0  |
| Krečisz et al28  | 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 al29     | 66 patients                 | Post-operatively (after 3–18 years) | Participants with THR | 1 | 1.5  |
|                  | 41 patients                 | –                       | Control group | 0 | 0.0  |
|                  |                             |                         | Awaiting revision THR | 5 | 12.5 |
| Miliavec-Puretić et al10 | 40 patients             | Post-operatively (after 7.6 years) | Participants with THR (MOP bearing) | 0 | 0.0  |
| Nater et al31    | 66 patients                 | Pre-operatively | Before THR | 0 | 0.0  |
|                  | 66 patients                 | Post-operatively (after 6–12 months) | After THR | 3* | 4.5  |
| Pazzaglia et al32 | 16 patients               | Post-operatively (after 10–13 years) | Participants with THR (MOP bearing) | 0 | 0.0  |
| Rooker and Wilkinson33 | 20 patients             | –                       | Control group | NR | NR   |
|                  | 69 patients                 | Pre-operatively | Before THR | 3 | 4.3  |
|                  |                             |                         | After THR (n = 54) | 1* | 1.9  |
| Shannamugham et al34     | 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)
of which suggested that testing should be obligatory. Three studies recommended considering the clinical relevance of patch tests and only to perform this investigation when there was a known history of hypersensitivity reactions.

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

Ten of the studies did not comment on the usefulness of patch testing in identifying nickel hypersensitivities (Table 6).

### 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. Five studies reported increased nickel sensitivity post-operatively and in three of those none of the patients experienced any complications of THR. Krczisz et al reported that three patients developed a positive reaction to nickel post-operatively and experienced periodical skin lesions, pain, swelling and erythema 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.

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. Several studies recommended further studies on a larger scale to establish the relationship between sensitization and THR, between increased metal hypersensitivity and THR failure and between post-surgical pain and metal hypersensitivity.
required. 

ber recommended that patch testing was not routinely recommended, but a similar number suggested that patch testing should not be mandatory. 28 But a similar number reported nickel hypersensitivity prevalence ranging from 0.0% to 25.0%, whereas in one study patients undergoing revision THR had known nickel hypersensitivity and the prevalence was 0.0% to 25.0%. 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

**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 al16                     | Patch testing a valuable diagnostic tool                           |
| Cranchi et al23                   |                                                                  |
| Thomas et al35                    |                                                                  |
| Thomas et al36                    |                                                                  |
| Zeng et al40                      |                                                                  |
| Deutman et al20                   | Recommend routine patch testing                                  |
| Frigerio et al22                  |                                                                  |
| Krečíz et al28                    |                                                                  |
| Nater et al31                     |                                                                  |
| Gustafson et al25                 | Consider clinical relevance and perform patch testing only in patients with a history of allergic reactions |
| Shannughum et al34                |                                                                  |
| Carlsson et al17                  | Did not recommend routine patch testing                          |
| Rooker et al33                    |                                                                  |
| Waterman et al19                  |                                                                  |
| Hallab et al26                    | Poor diagnostic tool                                              |
| Benson et al13                    | Did not comment on the utility of patch testing                   |
| Carlsson and Møller18             |                                                                  |
| Christiansen et al19              |                                                                  |
| Elves et al21                     |                                                                  |
| Hjorth et al27                    |                                                                  |
| Lodi et al29                      |                                                                  |
| Milavec-Puretić et al30           |                                                                  |
| Pazzaglia et al12                 |                                                                  |
| Thomas et al37                    |                                                                  |
| Thyssen et al38                   |                                                                  |

Seven of the studies did not support a link between nickel hypersensitivity and THR complications16,18,19,29,30,33,38 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 hypersensitivity16,23,35,36,40 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, 20,22,24,28,31,34,39 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

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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. 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 clearly reported the details of the implant used as well as the bearing or a breakdown of number of patients. Three of the studies 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. 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. Although they raised concerns about the metallosis that could occur, it was unclear what effect this had on the eventual outcome of the THR.

**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 and shoulder arthroplasties. However, the results of the patch testing of those patients were not stratified by the operation undergone, but only as a cohort. Eleven of the studies were published in the last 10 years, but the review also included studies dating back to 1975, with 12 of the papers being published in 1997 or earlier. 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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All authors declare no conflicts of interest relevant to this work.

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