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Nickel-related hypersensitivity reactions following endovascular interventions: A review of current evidence

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Abstract

Introduction: Nickel is a principal alloying agent in the production of vascular endoprostheses, despite persisting as the most habitually identified allergen. Variable nickel-related hypersensitivity manifestations following endovascular intervention were reported, challenging established paradigms in treatment and accuracy of prognostic assessments. The objective of this review is to critically evaluate current metrics to maximise patient-related outcomes.

Methods: A literature review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 statement. Patients indicative of nickel hypersensitivity reaction following endovascular intervention were discerned. A positive reaction was defined by patch testing, histological analysis, or anamnesis indicative of nickel hypersensitivity. Morphology of implicating prostheses, adverse events and postoperative complications, clinical course, diagnostic and therapeutic strategies alongside patient prognosis were recorded.

Results: Nickel-related hypersensitivity reactions following endovascular repair were identified in 36 patients with a median age of 44.5 years. 20 patients received nitinol-containing intervention. 28 (77.8%) patients are female. Multi-organ adverse reactions occurred in 21 (58.3%) patients with variable latency. 14 (38.9%) patients were presented with neurological adverse reactions manifesting mainly as unilateral hemiparesis. Dermatological reactions implicated 16 (44.4%) patients. Miscellaneous manifestations include suicidal ideation. 13 (36.1%) patients displayed previous metal intolerance and 32 (88.9%) patients had positive patch testing for nickel. Histological analysis of lesions and prostheses indicated lymphocytic infiltration. 5 (13.9%) patients experienced device-specific reactions as in-stent restenosis or auxiliary distal vessel stenosis. 11 (30.1%) patients received solely medical therapy and 5 (13.9%) patients received solely surgical therapy. 19 (52.7%) patients underwent both medical (oral corticosteroid) and surgical therapy (device retrieval). 26 (77.1%) patients achieved symptomatic cessation, 6 (16.7%) patients exhibited symptomatic persistence and 0 patients died.

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Conclusion: Prophylactic pre-assessment for a history of metal allergy and consideration of prostheses alternatives is recommended to minimise reaction risk and severity. Despite nickel's predominant usage, information paucity urges additional studies to emphasise its implications and maximise patient outcomes.

Keywords
Adverse events, complications, endovascular, nickel allergy

Background

Overview

Nickel is the most identified allergen following patch-testing, estimated to implicate 17% of females and 3% of males.[1] Nickel-related hypersensitivity reactions mainly present as contact dermatitis[2] but may advance to systemic multi-organ reactions, hypothesised to arise from a Type IV delayed hypersensitivity reaction.[3] However, nickel-based alloys including nitinol remain a widely used constituent of endovascular prostheses.[4]

Possessing shape-memory properties places nitinol as a vascular conduit for the deployment of self-expanding stents and baskets.[5] Initial developments in percutaneous coronary interventions relied solely on plain old balloon angioplasty (POBA) involving mechanical compression of atheromatous plaque. Currently, the practice of angioplasty with the insertion of a metal stent is preferred to optimise luminal diameter, whilst the alloy's resistance to corrosion makes it tolerant to physiological fluids.[6] Novel nitinol-based flow-diverting stents are also used to restore luminal blood flow in complex intracranial aneurysms.[7]

Nickel-based vascular occlusive devices are favoured in the management of various venous pathologies due to their elastic properties.[8] For example, nickel-based vascular coils are used to manage thrombotic and non-thrombotic venous obstruction such as pelvic congestion syndrome. Self-expanding nitinol stents are also used to manage nutcracker syndrome secondary to meso-aortic compression.[9] Endovascular stenting was noted of comparable efficacy to open surgery, whilst conferring reduced morbidity.[10]

Rationale

Hypersensitivity reactions following nickel-related endovascular intervention have been noted in the literature, ranging from dyspnoea to cutaneous pruritus.[11,12] Predicaments with relation to patient-centred treatment manifest from impairment of prostheses efficacy following a nickel-related hypersensitivity complication.[13] Hypersensitivity to eluted nickel ions was reported to induce in-stent stenosis upon coronary stenting, hypothesised by accelerating neointimal hyperplasia.[14] Diminished stent patency may demand secondary stent revision with the aim of symptomatic cessation, which may include autologous grafting or stent removal.[15] Such a solution may not always be facile, especially when tending cerebrovascular pathologies, where surgical interventions possess supplementary risks. Revision surgeries are additionally challenging, time exhaustive and costly to perform. Subsequently, the spectrum of clinical manifestations among patients is variable and challenging to prognosticate.[16]

The review explored case reports and case series concerning nickel-related adverse events and post-operative complications following endovascular repair. Despite the prevalence of

nickel allergy, there is a paucity of information paving importance in endovascular interventions. This review primarily aims to emphasise its potential implications, enabling clinicians to maximise patient-related outcomes when faced with the phenomenon.

Review objectives

The objectives of the review are listed below:

1. Understand the pathogenesis of variable localised and systemic hypersensitivity reactions following nickel-containing endovascular intervention
2. Identify correlations between the morphology of nickel-containing endovascular prostheses and its competence in predisposing an allergic reaction
3. Outline therapeutic and prophylactic mechanisms to improve patient outcomes following an adverse event concerning nickel-related endovascular interventions
4. Propose guidance to minimise adverse events following endovascular interventions and therefore improve patient care

Methods

Literature search strategies

A review of current evidence was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 statement. Electronic databases: PubMed, Google Scholar, Medline (OVIDSP) were accessed to perform a literature search, restricted to English language literature until February 2022.

The following search terms were employed to identify relevant literature in electronic databases: 'nickel allergy', 'endovascular repair', 'nickel', 'stent', 'hypersensitivity reaction' amongst others, as displayed in the supplementary document.

Study selection

Assessment for eligibility of literature was made following pre-determined inclusion and exclusion criteria. Eligibility of study was determined via a rigorous, 3-step screening process: initially beginning with a superficial reading of titles to sift irrelevant articles. This is followed by an assessment of the eligibility of abstracts and comprehension of the article's full text. This ensured the inclusion and exclusion criteria are reliable and reproducible.

Inclusion and exclusion parameters. Literature is suitable for the systematic review if they possessed the following *inclusive criteria* enlisted below:

1. Patient had an endovascular procedure with exposure to nickel
2. Patient experienced ANY adverse events/post-operative complications related to nickel allergy, as confirmed by a patch test and/or post-operative histological analysis following implant-retrieval/ biopsy of rash
3. Case studies and case reports written in the English language and published in databases

4. Relevant literature published from inception until February 2022

There were no parameters pre-specified for the age of the patient population.

The exclusion criteria is:

5. Patient experiencing adverse reactions developed from an allergen that is not nickel

In cases where the literature did not wholly fit with the pre-specified inclusion and exclusion criterias, for example: literature that described adverse events concerning nickel and other metal allergens, they are included. However, data was extracted to obtain information relevant to the review's outcome variables.

Data collection

Data extraction was performed from individual studies between the authors with reference to primary outcome variables of interest, as shown below:

1. Morphology of nickel-containing endovascular prostheses
2. Pathogenesis of adverse events upon administration of nickel-containing endovascular intervention
3. Clinical features upon administration of nickel-containing endovascular prostheses
4. Diagnostic interventions are useful in modelling nickel hypersensitivity reaction
5. Therapeutic interventions used in resolving adverse events upon nickel-related endovascular intervention
6. Patient prognosis upon administration of therapeutic interventions

The mentioned outcome variables were extracted from suitable literature. Information pertaining to the morphology of vascular endoprostheses was extracted from secondary resources to evaluate the material specifications of the implant. Implant competency was cross-checked via the Medicines and Healthcare products Regulatory Agency (MHRA).

Results

Eligible literature

In accordance with the PRISMA, a flow chart that summarised literature selection is depicted in Figure 1.

Adverse events and postoperative complications relating to nickel usage in endovascular interventions

The following outcome variables were extracted from 36 eligible pieces of literature and are summarised in Supplemental Table 1. The patient population was comprised of 36 patients with a median age of 44.5 years. The age range of identified patients is 68 years with the youngest patient being an 11 years old male[17] and the oldest patient a

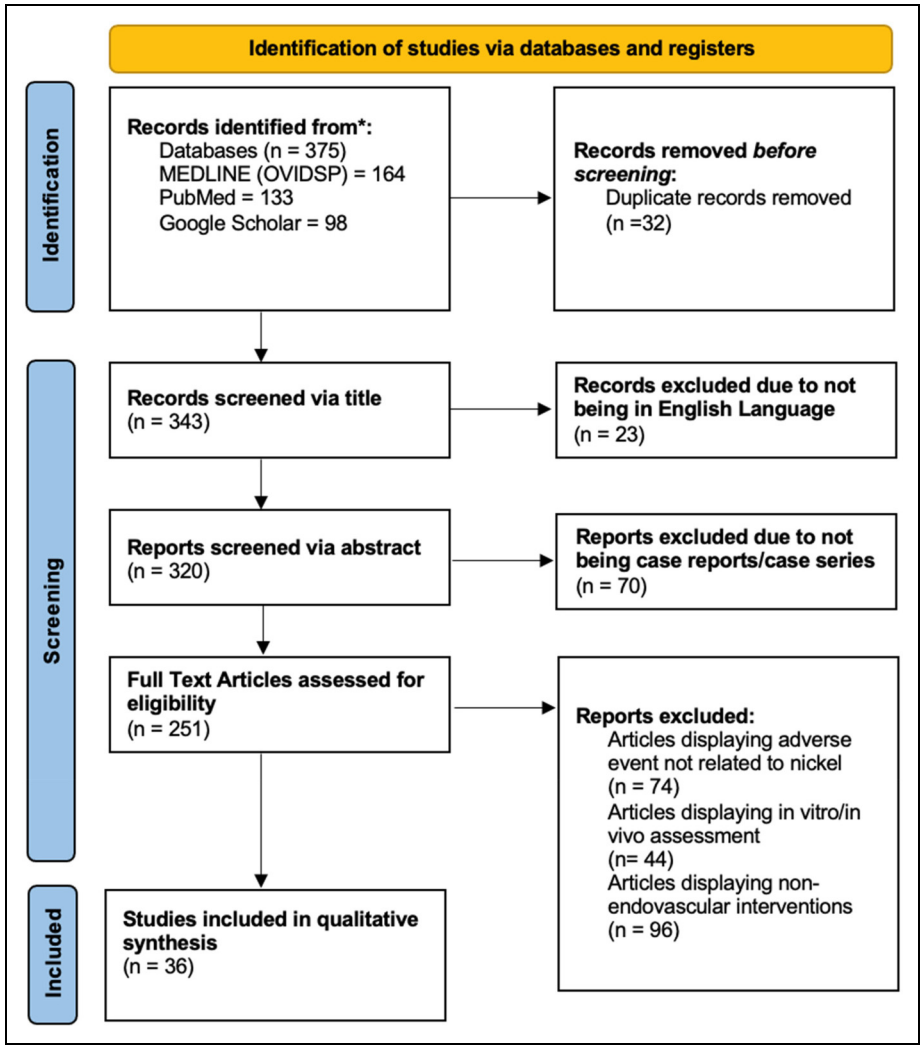

Figure 1. Flow chart summarising processes for study selection.

79 years old female.[18] There is a prevalence disparity amongst patient sex distribution, with a higher frequency reported amongst females ($n = 28$) as opposed to males ($n = 8$), with females representing 77.8% of the patient population. Following analysis, 3 papers reported their patient to be of Caucasian descent.[19–21]

Systemic manifestations

Dermatological manifestations. 16 patients reported cutaneous-related symptoms with 8 patients displaying exclusively cutaneous symptoms.[18,22–28] Cutaneous symptoms

displayed variable onset and symptoms emerged as early as 1 day[29] and latest by 12 months.[30] The Amplatzer Septal Occluder device vascular endoprosthesis implicated dermatological reactions in 9 patients, the most prevalent when considering the range of vascular endoprosthesis which presented dermatological-related adverse effects in the population.[23,28,31–35] All patients demonstrated positive patch-testing to nickel.

Predominantly, dermatological-related hypersensitivity reactions had manifested as cutaneous pruritus with eczematous and erythematous lesions. Localised dermatological lesions were observed in 1 case report where Tonetti et al. described the arousal of erythematous pruritus. However, this was observed following the appendage of an Endovascular Device or 'PED' as opposed to its administration. The lesion was localised to the site of fixation and occurred pre-operatively following a prophylactic patient assessment to predict risks of attaining a nickel-related adverse reaction.[36] Contrastingly, vesicular endogenous eczema was observed following the administration of a nickel-containing pacemaker.[24]

Dermatological reactions predominantly manifested in areas of intervention and a generalised presentation thereafter, likely due to the circulation of disseminated nickel ions. Giménez-Arnau et al.[18] described a patient with Vanguard vascular endoprosthesis who developed a cutaneous eruption. The rash initially presented in the lower limbs but disseminated into the abdomen, arms and back. Jetty et al.[37] reported a patient who presented with pruritic and eczematous dermatitis following implantation of nitinol stent in the right superficial femoral artery. Symptoms initially presented in the right leg, with a cutaneous biopsy demonstrating perivascular lymphocyte cuffing indicative of a hypersensitivity reaction.

Neurological or neurovascular manifestations. Neurological manifestations were present in 14 patients. 13 patients demonstrated positive patch-testing to nickel and 1 patient demonstrated a positive history of nickel-plated jewellery. This represented 38.9% of the total patient population.[19,21,30,31,33–35,38–41] Six of which underwent treatment for an unruptured intracranial aneurysm by clips, coiling or stents.[19,30,31,39–41] Neurological symptoms had emerged at variable onset amongst the patient population. Clinical presentation indicative of neurological manifestations included abnormal neurological reflexes, ranging from unilateral hand weakness to sensory disturbances. Typically, neurological deficits like reflex impairment presented unilaterally amongst patients, but occasionally advanced to bilateral presentation. Deficits had collectively presented alongside speech difficulties[19] or difficulties in undertaking movement.[42] Status epilepticus and migraines, implicated 2 patients[19,42] and 4 patients respectively of the sub-group of neurological adverse reactions.[21,33,35,38] In 2 patients, the migraine and headache collectively presented with aura.[35,43]

Radiological changes often accompany the neurological complaint, which includes multiregional lesions of variable intensity and secondary presentation of subcortical cerebral oedema.[20] MRI identifiable lesions were mainly localised to regions where intervention was administered, suggesting a spatial relationship between offending implant and local manifestations. Lobotesis et al.[39] described a right terminal internal carotid artery aneurysm treated with coils, complicated with lesions specific to the middle and anterior cerebral arteries.[30]

Neurovascular ischaemic events secondary to associated swelling were occasionally observed. Ringer et al. reported a patient with frontal lobe infarction after the placement

of a Yasargil aneurysm clip.[40] Schmidlin et al.[19] reported a delayed infarction of the left frontal lobe following administration of a nickel-containing clip. In such studies, histopathological assessment displayed peri-vascular lymphocyte infiltra, with such pronounced inflammatory response highly indicative of hypersensitivity reaction. Alternatively, patients may present with a delayed non-ischemic cerebral enhancing lesion, as described by Shotar et al.[30] Worth noting that however, some neurovascular conditions are better treated with open surgical procedure rather than using endovascular approaches, for example Moyamoya disease.[71]

Respiratory manifestations. Adverse effects on the respiratory system were minor and seen only in 7 patients, representing 19.4% of the patient population.[20,33,34,37,44,45] Clinical presentation was solely dyspnoea, with all but 2 patients having exhibited symptoms following intracardiac shunt closure. None of the patients demonstrated a prior history of respiratory conditions including asthma. Symptomatic onset ranged from 2 weeks to 3 months, with symptomatic worsening prior to treatment. Diagnosis of hypersensitivity to the offending device was made following positive patch testing to either nickel or offending device and/or histopathologic assessment indicative of an inflammatory hypersensitivity reaction.

Cardiovascular manifestations. Adverse effects concerning the cardiovascular system were observed in 6 patients from the patient population. Cardiovascular manifestations ranged from mild heart palpitations to pericardial tamponade.[19,20,30,39,41,45]

In extracted studies, cardiovascular manifestations were accompanied by ECG changes. Variability in ECG changes had accompanied spatial location of the implanted device. This was noted when Jain et al. reported a patient who displayed abnormal QRS complex voltage following septal defect closure with an Amplatzer device. Clinical presentation was indicative of pericardial effusion following hypersensitivity pericarditis, which manifested into pericardial tamponade. Supplementary diagnosis displayed right ventricle diastolic collapse and positive patch test to nickel, indicative of a probable restrictive cardiomyopathy secondary to nickel-hypersensitivity.[20]

Patients also presented with atypical chest sensations like pain and pressure. Following the application of an Amplatzer atrial Septal Occluder**,** Rabkin et al. described a 52 years old woman having 'burning' chest pain.[32] Multi-modal medical management was ineffective, with symptomatic cessation only achieved upon explantation of nickel-containing endograft. Furthermore, histopathological analysis demonstrates chronic inflammation and eosinophilia surrounding the endograft. Alternatively, Lai et al. described a patient who experienced cardiovascular adverse effects following implantation of a patent foramen Occluder device. Here the patient exhibited a pressure-like sensation in the substernal region. The patient also manifested pericarditis alongside pericardial effusion. Atypical heart rhythm was also discerned, recorded as atrial fibrillation.[43]

Multi-organ manifestations and gastrointestinal manifestations. Multi-organ manifestations were prevalent and observed in 22 patients, which represented 61.1% of the patient population. This ranges from musculoskeletal to gastrointestinal and depicts variable symptomatic onset. An atypical multi-organ manifestation included a severe, unilateral scapular discomfort of the left side, worsening on motion, such as during inhalation.

This accrued several days upon application of a patent foramen ovale Occluder device and concurrently involved ipsilateral 'tingling' sensations on the patient's hand.[43] Additionally, Jain et al. alluded to the use of life support in a patient with multi-organ dysfunction following implantation of an Amplatzer Septal Occluder device.[20] In such studies, nickel hypersensitivity was determined following a positive prior history and marked symptomatic resolution by intravenous steroids.

Gastrointestinal manifestations mainly manifest as non-specific oesophageal disorders. Park et al. described dysphagia complicated with facial and abducens nerve palsy following treatment of a wide neck aneurysm. Alternatively, in a case presented by Ross et al., the patient presented with abdominal pain upon administration of an aneurysm clip. The patient was diagnosed with acalculous cholecystitis and required supplementary cholecystectomy. Patch-testing to nickel was positive, with histopathological analysis of the clip was evidence of a delayed Type IV hypersensitivity reaction.[46]

Other manifestations. Psychological manifestations ranged from minor stress to suicidal ideation. Elevated body temperatures were also reported.[19,40,47] Non-specific symptoms, such as night sweats were reported by Fahrni et al., in a patient who underwent percutaneous coil embolisation for pelvic congestion syndrome.[48] Systemic symptoms manifested alongside pelvic pain and resolved following coil removal. Such presentation was hypothesised to occur secondary to hypersensitivity with endograft material, termed as post-embolisation syndrome (PES).

Device-specific reactions. Device-specific reactions were observed in 5 patients, demarcating 13.9% of the patient population.[26,30,40,41,48] Predominantly, device-specific manifestations range from in-stent restenosis (ISR) to total occlusion of the implanted stent. Eosinophilic infiltration and perivascular lymphocytic cuffing were noted upon histopathological assessment of invidious stents. Total occlusion was mentioned by D'Arrigo et al. in femoral artery stenting.[49] Konishi et al.[50] reported thrombus formation and concurrent in-stent stenosis of Driver^{TM} nickel- stent which led to ST-elevation myocardial infarction. Eosinophilic infiltra extracted from a thrombus was also demonstrated in post-mortem individuals who exhibited ST changes following endograft hypersensitivity. Such combined with positive patch testing to nickel indicated a high likelihood of nickel hypersensitivity reaction.

Diagnosis of nickel-related hypersensitivity reaction

Diagnosis of nickel-related hypersensitivity reaction was made via assessment of patient history, patch testing with suspected reagent, a biopsy of cutaneous manifestation and biopsy of the extracted sample. A negative patient history of known metal allergy was present in 23 patients, 68.6% of the patient group.

The patient-reported experience was generalised. Indicators for a likelihood or definitive nickel allergy were confirmed via patch test screening. This was undertaken by 33 patients, with 1 patient unable to undertake the test following the severity of her reactions[20] and 3 patients with unspecified methods of confirmation.[40,42,51] However, 5 patients also displayed allergies to other metals, including cobalt, mercury, and palladium. Two patients depicted positive cutaneous manifestations following patch testing of the soon-implanted metallic device.[36,52]

Findings of biopsy from cutaneous lesions include intercellular oedema of the epidermis with lymphocytic and eosinophilia infiltration, suggestive of a hypersensitivity reaction.

Immunohistochemistry found evidence of phagocytic macrophages and T-cell lymphocytes in the site of concern.[46] Intimal hyperplasia also suggested persistent inflammatory reaction.[22,49]

Therapeutic interventions for nickel-related adverse events

Medical treatment. Sole medical treatment was carried out in 11 patients. This represented 30.6% of the patient group. As described by Landwehr et al., one patient presented with Pompholyx 2 days after placement of a pacemaker. The patient had complete symptomatic cessation after a period of 2 months without treatment.[24]

The predominant agent used was oral corticosteroids. Additionally, oral antihistamines were used in 5 patients in conjunction with steroid therapy.[17,18,23,45,50] In 3 patients, anti-platelet medications were administered, with 2 patients administered clopidogrel following an adverse reaction for the treatment of congenital heart diseases.[34,35] Following the severity of the hypersensitivity reaction, Guerra et al. described one patient who was administered immunosuppressive therapy in the form of mycophenolic acid. The patient had undergone placement of a nitinol bare metal stent in the popliteal artery. The patient had to wear an occlusive suit for a period of 12 h with full body petroleum application.[22]

Jetty et al. highlighted the adjacent use of referral to an allergy specialist following corticosteroid therapy. The patient was advised by an expert in allergic dermatitis to minimise any potential occupational exposure as the patient was a machinist, with the aim of symptomatic management.[37]

An alternative intervention included a neuromodulation helmet for migraines, depicted by Fernandes et al. upon placement of a nitinol Septal Occluder Device.[38] Symptomatic improvements were variable amongst patients, ranging from 3 weeks to several years in other patients.[45]

Surgical and endovascular treatment. Sole surgical therapy was undertaken in 5 patients, representing 13.9% of the patient population.[33,44,48,51,52] Surgical therapy involved retrieval of the invidious device or graft replacement. Conversely, 15 patients underwent an initial course of conservative therapy followed by conclusive non-conservative treatment. This represented 41.7% of the whole patient population. Guerra et al. described the presentation of a pruritic rash with desquamation following implantation of a popliteal artery nitinol stent. Conservative treatment was ineffective. The patient subsequently underwent surgery for retrieval of the device.[22]

Fukahara et al. described the use of autologous grafting following the non-conservative removal of the PFO-Star device. The use of an autologous pericardial patch resulted in patient recovery. In another case, the invidious device was replaced with a material of different morphology.[52] Schmidlin et al. described removal of a nickel-containing aneurysm clip and replacement with a titanium clip for an intracranial aneurysm.[19]

Patient outcomes following nickel-related adverse events

Assessment of mortality and morbidity. Symptomatic cessation occurred in 27 patients, 6 patients reported symptomatic improvement with residual symptoms. Residual symptoms include intermittent recurrence of rash as described by Guerra *et al.*[18,22,39,42,43,46] 2 Patients reported radiological cessation, but 1 patient had merely improvement of radiological symptoms.[39] There was no reported death secondary to nickel-hypersensitivity reaction in the identified literature.

Significant morbidity was also observed. Symptomatic irresolution and worsening was observed in 1 patient as described by Schmidlin et al., which necessitated assisted ventilation.[19] Reduced quality of life was reported in 2 patients. Guerra et al. depicted the need for an occlusive suit, worn for a longer period of time following the severity of the cutaneous rash whilst taking immunosuppressants.[22] Fahrni et al. depicted a patient who acquired progressive pelvic pain after coil embolisation for pelvic congestion syndrome following which she became bedbound.[48]

Another significant morbidity presented was life-threatening allergic vasculitis upon a coil embolisation of an internal carotid artery aneurysm. Grande et al. described the clinical presentation to include seizures. Subsequent deterioration of her current health necessitated an induced coma. Her manifestation included encephalitis which contributed to abnormal neurological status, a significant morbidity.[40] Nevertheless, the patient had to be administered to a rehabilitation centre. Other significant morbidity included a refractory shock, observed in 1 patient as mentioned by Jain et al.[20] which progressed to life-threatening pericardial effusion and tamponade. The patient also presented with multi-organ dysfunction and required assisted ventilation alongside renal replacement therapy.

Discussion

Key literature findings

Despite the prevalence of nickel hypersensitivity in the population, this study only identified 35 patients, each demonstrating heterogeneity in symptomatic presentation. Adverse events may initially manifest as non-specific symptoms such as fever and lethargy, which is common following surgery. It is therefore difficult to prospectively discern such patients, leading to therapeutic delay and misdiagnoses in a possibly under-reported pathology.[53]

Variable onset and clinical presentation amongst patients are attributed to patient-specific factors including age, pre-existent comorbidities and previous nickel exposure.[54] Twin studies evaluating nickel contact dermatitis highlighted the significance of environmental factors and to a lesser extent, genetic predisposition.[55] Morphology of implanted devices is also noted as consequential, with various *in vivo* studies placing importance on the biological corrosion of stents as a source of nickel ion release, which exacerbates hypersensitivity.[56] An *in vivo* study by Elkiran et al.[57] evaluated serum nickel levels in paediatric patients following implantation of a nitinol Amplatzer Occluder device. The study noted a significant increase of serum nickel ion at 24 h which peaked at 3

months. This may explain the variable latency of reactions amongst the population which ranged from immediate to years.

Various studies were conducted to evaluate the efficacy of patch testing. Simonetti et al. conducted a comparative study where 2 patch tests for nickel allergy were placed on 30 patients' backs. Both tests contained 5% nickel sulphate prepared by different brands. 78% of the patient population demonstrated a positive reaction to both tests with only 11% showing a positive reaction to one patch test. This may be due to differing patch test formulations and dermatological reactivities, demonstrating the limitations of patch testing as a sole modality for pre-screening. Notably, patch test efficacy may also be diminished following risks of cross-reactivity if testing for more than one metal.[58]

Diagnostic intervention by patch testing of soon-implanted devices was also not indicative of developing a hypersensitivity reaction. Tonetti et al.[36] described the attachment of a Pipeline™ endovascular device to a patient's forearm which manifested cutaneous pruritus. However, the patient was asymptomatic following device implantation. Sensitising potential may be larger when placed epidemically due to epidemical absorption of nickel ions via direct device contact.[56]

Device-specific reactions, such as ISR described by Koster et al.,[59] may have been implicated following a hypersensitivity reaction to released metal ions in stainless steel stents. In a meta-analysis by Guéroult et al.,[60] patients exhibiting nickel-hypersensitivity demonstrated a statistically significant increased risk of ISR following coronary stenting. Alternatively, a study by Norgaz et al.[61] found no discernible relationship between nickel-allergy and ISR solely in patients with stainless steel stent. Conflicting findings in the literature emphasises the probable multi-modal pathogenesis underlying ISR. As current literature only evaluated its role in coronary stents, future large-scale studies are warranted.

With respect to device-specific reactions, the viability of the native vessel upon a nickel-induced hypersensitivity reaction poses a significant concern. ISR and thrombosis adversely implicates the efficacy of the implant, necessitating removal. In synthesised literature, ligated native vessels frequently demonstrate dense scar-like fibrinous tissue and thrombosis. This precludes future treatment options such as autologous reconstruction, which adversely implicates patient outcomes.[14]

Device alternatives should be considered to minimise plausible hypersensitivity reactions. *In vitro* studies conducted by Verma[62] contrasted the elution of nickel ions in various devices for atrial septal defects. This included a stainless-steel based sternal wire, the Amplatzer Septal Occluder device (St Jude Medical Inc, Minnesota, USA) and Gore Helex Septal Occluder (W.L Gore and Associates, Delaware, USA) and the new Gore Septal Occluder device (W.L Gore and Associates). The study found the Amplatzer Septal Occluder device eluted the highest amount of nickel in a period of 90 days. Notably, elevated nickel content may predispose a higher risk of developing hypersensitivity reactions.

Bioresorbable stents with steroid-incorporated vascular scaffolds have also been suggested as a novel alternative for symptomatic management, although information pertaining to its outcomes remains limited.[42] Novel embolic agents may be considered as alternatives to nickel-containing vascular occlusive devices in patients with nickel allergy. Gong et al.[63] highlighted the use of Glubran-2 cyanoacrylate adhesive to

achieve arterial embolisation in patients with acute renal haemorrhage. Rapid vascular occlusion is attributed to its prothrombotic characteristics, with technical efficacy achieved whilst preserving renal function in the study. However, more studies are warranted as its volatile cross-linkage may make it unsuitable in challenging vascular architecture. Therapeutic embolisation via embolic microsphere particulates has also been described in the literature. Embosphere microspheres' homogenous diameter prevents coalescence in catheters during deployment, compared to traditional particulates.[64] In a study by Kucukay et al.,[65] bronchial artery embolisation via embospheres was used to manage patients with haemoptysis. The study highlighted its safety and efficacy with favourable long-term outcomes, highlighting its efficacy *in lieu* of nickel-based Occluders.

Prior to nickel-related endovascular intervention, pre-operative history is recommended to evaluate the presence of probable or definitive nickel hypersensitivity in all patients. Details concerning past nickel-related hypersensitivity reactions and factors like frequency and severity of exposure should be considered to identify at-risk patients.[66] Due to the risk of cross-sensitivity with other metals, patch testing is recommended prior to surgery in patients with a prior history of nickel allergy. In a meta-analysis by Guéroult et al., positive patch-testing to nickel was associated with an increased risk of adverse events following nickel-related endovascular intervention. Referral to allergy specialists may also be conducted to evaluate suitability for device implantation following evaluation of hypersensitivity, in patients with suspected nickel allergy. The material composition of the prospective endograft must additionally be evaluated, alongside the risk-benefit ratio of proceeding with the intervention. Whenever possible, device alternatives made of differing materials and/or embolisation techniques must be considered.[60]

PES is a common complication following endovascular solid-organ embolisation.[67] Incidence of PES is reported as high as 20% in the literature and is characterised by pain, fever and leukocytosis following embolisation. PES is hypothesised to manifest following inflammation of vascular endothelium and/or material hypersensitivity of implanted endograft including nickel. Symptomatic resolution using NSAIDs and veno-active drugs have been reported following uterine artery embolisation, and clinicians should consider the application of such in suspicion of PES.[68,69]

Various studies have reported the utility of post-operative administration of corticosteroids and antihistamines for symptomatic management. Nevertheless, the utility of prophylactic corticosteroids and/or antihistamines to reduce the risk of a nickel-related hypersensitivity reaction remains up for debate. Limited consensus pertains to the route of administration, frequency and/or dosage for patients. Due to symptomatic heterogeneity, it remains unclear if symptomatic absence is attributed to drug efficacy or an inherent lack of reaction. Additionally, consideration of pre-existent comorbidities remains integral, due to the side effects of steroid administration.[70]

Limitations of the literature review

Reliance on patient-reported outcome variables subjects the review to recall bias. The role of patient-specific and device-specific factors may alter the patient's clinical status.

Various studies conducted collective patch testing with other metals, increasing the risk of cross-reactivity. As nickel-based alloys also include metals known to instigate hypersensitivity reactions, it is difficult to discern nickel as a definitive primary causative agent.[56] With just 36 case reports and studies, there is limited scope in analysis for the matter. Various studies also employed sole biopsy as their diagnostic tool which although indicates a hypersensitivity reaction, may not be one solely caused by nickel.

Conclusion

Prophylactic pre-assessment for previous history of nickel allergy is recommended, although may not be indicative of a definitive possible causation. Differing device morphology including nickel ion content may alter their effectiveness in eliciting adverse reactions. Due to variable patient factors, the clinical presentation is difficult to generalise. It remains challenging to conclude if nickel-based prostheses are safe or unsafe in patients with nickel allergy. Benefits outweigh the associated risk following a high percentage of symptomatic cessation in the patient group. Clinicians must evaluate possible alternatives to maximise patient outcomes. This may include autologous grafting and/or interventions without nickel.

An inceptive search yielded 345 papers, with 30 additional papers identified for literature screening following a screening of the articles' references. 343 papers were screened following the removal of duplicates. A total of 306 papers were excluded due to not meeting the inclusion criteria, which range from papers not being in English language or depicting adverse events not related to nickel following an endovascular intervention. A total of 36 papers were finalised and included in the qualitative synthesis.[17–52]

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Author Contribution

PZY conceived and supervised the project. VHT and PZY designed the study. VHT collected and analysed the data. VHT and PZY wrote the manuscripts.

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Supplemental material

Supplemental material for this article is available online.

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