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Clinical factors before or after device implantation in predicting metal hypersensitivity reactions: A retrospective study

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Abstract

Background: Metal hypersensitivity reactions (MHR) as a cause of implant-related complications are highly debated and recommendations regarding pre-procedural allergy evaluation vary dramatically.

Objective: To examine patients referred before or after device implantation and identify factors that could be useful to guide the value of patch testing.

Methods: Patients who underwent patch testing pre- or post-device implantation between July 2006 and September 2016 were analyzed retrospectively.

Results: A series of 127 patients underwent patch testing: pre-implantation (n = 40) and post-implantation (n = 87). In the pre-implant group, a history of metal allergy demonstrated high sensitivity (0.94; 95% CI: 0.83–1.00) and negative likelihood ratio (0.17; 95% CI: 0.02–1.29) for diagnosing MHR. No predictive value could be ascribed to any of the clinical symptoms (e.g. dermatitis, pain, swelling, implant failure, and/or other symptoms) for patients referred following orthopaedic and dental post device implantation. Eight patients in the orthopaedic group and six patients in dental group with relevant patch test reactions underwent implant revisions, and seven and five patients improved, respectively.

Conclusions: Pre-implant patch testing for selected individuals with a history of metal allergy can help guide implant choice. Post-implant patch testing may be helpful in some patients if other causes have been excluded, as patients with confirmed MHR benefited from revisions.

KEYWORDS

allergic contact dermatitis, metal hypersensitivity, patch testing, pre-implant testing, prostheses implant complications

1 | INTRODUCTION

Metal hypersensitivity reactions (MHR) to implanted devices are a growing concern. The significance and frequency of MHR are subject to debate and recommendations regarding pre-procedural metal hypersensitivity evaluation via patch testing differ. Amongst orthopaedic surgeons in the United Kingdom, MHR in the setting of orthopaedic implantation are considered inconsequential or non-existent.^{1,2}

German experts recommend the use of titanium implants in patients with concerns about metal reactions.³ In Sweden, “virtually no one is tested” before procedures,⁴ whereas the American Contact Dermatitis Society (ACDS) in the United States recommends metal patch testing for individuals with a history of metal reactions prior to implantation and for those with concern about metal allergy after the implant.^{5,6}

Few retrospective and prospective studies have been conducted on the association between implant complications and hypersensitivity.

TABLE 1 Characteristics of patients referred for patch testing (n = 127)

Characteristic	Patients n (%)	
	Pre-implant (n = 40)	Post-implant (n = 87)
Age (mean, range), y	48.7 (11–90)	58.3 (14–85)
Sex		
Female	32 (80)	62 (71.3)
Male	8 (20)	25 (28.7)
History of metal/jewellery allergy		
All implant types	32 (80)	32 (36.8)
Orthopaedic	16 (50)	17 (52.1)
Dental	6 (18.8)	12 (37.5)
Cardiovascular	7 (21.9)	1 (3.1)
Other	3 (9.4)	2 (6.3)
Type of implant		
Orthopaedic, all	21 (52.5)	49 (56.3)
TKA	12 (57.1)	27 (55.1)
Metal pins, rods, plates, screws	5 (23.8)	10 (20.4)
THA	2 (9.5)	5 (10.2)
Spinal implant	0 (0)	3 (6.1)
Spinal stimulator	0 (0)	2 (4.1)
Static knee implant	0 (0)	1 (2)
Shoulder arthroplasty	0 (0)	1 (2)
Nuss bar	2 (9.5)	0 (0)
Dental, all	8 (20)	28 (32.2)
Implant	3 (37.5)	18 (64.3)
Crowns	1 (12.5)	3 (10.7)
Temporomandibular joint implant	2 (25)	2 (7.1)
Orthodontics	2 (25)	2 (7.1)
Partial dentures	0 (0)	1 (3.6)
Partial bridge	0 (0)	1 (3.6)
Metal plates	0 (0)	1 (3.6)
Cardiovascular, all	7 (17.5)	4 (4.6)
ASD, PFO repair	7 (100)	0 (0)
Pacemaker	0 (0)	2 (50)
Stent	0 (0)	2 (50)
Other, all	4 (10)	6 (6.9)
Referring service		
Allergist	11 (27.5)	22 (25.3)
Dermatologist	2 (5)	21 (24.1)
Orthopaedic surgeon	11 (27.5)	19 (21.8)
Primary care physician	1 (2.5)	12 (13.8)
Dentist	1 (2.5)	7 (8)
Oral and maxillofacial surgeon	1 (2.5)	2 (2.3)
Self	4 (10)	2 (2.3)
General surgeon	1 (2.5)	1 (1.1)
Pain medicine	0 (0)	1 (1.1)
Paediatric surgeon	1 (2.5)	0 (0)
Interventional cardiologist	7 (17.5)	0 (0)

Abbreviations: ASD, atrial septal defect; PFO, patent foramen ovale; THA, total hip arthroplasty; TKA, total knee arthroplasty; y, years. Data are presented as n (%).

Given that allergic reactions occur infrequently following implantation, clinical data on MHR are valuable.³ In this study, we examined 127 patients referred for MHR evaluation prior to or following device implantation. Furthermore, we clinically characterized these patients and identified factors that could be useful to guide patch testing.

2 | METHODS

2.1 | Patients

Patients who underwent patch testing at the Massachusetts General Hospital Contact Dermatitis Clinic from July 2006 to September 2016 for suspected allergic contact dermatitis (ACD) in the context of an implanted device pre- and post-operatively, were identified retrospectively. Information regarding patch testing results and patients' age, sex, indications for patch testing, presenting symptoms, sites of dermatitis, type of implanted device, self-reported history to metal or jewellery allergy, were extracted from their electronic records. The type of implanted device was further divided into four groups: orthopaedic, cardiovascular, dental, and other devices (Table 1). For the pre-implant group, any changes to the metal or a component of the device implanted due to results of patch testing, as well as outcomes of the device implanted were recorded. For the post-implant group, symptoms were categorized as dermatitis, other skin eruptions, pain, swelling/inflammation, implant failure/loosening, and/or other symptoms. Patients could have more than one symptom. In addition, any implant revisions in the post-implant group, the reason for the revision, and outcomes were recorded. Patient records were cross-referenced with surgical and postoperative visit records when available. This study was approved by the Partners Healthcare Institutional Review Board.

2.2 | Patch testing

Patients were screened with the North American baseline series of 50 allergens (Chemotechnique Diagnostics, Vellinge, Sweden) and custom series (eg metal series, dental series, bone cement series) based on clinical history. Testing procedures and readings were conducted in accordance with international recommendations.⁷ Tests remained in place for 48 hours and sites were evaluated at day (D) 2 and D3 or D4. No late readings beyond D4 were performed. All interviews and interpretations of patch test reactions over the 10-year study period were performed by a single observer and senior author (PCS). Readings were classified according to ICDRG guidelines with '+' to '+++' reactions regarded as positive.

2.3 | Patch test interpretation

The relevance of positive patch test reactions (PPT) was defined as possible, probable, definite, past, or unknown. Possible relevance was assigned in situations where there was a positive reaction, but the

exact source was unknown or only suspected. Probable relevance was assigned to patients who had a positive reaction and there was an identifiable metal causing a clinical reaction. Definite relevance was assigned in cases where an allergen contained in the device alloy was tested positive and a reaction seen, or the offending device was removed with symptomatic clearance. Past relevance was used in situations where the patient had metal reactions in the past, but which were not contributing to current symptoms. Unknown relevance was assigned when physician and patient were unable to define a source of exposure to allergen. A positive patch test of possible, probable, and definite relevance was designated as a relevant PPT (RPPT).

2.4 | Statistical analysis

Statistical analyses were performed and descriptive frequencies calculated for categorical variables. Probabilistic measures, including specificity, sensitivity, likelihood ratios (LR), and their 95% confidence intervals (CIs), were used to assess the predictive values of various clinical findings in determining relevant MHR through patch testing using SAS version 9.4 (SAS Institute, Cary, North Carolina). A positive LR > 10 and negative LR < 0.1 provide strong evidence to rule in or rule out relevant metal hypersensitivity, whereas LR > 5 and LR < 0.2 provide good diagnostic evidence.⁸ Because of the limited number of cases in the post-implant cardiovascular and other devices groups, these latter measures were not applied for these groups.

3 | RESULTS

3.1 | Patient population

Over the 10-year study period, 127 patients were referred for evaluation of possible MHR in the context of an implanted device; 40 were referred pre-implantation (mean age 48.7 years, range 11–90 years) and 87 were referred post-implantation (mean age 58.3 years, range 14–85 years) (Table 1).

3.2 | Pre-implantation group results

Of the 40 patients referred for pre-implantation patch testing, 21 were evaluated prior to orthopaedic implants, eight were evaluated prior to dental implants, seven were evaluated prior to cardiovascular surgery for patent foramen ovale (PFO) or atrial septal defect (ASD) repair, and four were evaluated for other implanted devices such as copper intrauterine device, metal clips, or staples (Table 1). Patients in the pre-implant group were most often referred by an orthopaedic surgeon or allergist due to a history of metal or jewellery allergy. Of the 32 (80%) patients who had a self-reported history of metal or jewellery allergy, 17 patients (53.1%) had one or more relevant metal reactions. Eight patients who did not report a history of metal or jewellery allergy were referred because of physician or patient concerns.

TABLE 2 Patch test results of pre-implant evaluation

Allergen (metals)	PPT n (%)	RPPT n (%)
Any metal	25/40 (62.5)	18/40 (45)
Nickel sulfate 2.5/5.0 pet.	20/40 (50)	17/40 (42.5)
Cobalt chloride 1.0 pet.	9/36 (25)	6/36 (16.7)
Palladium chloride 2.0 pet.	16/33 (48.5)	2/33 (6.1)
Potassium dichromate 0.25 pet.	2/37 (5.4)	2/37 (5.4)
Vanadium 5.0 pet.	3/33 (9.1)	1/33 (3)
Gold sodium thiosulfate 0.5/2.0 pet.	12/32 (37.5)	0/32 (0)
Manganese chloride 2.0 pet.	2/33 (6.1)	0/33 (0)
Mercury ammonium chloride 1.0 pet.	2/33 (6.1)	0/33 (0)
Potassium dicyanoaurate 0.1 aq.	2/33 (6.1)	0/33 (0)
Stannous chloride 1.0 pet.	2/33 (6.1)	0/33 (0)
Mercury 0.5 pet.	2/34 (5.9)	0/34 (0)
Iridium chloride 10.0 aq.	1/33 (3)	0/33 (0)
Mercuric chloride 0.1 pet.	1/33 (3)	0/33 (0)
Zinc chloride 2.0 pet.	1/34 (2.9)	0/34 (0)

Abbreviations: aq, aqueous; PPT, positive patch test; pet, petrolatum; RPPT, relevant positive patch test.

Of these eight patients, only one patient had ≥ 1 RPPT. In the pre-implant group, 25 (62.5%) patients had ≥ 1 PPT to metals and 18 (45%) patients had reactions to metals that were proposed for their surgery. The top three relevant metals in the pre-implant group were nickel (42.5%), cobalt (16.7%), and palladium (6.1%) (Table 2).

3.3 | Pre-Implantation outcomes

Nine of the 18 patients with relevant MHR that were proposed for surgery had a documented change in implant choice or deferred surgical intervention. All patients with a change in implant choice did not report any complications or skin eruptions post-operatively (mean follow-up time 9.5 months, range 2–24 months). Two nickel allergic patients had the devices implanted as planned: one patient received a nitinol containing device for PFO repair and the other patient received an ASD occluder containing nitinol. Neither patient reported any complications at 12 months post-operative follow-up.

Of the 22 patients who did not test positive to components of their proposed device, seven patients proceeded with the device implanted as planned and none of these patients had any complications or skin eruptions post-operatively (mean follow-up time 7.4 months, range 1.5–12 months). Two patients did not proceed with surgery and 13 patients were lost to follow up.

3.4 | Post-Implantation group results

Of the 87 patients referred for post-implant testing, 49 received orthopaedic devices, 28 received dental devices, four received

cardiovascular devices, and six received other devices. The most common referrals for post-implant evaluation were from allergists and dermatologists (Table 1). Forty-five (51.7%) patients had ≥ 1 PPT to metals and 33 (37.9%) patients had ≥ 1 RPPT to metals that were a component of their implants. The top three relevant metals in the post-implant group were nickel (16.1%), cobalt (10.3%), and potassium dichromate (8%) (Table 3). A previous history of metal allergy or jewelry allergy was reported in 32 of 87 (36.8%) patients.

Of the 49 patients who were referred post-orthopaedic implants, dermatitis was the most common presenting symptom (20/49 patients [40.8%]) (Table 4). In 15 of the 20 patients with implants, dermatitis developed at sites overlying the implanted device or overlying the implanted device and distal sites; in four patients dermatitis developed at sites distal from the implanted device, and one patient developed generalized dermatitis. Patients who presented with dermatitis demonstrated a high prevalence of ≥ 1 RPPT to metals, in any distribution (35%) and over prosthesis (40%). Other skin findings (4/49 patients [8.2%]) included stasis dermatitis, prurigo nodularis, and urticaria. Non-cutaneous symptoms included pain (23/49 patients [46.9%]), swelling/inflammation (9/49 patients [18.4%]), joint loosening/implant failure (3/49 patients [6.1%]), and other symptoms (e.g. pruritus, metallic taste, poor wound healing, chronic effusion, osteolysis, nausea, and vomiting (10/49 patients [20.4%])).

There were 28 patients who were referred following dental implants. Dermatitis, oral ulcers, or oral lichen planus were the most common reasons for patch testing in this group (16/28 patients [55.2%]) (Table 4). Nine of the 16 patients with dermatitis, oral ulcers, or oral lichen planus developed skin/mucosal eruptions adjacent to the implanted device on the lips or perioral distributions. Patients who presented with these symptoms demonstrated a high prevalence of ≥ 1 RPPT to metals; any distribution (62.5%) and adjacent to implant, lips or perioral distribution (55.6%) (Table 4). Other skin findings included prurigo nodularis and urticaria. Non-cutaneous symptoms included pain (1/28 patients [3.6%]), swelling/inflammation (5/28 patients [17.9%]), implant failure/loosening (4/28 patients [14.3%]), and other symptoms (e.g. burning mouth syndrome, chronic sinusitis, gingivitis, and bone loss) (3/28 patients [10.7%]).

Ten patients received non-dental and non-orthopaedic implants (Table 4). Four patients received cardiovascular implants; one patient presented with generalized dermatitis only; one patient presented with generalized dermatitis, fatigue, and anorexia; one patient was referred because of chest pain and migraine; and one patient was referred because of chest pain and other symptoms such as fever and elevated C-reactive protein. Five patients received metal clips and one patient received a bladder pacemaker. Two patients presented with dermatitis, one patient presented with urticaria, and three reported other symptoms such as muscle pain, fatigue, and chronic sinusitis.

3.5 | Post-Implantation outcomes

In the post-implant orthopaedic group, 21/49 (42.9%) patients had ≥ 1 RPPT to a metal and/or bone cement allergen. The decision for

TABLE 3 Patch test results of post-implant evaluation, (n [%])

Allergen (metals)	All groups		Orthopaedic		Dental		Cardiovascular		Other	
	PPT	RPPT	PPT	RPPT	PPT	RPPT	PPT	RPPT	PPT	RPPT
Any metal	45/87 (51.7)	33/87 (37.9)	23/49 (46.9)	17/49 (34.7)	16/28 (57.1)	13/28 (46.4)	1/4 (25)	1/4 (25)	4/6 (83.3)	2/6 (33.3)
Nickel sulfate 2.5/5.0 pet.	15/87 (17.2)	14/87 (16.1)	7/49 (14.3)	6/49 (12.2)	6/28 (21.4)	6/28 (21.4)	0/4 (0)	0/4 (0)	2/6 (33.3)	2/6 (33.3)
Cobalt chloride 1.0 pet.	9/87 (10.3)	9/87 (10.3)	6/49 (12.2)	6/49 (12.2)	2/28 (7.1)	2/28 (7.1)	1/4 (25)	1/4 (25)	0/6 (0)	0/6 (0)
Potassium dichromate 0.25 pet.	8/87 (9.2)	7/87 (8)	4/49 (8.2)	4/49 (8.2)	2/28 (7.1)	1/28 (3.6)	1/4 (25)	1/4 (25)	1/6 (16.7)	1/6 (16.7)
Gold sodium thiosulfate 0.5/2.0 pet.	23/81 (28.4)	6/81 (7.4)	8/49 (16.3)	0/49 (0)	10/28 (35.7)	6/28 (21.4)	1/4 (25)	0/4 (0)	4/6 (66.7)	0/6 (0)
Manganese chloride 2.0 pet.	9/68 (13.2)	4/68 (5.9)	6/38 (15.8)	3/38 (7.9)	2/21 (9.5)	1/21 (4.8)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Palladium chloride 2.0 pet.	13/70 (18.6)	4/70 (5.7)	6/38 (15.8)	0/38 (0)	5/23 (21.7)	4/23 (17.4)	0/3 (0)	0/3 (0)	2/6 (33.3)	0/6 (0)
Vanadium 5.0 pet.	3/68 (4.4)	3/68 (4.4)	2/38 (5.3)	2/38 (5.3)	1/21 (4.8)	1/21 (4.8)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Potassium dicyanoaurate 0.1 aq.	4/68 (5.9)	2/68 (2.9)	1/38 (2.6)	0/38 (0)	3/21 (14.3)	2/21 (9.5)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Iron chloride 2.0 pet.	3/68 (4.4)	2/68 (2.9)	3/38 (7.9)	2/38 (5.3)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Vanadium chloride 1.0 pet.	4/68 (5.9)	1/68 (1.5)	3/38 (7.9)	1/38 (2.6)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Mercuric chloride 0.1 pet.	2/68 (2.9)	1/68 (1.5)	0/38 (0)	0/38 (0)	1/21 (4.8)	1/21 (4.8)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Mercury ammonium chloride 1.0 pet.	2/68 (2.9)	1/68 (1.5)	1/38 (2.6)	0/38 (0)	1/21 (4.8)	1/21 (4.8)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Stannous chloride 1.0 pet.	2/68 (2.9)	1/68 (1.5)	0/38 (0)	0/38 (0)	2/21 (9.5)	1/21 (4.8)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Titanium oxide 10.0 pet.	1/68 (1.5)	1/68 (1.5)	1/38 (2.6)	1/38 (2.6)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Mercury 0.5 pet.	2/70 (2.9)	1/70 (1.4)	1/38 (2.6)	0/38 (0)	1/23 (4.3)	1/23 (4.3)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Copper sulfate 2.0 pet.	5/70 (7.1)	0/70 (0)	2/38 (5.3)	0/38 (0)	2/23 (8.7)	0/23 (0)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Iridium chloride 10.0 aq.	3/68 (4.4)	0/68 (0)	2/38 (5.3)	0/38 (0)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Zinc chloride 2.0 pet.	3/68 (4.4)	0/68 (0)	3/38 (7.9)	0/38 (0)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Zirconium chloride 1.0 pet.	2/68 (2.9)	0/68 (0)	1/38 (2.6)	0/38 (0)	0/21 (0)	0/21 (0)	1/3 (33.3)	0/3 (0)	0/6 (0)	0/6 (0)
Cadmium chloride 1.0 aq.	1/68 (1.5)	0/68 (0)	1/38 (2.6)	0/38 (0)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Indium 1.0 pet.	1/68 (1.5)	0/68 (0)	0/38 (0)	0/38 (0)	1/21 (4.8)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Indium sulfate 10.0 aq.	1/68 (1.5)	0/68 (0)	1/38 (2.6)	0/38 (0)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Iridium 1.0 pet.	1/68 (1.5)	0/68 (0)	0/38 (0)	0/38 (0)	0/21 (0)	0/21 (0)	0/3 (0)	0/3 (0)	1/6 (16.7)	0/6 (0)
Lead acetate 0.5 aq.	1/68 (1.5)	0/68 (0)	0/38 (0)	0/38 (0)	1/21 (4.8)	0/21 (0)	0/3 (0)	0/3 (0)	0/6 (0)	0/6 (0)
Allergen (bone cement/dental series)										
2-Hydroxyethylmethacrylate 2.0 pet.	5/23 (21.7)	5/23 (21.7)	4/10 (40)	4/10 (40)	1/12 (8.3)	1/12 (8.3)	0/1 (0)	0/1 (0)	-	-
2-Hydroxypropyl methacrylate 2.0 pet.	1/12 (8.3)	1/12 (8.3)	1/8 (12.5)	1/8 (12.5)	0/3 (0)	0/3 (0)	0/1 (0)	0/1 (0)	-	-
Ethyleneglycol dimethacrylate 2.0 pet.	1/22 (4.5)	1/22 (4.5)	1/9 (11.1)	1/9 (11.1)	0/12 (0)	0/12 (0)	0/1 (0)	0/1 (0)	-	-
Methyl methacrylate 2.0 pet.	2/79 (2.5)	2/79 (2.5)	2/43 (4.7)	2/43 (4.7)	0/26 (0)	0/26 (0)	0/4 (0)	0/4 (0)	0/6 (0)	0/6 (0)
Ethyl acrylate 0.1 pet.	1/79 (1.3)	1/79 (1.3)	1/43 (2.3)	1/43 (2.3)	0/26 (0)	0/26 (0)	0/4 (0)	0/4 (0)	0/6 (0)	0/6 (0)

Abbreviations: aq, aqueous; PPT, positive patch test; pet, petrolatum; RPPT, relevant positive patch test.

Implant type and symptoms	n (%)	≥ 1PPT	≥ 1RPPT
Orthopaedic (n = 49)			
Dermatitis (any distribution)	20 (40.8)	8 (40)	7 (35)
Dermatitis (over prosthesis)	15 (30.6)	7 (46.7)	6 (40)
Skin eruptions (other)	4 (8.2)	4 (100)	3 (75)
Pain	23 (46.9)	10 (43.5)	8 (34.8)
Swelling/inflammation	9 (18.4)	6 (66.7)	4 (44.4)
Implant failure/loosening	3 (6.1)	0 (0)	0 (0)
Other	10 (20.4)	7 (70.0)	4 (40.0)
Dental (n = 28)			
Dermatitis, oral ulcers, lichen planus (any distribution)	16 (57.1)	11 (68.8)	10 (62.5)
Dermatitis oral ulcers, lichen planus (adjacent to implant, lips, perioral)	9 (32.1)	6 (66.7)	5 (55.6)
Skin eruptions (other)	2 (7.1)	0 (0)	0 (0)
Pain	1 (3.6)	1 (100)	0 (0)
Swelling/inflammation	5 (17.9)	1 (20)	0 (0)
Implant failure/loosening	4 (14.3)	1 (25)	1 (25)
Other	3 (10.7)	3 (100)	2 (66.7)
Cardiovascular (n = 4)			
Dermatitis (any distribution)	2 (50)	0 (0)	0 (0)
Pain	2 (50)	1 (50)	1 (50)
Other	3 (75)	0 (0)	0 (0)
Other (n = 6)			
Dermatitis (any distribution)	2 (33.3)	2 (100)	1 (50)
Skin eruptions (other)	1 (16.7)	1 (100)	0 (0)
Pain	1 (16.7)	1 (100)	1 (100)
Other	3 (50)	2 (66.7)	1 (33.3)

Abbreviations: PPT, positive patch test reaction; RPPT, relevant patch test reaction.

TABLE 4 One or more positive patch test and relevant positive patch test reactions to metals according to type of implant and symptoms

implant revisions varied and was based on the severity of symptoms and PPT, or reasons other than PPT. Six of these patients underwent device revision or removal due to PPT, two underwent device revision prior to patch testing, nine had no revisions, four were lost to follow up. Seven out of eight patients who underwent device revision or removal had symptomatic (eg dermatitis, pain, "metallic taste") improvement or complete resolution post-operatively (mean follow-up time 8.1 months, range 1–24 months). Of the nine patients with relevant MHR who did not have implant revision or removal, seven patients had persistent symptoms, one patient had resolution of symptoms after avoidance of chromium that was found in the patient's multivitamin supplements, and one patient was found to be allergic to the suture material used during the procedure (mean follow-up time 16.5 months, range 2–48 months). There were 28 symptomatic patients who had either non-relevant or negative patch test reactions, two patients underwent device revision due to presumed metal allergy, two underwent device revision prior to patch testing, one patient underwent revision due to positive lymphocyte transformation testing, and one underwent revision due to implant loosening. Of these patients, 5/6 patients (83.3%) reported symptom

improvement (mean follow-up time 7.2 months, range 3–12 months) and one was lost to follow-up.

In the post-implant dental group, 13 patients (46.4%) had ≥ 1 RPPT to a metal and/or a dental series allergen; six patients underwent device revision or removal due to patch test results, two had no revisions, five were lost to follow up. Of the six patients who underwent revision or removal, five had alleviation of symptoms (eg dermatitis, oral ulcers, implant failure, gingivitis, bone loss) and one patient had persistent symptoms despite removal of the implant (mean follow-up time 9.2 months, range 2–24 months). Fifteen patients had either non-relevant or negative patch test results. One patient, who was referred because of lip swelling, had the implant removed prior to patch testing and demonstrated symptom improvement despite a negative patch test result. Seven patients did not have device revision, and seven patients were lost to follow up. In the post-implant cardiovascular group, one patient had ≥ 1 RPPT to metals. This patient did not have revision of her stent and symptoms of chest pain, migraine persisted at 48 months follow-up. In the post-implant other devices group, two patients (33.3%) had ≥ 1 RPPT to metals, one patient did not have revisions and had persistent dermatitis at 17 months follow-

TABLE 5 Diagnostic value of clinical findings in discriminating relevant positive patch test results to metals

	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)
History of metal allergy				
Pre-implant	0.94 (0.83–1.00)	0.32 (0.12–0.51)	1.39 (0.94–1.82)	0.17 (0.02–1.29)
Post-implant	0.42 (0.28–0.56)	0.69 (0.55–0.84)	1.35 (0.56–2.15)	0.84 (0.57–1.11)
Orthopaedic ^a				
Dermatitis (any distribution)	0.39 (0.16–0.61)	0.58 (0.42–0.75)	0.93 (0.25–1.60)	1.05 (0.54–1.57)
Dermatitis (over prosthesis)	0.33 (0.12–0.55)	0.71 (0.55–0.87)	1.15 (0.14–2.16)	0.94 (0.56–1.32)
Pain	0.44 (0.21–0.67)	0.51 (0.34–0.69)	0.92 (0.32–1.51)	1.08 (0.48–1.67)
Swelling/inflammation	0.22 (0.03–0.41)	0.84 (0.71–0.97)	1.38 (0.42–4.48)	0.93 (0.65–1.20)
Implant failure/loosening	0	0.90 (0.74–0.98)	0	1.11 (0.98–1.24)
Other	0.23 (0.03–0.44)	0.81 (0.68–0.95)	1.25 (0.41–3.85)	0.94 (0.64–1.24)
Dental ^a				
Dermatitis, oral ulcers, lichen planus (any distribution)	0.77 (0.54–0.99)	0.60 (0.35–0.85)	1.92 (0.54–3.31)	0.38 (0.13–1.13)
Dermatitis oral ulcers, lichen planus (over prosthesis)	0.38 (0.12–0.65)	0.73 (0.51–0.96)	1.44 (0.49–4.27)	0.83 (0.38–1.30)
Pain	0	0.93 (0.66–1.00)	0	1.07 (0.92–1.22)
Swelling/inflammation	0.08 (0.00–0.22)	0.73 (0.51–0.96)	0.29 (0.04–2.27)	1.26 (0.81–1.71)
Implant failure/loosening	0.08 (0.00–0.22)	0.80 (0.60–1.00)	0.38 (0.05–3.26)	1.15 (0.79–1.51)
Other	0.15 (0.00–0.35)	0.93 (0.81–1.00)	2.31 (0.24–22.62)	0.91 (0.65–1.16)

^aPatients may have more than one clinical symptom.

up, and one had metal clips removed with no improvement of muscle pain, joint pain, and fatigue at 12 months follow-up.

3.6 | Diagnostic performance of clinical findings

Table 5 shows the diagnostic performance of a self-reported history of metal allergy in the pre- and post-implant group, as well as various clinical symptoms in patients who received orthopaedic or dental devices, in distinguishing relevant reactions to a metal component of the patient's implanted device. In the pre-implant group, a history of metal allergy demonstrated high sensitivity (0.94; 95% CI: 0.83–1.00) and low specificity (0.32; 95% CI: 0.12–0.51) for diagnosis of MHR. The LR positive (LR+) was 1.39 (95% CI: 0.94–1.82) and LR negative (LR-) was 0.17 (95% CI: 0.02–1.29). A self-reported history of metal allergy in the post-implant group had a sensitivity and specificity of 0.42 and 0.69, respectively, for the diagnosis of MHR. LR+ for post-implant, self-reported metal allergy was 1.35 (95% CI: 0.56–2.15) and LR- was 0.84 (95% CI: 0.57–1.11).

In the post-implant orthopaedic group, dermatitis over their prosthesis had a sensitivity of 0.33 (95% CI: 0.12–0.55), specificity of 0.71 (95% CI: 0.55–0.87), LR+ of 1.15 (95% CI: 0.14–2.16), and LR- of 0.94 (95% CI: 0.56–1.32). In terms of patients with implant failure or loosening in the post-implant orthopaedic group, none of the three patients had relevant metal allergies; however, two of the three patients demonstrated relevant patch test reactions to bone cement allergens. Therefore, a high specificity (0.90; 95% CI: 0.74–0.98) was

shown for implant failure and loosening; however, the LR did not confirm the discriminatory ability of this clinical finding.

In the post-implant dental group, dermatitis, oral ulcers, or lichen planus in any distribution demonstrated a sensitivity of 0.77 (95% CI: 0.54–0.99), specificity of 0.60 (95% CI: 0.35–0.85), LR+ of 1.92 (95% CI: 0.54–3.31), and LR- of 0.38 (95% CI: 0.13–1.13) for diagnosis of relevant MHR. Dermatitis, oral ulcers, or lichen planus adjacent to implant, on lips or perioral distribution demonstrated a sensitivity of 0.38 (95% CI: 0.12–0.65), specificity of 0.73 (95% CI: 0.51–0.96), LR+ of 1.44 (95% CI: 0.49–4.27), and LR- of 0.83 (95% CI: 0.38–1.30). Non-cutaneous symptoms such as pain, swelling/inflammation, and implant failure demonstrated high specificity; however, the LRs did not confirm the discriminatory ability of these individual symptoms.

4 | DISCUSSION

In this study, we present a summary of 127 patients referred to our centre for pre- and post-implant related metal allergy testing. Whether MHR lead to implant complications remains debatable and incompletely understood. Routine screening for all patients prior to implantation is not indicated. However, our findings suggest that a self-reported history of metal allergy has a high sensitivity for predicting relevant MHR. Surgeons should consider requesting this information during pre-operative implant visits to determine whether further testing is required.^{9,10} In addition, results from patch testing may help guide the choice of implant as none of the patients who had

a documented device change developed complications or skin eruptions during post-operative follow-up.

Our analysis found the value of post device implantation patch testing to be less clear, which aligns with previous reports that clinical findings alone may not be predictive of relevant metal allergy.^{1,2} Nonetheless, there are multiple reports documenting the association between MHR and adverse events post-implantation.^{11–15} The ACDS and other international groups have published recommendations for the evaluation of patients with MHR concerns.^{6,16} Evaluation to rule out MHR may be warranted after exclusion of other causes.^{5,6}

4.1 | Pre-implant patch testing

In the pre-implant group, 18 (45%) patients had ≥ 1 RPPT to metals. Similar rates have been reported in other studies in the setting of pre-implant testing.^{17–19} Patch testing is important in identifying relevant metal allergies. Results from patch testing seem to influence the surgeon's decision on the selection of implant, however, more studies are necessary to evaluate long-term outcomes in these patients. Our current data for outcomes in patients who had a change in device ranged from 2 months to 2 years, and for those who did not have a change in device ranged from 1–5 years.

In our study, nine patients with ≥ 1 RPPT to metals had a device change or deferred surgery based on patch test findings. The most common allergen-free alternatives in the study were oxidized zirconium-niobium or titanium alloys. Although two patients with nickel allergy received nitinol (nickel-based) intracardiac implanted device, neither patients developed any complications or skin eruptions at 1-year post-implantation. There is currently no consensus regarding the ability of patch testing to determine ACD within cardiac tissue. However, a recent study that surveyed 56 dermatologists and allergists, who were mostly ACD specialists, on the management of nickel allergy in the setting of intracardiac device implants recommended avoiding nickel-based intracardiac devices if patients have a nickel allergy on patch testing, or leaving the decision to the discretion of the cardiologist.²⁰

We recommend avoiding known allergens if or when replacement or revision is planned. Although there was a limited number of patients tested with bone cement allergens, obtaining a thorough history of acrylate allergy can allow for a more comprehensive pre-operative evaluation, to avoid post-operative complications.²¹ Furthermore, caution should be exercised when testing with metal disks of the prosthesis supplied by manufacturers. Testing with metal disks may be unreliable because it consistently gives negative or irritant results, possibly due to the lack of metal ion release from the disks.^{6,17,22} Further studies are warranted in standardizing pre-implant ACD evaluation.

4.2 | Post-implant patch testing

Dermatitis was the most common reason for a referral for evaluation of ACD because of a concern about hypersensitivity to a component

of the implanted device. Other symptoms that prompted referral included pain, swelling, device failure, and other non-specific symptoms. In our analysis of the post-implant orthopaedic and dental group, no predictive values may be ascribed to any of the clinical symptoms as the LR demonstrated that none of the commonly reported clinical symptoms were able to discriminate for relevant MHR. Nonetheless, there is evidence that metal hypersensitivity may have a role of in post-implant complications such as localized or generalized dermatitis, chronic pain, and failure.^{17,21,23} This is demonstrated by patients in the post-orthopaedic implant group with relevant MHR who underwent implant revision or removal and had complete resolution or improvement of their symptoms, whereas patients who did not have revision with relevant metal hypersensitivity had persistent symptoms. Previous studies have also reported similar findings in remission of symptoms after revision with prostheses free of metals to which the patient tested positively.^{19,21}

Among patients being evaluated for dental or oral implants, relevant metal reactions were common overall, although no predictive values may be ascribed to any of the clinical symptoms in discriminating for relevant MHR. However, there have been many reports of symptoms of skin and oral mucosa associated with dental metal allergies.^{24–27} Dental metal allergy, specifically to gold and mercury, has also been suggested to be a cause of oral lichen planus.^{25–28} One of our patients who presented with oral lichen planus had a relevant positive allergy to gold on patch testing, and gold was a component of the patient's implant. Furthermore, a small proportion of our patients (6 out of 13 [46.2%]) underwent implant removal based on presumed association with relevant patch test findings and 5 out of 6 patients had symptom improvement. A recent study of 925 patients who were patch tested for metal allergy after undergoing dental implant surgery found that over half (55.6%) of the patients who underwent implant removal demonstrated improvement of symptoms of the oral mucosa and skin.²⁴ Therefore, patients with confirmed contact sensitization through patch testing may benefit from dental implant revision or removal.

Patients with debilitating symptoms and positive patch testing may benefit from implant removal or revision with an implant free of relevant allergens, however, patients should be informed that improvement of symptoms is not guaranteed.²¹ Thorough ACD evaluation for post-implantation patients with significant concerns of implanted device hypersensitivity may also provide psychosocial benefit and potentially promote improved post-operative outcomes.²⁹ Preserving function, improving quality of life, and lastly, avoiding allergic reactions should be guiding principles.

4.3 | Limitations

All patients were specifically referred for suspected metal allergy, therefore, our data is subject to selection bias. This study is retrospective in nature, thus, some patients had missing information and long-term outcomes, respectively. Late positive reactions might have been missed or read as false-negative because readings were done at D3 or

D4. Furthermore, the number of patients in certain subgroups was small, limiting conclusions. The authors feel the strengths of this study, specifically the consistent interpretation from an ACD expert (PCS) and statistical analysis of a rare diagnosis, far outweigh the limitations.

5 | CONCLUSION

ACD to implanted devices is controversial with few definitive guidelines for surgeons, allergists, dermatologists and, most importantly, patients. While this study describes a group with short-term outcomes following surgery, it is the authors' opinion that pre-implant evaluation by patch testing can be useful in guiding implant alloy choice for selected individuals with a clear history of metal or jewellery allergy. Although our analysis did not suggest that individual clinical factors are predictive, a combination of symptoms can possibly provide better predictive value. Post-implant ACD evaluation may be reasonable when all other causes of adverse effects related to the implant device have been ruled out. Removing/replacing an implanted metal device containing metal(s) identified as allergenic may be beneficial in resolving morbidity likely caused by implant related MHR. Well-designed, large, prospective cohort studies on metal hypersensitivity to implanted devices are needed to better understand this growing area of concern.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Idy Tam: Data curation; formal analysis; investigation; methodology; validation; writing-original draft; writing-review and editing. **JiaDe Yu:** Conceptualization; formal analysis; investigation; methodology; supervision; validation; writing-original draft; writing-review and editing. **Lauren Ko:** Data curation; methodology; writing-original draft; writing-review and editing. **Peter Schallack:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; validation; visualization; writing-review and editing.

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