

Associations of Nickel Co-Reactions and Metal Polysensitization in Adults

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Background: Allergic contact dermatitis to metals is a significant clinical and public health problem. Little is known about the determinants of polysensitization to metals.

Objective: The aim of the study was to determine the frequency and predictors of nickel co-reactions and metal polysensitization.

Methods: This is a retrospective chart review of 686 adults (age ≥ 18 years) who were patch tested from 2014 to 2017.

Results: Overall, 267 patients (38.9%) had 1 or more positive patch-test reactions to a metal allergen, most commonly nickel (17.4%), mercury (12.3%), and palladium (9.2%). Nickel reactions were inversely associated with age (logistic regression; adjusted odds ratio [95% confidence interval], 0.39 [0.29–0.78]). Among patients with positive reactions to nickel, 34.5%, 15.1%, and 5.0% had positive reactions to 1, 2, or 3 additional metals, respectively. The most common nickel co-reactors were palladium, mercury, and gold. Polysensitization to metals occurred in 11.8% of patients. Polysensitization to metal allergens was associated with female sex (6.67 [1.01–44.21]) and inversely associated with age (0.40 [0.18–0.88]).

Conclusions: Nickel-sensitized patients have high rates of metal co-reactions. Polysensitization to metals is common in adults. These results may help guide future strategies for allergen avoidance.

Allergic contact dermatitis (ACD) to metals is a significant clinical and public health problem. In particular, nickel is a common culprit in ACD. Because of the increasing prevalence of nickel allergy in Europe, the European Union Nickel Directive was introduced in 1994 to diminish nickel sensitization in the population. Several studies showed that this regulation helped limit the amount of nickel allowed in jewelry and other products.^{1–3} However, despite these improvements, nickel still remains a common and troublesome allergen,^{4,5} especially in nondirective countries. For instance, higher proportions of earrings that had excessive amounts of nickel were reported in the United States (30%) and in Thailand (29%), compared with those in European countries (4%–18%). In the United States, rates of nickel allergy continue to increase because there are limited regulations on nickel-containing items.⁶

In addition, because of the mixing of various metal alloys, some patients may become sensitized to multiple metals. For example,

cobalt, chromium, and gold may be present in nickel-containing products, such as jewelry, belts, and phones.^{7–10} Because of these common exposures containing multiple metals, individuals may develop multiple metal allergies, thereby complicating allergen avoidance strategies of patients and manufacturers.

Because little is known about nickel co-reactions and polysensitization to metals, the aim of the study was to determine their frequency and predictors.

METHODS

Study Design

A retrospective chart review was performed on 686 “deidentified” adults (age ≥ 18 years) who were patch tested at the patch-testing clinic from 2014 to 2017 for possible ACD to metals. Patients were patch tested with the North American Contact Dermatitis Group standard series and a supplemental metal allergen series. Data on patient demographics, pertinent exposures, and patch-testing results were extracted from the clinical database. The local institutional review board approved the study, and informed consent was waived.

Patch Testing

Allergens were purchased from SmartPractice Dermatology (Phoenix, AZ). Patches were applied to the upper back and removed after

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48 hours. Patches were initially evaluated at 48 hours and again at 72 to 96 hours when final patch-test results were recorded. Positive reactions were further classified as +, ++, and +++ per the International Contact Dermatitis Research Group's scoring system.¹¹ Negative reactions included irritant responses. Patients were evaluated with a standardized medical history, including self-report of jewelry and metal eyelash curler use, and a skin examination by a dermatologist before patch testing.

Positive patch-test reactions to metals may be delayed in a small subset of patients and occur up to 2 weeks after patch-test placement.^{12,13} To address this concern, a series of photographs was taken at the final patch read and patients were encouraged to monitor their back for delayed reactions for 3 weeks. Delayed reactions were identified via photographs.

Statistics

All data processing and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). χ^2 Tests were used for bivariable analysis of association between categorical variables. Given that positive reactions for some metals were rare, analyses were limited to those metals with at least 5 events per cell in a 2×2 table. A 2-sided *P* value of less than 0.05 was taken to indicate statistical significance for all hypothesis tests. Stepwise selection was used to determine the significant predictors of nickel hypersensitivity and polysensitization to metal allergens ($\alpha = .1$). Sex (male/female), race (white/nonwhite), age ($<40/\geq 40$ years), history of wearing jewelry (yes/no), using metal eyelash curlers (yes/no), and atopic dermatitis (yes/no) were included as covariates. Adjusted odds ratios and 95% confidence intervals were estimated.

RESULTS

Patient Characteristics

The total cohort consisted of 686 adults, including 519 women (75.6%) and 490 whites (71.4%). The mean (SD) age at enrollment was 46.0 (15.7) years. Positive patch-test reactions to 1 or more metal allergens were observed in 267 patients (38.9%), with nickel (17.4%), mercury (12.3%), and palladium (9.2%) being the most common. Most final patch-test readings were performed at 72 to 80 hours (82%), with the remainder performed at 96 to 104 hours (18%). Overall, there were 89 doubtful reactions (1.1%) to metals observed.

Co-Reactions With Nickel

One hundred nineteen patients were sensitized to nickel, of which 65 (55.6%) also had a positive reaction to another metal. Positive reactions to 1, 2, or 3 additional metals occurred in 41 (34.5%), 18 (15.1%), and 6 (5.0%) of nickel-sensitized patients, respectively. The most common co-reactors with nickel were palladium (37.0%), mercury (16.0%), and gold (15.0%). Delayed reactions (>96 hours) to nickel occurred in 1 patient (0.8%) and to gold in 3 patients (2.5%).

There were 16 doubtful reactions (2.8%) to nickel. Among those with a positive reaction to nickel, the frequency and proportion of doubtful reactions to other metals were as follows: 4 (5.1%) for mercury, 3 (3.8%) for gold, 2 (2.5%) for palladium, 2 (2.1%) for chromium, 1 (1.0%) for cobalt, 1 (1.9%) for titanium, 1 (1.9%) for copper, and 1 (1.9%) for cadmium.

A positive reaction to nickel was significantly associated with co-reactions to palladium, cobalt, and gold (Table 1). Multivariable logistic regression models of nickel hypersensitivity with stepwise selection found that older age (adjusted odds ratio [95% confidence interval], 0.39 [0.29–0.78]) and use of metal eyelash curlers (2.12 [1.01–4.48]) were the only significant predictors.

Metal Reactions in Non-Nickel-Sensitized Individuals

Among the 566 individuals not sensitized to nickel, 131 (23.1%) had positive patch reactions to other metals. The most common allergens were mercury (11.6%), gold (7.3%), and chromium (4.2%). Of note, only 3.5% of non-nickel-sensitized patients had a positive reaction to palladium. Fifteen (2.7%), 1 (0.2%), and 0 individuals had positive reactions to 1, 2, or 3 additional metals, respectively.

Risk Factors for Metal Sensitization

Female sex was a risk factor for having a positive patch test to 1 or more metals, specifically nickel and palladium. There were no significant associations between jewelry use and metal hypersensitivity ($P = 0.56$). Patients who used metal eyelash curlers had significantly higher rates of positive patch-test reactions to at least 1 metal compared with those who did not (57.9% vs 36.0%, $P = 0.0001$), particularly to nickel (26.3% vs 14.0%, $P = 0.005$) and mercury (20.0% vs 10.2%, $P = 0.01$).

Body Distribution

Body distribution of skin lesions was categorized by individuals with 0, 1, and 2 or more metal reactions. Eyelids were the most commonly affected site in those with 0 and 1 metal reaction, whereas the hands/wrists were the frequent location of skin lesions in polysensitized patients. As expected, dermatitis of the earlobes was significantly associated with having 1 or more metal reactions ($P = 0.002$). Cheilitis was present in 9.3%, 10.8%, and 16.1% of patients with 0, 1, or 2 or more metal reactions, respectively. The most common metals associated with cheilitis were nickel (26.4%), gold (14.3%), palladium (11.3%), and mercury (11.3%).

Risk Factors for Polysensitization

Overall, polysensitization to metals occurred in 11.8% of patients and was significantly more common among adults with versus without a positive reaction to nickel (54.6% vs 10.9%, respectively; $P < 0.0001$). In bivariable analyses, patients with polysensitization to metals were significantly younger (mean [SD], 40.6 [12.7] vs 46.7 [15.9]; $P = 0.001$), were more likely to be female (92.4% vs 74.8%, $P = 0.0005$), were more likely to be polysensitized to

TABLE 1. Association Between Nickel and Other Metals

Metal	Nickel		P
	Negative (n = 547)	Positive (n = 117)	
	n (%)	n (%)	
Palladium			
Negative	447 (96.4)	63 (63.0)	<0.0001*
Positive	18 (3.6)	37 (37.0)	
Chromium			
Negative	523 (95.6)	115 (98.3)	NA
Positive	24 (4.4)	2 (1.7)	
Cobalt			
Negative	539 (98.5)	100 (85.5)	<0.0001*
Positive	8 (1.5)	17 (14.5)	
Gold			
Negative	468 (92.7)	85 (85.0)	0.01*
Positive	37 (7.3)	15 (15.0)	
Mercury			
Negative	436 (88.1)	84 (84.0)	0.26*
Positive	59 (11.9)	16 (16.0)	
Titanium			
Negative	335 (100)	68 (100)	NA
Positive	0 (0)	0 (0)	
Molybdenum			
Negative	335 (99.7)	68 (100)	NA
Positive	1 (0.3)	0 (0)	
Vanadium			
Negative	335 (99.7)	67 (98.5)	NA
Positive	1 (0.3)	1 (1.5)	
Zirconium			
Negative	335 (100)	68 (100)	NA
Positive	0 (0)	0 (0)	
Aluminum			
Negative	334 (99.7)	68 (100)	NA
Positive	1 (0.3)	0 (0)	
Copper			
Negative	329 (97.9)	67 (98.5)	NA
Positive	7 (2.1)	1 (1.5)	
Zinc			
Negative	330 (99.4)	67 (100)	NA
Positive	2 (0.6)	0 (0)	
Silver			
Negative	330 (99.4)	66 (98.5)	NA
Positive	2 (0.6)	1 (1.5)	
Tin			
Negative	332 (100)	66 (98.5)	NA
Positive	0 (0)	1 (1.5)	
Indium			
Negative	331 (99.7)	67 (100)	NA
Positive	1 (0.3)	0 (0)	
Manganese			
Negative	332 (100)	67 (100)	NA
Positive	0 (0)	0 (0)	

TABLE 1. (Continued)

Metal	Nickel		P
	Negative (n = 547)	Positive (n = 117)	
	n (%)	n (%)	
Tungstic			
Negative	332 (100)	67 (100)	NA
Positive	0 (0)	0 (0)	
Ferric			
Negative	330 (99.4)	66 (98.5)	NA
Positive	2 (0.6)	1 (1.5)	
Cadmium			
Negative	331 (99.7)	67 (100)	NA
Positive	1 (0.3)	0 (0)	

Bold font indicates P-value is statistically significant and ≤ 0.05 .

** χ^2 tests of association comparing nickel and other metals.*

NA indicates not applicable.

nonmetal allergens (57.4% vs 37.6%, $P = 0.005$), and use metal eyelash curlers (35.6% vs 21.1%, $P = 0.03$) (Table 2). No significant differences of race (28.4% vs 28.6%, $P = 0.97$), atopic dermatitis (17.3% vs 22.5%, $P = 0.29$), and jewelry use (84.9% vs 79.2%, $P = 0.32$) were observed between those with versus without polysensitization to metals. In multivariable logistic regression models of polysensitization to metal allergens with stepwise selection, female sex (6.67 [1.01–44.21]) and older age (0.40 [0.18–0.88]) were the only significant associations.

TABLE 2. Associations of Polysensitization to Metals

Characteristic	Polysensitization to Metal Allergens		P
	No (n = 605)	Yes (n = 81)	
Age, y			
Mean (SD)	46.7 (15.9)	40.6 (12.7)	0.001
n (%)			
<40	221 (36.8)	43 (54.4)	0.003
≥ 40	379 (63.2)	36 (45.6)	
Sex, n (%)			
Female	446 (74.8)	73 (92.4)	0.0005
Male	150 (25.2)	6 (7.6)	
Race, n (%)			
White	432 (71.4)	58 (71.6)	0.97
Nonwhite	173 (28.6)	23 (28.4)	
Atopic dermatitis, n (%)			
Negative	469 (77.5)	67 (82.7)	0.29
Positive	136 (22.5)	14 (17.3)	
Jewelry use, n (%)			
No	79 (20.8)	8 (15.1)	0.32
Yes	300 (79.2)	45 (84.9)	
Metal eyelash curler use, n (%)			
No	288 (78.9)	34 (65.4)	0.03
Yes	77 (21.1)	18 (34.6)	

χ^2 Tests of association were used to compare age, sex, race, atopic dermatitis, jewelry use, and metal eyelash curler use in individuals polysensitized versus non-polysensitized to metals. Less than 2% of patient data were missing for all variables.

DISCUSSION

The present study found high rates of patch-test positivity to 1 or more metals, most commonly nickel, mercury, and palladium. The high rate of nickel sensitization (17.4%) was similar to previous studies in the United States¹⁴ and European countries abiding by the Nickel Directive.⁴ In particular, more than half of patients with nickel hypersensitivity had high rates of co-reactions to another metal. Furthermore, patients with nickel hypersensitivity were significantly more likely to have co-reactions to palladium, cobalt, and gold, with polysensitization to other metals. Cobalt, chromium, and gold have been the commonly reported co-reactors in patients with nickel allergies.^{7–10} More recently, palladium has been found to be a common co-reactant of nickel.^{15,16} In this study, palladium was the most common co-reactor among nickel-sensitized patients, although not a common allergen among non-nickel-sensitized patients. High rates of co-reaction between nickel and palladium are clinically relevant. Palladium has become a rising problem in contact dermatitis patients, and can be found in dental/medical devices, jewelry, and auto industry.¹⁷ A previous study of patch testing to metal allergens in more than 1000 patients also found high reaction rates to palladium.¹⁸ Whereas cobalt and chromium are typically assessed in standard allergen screening series, for example, the American Contact Dermatitis Society and North American Contact Dermatitis Group series, palladium is not. Thus, patients with nickel hypersensitivity may benefit from additional patch testing to palladium or empiric avoidance of palladium.

We found that female patients had higher rates of nickel and palladium hypersensitivity, yet the exact exposures and risk factors that dually sensitize patients to nickel and palladium are yet to be determined.^{15,17} Earlobes were the only body part significantly associated with having metal hypersensitivity. These results are consistent with previous studies that showed cephalic body sites to be significantly related to positive reactions to metal allergens.⁸ This association is most likely due to ear piercings.^{19,20} Warshaw et al¹⁹ analyzed 17,912 patch-test data from the North American Contact Dermatitis Group and found nickel sensitivity to be significantly associated with piercing in both men and women. Interestingly, we did not find jewelry use in general to be significantly associated with having a metal allergy as well as with polysensitization to metal allergens. However, using metal eyelash curlers was significantly associated with nickel and mercury allergies, suggesting that eyelash curlers may be a more common source of metal sensitization than previously recognized. These results are consistent with an earlier report that hypothesized that eyelash curlers and nickel ferrules on the shaft of makeup applicators may also sensitize patients to nickel.²¹ Although metal eyelash curlers were significantly associated with polysensitization to metals in bivariable analyses, this association did not remain significant in the multivariable model. Moreover, nickel, gold, palladium, and mercury were commonly implicated allergens in those with cheilitis, underscoring the importance of metals allergens in oral diseases.²²

In addition, polysensitization to metals was associated with female sex and inversely associated with older age. The association

between polysensitization and female sex has been found in other studies.^{23,24} A study of the German Information Network of Departments of Dermatology found a female predominance in the number of positive patch-test reactions for both nickel and cobalt.²⁵ Previous studies have also found that polysensitization to metals is inversely associated with older age, likely because of the decreased use of imitation jewelry and different rates of ear piercing among various generations.²⁶ Our study found no association between polysensitization and race/ethnicity. These results differ from those of another study conducted in Kansas City, MO, that examined patch-test data from 1187 patients at 1 medical center. They found that nonwhite race/ethnicity was significantly associated with metal, particularly cobalt, allergy, possibly because of sociocultural exposures or an inherent susceptibility to cobalt.²⁷

Given the burden of ACD to metals, countries have tried to control metal use in consumer items. The European Union Nickel Directive has been pivotal in changing the epidemiology of nickel allergy in Europe.²⁸ The amount of nickel release in products anticipated to have direct and prolonged exposure with the skin is limited to less than 0.5 µg/cm² per week.²⁹ Because of this restriction, there has been a significant decrease in the incidence of nickel allergy among women across several age groups.³⁰ In contrast, palladium does not have a similar legislation. Given the association of palladium with women and co-reactions with nickel, it is likely that piercings/earrings are contributing factors. Thus, directives aimed at reducing jewelry/earring dermatitis should consider improvement of labeling for palladium and tighter regulation of its use.

Limitations of this study include not being able to track individual metal exposures through the life course of patients. In particular, the use of piercings was not assessed. In addition, we were unable to examine the effect of occupation because of insufficient power for specific occupations. There was a predominance of female patients and eyelid dermatitis in the cohort, which may limit the generalizability of these results. Moreover, most final patch readings were performed at 72 to 80 hours, which may miss a small subset of delayed reactions to metals.^{12,13}

In conclusion, this study shows high rates of nickel co-reactions and polysensitization to other metals. Furthermore, we found particularly high rates of co-reactions to palladium, which is highly relevant for allergen avoidance strategies because patients with nickel allergies may benefit from empiric avoidance of palladium.

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