

Comparison of Nickel Sulfate 2.5% and Nickel Sulfate 5% for Detecting Nickel Contact Allergy

Ari M. Goldminz, MD and Pamela L. Scheinman, MD

Background: Nickel is among the most common contact allergens found on patch testing worldwide and, because of its ubiquitous nature in our environment, often has important implications for allergen avoidance strategies. In both North America and Europe, nickel positivity is found in approximately 20% of patients who undergo patch testing. Whereas in North America, nickel sulfate is typically tested at a concentration of 2.5%, in Europe, it is tested at a 5% concentration.

Objective: The primary objective was to assess the differences in patch test positivity to nickel sulfate 2.5% and 5%.

Methods: We investigated 205 consecutive patients between September 2017 and February 2018 who were tested to nickel sulfate at concentrations of both 2.5% and 5%.

Results: Among the 205 patients tested, 33% were positive (+, ++, or +++) to at least 1 concentration of nickel sulfate, 20% were positive to nickel sulfate 2.5%, and 31% were positive to nickel sulfate 5% ($\chi^2(N=205) = 16.1, P=0.0001$). Patients were 6.5 times more likely to have a positive reaction to nickel sulfate 5% than 2.5% (odds ratio 95% confidence interval, 2.3–25.6).

Conclusions: Given our findings, we propose an additional evaluation of nickel sulfate 5% as a standard allergen for patch testing in North America.

Nickel is among the most common contact allergens found on patch testing worldwide and, because of its ubiquitous nature in our environment, often has important implications for allergen avoidance strategies. In Europe, there has been an organized effort, through the European Nickel Directive, to reduce nickel release from items that have direct and prolonged skin contact.¹ Subsequently, for the last several decades, nickel sensitization rates have declined in Europe. The prevalence of positive reactions to nickel in a Swedish study decreased from 21.4 to 19.8 to 17.6 in 1992, 2000, and 2009, respectively (Fig. 1).² Conversely, the North American trend is toward an increase in nickel sensitivity from 16.9% in 1991–1992 to 20.1% in 2013–2014.³ In addition, nickel has generally been tested at a concentration of 5% (N5) in Europe compared with 2.5% (N2.5) in North America, and therefore, differences in nickel positivity between the 2 continents may be underestimated.

From the Department of Dermatology, Brigham and Women's Hospital, Chestnut Hill, MA.

Address reprint requests to Ari M. Goldminz, MD, Department of Dermatology, Brigham and Women's Hospital, 850 Boylston St, Suite 437, Chestnut Hill, MA 02467. E-mail: agoldminz@bwh.harvard.edu.

A.M.G.'s wife owns stock in Johnson and Johnson. P.L.S. is a consultant for Squire Patton Boggs law firm, a lecturer for Brigham and Women's Hospital Allergy Department, and an author for UpToDate.

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METHODS

Consecutive dermatitis patients undergoing routine patch testing in our contact dermatitis program between September 2017 and February 2018 were included (Brigham and Women's Institutional Review Board protocol #2016P000751). All patients were tested to N2.5 and N5, which are both on our standard series of allergens. Any patients who were not tested to either or both nickel concentrations, such as those with known nickel contact allergy, were excluded from the analysis. Allergens (Chemotechnique Diagnostics, Malmö, Sweden) were placed in Finn Chambers (Smart Practice, Phoenix, AZ) on Scanpor tape. Nickel sulfate was the metal salt tested in both concentrations of nickel.

Allergens were adhered to the skin of each patient and left in place for 48 hours. After 48 hours, the patches were removed and an initial reading was performed. Patients returned for a final, in-clinic reading 3 to 7 days after patch placement. Reactions were graded from 0/no reaction to ?/questionable reaction, +/-weak positive reaction, ++/strong positive reaction, and +++/extreme reaction. For data analysis, all 0 and ? reactions were considered negative. McNemar test for matched data was performed using STATA.⁴

RESULTS

A total of 205 consecutive dermatitis patients were evaluated with N2.5 and N5. Among all patients tested, 33% (67/205) were positive

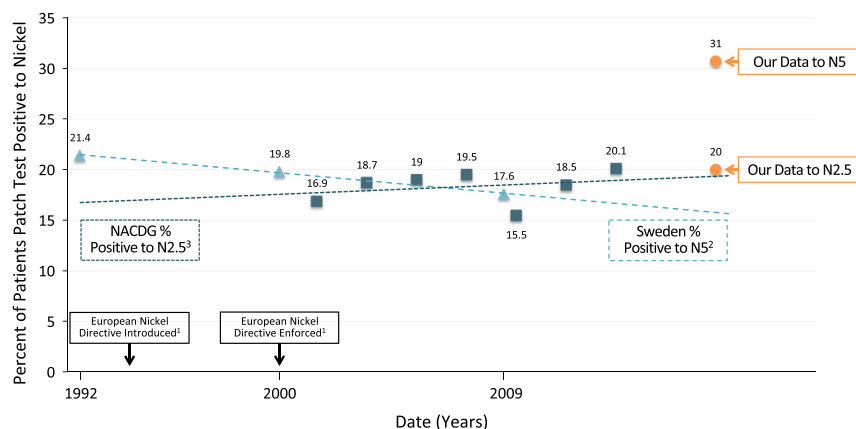


Figure 1. Scatterplot showing percentage of the patients positive to nickel on patch testing over time in Sweden (N5, turquoise triangles) and North America (N2.5, teal squares) and data from the current study (N2.5 and N5, orange circles).

(+, ++, or +++) to at least 1 concentration of nickel, 20% (41/205) were positive to N2.5, and 31% (63/205) were positive to N5 (χ^2 ($N = 205$) = 16.1, $P < 0.0001$; Fig. 2). No irritant or pustular reactions were observed. In our cohort, 61% (41/67) of nickel-positive patients were detected by N2.5 compared with 94% (63/67) detected by N5 (Fig. 3). In addition, patients were 6.5 times more likely to have a positive reaction to N5 than N2.5 (odds ratio [OR] 95% confidence interval [CI], 2.3–25.6).

When considering only ++ and +++ reactions as positive, 24% (49/205) of the patients were positive to at least 1 concentration of nickel. Nickel sulfate 2.5% detected strong or extreme reactions in 14% (29/205) of the patients compared with 22% (46/205) detected by N5 (χ^2 ($N = 205$) = 12.6, $P = 0.0005$). Whereas 49 patients had a ++ or +++ reaction to at least 1 concentration of nickel, only 59% (29/49) of these were detected by N2.5 compared with 94% (46/49)

detected by N5. Patients were 6.7 times more likely to have a ++ or greater reaction to N5 than N2.5 (OR 95% CI, 2.0–35.0).

Final read visits were 3 to 7 days after patch placement, with 43% falling on day 3 and 57% between 4 and 7 days. There was a 4.5 greater chance of detecting nickel positivity with N5 than N2.5 for day 3 final reads (OR 95% CI, 0.9–42.8) compared with an 8.5 greater chance for more delayed, day 4 to 7, final reads (OR 95% CI, 2.0–75.9).

From the initial read (48 hours) to the second, final read (range, 72–168 hours) negative, ?, and + reactions all showed a crescendo effect, with intensification of the patch test reaction; ++ and +++ reactions were either stable between the initial and second, final read or intensified.

Twenty-one percent of the patients without a history of dermatitis secondary to metallic objects, such as jewelry, were positive to at least 1 concentration of nickel on patch testing; the positive and negative predictive values for reported history of jewelry dermatitis and nickel reactivity on patch testing were 49% and 67%, respectively.

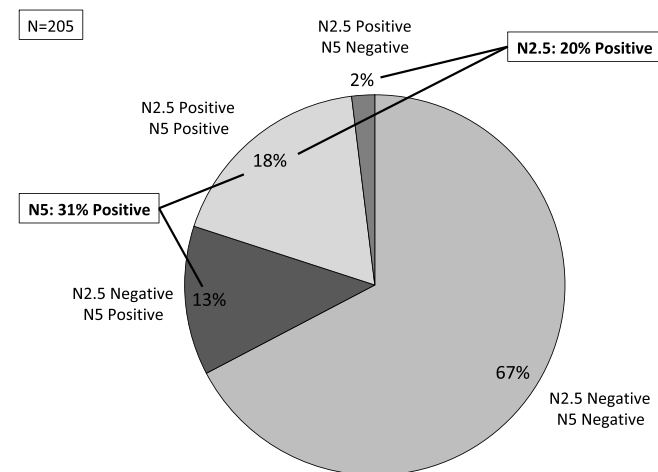


Figure 2. Pie chart showing percentage of the patients tested in the current study ($N = 205$) who are negative to both N2.5 and N5 (67%), positive to both N2.5 and N5 (18%), positive to N2.5 only (2%), and positive to N5 only (13%) (χ^2 ($N = 205$) = 16.1, $P < 0.0001$). Positive reactions for this chart included those demonstrating at least a + reaction at the final read visit.

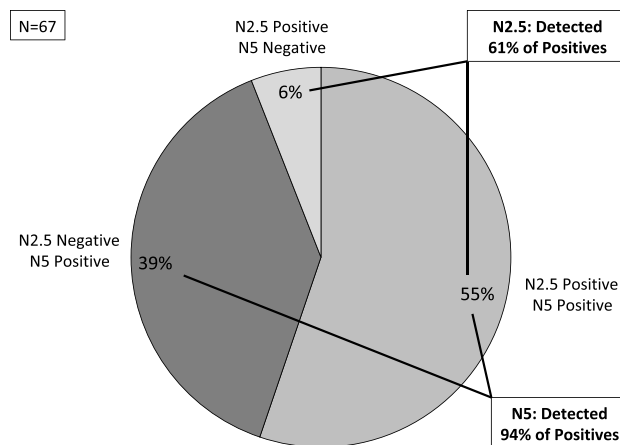


Figure 3. Pie chart showing percentage of the nickel-positive patients ($n = 67$) detected by both N2.5 and N5 (55%), N2.5 only (6%), and N5 only (39%). Positive reactions for this chart included those demonstrating at least a + reaction at the final read visit.

DISCUSSION

Nickel is among the most common contact allergens identified on patch testing and often has clinical relevance. The North American Contact Dermatitis Group calculated that nickel was the second most clinically relevant allergen based on an assessment of clinical significance and prevalence of patch reactions of 4850 patients tested in 2013 to 2014.³ Therefore, accurate identification of nickel sensitivity on patch testing can be critical in developing allergen avoidance strategies. In the North American Contact Dermatitis Group's most recently published data, 20.1% developed positive reactions to N2.5 and 12.4% developed ++ or +++ reactions to N2.5.⁵ In our cohort, positivity rates to N2.5 were similar, with 20% developing at least a + reaction ($P = 0.97$) and 14% developing at least a ++ reaction ($P = 0.47$).

Nickel-positive patients in our study demonstrated an intensification, crescendo effect of their reactions from the initial to final read or a stable, strong, or extreme reaction at both reading visits. These findings are consistent with allergic, not irritant-type, contact reactions. There were 4 patients in our study who demonstrated at least a + reaction to N2.5 but no reaction to N5. When considering the proportion of positives that were detected only by the lower allergen concentration, our findings on N2.5 and N5 were similar to those of several previous studies comparing formaldehyde 1% and 2% (range, 2.1%–6.5%).^{5–7} We hypothesize that the volume of allergen, actual concentration of nickel dispensed, or strength of patch adhesion may be responsible for this discordance. However, although a certain small degree of variation may be expected, N5 detected significantly more positive reactions than N2.5.

Patch test reactions to metals such as nickel may occur later than other allergens.⁸ We also found that differences between N2.5 and N5 positivity were greater at the more delayed, 4- to 7-day readings (OR, 8.5) than day 3 readings (OR, 4.5). The discordance between history of jewelry dermatitis and nickel positivity on patch testing is also well established.⁹ In our study, only 49% of the patients with a clinical history suggesting metal sensitivity were patch test positive to at least 1 concentration of nickel. One explanation is likely reactivity to other metals present in jewelry such as gold and cobalt. In a previous study, patch testing with an extended metal series identified a higher percentage of metal-reactive patients among those with a history of jewelry dermatitis compared with the standard series.⁹

Our study has several limitations. We are part of a specialized contact dermatitis program, and therefore, our findings may not be generalizable to a non-tertiary care setting. In addition, we may

detect more weak reactions than other practitioners given our use of a magnifying lamp. However, the analysis that included only the ++ and +++ reactions to nickel sulfate as positive, reactions unlikely to be missed, detected significantly more positive reactions to N5 than N2.5. Although a measuring device was not used to dispense allergens, the same nurse loaded both the N2.5 and N5 onto Finn Chambers during the entire study period.

CONCLUSIONS

An accurate evaluation of nickel contact allergy is crucial because of the high frequency of clinical relevance and prevalence of positive reactions. We demonstrate that N5 is significantly more sensitive in the detection of nickel allergy compared with N2.5. Moreover, the findings in our study suggest that the burden of nickel allergy in the North American population may be underestimated by the use of N2.5 as a screening tool. We therefore propose further investigation of N5 as a replacement for N2.5 as the standard nickel allergen used for patch testing in North America.

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