

Prevalence of nickel allergy among Finnish university students in 1995

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Nickel allergy was studied in a sample of 1st-year university students starting their studies in 1995. A total of 296 subjects (72%) of 413 invited participated in the clinical examination, and 284, 96 male and 188 female, were patch tested (69%). A history of nickel sensitization was enquired for. Prick tests and serum specific IgE levels were determined. Occurrence of atopic dermatitis, hand eczema, and current exposure to metals were recorded. Nickel allergy was encountered in 39% of all female students, in 42% of females with pierced skin, and in 14% of females without pierced skin. The corresponding figures for males were 3%, 7% and 3%. In the multiple regression analysis, the risk factors for nickel allergy were female sex (OR 8.1, $p < 0.01$), current metal exposure at examination (OR 4.1, $p < 0.01$) and skin piercing (OR 3.6, $p < 0.05$). Positive prick tests or elevated IgE levels to common allergens were not significantly associated with nickel allergy. In female students, the prevalence of nickel allergy has increased from 13% in 1986 to 39%. The prevalence among males has remained low at 3%. The results indicate that, in addition to skin piercing, current metal contacts are important risk factors for nickel allergy. This finding gives support to the EU Nickel Directive.

Key words: nickel allergy; atopy; skin piercing; clinical epidemiology. © Munksgaard, 2001.

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Nickel is the commonest cause of contact allergy in Western countries. During the last few decades, the prevalence of nickel allergy has increased, especially among females (1–8). The increase has been particularly strong among young females (1–7). In Finland, in the middle of the 1970s, the prevalence among schoolgirls was found to be 1% (9), 10 years later 16% (2). In the 1990s, the prevalence of 30% was reported among female adolescent population (7). The prevalence of nickel allergy in males is considerably lower, but has shown a tendency to increase (10, 11). Nickel allergy is often connected with chronic dermatitis, especially chronic hand dermatitis (12, 13).

Today, the major nickel exposure occurs through jewellery and everyday goods (14). In several studies, a clear relationship between ear piercing and nickel sensitization has been found (1–8, 10, 11).

According to a study among Finnish 1st-year university students in the middle of the 1980s, nickel allergy was found to be 13% in females, and 3% in males (3). In connection of a larger study “Allergy 95” (15), we examined the point preva-

lence of nickel allergy among Finnish 1st-year university students, and compared the sensitization rate with specific IgE levels and prick test results.

Subjects and Methods

A postal survey, called “Allergy 1995” (15), evaluating possible risk factors for asthma and allergic diseases was sent to all 14,200 Finnish 1st-year university students aged 18–26 years. A total of 10,667 (75.0%) students responded. For questionnaire validation purposes, 413 students were invited for clinical examination. The clinical sample was chosen from the city of Turku, where the 3 universities have students coming from all parts of Finland. To obtain enough subjects with asthma symptoms, a random sample of 195 students with asthmatic symptoms during their lifetime was selected. A random sample of students without asthmatic symptoms formed a sex-matched control group ($n=218$). A total of 296 students (72.0%) from 413 invited participated in the clinical study in 1996–1997. Among them, 152 were symptomatic for asthma and 144 were non-

symptomatic. The mean age of the subjects was 21.5 years (range 18.7–26.6 years).

Clinical examination was performed by a chest physician and by a dermatologist. A total of 284 students (68.8%) underwent patch testing with 5% nickel sulfate hexahydrate in pet. (Chemotechnique, Malmö, Sweden). The characteristics of the subjects patch tested are shown in Table 1. The reasons for not attending the tests were pregnancy in 1 person, and in the others ($n=11$) the unsuitable time schedule of the test. Informed consent was obtained from all the students. For comparison, 270 students were also tested with 1% nickel chloride in petrolatum. Prick tests and blood tests for specific IgE levels were carried out.

Dermatological examination

Signs possibly due to contact with metals, signs of atopic dermatitis (AD) (16) and hand eczema were registered. The diagnosis of hand eczema was made, if 1 or more of the following signs, erythema, scaling, lichenification, vesiculation on dorsal or ventral aspects of the hands or fingers, were present. The history of skin piercing was recorded in detail (number and sites of skin piercing, age at 1st skin piercing). All metal items worn by the students, including, e.g., jewellery, metal buttons, metal parts of wrist watches, spectacle frames, hairpins, belt buckles and metal zips, were noted. Dimethylglyoxime test was not performed.

Patch testing

Finn Chambers[®] on Scanpor[®] (Epitest, Tuusula, Finland) were used for patch testing. Tests were applied to the upper back, removed at 2 days and read at 4 days. The results were interpreted according to recommendations of the International Contact Dermatitis Research Group (ICDRG), and positive reactions from + to +++ were regarded as allergic.

Skin prick testing

The skin prick test panel included birch, timothy and mugwort pollens, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Pityrosporum ovale*, cat, dog and horse epithelia and house dust mite (*D. pteronyssimus*) (Soluprick[®], ALK-Abelló, Denmark), and natural rubber latex allergen (Stallergenes[®], France). Histamine dihydrochloride 10 mg/ml was used as a positive and diluent as a negative control. To optimize the result, the tests were carried out in duplicate, on the volar aspects of both forearms. The mean diameter of the 2 weals was calculated, and the test was considered as positive if the mean diameter was at least 3 mm (17).

Specific IgE

Assays for specific IgE antibodies against common inhalant allergens (Phadiatop[®], including cat, dog, horse, birch, timothy grass, mugwort, *D. pteronyssimus*, and *Cladosporium*) and food allergens (F×5[®], including milk, egg ovalbumin, wheat, soy bean, codfish, and peanut), both from Pharmacia-Upjohn, Uppsala, Sweden, were performed. The tests were regarded as positive when at least 0.35 kU/l.

Statistical analysis

Pearson's χ^2 test was used to test the association between nickel sensitization and possible risk factors. Multiple logistic regression analysis (SAS) was used to calculate independent association between the possible risk factors and nickel sensitization.

Results

In total, positive patch test results to 5% nickel sulfate were seen in 27% (76/284) of all students, 39% (73/188) of female students and 3% (3/96) of male

Table 1. Characteristics of the clinical study subjects patch tested with 5% nickel sulfate. Current diagnoses on clinical examination

	Women $N=188$ (%) (n/N)	Men $N=96$ (%) (n/N)	All $N=284$ (%) (n/N)
positive prick test (≥ 3 mm)	53.2 (100/188)	60.4 (58/96)	55.6 (158/284)
positive Phadiatop [®] or F×5 [®] $\geq 1^*$	57.0 (106/186)	67.7 (65/96)	60.6 (171/282)
atopic dermatitis [†]	19.7 (37/188)	10.4 (10/96)	16.5 (47/284)
hand eczema [†]	12.2 (23/188)	6.2 (6/96)	10.2 (29/284)
allergic rhinitis [‡]	40.8 (75/184)	47.4 (45/95)	43.0 (120/279)
allergic conjunctivitis [‡]	39.7 (73/184)	43.2 (41/95)	40.8 (114/279)
asthma [#]	28.5 (53/186)	24.2 (23/95)	27.0 (76/281)

* Phadiatop[®] (inhalant allergens) and/or F×5[®] (food allergens) >0.35 kU/l. [†] On dermatologist's examination. [‡] Based on positive history at physician's interview, and positive prick test or positive specific IgE result. Subjects with complete data included. [#] Based on physician's interview, and lung function tests.

Table 2. Prevalence of nickel allergy among female and male university students, with skin pierced or skin not pierced

	Positive patch test result to 5% nickel sulfate		
	Skin not pierced (%) (95% CI) n/N	Skin pierced (%) (95% CI) n/N	In total (%) (95% CI) n/N
women	14.3 (0.0–29.2) (3/21)	41.9*** (34.4–49.4) (70/167)	38.8 (31.9–45.8) (73/188)
men	2.5 (0.0–5.8) (2/81)	6.7 (0.0–19.3) (1/15)	3.1 (0.0–6.6) (3/96)
all	4.9 (0.7–9.1) (5/102)	39.0*** (31.9–46.1) (71/182)	26.8 (21.6–31.9) (76/284)

*** $p < 0.001$ between subjects with pierced and non-pierced skin.

students ($p < 0.001$, Table 2). The results of patch testing with 5% nickel sulfate hexahydrate and 1% nickel chloride were quite similar: only 5% (3/65) of subjects with a positive patch test to 1% nickel chloride were negative to 5% nickel sulfate. The percentage of nickel sulfate-positive, but nickel-chloride-negative, cases was 9% (6/68).

Skin piercing was present in 89% (167/188) of female students and in 16% (15/96) of males. The piercing was mainly in the ears: in 10 students also elsewhere, most often in the nose. The maximum number of sites of skin piercing in 1 subject was 20. The mean age at the time of skin piercing was 11 years for women and 16 years for men. The total prevalence of nickel allergy was 39% (71/182) among those with pierced skin, and 5% (5/102) in those with non-pierced skin (Table 2). In female students nickel allergy associated significantly with skin piercing, but the correlation was not significant in males (Table 2). In females, the prevalence of nickel allergy was not linearly associated with the number of sites of skin piercing, 37% (38/104) with 1–2 sites and 42% (33/78) with 3 sites or more being sensitized to nickel. There was no statistically significant association between the age of the 1st skin piercing and nickel sensitization.

Of female students, 53% (99/188) and 15% of male students (16/105) reported a history of metal contact dermatitis. The primary site reported by these 115 students was on the earlobes in 57% of females and on the wrists in 50% of men. Among the female students 40% with a positive history had a negative patch test result. Only 13% of male students with a positive history of metal dermatitis were allergic to nickel.

Among female students, current hand eczema (HE) was found in 14% (10/73) of nickel-allergic, and in 11% (13/115, $p > 0.05$) of non-allergic, sub-

jects. Of subjects with atopic dermatitis 34% (16/47) were allergic to nickel.

Metal items in contact with the skin were recorded at the dermatologist's examination in 82% of female students and in 74% of males. Nickel allergy was positively associated with metal exposure at examination. Of female students with current metal exposure, 45% had nickel allergy, compared to 18% without metal contacts ($p < 0.01$). Each of the 3 male students with a positive patch test result to 5% nickel sulfate had metal exposure at examination.

In the clinical sample the prevalence of atopy, defined by at least 1 positive prick test result, was 53% in women and 60% in men ($p > 0.05$, Table 1). At the dermatologist's examination 20% of women and 10% of men had current atopic dermatitis ($p < 0.05$), and hand eczema was also more prevalent in women than in men, 12% versus 6% ($p > 0.05$), respectively (Table 1). The prevalence of nickel allergy was 23% (37/158) in prick-test-positive students and 31% (39/126) in prick-test-negative students. The corresponding rates for nickel allergy among specific-IgE-positive (at least 1 specific IgE > 0.35 kU/l in Phadiatop® or F×5®) and -negative students were 25% (43/171) and 30% (33/111). Of subjects with current atopic dermatitis 34% (16/47) were allergic to nickel. 52% of atopic students with a history of metal contact dermatitis had a positive patch test compared to 57% of non-atopic students. The differences were not statistically significant.

In the univariate analysis, female sex (OR 19.7, 95% CI 7.9–48.9) and skin piercing (OR 12.4, 95% CI 5.6–27.4) were the strongest risk factors for nickel allergy (Table 3). The corresponding unad-

Table 3. Prevalence of nickel allergy, unadjusted odds ratios and 95% confidence intervals for nickel allergy by sex, current metal exposure, skin piercing, and atopy (Finnish university students aged 19–26 years)

	Prevalence* (%)	n/N*	Unadjusted OR*	95% CI
sex				
male	3.1	3/96	1.0	
female	38.8	73/188	19.7	7.9–48.9
skin piercing				
no	4.9	5/102	1.0	
yes	39.0	71/182	12.4	5.6–27.4
current metal exposure				
no	10.7	6/56	1.0	
yes	32.5	68/209	4.0	1.7–9.4
atopy†				
no	31.0	39/126	1.0	
yes	23.4	37/158	0.7	0.4–1.2

* Using all available data. † At least 1 prick test ≥ 3 mm.

Table 4. Adjusted odds ratios and 95% confidence intervals for nickel allergy by sex, current metal exposure, skin piercing, and atopy (Finnish university students aged 19–26 years)

	Adjusted OR*	95% CI	p-value
sex			
male	1.0		
female	8.1	2.1–30.8	<0.01
skin piercing			
no	1.0		
yes	3.6	1.2–10.8	<0.05
current metal exposure			
no	1.0		
yes	4.1	1.6–10.7	<0.01
Atopy†			
no	1.0		
yes	0.6	0.3–1.2	NS

* Adjusted for all the other variables in the table, includes 265 subjects with complete data on all the variables. † At least 1 prick test ≥ 3 mm.

justed odds ratios for current metal exposure were 4.0 (95% CI 1.7–9.4) and atopic sensitization (prick test at least 3 mm) 0.7 (95% CI 0.4–1.2, Table 3). In the multiple regression, adjusted for current metal exposure and atopy, female sex remained as the strongest independent risk factor (OR 8.1, 95% CI 2.1–30.8), whereas skin piercing (OR 3.6, 95% CI 1.2–10.8), and current metal exposure (OR 4.1, 95% CI 1.6–10.7) were equal risk factors (Table 4). Atopic sensitization was not significantly associated with nickel allergy (OR 0.6, 95% CI 0.3–1.2) (Table 4).

Discussion

The result of the present study indicates a considerable increase in the prevalence of nickel allergy among female university students during the past 10-year period 1985–1995. The prevalence increased from 13 to 39% (3). This has taken place despite of active information about risks for nickel sensitization given at many levels, e.g., at schools in Finland.

According to a population study in 1975 in Finland, the prevalence of nickel allergy among women was 10%. Among schoolgirls it was 1% (9), and 10 years later 16% (2). At the same time the increase among young females was not as steep, 8% (9) v 13% (3). In 1990, the prevalence among Finnish female adolescents was 30% (7). In population-based studies in Denmark and Norway in the 1990s, the prevalence of nickel allergy among young Danish females (5), as well as among Norwegian schoolgirls, was about 20% (6) and among Norwegian women 31% (8). The figures reported of nickel allergy among Finnish schoolboys and

young males during the past about 20-year period were only 1–3% (2, 7, 9).

The main sources of nickel sensitization have varied over the decades, largely reflecting the variability of fashion. Today ear-ornaments, wrist-watches and buttons are the objects most often causing dermatitis (14). A clear relationship between ear piercing and nickel sensitization has been found in several studies (1–8, 10, 11). In population studies from Scandinavian countries, the prevalence of nickel allergy among young females with pierced skin has varied from 13 to 20% in the 1980s (1–3), and in the 1990s it has been reported to be roughly 30% (6, 7). Among young men nickel allergy is not as common. In Nordic population studies from the last 20 years, the figures have varied from 2 to 8% if skin not pierced, and from 4 to 9% if pierced (5–7, 10, 11).

In agreement with previous and recent studies (1–8), sensitization to nickel associated clearly with skin piercing in females. Multiple sites of piercing (3 or more), though frequent in our study, did not significantly increase the risk of nickel allergy compared with 1–2 sites, though some tendency could be found. Studies among Nordic schoolchildren (1, 2, 6), in contrast to our study, support increased risk with multiple sites of piercing.

Current exposure to metal items was positively associated with nickel sensitization. Interestingly, the 4× risk was equal to that of skin piercing. The result is parallel to a recent study suggesting that metal exposure is the route for nickel exposure, eliciting or maintaining nickel allergy (14) or nickel dermatitis (18). The only way to evaluate personal behaviour is to inspect the patient. Therefore we evaluated metal exposure by inspection. Dimethylglyoxime test was not used, because it reveals the release of nickel only from items worn at the very moment of the investigation. In clinical practice young people often claim, that they never use jewellery that contains nickel. However, using cheap jewellery is popular and there has been no limitation of nickel in metals in close association with skin. Strictly avoiding constant metal contacts, especially in clothing and jewellery, has been shown to improve the prognosis of metal dermatitis (18).

History of metal intolerance may lead to over-diagnosing of nickel sensitization (6, 19, 20). Transient irritation under metal items can easily be recorded as nickel sensitization. Positive history but negative test result has been related to atopy (3, 6, 19), but not in all studies (20). In the present study, nickel allergy was found in 57% of non-atopic and 52% of atopic subjects with a positive metal history, suggesting that atopic subjects somewhat over-report nickel allergy.

Nickel chloride, tested at 2.5% or higher concentrations, has appeared to be a more sensitive but also more irritating patch test agent than 5% nickel sulfate hexahydrate (21). To avoid such irritation, we used a lower concentration. However, the results with 1% nickel chloride were parallel with 5% nickel sulfate hexahydrate.

In the present study, female sex independently increased the risk of nickel sensitization. The finding is in line with experimental data on sensitization to dinitrochlorobenzene, suggesting that women are more easily sensitized (22). Moreover, several population studies (3, 5, 7, 8), as well as a patient study (4), have shown a different prevalence rate among males and females with pierced earlobes, thus providing indirect evidence to support the theory. Length of exposure due to lower age of skin piercing in females, might be a valid explanation for the sex difference. In this study, however, the age of 1st skin piercing was not associated with nickel sensitization. Quantity of exposure (23) might be another explanation, e.g., nickel release when sweating, and possibly racial differences, could explain the result. In 1985, according to a patient study in Nigeria, where men also commonly wear cheap jewellery, equal rates of sensitization were found among men and women (24).

In female students atopic sensitization (a positive prick test to common allergens, or serum specific IgE) seemed to decrease the risk of nickel allergy, though not significantly. This observation is in line with previous studies among university students (3), and atopic eczema patients (4), as well as in the Danish population (25), which found no association between elevated total serum IgE, or positive prick test results, and the development of delayed hypersensitivity.

It has been suggested that nickel allergy increases the risk of hand eczema (10, 26), though the finding is not supported by all studies (4, 11, 27). In the present study no association was found between nickel allergy and current hand eczema in females. The occurrence of atopic sensitization in combination with nickel allergy did not increase the hand eczema risk, either, in contrary to earlier studies (3, 27). However, in those studies, the definition of atopy was based on symptomatic atopic diseases.

The present study addresses the importance of the EU Nickel Directive (28), in which not only exposure during epithelialization after skin piercing, but also exposure to nickel-releasing materials in direct and prolonged contact with skin is regulated. In Denmark strict national legislation on nickel-releasing objects has been in place since 1990 (29) and, as a result, the prevalence of nickel

allergy among adolescents has resulted in a decrease in nickel allergy (30). We await a similar development in other EU countries in the coming years.

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