

Nickel Levels in Serum and Urine in Five Different Groups of Eczema Patients Following Oral Ingestion of Nickel

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Patients with nickel allergy and different types of eczema with and without atopy were given a single oral dose of nickel sulfate. Blood levels and urinary excretion were determined by atomic absorption spectrophotometry. Urinary excretion of nickel was found to be dependent on age, decreasing with increasing age. When difference in age between the eczema groups was taken into account, the level of nickel in urine was significantly ($p < 0.005$) higher in the two atopy groups compared to the controls. This may indicate a higher intestinal absorption of nickel in atopic skin disease. Key words: pompholyx; atopy; absorption.

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Since 1975 (1) it has been shown in several studies that oral challenge with nickel causes exacerbation of vesicular hand eczema in nickel-sensitive patients, along with other manifestations such as flare-up reactions of earlier patch test sites.

From these studies it seems relatively clear that these flare-up reactions are dose-dependent and that doses between 0.5-5.6 mg are usually required (1-3). The reaction to an oral challenge with nickel is probably also dependent on individual sensitivity. The amount of nickel in urine varies considerably between individuals, maybe in consequence of a varying degree of absorption (2-5). Some studies indicate that the excretion of nickel increases in association with outbreaks of vesicles (6).

In a long-time follow-up by Christensen (7) it was shown that patients with nickel allergy, hand eczema of the pompholyx type, and atopy had a less favourable prognosis than patients with this type of hand eczema without atopy. In several oral provocations with nickel, we have also observed strong flare-up reactions in atopic patients.

In a recently published epidemiological and allergological

study on pompholyx by Lodi et al. (8) it was found that nickel was the most common allergen in patients with pompholyx. It is interesting to note that 57% of these also had a personal or family history of atopy.

Therefore, in the present study we investigated the concentration of nickel in serum and urine in different eczema groups related to a fixed oral intake of nickel, with the aim of establishing if there is any difference between these eczema groups with or without atopy.

MATERIAL AND METHODS

Fifty-two female patients with five different types of eczema were enrolled in the study after approval by the Ethics Committee at Lund University. The different eczema groups are presented in Table I.

Urine was collected in polyethylene acid-washed bottles during a 24-h period before ingestion of nickel. Approximately 15 ml from each sample was taken and stored frozen until nickel analysis.

The patients were instructed not to eat or drink from midnight before coming to the clinic at 8:00 a.m. A venous blood sample of 10 ml was taken in a test tube without additive by puncturing the elbow flexural vein. The blood sample was centrifuged and stored frozen until analysis. Each patient then swallowed a capsule containing 4.48 mg nickel sulfate ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) in lactose, the nickel content being 1 mg. The patients were instructed not to eat until 1 h after ingestion of nickel.

Three hours later a second venous blood sample of 10 ml was taken and treated as mentioned above. During a 24-h period after ingestion of nickel urine was collected and stored as mentioned above.

The analysis of nickel in serum and urine was carried out on an atomic absorption spectrophotometer with a Hitachi Z-7000 instrument equipped with a graphite furnace (4,9). The accuracy of the analytical method was ascertained with duplicate analysis resulting in a coefficient of variation of $\pm 5\%$. The detection limit for Ni/serum was 25 nmol/l and Ni/urine 50 nmol/l.

Urinary excretion of nickel was found to be dependent on age. Therefore multiple regression analysis was used in order to eliminate this confounding effect of age. Thus, the concentration of nickel in serum and urine, respectively, was set as dependent variables. Age and a classification variable (0 = control group, 1 = test group) were used as independent variables.

Table I. The different eczema groups

Group	Diagnosis	n	Mean age	Definition
1	Atopy	12	32	Previous or present, lichenified, flexural dermatitis and/or head, neck and shoulder dermatitis
2	Atopy + pompholyx	11	41	Atopy plus recurrent vesicular eruption of palms
3	Nickel allergy	10	40	Contact dermatitis from metals of jewellery or clothing and positive patch test with nickel sulfate (5% pet)
4	Nickel allergy and pompholyx	10	47	As group 3 and recurrent vesicular eruptions of palms
5	Controls	9	41	Seborrhoeic dermatitis without contact dermatitis and no atopic background

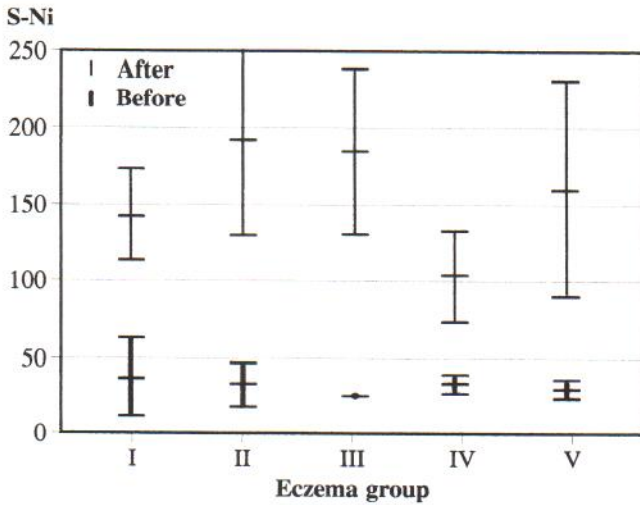


Fig. 1. Eczema group.

RESULTS

The mean value and SD for nickel concentration in serum before and after ingestion of nickel in the five patient groups are presented in Fig. 1. There were no significant differences in the mean values of nickel in serum between the five groups.

Individual values for urinary excretion of nickel before and after ingestion of nickel are given in Table II. Nickel concentration in urine was found to decrease with increasing age ($p < 0.01$). When we first studied the mean values of nickel in urine, no significant difference was found between the different groups, but when difference in age between the eczema groups was taken into account the level of nickel in urine was significantly higher ($p < 0.005$) in the two atopy groups, respectively, compared to the control group; no other inter-group significant differences were found.

Two patients in group IV (nickel allergy and pompholyx) had a clinical flare-up reaction following the administration of oral nickel. Both patients showed increased vesicular eruptions of

the palms and one of them also had flare-up reactions on earlier eczema sites, including the patch test. These two patients had the highest levels of urinary nickel in their group.

DISCUSSION

Many studies have shown that oral intake of nickel can cause flare-up of dermatitis in nickel-sensitive patients. The amount of nickel required has usually been higher than the normal daily intake of nickel (10), but in some patients a flare-up has been reported even in such low doses (5). In the present study a low oral dose of 1 mg nickel was chosen to avoid strong clinical reactions. Nevertheless, the two patients with the highest urine concentration had flares of their nickel dermatitis, an indication that individual sensitivity might be related to increased absorption.

An earlier study (4) has shown that urine is the most reliable parameter to follow after oral intake of nickel even though both serum and urinary levels of nickel reflect the nickel intake. A study by Sunderman et al. (11) indicates that food reduces the possibility of intestinal absorption of nickel and that a standardized schedule, as in the present study, for fasting and eating is required when measuring the absorption of nickel.

It is possible to increase or decrease the urinary excretion of nickel by giving a nickel-rich or nickel-poor diet, respectively (12, 13). A low-nickel diet has been tried in patients with nickel dermatitis (14); after 1 to 5 years, 59% reported an improvement if they continued their diet. There were no control groups in this study. A diet with a high content of natural nickel has been shown to worsen the hand eczema in nickel-sensitive patients (12). This may indicate that nickel in the diet has some effect on the eczema in nickel-sensitive patients.

Earlier studies have not, as far as we know, shown the nickel concentration in urine and serum to be influenced by age (15). We found the urinary excretion of nickel to be dependent on age, to decrease with increasing age. In this study we found significantly higher levels of nickel in urine in the two atopy groups compared to the control group, when difference in age

Table II. Individual and mean values for urinary nickel excretion before and after nickel ingestion in five eczema groups

	Group I		Group II		Group III		Group IV		Group V	
	Age	Before/after nmol/l	Age	Before/after nmol/l	Age	Before/after nmol/l	Age	Before/after nmol/l	Age	Before/after nmol/l
	19	75/4150	18	<50/3350	23	50/2450	72	125/1025	39	<50/1400
	25	100/3925	35	<50/1300	35	<50/2200	34	<50/775	49	<50/800
	39	<50/3150	36	<50/1275	61	<50/1000	33	50/675	23	50/625
	31	175/3000	40	<50/1100	26	<50/950	35	<50/600	35	<50/600
	26	50/850	51	<50/375	70	50/925	45	<50/350	43	<50/500
	29	<50/725	73	75/350	29	<50/650	44	<50/250	48	<50/425
	35	50/600	35	<50/250	28	<50/575	47	<50/225	29	<50/100
	40	50/500	39	<50/200	43	<50/525	68	50/125	54	<50/100
	30	50/425	40	125/200	38	<50/225	26	<50/125	51	<50/100
	31	<50/375	25	<50/175	51	<50/75	66	<50/75		
	33	<50/200	54	75/50						
	43	<50/200								
Mean value and SD	32 ±7	67±37/1508±1552	41 ±15	61±23/784±971	40 ±16	50±0/957±783	47 ±16	57±24/423±327	41 ±11	50±0/516±420

between the eczema groups was taken into account. Maybe patients with atopy have a higher degree of absorption of nickel. In atopic children an increased intestinal permeability to macromolecules has been demonstrated (16), but in adult patients with atopic eczema no such increased permeability has been found (17). To our knowledge there is no increased absorption to molecules of low-molecular weight in atopic patients.

We did not find any excessive increase of urinary nickel in patients with nickel pompholyx without atopy but an increase of approximately the same magnitude as that in the two other groups without atopy. Obviously, atopy seems to be the most decisive variable for the degree of intestinal absorption. Thus, patients with a combination of nickel allergy and pompholyx do not seem to have an increased absorption of ingested nickel. Although there were relatively few patients in each group, it does not seem that oral intake of nickel is of major importance in this group. However, as mentioned earlier (8), the combination of nickel allergy and atopy is frequent in patients with pompholyx.

The practical consequence of our findings is a matter of discussion. It seems reasonable that a low-nickel diet should be tested primarily in nickel patients with an atopic background. Further studies on nickel absorption and excretion are, however, needed.

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