

The role of nickel in foods exacerbating nickel contact dermatitis

Purello D'Ambrosio F, Bagnato GF, Guarneri B, Musarra A, Di Lorenzo G, Dugo G, Ricciardi L. The role of nickel in foods exacerbating nickel contact dermatitis.

Allergy 1998; 53 (Suppl 46): 143–145. © Munksgaard 1998.

**F. Purello D'Ambrosio¹, G. F. Bagnato¹,
B. Guarneri², A. Musarra¹, G. Di
Lorenzo³, G. Dugo⁴, L. Ricciardi¹**

Schools of ¹Allergy and Clinical Immunology, and
²Dermatology and ⁴Department of Pharmacochimistry,
University of Messina, Messina ³Department of
Internal Medicine and Geriatry, University of Palermo,
Palermo, Italy

Prof. F. Purello D'Ambrosio
School of Allergy and Clinical Immunology
University of Messina
98125 Messina
Italy

Nickel is a very common metal; it is the fourth most frequently used metal in the world and the principal cause of allergic contact dermatitis (CD). The prevalence of nickel sensitization in the general population is estimated at around 7–10% with a predominance in women; there is a F/M ratio of 7–14/1. Nickel is responsible for 35% of occupational and nonoccupational allergic CD. The average age for its onset is 21–30 years (1).

Nickel is commonly present in metal objects (fashion jewelry, glasses, tools, crockery) and in dyes (for porcelain, glass, earthenware, detergents, and food).

The nickel atom has two unpaired electrons in its peripheral orbit: this allows binding with organic peptides or proteins, which form antigen complexes capable of inducing an allergic reaction. It is absorbed through the cutis by inhalation, parenterally, by direct contact, or through the digestive tract.

Recent studies on nickel have shown that it plays an important role in alimentation. Firstly, it favors the absorption of trivalent iron, mostly in the case of low blood levels of iron, causing the synthesis or maintaining the integrity of a lipophilic complex involved in the transportation of the oxidized iron through the mucosa layer.

It also activates unspecifically several enzymes such as tyrosinase, arginase, deoxyribonuclease, and phosphoglucomatase (2).

In man, the blood levels of nickel vary from 1.6 to 7 µg/l, and the urine levels from 2 to 5 µg/l.

In the case of low levels of nickel, different kinds of alterations may occur according to the animal species considered. In man, clinical pictures due to nickel deficit have not been described, as the daily intake of this metal, about 50 µg, is covered by a normal diet even if it can differ from nation to nation because of dietary diversities, and the presence of the metal in the subsoil and in drinking water. The daily intake of nickel has been estimated at 300 µg per day in Italy, 300–600 µg in the USA, 347–576 µg in Canada, and from 200 µg to 4.5 mg in Sweden (3).

It has been shown that vegetables are the main source of nickel in diet; animal products have a low nickel content, but, among them, eggs have the highest. In a normal diet, 50% of the daily nickel supply is supplied by cereals and pulses, followed by fats, dairy products, and fruit (4).

Over the last 20 years, several studies reported a high percentage of patients with allergic CD from nickel who had cutaneous lesions in areas where there had been no direct contact with the metal. Because of the symmetry of the eczematous lesions, they were attributed to the systemic introduction of nickel (parenterally, by inhalation, in food).

The clinical features include scaly keratotic eczema localized on the flexor surface of the forearms and arms, the knee flexures, the eyelids, the neck, and the internal surface of the thighs. The disorder has been termed by some authors "Shannon's pseudoatopy".

With the introduction of nickel in food, other clinical pictures have later been correlated such as chronic erythematous papulovesicular dermatitis, urticaria, and purpura (5).

It has been observed that the intake of metal in food is capable of provoking relapses and/or causing contact eczematous lesions due to nickel to become chronic, particularly as in chronic dysidrotic dermatitis of the hands; it has been hypothesized that the latter is more likely to be caused by nickel ingestion than by contact (6).

In recent years, cases of chronic urticaria due to the intake of nickel in food have been reported to be caused by either type I or type IV pathogenetic mechanisms (7). In addition, it has been suggested that disorders such as allergic vasculitis and polymorphic erythema can become chronic after ingestion of nickel (8). All these different clinical pictures can be defined as "systemic contact-type dermatitis" caused by the systemic introduction of a metal, including nickel, cobalt, or chromium, in patients already sensitized to them.

Although some studies have underlined that cooking utensils of stainless steel can free nickel ions during cooking, recent studies by Flint & Packirisamy (9) have demonstrated that the amount of nickel from this source is almost negligible. These authors also state that the quantity of nickel released from a portion of food cooked in already used pans is lower than that contained in 5 g of chocolate (2.6 µg/g).

Up to now, immunologic or extraimmunologic mechanisms which may cause reactions induced by food containing nickel, in subjects sensitized to this metal, have been taken into consideration. Flare-ups of skin areas previously affected by contact eczema from nickel clearly indicate a delayed hypersensitivity reaction, as the ingestion of nickel in sensitized subjects induces increased lymphocyte proliferation.

Christensen demonstrated that a type IV reaction occurs, causing the relapse of eczematous lesions evoked by a nickel patch test after the oral ingestion of nickel.

A type III hypersensitivity mechanism has been hypothesized by Veien et al., as antinickel antibodies have been detected in sensitized patients after a positive oral nickel challenge (10).

This mechanism is evidenced by the delayed appearance of the reaction after an oral challenge, usually after 24 h, and the possibility of cutaneous features such as urticaria, polymorphic erythema, and systemic clinical features.

A type I hypersensitivity reaction has been hypothesized to cause immediate urticaria reactions (in this case, it is possible to evoke a positive prick test with a watery solution of 0.5–2.0% of

NiSO₄); specific IgE have also been found in patients with nickel-induced asthma.

Nevertheless, clinical reactions due to nickel may not be caused by immunologic mechanisms, but they can be secondary to the cytotoxic and pharmacologic effects of nickel. This metal, in fact, induces the unspecific proliferation of lymphocytes (11), has a cytotoxic effect on the macrophages (12), and induces pharmacologic degranulation of mastocytes and basophils (13). Some authors (14) have also hypothesized that the clinical features previously described may be caused by digestive food intolerance of the nickel salts.

Christensen & Moeller (15) were the first authors to show that nickel contained in foods may cause a flare-up of the eczema of the hands in patients already sensitized to the metal. Several studies have also confirmed that a flare-up of CD may be induced after oral challenge with varying doses of nickel from 0.5 to 5.6 mg, even if the results are contradictory; in most of them, in fact, it was found that a clinical flare-up could be evoked in more than 50% of the patients with an oral nickel challenge of 2.5 mg of Ni²⁺, which is a higher dose than the normal daily intake of the metal in foods.

For this reason, several authors recommend as main treatment in patients with endogenous CD from nickel not only the avoidance of direct contact with the metal but also a low-nickel diet for a period of not less than 6 months (16).

Other therapeutic approaches are represented by the administration of Antabuse (17) or disodium cromoglycate (18). The former has been banned because of its hepatotoxicity.

More encouraging results have been reached with disodium cromoglycate, especially if administered with a low-nickel diet, as it reduces intestinal permeability to the metal.

A new therapeutic approach is oral nickel-specific hyposensitization (19); nickel may be administered daily (with doses of 0.5 mg) or weekly (with doses of 5 mg). The mechanism of action is not yet well known; it has been hypothesized that the intestinal cells may become impermeable to nickel or that an activation of T suppressors may occur (20). In order to obtain the stimulation of these cells, immunomodulators such as thymopentine have been used with good results (21).

In conclusion, in the light of what has been reported, there are still some aspects of CD, as exacerbated by nickel contained in foods, which need further investigation:

- 1) additional knowledge of the mechanism of action

- 2) possible identification of other clinical features which could be considered as signs of this kind of sensitization
- 3) the standardization of the doses to administer during oral hyposensitization.

References

1. Schollhammer M, Guillet MH, Guillet G. Nickel and skin. *Ann Dermatol Venereol* 1994;121:338-45.
2. Nielsen FH, Ollerich DA. Nickel: a new essential trace element. *Fed Proc* 1974;33:1767.
3. McIlveen WD, Negusanti JJ. Nickel in the terrestrial environment. *Sci Total Environ* 1994;148:109-38.
4. Tsoumbaris P, Tsoukali-Papadopoulou H. Heavy metals in common foodstuff: quantitative analysis. *Bull Environ Contam Toxicol* 1994;53:61-6.
5. Purello D'Ambrosio F, Levanti C. Nichel e alimenti. In: *Atti del Meeting Annuale SIAIC, Giardini Naxos*, 1996:208-16.
6. Angelini G, Vena GA. Allergia da contatto al nickel. Considerazioni su vecchie e nuove acquisizioni. *Boll Dermatol Allergol Professionale* 1989;4:5-29.
7. Abeck D, Traenckner I, Steinkraus V, Vieluf D, Ring J. Chronic urticaria due to nickel intake. *Acta Derm Venereol* 1993;73:438-9.
8. Veien NK, Krogdaki A. Is nickel vasculitis a clinical entity? In: Frosh PJ, et al., editors. *Current topics in contact dermatitis*. Berlin: 1989:172-7.
9. Flint GN, Packirisamy S. Systemic nickel: the contribution made by stainless steel cooking utensils. *Contact Dermatitis* 1995;32:218-24.
10. Veien NK, Svejgaard E, Mennè T. *In vitro* lymphocyte transformation to nickel: a study of nickel sensitive patients before and after epicutaneous and oral challenge with nickel. *Acta Derm Venereol* 1979;59:447-51.
11. Spruit D, Bongaarts PJM. Nickel content of plasma urine and brain in contact dermatitis. *Dermatologica* 1977;154:291.
12. Gawrodder DJ, Shuttler IL, Delves HT. Nickel dermatitis and diet: clinical improvement and reduction in blood and urine nickel levels with a low nickel diet. *Acta Derm Venereol Suppl (Stockh)* 1988;68:453.
13. Veien NK, Christiansen H, Svejgaard E, Kaaber K. Antibodies against nickel-albumin in rabbits and man. *Contact Dermatitis* 1990;22:27.
14. Antico A, Soana R, Baioni R, Livio L. Dermatopatie croniche generalizzate da intolleranza alimentare ai sali di nickel. *Minerva Gastroenterol Dietol* 1990;36:165.
15. Christensen OB, Moeller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. *Contact Dermatitis* 1975;1:136.
16. Purello D'Ambrosio F, Gangemi S, Levanti C, Ricciardi L, Cuzzocrea S. Dermatite da Nichel introdotto con gli alimenti. *G Ital Allergol Immunol Clin* 1996;6:4-9.
17. Kaaber K, Menne T, Veien N, et al. Treatment of nickel-dermatitis with Antabuse: a double blind study. *Contact Dermatitis* 1983;9:297.
18. Pigatto PD, Gibelli E, Fumagalli M, Bigardi A, Morelli M, Altomare GF. Disodium cromoglycate versus diet in the treatment and prevention of nickel positive pompholyx. *Contact Dermatitis* 1990;22:27.
19. Sjoval P, Christensen OB, Möller H. Oral hyposensitization in nickel allergy. *J Am Acad Dermatol* 1987;17:774.
20. Lowney ED. Immunologic unresponsiveness to a contact sensitizer in man. *J Invest Dermatol* 1968;51:411.
21. Rantuccio F, Colizzi M, Polignano A, Sinisi DA, Antonaci S. Modulazione *in vivo* della risposta immunitaria con timopentina nelle dermatiti allergiche da contatto. *Ann Ital Dermatol Clin Sper* 1988;42:105.