

S. PIZZUTELLI

# Reply to: Update on Systemic Nickel Allergy Syndrome and Diet

Pediatric Allergology, Frosinone General Hospital, Frosinone, Italy

**Corresponding author:**

E-mail: sipizzut@tin.it

Dear editor,

I am glad to reply to Goldenberg and Jacob's observations, whom I thank for the kind attention given to my article.

As a preliminary consideration, I wish to reiterate that my paper discussed exclusively the exposure to nickel via food; it didn't discuss the other routes of systemic exposure. It distinguished allergic contact dermatitis (ACD) from systemic nickel allergy syndrome (SNAS) and, within the SNAS, systemic contact dermatitis (SCD, which has only cutaneous signs and symptoms) from extra-cutaneous (i.e. gastrointestinal, respiratory, neurological, etc.) signs and symptoms (see **table 1**) (1).

In what follows, I will discuss: diagnostic steps for nickel pathology (Section 1); and some possible differences in the management of the three forms of nickel pathology discussed (Section 2).

## 1. Diagnostic steps for nickel pathology

According to some authors, the following events would prove a relationship between the three forms of nickel pathology (ACD, SCD and extra-cutaneous SNAS) and nickel food intake (2):

- Improvement of eczema or of other symptoms with a low-nickel diet,
- Relapse or worsening with nickel oral challenge (NOC);
- Management with low-nickel oral hyposensitization treatment (NiOHT).

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**Table 1** - SNAS.

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- Cutaneous symptoms (SCD: Systemic Contact Dermatitis)
    - involvement of areas previously exposed to metal with flare-ups of previous eczematous lesions and patch test;
    - involvement of areas not previously exposed in the form of:
      - pompholyx;
      - baboon syndrome;
      - maculopapular exanthema;
      - flexural eczema;
      - urticaria;
      - itching;
      - vasculitis-like lesions.
  - Extra-cutaneous symptoms
    - gastrointestinal symptoms (abdominal pain, diarrhoea, vomiting, swelling, heartburn, nausea, constipation, etc.);
    - respiratory symptoms (rhinitis and asthma);
    - neurological symptoms (headache);
    - general symptoms (fever, fibromyalgia, joint pain, chronic-fatigue syndrome, etc.).
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The first two events are the two essential steps for the diagnosis of all allergies and food intolerances (diagnostic elimination diet and oral provocation test or challenge). As there is no specific laboratory test for the diagnosis of SNAS caused by nickel in food (both cutaneous and extra-cutaneous) the oral challenge is the diagnostic golden standard (3,4). Any other tests, such as the patch, are indicative but are not considered diagnostic. In the following paragraphs I will discuss each event with respect to nickel pathology.

#### a. Elimination diet

As underlined by Sharma himself, the effectiveness and reliability of the elimination diet in nickel pathology is sensitively reduced by the following factors (5):

- Strictly speaking, the elimination diet doesn't exist, because nickel is ubiquitous and cannot be eliminated from the diet.
- The nickel content of every single meal and therefore the daily intake of the metal are impossible to know. Nickel content in the same food varies sensibly because it is strongly influenced by nickel concentration in soil, which varies from place to place up to 100 times (5-500 µg/ gram), depending on the type of soil, the use of synthetic fertilizers and pesticides, soil contamination by industrial effluents and urban wastes etc. There are variations even in different batches of the same food in the same place. Variability factors of nickel content in the same food include: the season (more nickel in spring and autumn, less in midsummer); the part of the plant (more nickel in leaves than in stems and roots; more nickel in old leaves than in young leaves); etc. (5).
- The low-nickel diets suggested in literature differ from each other, sometimes substantially (1). This is also the case of the diets recently developed by Braga and Mislankar, notwithstanding their greater desirability and easier management (6,7).

Sharma notes that, because of the variability of nickel content in foods and, therefore, of its daily intake also in subjects following a low-nickel diet, the benefits gained from a particular low-nickel diet may not be uniform in all seasons and in every patient. The benefits gained from one type of low-nickel diet by one group of patients in one place may not be observed by another group in a different place (5). In a 2011 Italian study, 62,5% of subjects diagnosed as SNAS-affected did not respond to a six-month low-nickel diet (8).

According to the 2009 guidelines of the British Association of Dermatologists, there is only some evidence of the benefit of low-nickel diets in nickel-sensitive patients (Quality of evidence IV; Strength of recommendation C) (9).

The problems inherent in the low-nickel diets are schematically summarised in **table 2** (1,5,10).

As the low-nickel diet is manifestly unable to determine all the hypothetically affected subjects, it cannot be considered as a reliable diagnostic tool. Consequently, all the scientific studies on subjects

affected by SCD or SNAS, for which the patients were selected after a positive response to a low-nickel diet, must be considered methodologically weak and deprived of the necessary accuracy.

In the diagnostic iter of food allergies and intolerances the exclusion diet is followed by the evaluation of the improvement caused by such exclusion. However, such evaluations are contradictory. On one hand, Sharma underlines that one cannot expect the dermatitis to disappear completely during the diet, as the diet is only likely to lead to fewer and milder flare-ups (5,11). On the other hand, many studies, including recent ones, declare the complete resolution of the cutaneous pathology after the diet (12,13,14). Even greater problems in the interpretation of the results of the diet can be noted with respect to the extracutaneous SNAS and, above all, the neurological and gastrointestinal symptoms, which are subjectively reported by the patient and cannot be objectively evaluated by the physician.

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**Table 2 - Problems and perplexities about the low-nickel diet.**

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- a. Complete elimination of nickel from the diet is impossible (nickel is ubiquitous).
  - b. Nickel content in the same type of food varies from place to place, season to season, even widely.
  - c. Therefore, the food nickel intake of a person following a restriction diet cannot be determined with certainty.
  - d. The beneficial effect of a low-nickel diet is not guaranteed. It is not uniformly seen in all patients being prescribed such a diet for nickel dermatitis (Sharma).
  - e. Opinions vary about the nickel content which would determine the threshold of a low-nickel diet.
  - f. The low-nickel diets suggested in scholarly articles vary widely under several respect. In particular, there is no unanimity about allowed and forbidden foods:
    - In the 7 low-nickel diets considered, only cocoa, chocolate, peas and canned foods are always forbidden;
    - Six out of 7 diets forbid hazelnuts and peanuts;
    - Five out of 7 diets proscribe beans, lentils, shellfish, tea, spinach;
    - Tomatoes, fish, vegetables are allowed in some diets, not allowed in others.
    - Although having low nickel content, beer, red wine, herrings, mackerel, tuna, raw tomatoes, onions, carrots, apples, citrus fruits and their juices are forbidden in some diets because considered to worsen nickel eczema;
  - g. Opinions vary about inox steel pans and kitchen tools, which are not universally prohibited.
  - h. Using tap water is prohibited in some diets, prohibited under some conditions (first water of the morning) or allowed in others.
  - i. Although nickel allergy is life long, it is not clear how long a low-nickel allergy should last.
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### b. Nickel Oral Challenge (NOC)

The NOC after a low-nickel diet should allow to evaluate the reappearance (or new appearance) of symptoms connected to the intake of suitable quantities of food nickel. The NOC, however, does not reproduce natural exposure, either in terms of quantity of nickel intake or in terms of distribution during the day and various meals.

In many studies, the doses given in the challenge were much higher than the amount of nickel taken progressively throughout the day in a regular diet (15,16). In a study, patients sensitized to nickel seem to react to doses of 4 mg (about 10 times the contents of a normal diet) significantly more than to placebo, but not as frequently to doses of a normal diet (0.3 mg) or to a diet rich in nickel (1.0 mg), unless these doses are added to the usual food exposure (17). In the more recent Sicilian study the administered doses are elevated to 1,25-3,75 mg (18).

A dose of 4 mg of nickel corresponds to the assumption in one time of more than 3 Kg of milk chocolate or of nearly 10 Kg of beans (19). This form of intake may lead to differences in absorption and biokinetics of the element (20). One cannot exclude a dose-dependent toxic effect (21,22,23).

### c. Nickel Oral Hyposensitizing Treatment (NiOHT)

The nickel oral hyposensitizing treatment (NiOHT), predominantly discussed in Italian studies (12,24,25,26,27), was out of the scope of my precedent work. These studies, however, present the limitations mentioned above with respect to sample selection, based on an unreliable low-nickel diet and a NOC far away from natural exposure. Therefore they cannot be used to demonstrate the relationship between food nickel and symptoms of SNAS.

Additionally, NiOHT results with respect to cutaneous manifestations, which are objective and objectively appraisable, would not reach statistical significance, while such significance would be reached with respect to gastrointestinal symptoms (above all meteorism, but also abdominal pains, gastric acidity etc.), which are all subjective symptoms, reported by the patient and not objectively appraisable (12).

In conclusion, diagnostic difficulties and limitations in the clinical studies, resulting in non univocal results, do not allow me to reconsider the perplexities about food nickel allergy expressed in my previous paper.

## 2. Possible differences in the management of ACD, SCD and extracutaneous SNAS

The three types of nickel pathology discussed here (ACD, SCD and extracutaneous SNAS) may present some differences (table 3).

**Table 3 - Evidence of relationship with nickel and utility of diet in clinical manifestations of nickel allergy.**

Clinical form relationship with nickel	Evidence diet utility	
	YES	NO
<b>ACD</b>		
<b>SNAS</b> Cutaneous manifestations (Systemic contact dermatitis: <b>SCD</b> )	??	??
- flare-up		
- pompholyx,		
- baboon syndrome		
- maculopapular exanthema		
- flexural eczema		
- urticaria		
- itching		
- vasculitis-like lesions		
Extracutaneous manifestations	NO	NO
• Gastrointestinal		
- heartburn		
- abdominal pain		
- nausea		
- vomiting		
- meteorism		
- constipation		
- abdominal distension		
• Respiratory	YES	NO
- rhinitis		
- asthma		
• Other	NO	NO
- headache		
- chronic-fatigue syndrome		
- arthralgia		
- fibromyalgia		
- fever		

### ACD

The relationship of ACD with cutaneous contact with nickel is undisputed; however, the symptoms are not affected by high or protracted oral nickel intake. Therefore, although dietary restrictions are commonly imposed on many patients, a low-nickel diet has no utility in localised ACD (6,28).

Additionally, there is no substantial support for the purported "preventive" effect of low-nickel diet on cutaneous and gastrointestinal symptoms of the SNAS, either in recent literature or in the studies quoted by Goldenberg and Jacob. On the contrary, according to Röhrl and Stenberg, a vegetarian diet, by definition at high-nickel diet, is not associated with an increased preva-

lence of hand eczema, frequent manifestation of SCD, in sensitized individuals (29).

### SCD

Because of the weakness of the diagnostic methods and the lack of their standardization, different authors report widely varying prevalence of SCD manifestations. Sharma considers SCD to be a rare pathology, affecting a few patients (5,11); a Sicilian statistic study, on the other hand, maintains that SCD affects 3% of a population not selected for nickel sensitization (18); according to a recent report, SCD affects 20-30% of Ni-Patch positives (3). There seems to be some evidence of the relationship between food nickel and flare-ups in the site of previous injuries and previous patch tests, as well as of the relationship between food nickel and vesicular eczema of the hands (pompholyx), but only for very high doses (up to 10 times the amount that is deemed present in a normal diet). Lower doses do not cause more reactions than placebo (30). According to Hindsen, the flare-up induced by nickel in previous patch tests appears to be linked not only with the dose, but also with the intensity of the previous reaction and its proximity in time (31).

Admittedly, Jensen's meta-analysis of 17 clinical trials, quoted by Goldberg and Jacob, affirms that 1% of nickel allergic patients may have a systemic reaction to the nickel contained in a normal diet (0.22 mg or 0.35 mg or 0.55 mg) and 10% may react when exposed to quantity of food nickel between 0.55 and 0.89 mg (a quantity which could be reached by having a diet rich in high-nickel foods, drinking nickel-contaminated water from pipes and taps and/or drinking on an empty stomach a large amount of high metal content water). However, the authors themselves have pointed out that the subjects included in the studies and tested are not representative of the general population, as they are a selected sample of nickel allergic individuals, with symptoms that were so strong or so persistent to lead them to consult specialized dermatologists (16). One per cent of a population selected among nickel allergic individuals according to the severity of their symptoms would appear in line with what reported by Sharma about the rarity of the pathology (5,11).

The most recent studies, which are numerically modest and often case reports, do not offer elements of novelty and explanation (14,32,33). On the contrary, they are affected by the same, effectively inevitable, methodological errors that affected previous studies.

The perplexities already expressed subsist also with respect to the low-nickel diets recently designed for both the diagnostic avoidance phase and the therapeutic phase, despite the excellent work by Braga and Mislankar to suggest more desirable, acceptable and easily applicable low-nickel diets (6,7).

Based on the considerations above, I cannot but confirm that the treatment with low-nickel diet, because of its evident limits,

could be hypothetically suggested only for highly selected patients, i.e. for patients with wide and chronic manifestations of allergic dermatitis and nickel contact sensitization when topical avoidance does not appear sufficient, and a clear dependence between diet and clinical manifestations is shown. A low-nickel diet should not be a routine prescription or a first-step approach, as underlined in Matiz and Jacob's study (14).

However, for the same reasons explained above, the opinions about the use of a low-nickel diet, even in the limited cases suggested here, cannot be unanimous. In this sense, I reported that the therapeutic use of a low-nickel diet is controversial, i.e. debated and not unanimously shared. Unfortunately, this is still the case in the light of recent studies in literature.

### Extracutaneous SNAS

With respect to extracutaneous SNAS, the most recent medical studies do not add much to what I reported in my previous paper. Nowadays, these studies appear to give less prominence to headache, dizziness and respiratory phenomena among the symptoms potentially due to food nickel (3,12), while gastrointestinal symptoms would be dominant (18). The Sicilian study reports that 5% of a sample of patients not selected for nickel sensitization are affected by gastrointestinal troubles due to food nickel.

Moreover, recent medical studies are few in number. The majority of them is of Italian production and many of them have been published in the same scientific magazine. A big part of them considers the existence of gastrointestinal troubles induced by nickel in foods to be acquired and verified as fact. Quotations very often refer back to other quotations; sometimes the bibliographical reference is entirely missing or lack the support of a clear evidence (12,25,26,27,34,35,36,37).

According to some of these studies, SNAS would even show itself with isolated gastrointestinal symptoms, in the absence of correlated cutaneous manifestations or of patch positiveness (18). This would allow to formulate an hypothesis of gastrointestinal troubles due to nickel on the basis of an exclusively anamnestic approach.

However, such symptoms (in particular meteorism, appearing to be dominant (18), but including also abdominal pain, nausea, constipation, heartburn, vomit, diarrhea) are numerically limited, not specific and not always objectively assessed. They are shared by the greatest part of gastrointestinal illnesses: infectious, inflammatory, due to enzymatic deficit, neoplastic, at times even psychosomatic. In similar cases, identical symptoms are often attributed to not celiac gluten-sensitivity or to food intolerance, two conditions that share with nickel allergy the difficulty of a supported diagnosis. Lactose intolerance due to lactase deficit as well can show the same symptoms as gastrointestinal SNAS. One risks considering lactose intolerant patients

(breath test positive) who are casually positive to the nickel patch test to be affected by gastrointestinal SNAS (38).

To add a further confusing element, in all these pathologies gastrointestinal symptoms are not always objectively appraisable and often lack objective parameters to assess their improvement in the elimination diet and their worsening or the relapse in the provocation test. Meteorism, flatulence, heartburn, nausea and so on are subjective symptoms and they could sometimes have a strong psychosomatic component.

## Conclusions

In conclusion:

1. While SCD caused by food nickel might exist, the quality of the evidence is modest, the diagnostic tools are not orthodox and a possible diet has many limitations. Therefore, the prescription of a low-nickel diet is quite empirical and dictated by individual evaluations and its effectiveness, in any case, very uncertain and inconstant.

2. Extracutaneous SNAS caused by food nickel is much more doubtful, particularly the gastrointestinal type. In this case, besides the limits of the diagnostic iter described here, common to the whole suspicious nickel pathology, there are additional factors of doubt: the subjectivity of the symptoms, their not infrequent psychogenic component and the overlapping with gluten-sensitivity, food intolerances, and lactose intolerance.

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