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Systemic nickel hypersensitivity and diet: myth or reality?

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Key words

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Summary

Nickel is a very common metal contained in many everyday objects and is the leading cause of ACD (Allergic Contact Dermatitis). Nickel is present in most of the constituents of a normal diet, but some food groups are usually considered to be richer. However, the nickel content of specific food can vary widely, depending on many factors. Thus, the daily intake of nickel is also highly variable both among different populations and in a single individual, in different seasons and even in different days. Measuring precisely the daily intake of nickel from food and drinks is extremely difficult, if not impossible. The relationship between ACD and contact with nickel is undisputed and widely confirmed in literature. The situation is different for systemic nickel allergy syndrome (SNAS). The SNAS can have cutaneous signs and symptoms (Systemic Contact Dermatitis or SCD) or extracutaneous signs and symptoms (gastrointestinal, respiratory, neurological, etc.).The occurrence of SCD as a systemic reaction to the nickel normally assumed in the daily diet is very controversial. A rigorous demonstration of the relationship between SCD and nickel is extremely difficult. In particular, further and larger studies are needed to assess the reality and the prevalence of nickel urticaria. With respect to nickel-related gastrointestinal symptoms, as well as chronic fatigue syndrome, fibromyalgia, headache, recurring cold sores and recurrent infections in general, the data available in literature are not conclusive and the studies lack the support of clear, first-hand evidence. With respect to respiratory disorders, the role of food nickel and the effectiveness of a dietary treatment have been assumed but not proven. In fact, the usefulness of a therapeutic low-nickel diet is controversial: rare, if not exceptional, and limited to very sporadic cases of SCD. Additionally, the quantitative and qualitative composition of a low-nickel diet presents few certainties and many uncertainties. The low-nickel diets suggested in literature are highly variable, both in the extension of the restrictions and in their details - and the differences are not marginal. Conclusion: an evaluation of the data presented by medical literature about SNAS and its relationship with oral nickel does not allow to draw final conclusions. In the absence of genuine certainty we can only conclude that further and broader studies, more rigorously conducted, are needed.

Introduction to nickel allergy

Nickel is a very common metal that occurs in soil, water, air and in the biosphere. It is combined with other metals to form alloys. Most of the nickel produced worldwide is used for the production of stainless steel (1, 2). Nickel is contained in many everyday objects and is also used for detergents, soaps and cosmetics. Because of this wide exposure it is the leading cause of ACD (Allergic Contact Dermatitis).

The prevalence of nickel allergy appears to vary in different studies and selected populations. However, in recent years a marked upward trend has been recorded, primarily, though not exclusively, due to the increase in the practice of piercing (3, 4). A 2004 polycentric statistical study by the ESSCA (European Surveillance System of Contact Allergy), confirming other epidemiological studies (5), found that the prevalence of positive patch in the general population in Europe is about 20%. In particular, Italy is a leading country in Europe for the prevalence of individuals suffering from nickel allergy (32.1%) (6). Women are more strongly affected than men with a high F/M ratio ranging between 3:1 and 14:1. In two non-selected Norwegian populations, the prevalence of nickel allergy among women was found to be respectively 27.5% and 31.1% (7). In men, occupational exposure is the most responsible factor for raising sensitization and the prevalence of sensitization in unselected populations varies between 2 and 8%. In paediatric patients the prevalence is around 15-16%. Although sensitization is more common among teenagers, even newborns and infants can be sensitized to nickel, as well as other contact allergens (8-10). Nickel allergy may develop at any age but prevails in the third decade of life. Once developed, it persists for many years, often life-long (2, 8).

Nickel and food

Nickel in soil and water is taken up by living organisms, plants and animals, that are food sources for humans. Nickel is therefore present in most of the constituents of a normal diet. The nickel content in fruit and vegetables (0.5-5 μg/gr) is on average four times higher than in meat, milk, dairy products, eggs and other food of animal origin (0.1-5 μg/gr). However, the nickel content of specific food can vary widely, depending on the nickel content in the soil (ranging between 5 and 500 μg/gr) and water (between 5 and 100 μg/litre) (2, 11). There are therefore differences from region to region but also from place to place, depending on the type of soil, the use of synthetic fertilizers and pesticides, soil contamination by industrial and urban waste, the distance from nickel foundries. The nickel content of food also varies according to climate and season: an increase was observed in the concentration of nickel in fruit and vegetables in spring and autumn and a halving in summer (12). For these reasons, data on the nickel content in individual foods often appear to vary according to the sources, and differences are sometimes significant.

Because the nickel content of specific food can vary widely, the daily intake of nickel is also highly variable among different populations but also in a single individual in different seasons and even in different days. Of course, national and local dietary habits, as well as the diversity of the daily menu contribute to this variability. Other factors could make the daily dietary intake of nickel even more variable, such as drinking water possibly contaminated by nickel, drinking the first water that comes out of taps in the morning (the type of tap may also be important), drinking on an empty stomach, using hot rather than cold water (13). Additionally, the use of stainless steel pots and utensils (or at least the first use of new pots or pans) particularly when cooking acidic foods, as well as eating contaminated canned foods (by erosion of the metal containers), could be important. Food nickel contamination could occur also during the preparation process with equipment containing nickel. This is, however, still a very controversial subject-matter. According to some sources, the contribution of water, pots, pans, and kitchen utensils to the daily intake of nickel would be quite negligible (14, 15). Finally, the variable contribution of cigarette smoking should not be forgotten, as one cigarette can contain 1-3 μg of nickel (9, 16, 17).
Thus the daily intake of nickel is variable. Measuring precisely the daily intake of the nickel from food and drinks is extremely difficult, if not impossible. Furthermore, only a part of nickel taken with food, varying between 1 and 10%, is absorbed in the gastrointestinal tract. One of the factors that influence, reducing it, the absorption of nickel from food is the co-ingestion of vitamin C and iron.
To simplify, a worldwide average daily intake of nickel in human beings is approximately between 0.2 and 0.6 mg; these findings appear to be consistent in the different studies (18). The minimum daily requirement is estimated at around 50 μg (0.05 mg) and is covered by a normal diet (19). In the usual diet, these quantities are reached pri-

Table 1 - Daily intake of nickel in specific populations

Italy	0,3 - 0,4 mg
United Kingdom	0,12 - 0,21 mg
Finland	0,13 mg
U.S.A	0,17 – 0,6 mg
Canada	0,207 - 0,576 mg
Denmark	0,15 - 0,9 mg
Sweden	0,2 - 4.5 mg

marily through the intake of fruit and vegetables. 50% of the average daily nickel supply is provided by cereals and pulses, followed by fats, dairy products and fruits (20). Considering the specific populations (Table 1) the wide variation in the intake of nickel of the Scandinavians, up to significant quantities, is related to particular dietary habits involving the frequent intake of oatmeal, legumes, including soy, nuts, cocoa, chocolate (1, 21, 22).

Table 2 – Food with high nickel content according to different sources

	a	b	c	d	e	f	g	h	i	l	m
Almonds	■				■		■		■		■
Apricots					■						
Asparagus			■		■						
Avocado					■						
Baking powder		■				■					■
Beans	■	■	■	■	■	■		■	■		■
Beer			■			■					■
Broccoli					■						
Cabbage			■								■
Carrots					■	■					■
Cashew nuts										■	
Cauliflower					■						■
Cocoa and chocolate	■	■	■	■	■	■	■	■	■	■	■
Coconut powder									■		
Coffee											■
Corn			■		■						■
Crustaceans (Lobster)					■						■
Dried fruits		■				■					■
Figs					■					■	
Garlic											■
Hazelnuts		■	■		■	■	■	■	■		■
Herring		■	■			■					■
Lentils	■				■	■	■	■	■	■	■
Lettuce			■								■
Licorice		■			■	■		■	■		■
Linseed									■		
Mackerel						■					■
Margarine			■		■						
Mushrooms			■		■						

	a	b	c	d	e	f	g	h	i	l	m
Nuts	■			■	■	■	■	■	■	■	■
Oats (porridge)	■	■		■	■	■	■	■	■		■
Onion			■		■	■					■
Peanuts	■	■			■	■	■	■	■		■
Pears fresh and cooked			■		■						
Peas	■	■	■		■	■		■	■		■
Pistachio									■		
Poppy seeds									■		
Potato					■						
Prunes					■						
Raisins			■		■						
Raspberries										■	
Rhubarb			■		■						
Rye		■				■					■
Salmon											■
Shellfish					■	■		■	■		■
Soybean seeds and products	■	■				■		■	■	■	■
Spinach					■						■
Sunflower seeds		■				■					■
Tap water (initial flow)											■
Tea		■	■		■	■					■
Tomatoes			■		■		■				■
Tuna						■					■
Whole wheat flour		■	■		■	■		■	■		■
Wine (red)			■			■					■
Canned foods			■			■					■
Foods cooked in stainless steel			■					■			■

a) Flynholm 1984 [22], b) Veien [23, 24]; c) 1994 Venuti [25] d) Christensen 1999; e) Schiavino et al. 2006 [26] f) Sharma 2007 [2], g) Falagiani, Schiavino et al. 2008 [27] h) Veien, 1993 [47], i) Swedish Food Administration [28], l) Fonacier 2010 [29]; m) Picarelli 2010 [30].

Although nickel is widely distributed in food, some food groups are usually considered to be richer. However, the lists of foods with high nickel content available in literature are not consistent and difficult to compare (Table 2). These differences influence the prescription of a nickel-free diet both in diagnostics and in therapy and can influence the comparability of the diagnosis of nickel food allergy.
The reason for these differences is that no consistent threshold for defining a food as "high in nickel" (concentration of nickel in mg/kg) is determined and different thresholds are used by different authors or institutions. Sometimes even the same authors use variable thresholds at different times and in different publications. So, for example, the threshold can fluctuate from >0.5 mg/kg for the Swedish Food Administration, to >0.03 mg/kg in the 2006 study by Schiavino and others, and to >1.0 mg/kg in the 2008 review by Falagiani et al. With a threshold at 0.03 mg/kg many foods are considered high in nickel, including, for example, raisins, carrots, apricots, figs, mushrooms, pears and tomatoes, which have a content not exceeding 0.1 mg/kg and are not included in more restrictive lists.

Despite these inconsistencies, some foods are widely considered to be high in nickel content, regardless of the nickel content of the soil where they grow: peanuts, beans, lentils, peas and soybeans, as well as oats, cocoa (and chocolate), nuts, whole wheat.

Clinical forms and diagnosis

Nickel allergy can present itself in various forms: cutaneous, localized or systemic, and extra-cutaneous. Schematically we can distinguish
- The Allergic Contact Dermatitis (ACD)
- The Systemic Nickel Allergy Syndrome (SNAS), which can have cutaneous signs and symptoms (so-called Systemic Contact Dermatitis, or SCD) or extracutaneous signs and symptoms (gastrointestinal, respiratory, neurological, etc.).

Allergic Contact Dermatitis (ACD)

The classic clinical presentation of nickel allergy is Allergic Contact Dermatitis (ACD). Nickel causes 35% of the ACDs, both occupational and non-occupational. A dermatitis caused by contact with nickel is usually easy to recognize: it appears as a local eczema confined to skin sites in close contact with nickel-releasing objects, such as earlobes (earrings), wrist (watches), neck (necklaces), the umbilical region (jeans buttons). The face and scalp may be affected by contact with cell phones, piercings and hair clasps (31). These recurrent eczematous eruptions in places of contact with nickel are also called primary eruptions.
The diagnosis of nickel Allergic Contact Dermatitis uses, of course, the patch test, which is the specific test of ACD and explores local reactions of delayed cell-mediated hypersensitivity. It reproduces the mode of patient exposure to the metal, i.e. skin contact. The patch test only expresses a state of sensitization and a positive result is not necessarily an indicator of clinical disease (allergic sensitization does not mean allergy) (8).

Systemic Nickel Allergy Syndrome (SNAS)

In the '70s some authors (32) noted that a considerable number of patients sensitized to nickel presented dermatitis in locations other than those which had been in contact with nickel-plated objects. On the basis of the symmetry of these so-called secondary eruptions, the responsibility of systemic intake of nickel was suspected. In the following years, the possibility of systemic nickel allergy syndrome (SNAS) was investigated and presently it is considered that it may manifest itself clinically with

1. 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.

2. extracutaneous symptoms
- gastrointestinal (abdominal pain, diarrhoea, vomiting, swelling, heartburn, nausea, constipation, etc.),
- respiratory (rhinitis and asthma),
- neurological (headache),
- general (fever, fibromyalgia, joint pain, chronic-fatigue syndrome, etc.).

The nickel Systemic Contact Dermatitis (SCD) (33, 34) consists in cutaneous lesions not limited to sites of contact

with the metal. These lesions would occur in persons sensitized and exposed to hapten in a systemic way, i.e. oral, transdermal, subcutaneous, intravenous, intramuscular, or respiratory. The prevalence is not unique in studies. According to Sharma and Raison-Peyron (2, 35) SCD is rarely seen; according to other authors it is much more frequent and some Italian data (36) would imply the involvement of almost half of the subjects allergic to nickel.
The hand eczema, due to chronic contact with detergents containing nickel, nickel-plated artifacts, or coins, in some cases could flare-up because of oral intake of nickel. This is often a late manifestation after an initial sensitization and is reported to be the most common manifestation of nickel SCD.
Pompholyx is a recurrent vesicular eczema of the palms (32). It is reportedly associated with nickel allergy and its oral intake; however, the association is still controversial.
The baboon syndrome may be a manifestation of SCD (37-40). It is a generalized skin rash with particular involvement of the gluteal areas, the upper inner surfaces of the thighs, the ano-genital region, the flexor surfaces (eg, axillary regions) and eyelids. The peculiar involvement of the ano-genital area and of the buttocks, as well as the colour, from dark purple to pink, give a similar appearance to the typical buttocks of baboons. The acronym SDRIFE (Symmetrical Drug Related Intertriginous and Flexural Exanthema) has also been proposed for this syndrome. It's a benign and rare morbid phenomenon, just over 100 cases having been described in the world, not specific of nickel allergy. Its most common cause is, in fact, mercury and, after that, medications such as beta-lactam antibiotics. The maculopapular exanthema involving the flexor regions appears as a symmetrical eruption of the neck, face, eyelids, flexures of elbows and forearms, hands, inner thighs, ano-genital region. It can be generalized.
Rarely, nickel can cause non-eczematous dermatitis such as contact urticaria, vasculitis-like lesions, erythema multiforme. Only sporadic cases of these diseases are reported in literature. The literature also reports sporadic cases of chronic urticaria due to nickel taken orally and mediated by either a type I or a type IV pathogenetic mechanism. Nevertheless, in some Italian studies the prevalence of chronic urticaria caused by systemic nickel allergy via food is quite remarkable and the urticaria would be by far the main manifestation of cutaneous SNAS (36). According to data by Schiavino, 38% of individuals allergic to nickel would have, in addition to nickel ACD, urticaria-angioedema as clinical manifestation of systemic allergy. In another study, the patch positivity to nickel represents a significant part of the patch positivity to various elements detected in approximately 41% of chronic urticaria (41).
As mentioned above, clinical manifestations not confined to the skin are also attributed to nickel, in particular gastrointestinal symptoms, such as vomiting, diarrhoea, abdominal pain, meteorism and abdominal distension, constipation, heartburn as well as respiratory symptoms. In particular, cases of rhinitis and asthma due to occupational exposure have been reported. The possibility of occurrence of nasal and lung cancer is attributed to industrial exposure. Other disorders related to nickel are sometimes reported in the literature.
The diagnosis of Systemic Nickel Allergy Syndrome (SNAS), both cutaneous (systemic contact dermatitis) and extra-cutaneous is far more complex than the diagnosis of ACD. The only possibility of definitive diagnosis is one that mimics natural exposure, i.e. the exposure or provocation test. In the case of exposure via food the diagnostic procedure would consist of, as for all allergies and food intolerances, an oral provocation test with the suspected food, after the diagnostic elimination diet of the same food. Any other tests, such as the patch, as well as the prick with nickel sulphate, sometime performed, are only indicative but are not considered diagnostic. While the diagnostic certainty of SNAS from nickel in food would require a rigorous process, however, each stage of the diagnostic procedure presents problems.
First, the elimination test cannot be carried out because, as nickel is a metal ubiquitously present, it is not possible to completely eliminate its oral intake. Suggested diets contain less nickel than it is normally assumed, but there is not certainty in the nickel content of any given diet, more or less restrictive, and it is impossible to know the exact amount of nickel taken daily, in the course of normal supply. One can not, therefore, objectively define a threshold of tolerance for nickel food in sensitized subject. In other words, it is impossible to determine how much lower the nickel content of an individual diet should be, that is which and how many foods are to be prohibited or allowed. In addition, other indications are very controversial in literature: using some cooking utensils rather than others; somehow limiting the intake of tap water; avoid drinking on an empty stomach; eliminating cigarettes.
Second, the elimination diet should obtain an improvement of the diseases attributed to nickel at a rate of at least 80%, without interference due to concomitant medications. Nevertheless, this is not an objectively defined

score to evaluate the improvement and in some cases one must rely on the subjective sensations of the patients, not always reliable.
Third, the provocation test should be performed with double-blind placebo-controlled challenge, with an amount of nickel similar to what is taken normally and with the same distribution during the day. The double-blind, placebo controlled (DBPC) challenge test is the gold standard in the diagnosis of oral allergy to nickel and is highly recommended and generally necessary for a correct diagnosis (42). In real life, however, it is not carried out in current practice and almost never even in scientific studies. Even when the DBPC challenge test is used in the studies, natural exposure is never reproduced, either in terms of quantity of administered nickel or in terms of distribution during the day and various meals.

SNAS and food nickel

The relationship between ACD and contact with nickel is undisputed, quite clear and widely confirmed in the literature. The pathological effect is related exclusively to skin contact and lesions are not affected by high or protracted oral nickel intake. Therefore, a low-nickel diet has no utility in localised ACD, although dietary restrictions are commonly imposed on many patients affected by this unique disorder (43).
The situation is different for systemic nickel allergy syndrome (SNAS). The aim of this research is to evaluate

- Whether there is evidence, in scientific literature, of the existence of systemic nickel allergy syndrome (SNAS) - in other words whether nickel, mainly when taken orally, is responsible for the genesis of systemic disorders.
- Whether there is evidence that a low nickel diet may have therapeutic utility.

The answers to these questions are difficult, controversial and apparently not univocal (Table 3: Evidence of the relationship with nickel and utility of diet in clinical manifestations of nickel allergy).

Systemic contact dermatitis (SCD) and food

Limiting the assessment to oral exposure only, which is the interest in our research, the relationship between systemic contact dermatitis and nickel intake is controversial and not unanimously accepted. Studies that conclude positively on the role of food nickel in the genesis of symptoms (23, 24, 26, 36, 41, 44-48) are opposed to studies that exclude it (49-51).
According to Röhrl and Stenberg, a vegetarian diet, by definition at high nickel content, is not associated with an increased prevalence of hand eczema in sensitized individuals. There seems to be some evidence of the relationship between food nickel and flare-up in the site of previous injuries and previous patch tests, as well as of the relationship between food nickel and vesicular eczema of the

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

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

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 (52, 53). 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. In another 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) (54). Nickel SCD, therefore, seems to present a clear dose-response relationship, as confirmed by a meta-analysis of 17 clinical trials (55). In this meta-analysis it was statistically estimated that only l% of patients allergic to nickel may have a systemic reaction to the nickel contained in a normal diet (0.22 mg or 0.35 mg or 0.55 mg). 10% would react when exposed to quantity of food nickel from 0.55 to 0.89 mg, which could be reached by having a diet rich in high-nickel foods, by drinking water which is contaminated by nickel from the pipes and taps and/or by drinking on an empty stomach a large amount of water with a high metal content. The authors have pointed out, however, that the subjects included in the studies and tested are not representative of the general population but are selected samples of individuals allergic to nickel, with symptoms that were so strong or so persistent to lead them to consult specialized dermatologists.

The non univocal results of the studies depend certainly on the difficulties of diagnosis mentioned above. However, they also depend on the lack of standardization and uniformity in the protocols (55):

- the criteria for selection and inclusion appear to be different among the studies (in some cases they are limited to patch positivity only, in others to presence of hand eczema only, even without patch positivity),
- the studies prescribed different elimination low-nickel diets,
- the exposure or challenge test was not performed in all studies (in some cases the diagnostic process was limited to elimination diet),
- in some cases the exposure test was performed only with some extra nickel, in some others it was performed in open,
- in the trials in which the double-blind placebo-controlled challenge was performed, the following have not been standardized:
  - the administration of the dose (single or double bolus),
  - the amount of nickel sulphate administered,
  - the observation time (variable in different studies from 0 to 72 hours or more),
  - the criteria for identifying a positive reaction.

Usually, the doses administered in the challenge were very much higher (8, 55) than the amount of nickel taken progressively throughout the day in a regular diet - a form of intake which may lead to differences in absorption and biokinetics of the element. Studies do not always specify whether or not ingestion happened on an empty stomach or whether or not patients followed some other diet restrictions. Additionally, most studies have not taken into account the natural daily intake of nickel and dietary factors that may influence the absorption; these are two highly variable aspects which are difficult to determine accurately. Finally, the flare-up of a recurrent vesicular hand eczema, end point used in some studies, is a very complex disorder and may be precipitated by a number of stimulants (55).

In light of these considerations on the limits of clinical trials, it is not surprising that the occurrence of systemic contact dermatitis as a systemic reaction to the nickel normally assumed in the daily diet is very controversial. Actually, the rigorous demonstration of the relationship between SCD and nickel is extremely difficult, as considered above. Until additional and clarifying data from methodologically more correct studies become available, a therapeutic low nickel diet for manifestations of systemic dermatitis in patch positive patients could be recommended only to very carefully selected patients (34), i.e. in patients sensitized to nickel with extensive and chronic skin disease when there is clearly a demonstrated dependence between diet and clinical manifestations (42).

In the literature there are various reports of urticaria related to the nickel. In particular, cases of hives, but not only, related to the use of dental or orthopaedic prosthesis have been reported (56, 57). Some more in-depth statistics have shown, however, that unselected individuals subjected to hip or knee arthroplasty have a prevalence of allergic reactions significantly lower (4% against nickel) than the prevalence emerging from various dermatological studies and that the vast majority of allergic patients tolerate the implant without problems (58). There is a general agreement that nickel allergy is not a contraindication for the application of a stainless steel hip (8). Similarly, a statistical study on a sample of over 33,000 patients with orthodontic appliances suggests a prevalence of only 0.03% of (modest) intra-oral and extra-oral reactions. Only one patient, in particular, is reported for urticaria (59). The possibility that contact sensitization to chemicals, additives and metals (including nickel) can play a

valuable role in the genesis of chronic urticaria was also evaluated. In the aforementioned study by Guerra et al. (41), 41% of patients with chronic urticaria was patch test positive. Within one month, all patch positives subjected to "measures of avoidance" had experienced resolution of symptoms. This study, however, raised several concerns (60, 61) in relation both to the methodology and to the results. In particular, these results are contrary to all the most recent findings on the epidemiology and pathogenesis of chronic urticaria (29, 62, 63). Cases of chronic urticaria due to the presence of nickel in foods have also been reported (64) and correlated with a type I or IV immunological mechanism. The most frequent citations and the largest sample of patients with urticaria due to systemic nickel allergy taken orally seem to be the studies by Schiavino et al. (26, 27, 36, 65, 66). Some elements of these studies, however, raise questions and would probably require more precise definitions and methodologies. From a statistical point of view, for example, the individuals with SNAS manifestations in general (537/1086 = 49.5%) and with urticaria in particular (417/1086 = 38%) seem to be too many, in the patch positive population selected. In most other studies (2, 35) the SNAS is considered to be infrequent or it is rarely observed. With regard to chronic urticaria, in particular, we know that nickel patch positivity is characteristic of a percentage of the general population which varies, in different statistical studies, from 10 to 30%, with peaks up to 38% for certain professional groups. If one accepts that 38% of nickel patch positive individuals has chronic urticaria, the resulting prevalence of chronic urticaria in the general population should be between 7.6 and 11.4%, with peaks of 14.4% in occupational groups at particular risk of nickel sensitivity (such as hairdressers) (67). In paediatric patients, for whom the prevalence of sensitization to nickel is about 15-16%, one would expect a prevalence of 5-6% of chronic urticaria from nickel only. These data are clearly divergent and incompatible with the values of the remaining current literature about both nickel chronic urticaria (2) and chronic urticaria as a whole, as well as with the latest findings on the disease's pathogenesis (29, 62, 63, 68, 69).

In conclusion, the available data are insufficient to draw definitive conclusions. Further and larger methodologically impeccable studies are needed to assess the reality and the prevalence of nickel urticaria

Extracutaneous manifestations of SNAS and food

Considerations largely similar to those above can be made about nickel-related gastrointestinal symptoms. The specific characteristics of gastrointestinal symptoms must be added to the methodological difficulties already discussed at length. These symptoms (abdominal pain, bloating, nausea, constipation, heartburn, vomiting, diarrhoea) are limited in number, non-specific and not always objective. They are shared by the majority of gastrointestinal diseases, both infectious and inflammatory, neoplastic and from enzyme deficiency, organic and, it must be noted, sometimes psychogenic.

Furthermore, these symptoms are not always objectively evaluated in a challenge; objective parameters to evaluate their improvement in the elimination test, as well as their worsening or relapse in provocation test are often difficult to determine. A rigorous double-blind placebo-controlled challenge with natural amounts and natural distribution of intake would be necessary to ascertain the correlation of symptoms with the metal intake. The literature in this regard, however, is very poor. Some schools seem to consider the possibility that SNAS may occur with gastrointestinal symptoms and that these symptoms can be isolated in absence of skin lesions or patches related positivity. This scientific literature, however, (which is mainly, if not exclusively, Italian), is not demonstrative. For the majority, it considers the existence of gastrointestinal disorders induced by food nickel as an acquired and confirmed finding. In fact, these studies lack the support of clear, first-hand evidence: they very often quote other citations and sometimes lack bibliographic references (8, 26, 27, 30, 36, 42, 65, 66, 70 , 71).

Only a few clinical studies are available, which suffer from the methodological flaws described above. In the study by Picarelli and others, for example, the patients are selected only on the basis of a clinical history of gastrointestinal disorders allegedly related to nickel intake. In addition to inadequate selection, the lack of a control group and of exposure test in double blind allow to express doubts about the validity of its results. Some alterations of the intestinal mucosa and an increase in the infiltration in the lamina propria of CD45RO + memory with a reduction of CD8 + (42, 72-74) during the challenge with nickel in sensitized patients were certainly demonstrated. These changes, however, are non-specific (27, 42) because any recurrent contact with any antigen can induce an increase of CD45RO + (i.e. a maturation of T lymphocytes from virgin cells to memory cells). It should be remembered, in any event, that the mucosal alterations are associated with non-natural and unusual metal doses, very close to the toxic dose.

With the exceptions of the studies cited above, the litera-

ture reports a correlation between nickel and abdominal symptoms only in cases of acute or chronic intoxication in electroplating workers and dialysis patients (75, 76); or in carriers of dentures (77); or in patients who have swallowed coins (78). Nickel is therefore a metal characterised by acute or chronic toxicity. A possible toxic effect of high doses of nickel in the bolus challenge could be suggested. These doses are from 5 to 20 times higher than those usually taken on a daily basis. Considering that the natural daily intake is diluted, because it is distributed during daytime hours, with peaks during the two main meals, the bolus challenge dose could even be from 15 to 50-60 times higher than the dose normally assumed in a single meal. The effects caused by the challenge could therefore be the expression, at least in part, of a toxic, rather than immunological, reaction. These doubts have already been expressed, with some elements of objective confirmation (79).

In conclusion, while dietary restrictions appear to be often imposed on patients with gastrointestinal disorders attributed to nickel, in fact, the data from the literature are not conclusive at all.

Finally, with respect to respiratory disorders, the literature describes very sporadic cases of rhinitis and asthma, although the sensitization to nickel is more prevalent in asthmatic individuals, compared with atopic non-asthmatics and healthy control individuals (80). These diseases are often occupational, linked to conditions in the workplace (81). Workers of the galvanic, mechanical engineering industry and metallurgical industry appear to be at risk. Inhalation through the respiratory tract appears to be an important factor in these diseases. The role of food nickel and the effectiveness of a dietary treatment have been assumed but not proven (82).

Food nickel has been associated with chronic fatigue syndrome and fibromyalgia (17), as well as with headache (42), recurring cold sores and recurrent infections in general. No confirmation supported by appropriate studies exists with respect to any of these associations.

Low-nickel diets: indications and limits

A rigorous review of the literature suggests that the usefulness of a therapeutic low-nickel diet is controversial: rare, if not exceptional, and limited to very sporadic cases of systemic contact dermatitis. In the absence of clear and unambiguous data, supported by evidence, prescribing a low-nickel diet appears to be an empirical choice, dictated by personal evaluations.

In addition, many uncertainties and different opinions exist about how the prescribed diet should be articulated. As nickel is a ubiquitous metal, complete elimination is not possible and probably not desirable. However, the low-nickel diets suggested in the literature are highly variable, both in the extension of the restrictions and in their details (Table 4: Food restrictions suggested in low-nickel diets).

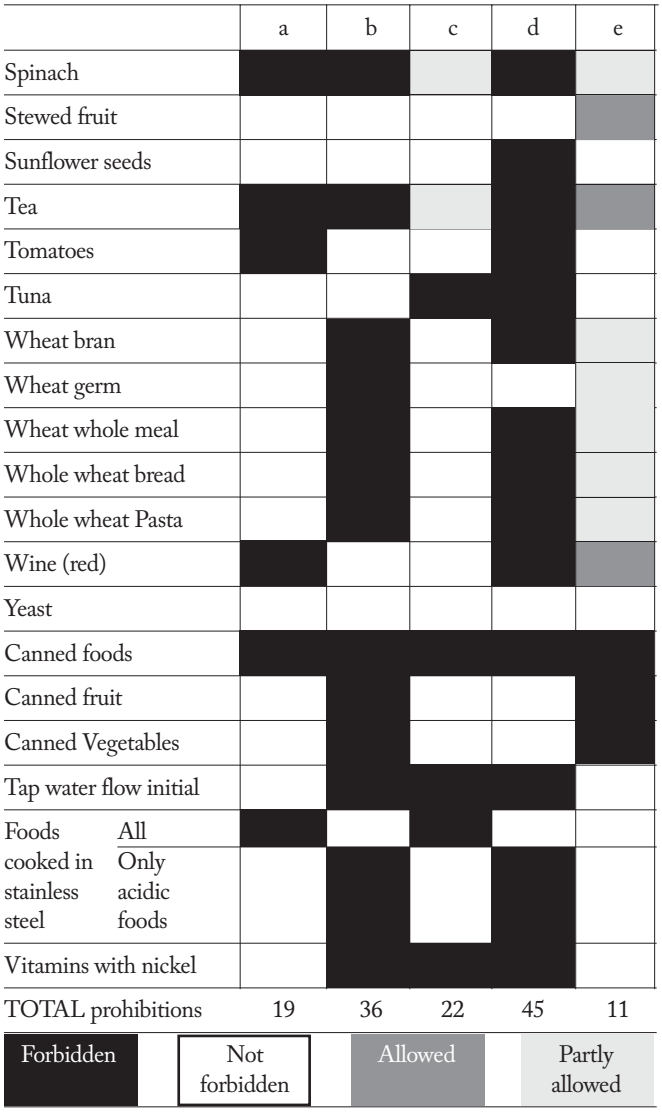
In some cases the exclusion is limited to foods unanimously considered quite high in nickel content, in other cases it is more extensive and involves foods lower in nickel content. Within the same kind of diet, which could be more or less restrictive, specific foods may be prohibited in certain lists but not in others. In the low-nickel diet suggested by the New Zealand Dermatological Society, for example, there are 11 prohibition points (i.e. recommendations to avoid particular foods or particular storage or cooking techniques); in Picarelli's list, on the other hand, the prohibition points are 4 times higher in number.

A detailed analysis revels that there is consensus only on the need to avoid cocoa and chocolate, peas and canned foods. The consensus about the need to avoid other legumes (beans and peanuts), shellfish, hazelnuts and walnuts is almost unanimous, but non completely unanimous. All other indications are not univocal and are often quite contradictory. Foods such as bananas and oranges are sometimes prohibited, despite not being included in lists of high-nickel foods. Other food (such as apricots, avocados, figs, raspberries, etc.), although mentioned as high-nickel foods, are never prohibited in the recommended diets analysed. Potatoes and cabbage, foods which are considered nickel-rich in some documents, are only allowed in small portions in the New Zealander indications, but completely permitted in those by Sharma. Some foods (e.g. green leafy vegetables, broccoli, garlic, mushrooms, tea, coffee) are completely prohibited in some recommended diets, only partially prohibited in other recommended diets, not mentioned or even explicitly allowed in others. Tomatoes, food with low nickel content (0.09 mg / kg) (26), are allowed by some authors and prohibited by others. The "prohibitionist" attitude may be affected by the disputed opinion that, being an acidic food, tomatoes can facilitate the release of nickel from stainless steel pots and pans; as well as by the objective fact that nickel concentration is higher in tomato paste. The attitude towards fish in general and various species of fish in particular is similarly contradictory among authors and sources of literature. Some recommended low nickel diets explicitly allow all fish, while others prohibit some species (such as

Table 2 - Restrictions suggested in low-nickel diets

	a	b	c	d	e
Almonds					
Apples					
Apricots					
Asparagus					
Avocado					
Baking powder					
Banana					
Beans					
Beans in tomato sauce					
Beer					
Beet					
Bread multigrain					
Broccoli					
Brussels sprouts					
Cabbage					
Carrots					
Cauliflower					
Cereals multigrain					
Chickpeas					
Cocoa and chocolate					
Coconut powder					
Coffee					
Corn					
Corn refined (popcorn, corn flakes)					
Crustaceans					
Cucumber					
Dried fruits					
Figs					
Fish (canned)					
Fishes (other)					
Fruit (all except specified)					
Garlic					

	a	b	c	d	e
Grain refined products (pasta, white bread, white flour)					
Green leafy vegetables					
Hazelnuts					
Herring					
Kale					
Leeks					
Lentils					
Lettuce					
Licorice					
Linseed					
Mackerel					
Margarine					
Mushrooms					
Nuts					
Oats (porridge)					
Onion					
Oranges and citrus					
Peanuts					
Pears fresh and cooked					
Peas					
Pistachio					
Potato					
Prunes					
Raisins					
Raspberries					
Rice					
Rye					
Salmon					
Seeds all					
Shellfish					
Soy sprouts					
Soybean seeds and products (tofu, salsa)					



a)Schiavino, Patriarca e al 1995[83]; b) Zirwas 2009[84]; c) Sharma 2007[2]; d) Picarelli 2010[30]; e) New Zealand Dermatological Society

tuna, mackerel, salmon and herring). According to other views fresh fish is never forbidden, regardless of species, while canned fish is prohibited because of the risk of nickel release from the container (84).

It is not without significance to note that some recommended diets (27, 85) while explicitly mentioning several foods and drinks as low in nickel content, nonetheless claim that they are to be avoided because potentially capable of aggravating the nickel eczema. This is the case of beer, wine (especially red), fish such as herring, mackerel and tuna, raw tomatoes, onions and carrots, apples and citrus fruits and their juices (22). However, it is contradictory and inconsistent to imply that systemic manifestations of nickel allergy, which are usually accepted to be linked exclusively to an exuberant presence of nickel in the daily food intake, can worsen rather than improve because of the intake of foods with low metal content.

There is no unanimity of views on the alleged risk linked to canned foods, as well as to the use of stainless steel cookware and tableware (pots, pans, kettles). Some dietary guidelines do not include these prohibitions. In fact, past concerns that stainless steel tools may release nickel during cooking have been overtaken by the finding that the nickel released is almost negligible (86). The nickel contained in a portion of food cooked in already used pots is less than the amount contained in 5 gr of chocolate. According to other opinions, however, the problem may be real, at least in the case of acidic foods like tomatoes, vinegar and lemon, which would increase the release of nickel from pots and pans. The negative studies mentioned could then have been affected by a prominent use of non-acidic foods, linked to specific national habits. Furthermore, the problem of nickel release from stainless steel cookware may be limited only to the first use of new pots or pans or to the first use of new pans in combination with acidic foods (87). After the first use the phenomenon would end, even when the inner surface of the pottery was cleaned causing abrasions. In this as in other aspects of low-nickel diet, therefore, the attitude is certainly not unique and the variability is absolute: recommendations can range from the exclusion in full of stainless steel kitchenware, to the exclusive ban of their use with acidic foods, to the only prohibition of the consumption of acidic foods cooked in new utensils, until the admission, without hesitation, of all use of stainless steel utensils.

In most studies, the nickel contained in source water and tap water is considered to be very small (1-10 μg/liter) (55) and the assumption of nickel through drinking water or other drinks is considered negligible. Possible exceptions are however reported: the water could be contaminated and the nickel content of water for domestic use could increase due to corrosion from pipes and taps, in particular with respect to hot water and the first water flowing from the tap in the morning after night stagnation (13). Despite these reports in the literature, not all diets recommend care in this regard.

Other contradictory aspects concern the effects of a recommended diet, its duration, as well as the role of cigarette smoke. Sharma points out explicitly in his review that dermatitis will not clear completely as a result of the diet, but likely there will be only a reduction of the inten-

sity and frequency of flare-ups (2). In many studies, in contrast, low nickel diet, despite the limits discussed above, seems to be able to determine the complete disappearance of all allergy symptoms, both cutaneous and extracutaneous. Additional uncertainties are related to the duration of the diet, which is quite well defined for the diagnostic elimination phase (one to two months) (8, 47) but is not for the therapeutic phase. Some believe that the diet should be continued for at least six months (88). However, follow up studies do not seem to be available in literature, despite the fact that nickel allergy is a life long disease. Finally, recommended diets never mention the utility of abstaining from smoking cigarettes, despite mentions in literature of the nickel contained in cigarettes and suspicions that severe exposure to cigarette smoke may be either a nickel sensitizer (8) or, at least, a potential trigger for manifestations of hyperreactivity in persons already sensitized (17). In other words, it could not be excluded, it is claimed, that some disorders caused by oral nickel intake in sensitized subjects may actually be related to the effects of cigarette smoke.

The quantitative and qualitative composition of a low-nickel diet presents, therefore, few certainties and many uncertainties. Differences are clearly not marginal. If real, they should have a clear reflection on the reduction of dietary nickel intake and should be accompanied by sensibly different clinical efficacy, which is not found in the clinical studies reviewed.

Conclusions

An evaluation of the data presented by medical literature about systemic nickel allergy does not allow to draw final conclusions. The uncertainties, contradictions, inconsistencies appear to be numerous and repeated. Doubts and lack of clear evidence exist regarding both the clinical aspects and the real relationship with nickel intake. There are also doubts about the validity of the diagnostic procedures used in clinical practice, as well as of the whole of the procedures of the clinical trials reviewed. Finally, there are doubts about the composition and the therapeutic value of the low-nickel diet itself.

In the absence of genuine certainty about these important aspects, we can only conclude that further and broader studies, more rigorously conducted, are needed to answer more firmly the questions considered in this article.

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