

## Nickel Hypersensitivity: A General Review on Clinical Aspects and Potential Co-Morbidities

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### Abstract

Allergic contact hypersensitivity to metals is a delayed-type allergy. Although various metals are able to induce an allergic reaction, nickel is the most frequent cause of metal allergy worldwide. The high prevalence of skin sensitization to that metal is the result of an ubiquitous exposure, being contained in different everyday things, such as detergents, cheap jewelry, cosmetics, coins, buttons, zippers, eyeglasses, buckles, clasps, inks, dental prosthesis and foods even. However, nickel is able to induce a wide range of morphological and clinical patterns, ranging from simple allergic contact dermatitis to systemic contact dermatitis and systemic nickel allergy syndrome. The latter seems to be promoted by nickel rich-foods or through endogenous route caused by metal implants which seem to elicit mainly in loco symptoms, sometimes with catastrophic consequences as aseptic bone necrosis following the implantation of hip prosthesis.

**Keywords:** Nickel; Allergic contact dermatitis; Hypersensitivity; Systemic nickel allergy syndrome; Heavy metal induced asthma; Metal implants

### Introduction

Nickel (chemical symbol Ni) is an element with atomic number 28. It is a silvery-white lustrous metal with a slight golden tinge, hard and ductile. It belongs to the group of transition metals, which includes iron, chrome, cobalt, zinc, copper and titanium even.

Ni is found ubiquitously in the environment and it is used with a high frequency in different applications, because of its high ductility. It has been widely used in many alloys, particularly in stainless steel. Furthermore, Ni is contained not only in costume jewelry, coins, mobile phones, and dental materials, but even in many everyday objects as detergents, soaps and cosmetics.

Ni is the most frequent cause of allergic contact dermatitis (ACD) worldwide. The mechanism of allergic contact dermatitis to Ni has been deeply elucidated and understood at the immunological and molecular level [1,2], however, for being such a simple hapten, Ni causes heterogenous and intricated clinical pictures.

### Morphological Aspects of Nickel Hypersensitivity

Pizzutelli has recently reviewed the diseases related to nickel exposure [3], but, in the light of new studies, such classification should be updated.

Ni causes ACD, usually localized at the cutaneous contact sites of metal. However, in the 70s, Scandinavian authors noted that a considerable number of nickel-sensitive patients developed dermatitis flare-up at sites different from those that have been in direct contact with nickel-plated items, so they speculated an endogenous exposure to Ni [4]. Because a genuine endogenous exposure has been suggested

in patients with hip prosthesis or dental alloys [5,6], it has been proposed that a diet with a Ni rich-foods, showed in Table 1, could cause an extension or a flare-up of contact dermatitis.

#### Foods containing high level of Ni

Whole wheat, rye, oats, cocoa, tea, gelatin, baking powder, kippered herrings, red kidney beans, peas, peanuts, hazelnuts, sunflower seeds, strong licorice and dried fruits margarine, pineapples, strawberries, raspberries, lentils, soy protein powder, spinach, rabe, kale, spinach, asparagus, onions, tomatoes, leeks, chocolate, carrot, apples citrus fruits (juice).

**Table 1:** Foods containing high level of Ni [3]

Although the diet as factor eliciting a generalized cutaneous contact dermatitis is controversial, however some aliments like tomatoes and apples have an acid pH which causes an increased release of Ni<sup>+</sup> ions when they are cooked in stainless steel pots, thus an aliment already enriched by Ni may increase its allergenic load [7].

For that reason, Ni can introduced by diet may induce systemic contact dermatitis with different clinical features in the form of

- Itching
- Pompholyx
- Maculopapular exanthema
- Flexural eczema
- Urticaria
- Vasculitis-like lesions

Then it is necessary to examine two other clinical pictures of generalized dermatitis Baboon syndrome and Shannon pseudo-atopic dermatitis, which are two kind of flexural eczema.

The term “Baboon syndrome” was used firstly in 1984 by Andersen et al. to describe a generalized dermatitis of the buttocks, anogenital area, flexures, and eyelids, frequently observed in patients with systemic contact dermatitis to nickel [8] as Shannon pseudo atopic dermatitis was firstly identified by Shannon as a variant of flexural eczema resembling an atopic dermatitis induced by chrome, but it can be elicited by Ni too [9].

It has been suggested Shannon pseudo atopic dermatitis could be due to Ni traces in sweat, because nickel concentrations in sweat have been reported to be 10 to 20-folds higher than concentrations in urine [10], so there is a further contact of skin with Ni ions excreted by sweat, especially on flexural areas.

Although the acronym SDRIFE (Symmetrical Drug Related Intertriginous and Flexural Exanthema) has been suggested as alternative to the term baboon syndrome, other authors argued the term SDRIFE should be used only when the causative hapten is a medication [11].

Another particular aspect of Ni systemic contact dermatitis is the pompholyx, which is a vesicular eruption of extremities, hands, and sometimes feet, without any involvement of body. Although the pathogenesis of pompholyx, known previously as dyshidrosis or dyshidrotic eczema, has been widely investigated and it has been evidenced that pompholyx is an allergic reaction to dermatophytosis (dermatophytid) in most of the cases and it occur often in patients with a previous atopic dermatitis [12], however, in a minority of patients affected by pompholyx, it has been demonstrated the importance of the endogenous route of a contact allergen to induce a further exacerbation of hand or foot vesicular dermatitis after an oral challenge test [13] and Ni sulphate resulted the commonest offending hapten [13]. At anyway, Magina et al. did notice differences in clinical patterns of hand eczema among patients with irritant contact dermatitis, atopic dermatitis and allergic contact dermatitis, allowing a differential diagnosis, except that dorsal involvement was more frequent in atopic patients [14].

Yet, the contact dermatitis to Ni may assume various morphological aspects different from classic eczematous eruption, so generalized maculopapular exanthema, purpuric rash and erythema multiforme-like eruption have been described following Ni ingestion or exposure [15], including the airborne pathway [16,17].

As far as urticaria induced by Ni is concerned, it is possible to distinguish 2 clinical patterns: a chronic urticaria which represents an urticarial like contact dermatitis [15], due to occult exposure to low doses of the metal through containing Ni-foods [18] or to dental alloys implants [19] and a more rarely and undervalued acute urticaria eruption, above all a contact urticarial, due to a genuine reaginic pathomechanism [20-22]. Sometimes, both the reaginic and cell-mediated pathomechanisms may coexist in the same patient [15,20].

Although contact urticaria to Ni have been described as a rare occurrence in literature, recently Salujia et al. identified 11 patients with a contact urticarial to Ni and skin prick tests positive to Ni diluted at 2,5 % and 5% in aqueous solution, but patch tests negative, so suggesting immediate type reactions to Ni are yet undervalued and misdiagnosed [23]. Such an investigation confirmed a previous study of Büyüköztürk et al. who have suggested the oral exposure to Ni may elicit an immediate type sensitization to the metal as they observed in a cohort of 69 patients [24].

Interestingly, IgE mediated asthma due to Ni has been previously identified and studied mainly in professionally exposed metal workers [25-27] and a technique to isolate specific IgE to Ni or other heavy metals was developed and available since 1983 [28], but it has been poorly used [28]. In 1992, Shirakawa et al. described two methods to isolate specific IgE to Ni, using a nickel-conjugated human serum albumin (Ni-HSA), and nickel-conjugated exchange resin in twenty-one workers with asthma due to hard metals [29].

On the other side, Brera and Nicolini in a study on 20 female patients with chronic rhinitis evidenced positive patch tests to Ni sulphate and a nasal challenge test positive to an aqueous solution 10 mg/ml Ni sulphate induced rhinorrhea, sneezing and mucosal edema 15-30 minutes after the inhalation of Ni solution as rhinomanometry demonstrated an increase in nasal resistance compared with baseline conditions [30]. Furthermore 11 patients showed a metacholine challenge test positive, so suggesting patients suffered asthma too. For that reason, authors argued in female population Ni can induce respiratory symptoms without any professional exposure [30].

Exceptionally, Ni may induce cutaneous generalized or localized lichenoid eruption [31], while mucosal lichen lesions due to Ni have been described more frequently in literature as result of a contact sensitization caused by dental alloys, prostheses or metal bridges [32,33], but sometimes lichenoid cutaneous eruption and mucosal lesions may be associated [34]. Ni released by these materials can be responsible for certain cases of burning mouth syndrome and gingival hyperplasia [35,36], but gingival hyperplasia has been doubtfully attributed to an immunologic mechanism [37].

### The Systemic Nickel Allergy Syndrome (SNAS)

It has been observed that maculopapular rash and vasculitic eruptions can be often associated with systemic symptoms such as diarrhea, vomiting, fever, arthralgia, asthenia, headache, and malaise [38]. In 1975, Christensen and Möller firstly observed in a double blind study on 12 nickel-sensitive individuals provoked with an oral dose of 5.6 mg nickel, that 9 of them reacted with systemic contact dermatitis after an average of 8 h and with extra cutaneous symptoms too [4]. Because in Ni sensitive patients, the intestinal route of nickel adsorption seemed to be associated with gastric symptoms as recurrent aphtosis, abdominal bloating and gastric pain, diarrhea or constipation, vomiting and nausea, Italian researchers investigated with biopsies performed on the antrum and on the duodenal mucosa obtained by endoscopy a group of 20 patients reporting a worsening of their contact dermatitis to Ni as consequence of Ni containing food ingestion and confirmed by a Ni oral challenge test [39]. Histological and immune-histochemical examination evidenced inflammatory alterations of gut mucosa with infiltrate of lymphocytes and plasma cells with oedema in the lamina propria and a slight flattening of the villi in 16 patients. The clinical picture was suggestive of a chronic inflammatory gastro-duodenitis.

Later, the same authors suggested that patients, whose Ni dermatitis worsened after an oral challenge test with Ni 10 mg, showed a decrease of CD8+ T cells and an accumulation of T memory cell CD45RO+ in the lamina propria and epithelium of gastrointestinal mucosa investigated through biopsy specimens, performed two days after the challenge, but such T cell modifications did not occur in the control group of patients with Ni induced ACD only [40]. However, being the cohort of subjects recruited very small (twelve patients only, shared in

two sub-groups), such observations should be considered suggestive, but inconclusive.

Other Italian researchers have suggested to consider Ni allergy a paradigm for T-cell mediated food allergy [41], demonstrating Ni sensitive patients who reported dermatitis exacerbation following Ni ingestion showed to have Interleukin-12 (IL-12) levels more elevated than healthy patients or patients with a simple contact dermatitis to Ni [41].

On the other hand, Jensen et al. observed a statistically significant increase of serum IL-5 and a Th2 oriented response occurring within 24 hours after oral challenge with Ni [42].

IL-5 is a cytokine which play a fundamental role in eosinophils proliferation and maturation [43], a cellular type frequently involved in allergic skin diseases and recently German dermatologists have evidenced an eosinophilic gastritis in a 46 year old patient who had lichenoid mucosal lesions of the gum near the metal bridge and crown recently implanted, because, following implantation the patient suffered from stomach pains [44], but patch tests resulted positive to various metals, including Ni, [44], so it was difficult to establish as the gut contact mucositis can show different clinical pictures as elicited by Ni containing foods or by Ni released by dental alloys, because the role of the other metals cannot be excluded [44]. Previously, another allergic gastritis has been described in a young Ni sensitive patient who had accidentally ingested a metallic foreign body represented by a nickel-containing coin [45]. She did not report any gastrointestinal symptoms or pain, but a flare up of her dermatitis occurred as biopsies taken during gastro-duodenoscopy, performed few days later to remove the coin, confirmed a gastro-duodenitis with an increased eosinophils, lymphocytes and plasma cells in the gastric mucosa [45].

Pizzutelli [3] proposed to distinguish Ni hypersensitivity in allergic contact dermatitis, systemic contact dermatitis and systemic nickel allergy syndrome when a contact dermatitis and/or cutaneous rash due to nickel is associated with gastro-enteric or other extra-cutaneous symptoms. SNAS should be suspected when patient with ACD, a patch test positive to Ni and an oral challenge test positivity to nickel versus placebo, shows an improvement of his cutaneous symptoms a month after a Ni-free or Ni-low diet [39]. Although in 2006 a meta-analysis had suggested that a systemic contact dermatitis might occur in 1% of Ni sensitive patients only [46], in 2011, an Italian multicenter study performed in 4 Sicilian Allergy Units on 1.696 patients, diagnosed SNAS in 98 patients, with a prevalence of 5.78% [47]. Apparently, there is a strong discrepancy between the Italian study and the Scandinavian meta-analysis results, but it is necessary to consider that nickel content in food is strongly influenced by the concentration of nickel in the soil (ranging between 5 and 500 µg/gr) and water (between 5 and 100 µg/litre) which may vary from place to place [48].

An interesting and dangerous consequence of Ni hypersensitivity is represented by Kounis syndrome 3° type in patients with implanted coronary stents. Kounis syndrome (KS) is the concurrence of acute coronary syndromes with a hypersensitivity reaction, due to a coronary vasospasm triggered by the vasoactive inflammatory mediators which are released during the allergic insult [49]. 3 variants of KS have been described:

Type I or with normal coronary arteries without predisposing factors for coronary artery disease;

Type II or with culprit but quiescent pre-existing atheromatous lesions, which are more likely to plaque erosion or rupture manifesting as acute myocardial infarction;

In type III KS hypersensitivity reactions occur following implantation of drug-eluting stents with stent thrombosis, because thrombotic specimens stained with hematoxylin-eosin and Giemsa demonstrated the presence of eosinophils and mast cells, respectively [49]. Although T-cell mediated response may be addressed towards the drug component of the stent (rapamycin, paclitaxel, everolimus and zotarolimus), it has been evidenced drug eluting stents contain a higher Ni concentration than the bare metal stents [49].

Then, it has been surprisingly observed that patients bearing drug eluting stents develop a catastrophic stent thrombosis immediately after an acute allergic reaction, induced by drugs or insect sting, with acute myocardial ischemia, suggesting that stents promote a local inflammatory reaction through mast cell recruitment and platelet activation [49,50]. Previously a German study examined 131 patients with 171 stents 6 months after stent implantation and underwent epicutaneous patch tests for nickel, chromate, molybdenum, manganese, and small 316L stainless-steel plates. In-stent restenosis occurred in 89 patients [51]. Among them, 10 patients with positive patch-test results had re-stenosis. Four male patients had positive reactions to molybdenum, and seven patients (4 male, 3 female) had reactions to nickel. Moreover all patients with patch test positive results showed recurrent angina pectoris and needed target-vessel revascularization [51] and a careful review of literature has been dedicated to that argument [52] Other intra-cardiac implants or devices such as septal occluder devices, implantable cardioverter-defibrillator or pacemaker have shown to elicit local or systemic symptoms [53], because Ni is present in the composition of various alloys Table 2.

Main metal alloys used in medical devices	
Name	Composition
Vitalium	Cobalt - Chromium - Molybdenum - Nickel
Stainless Steel	Chromium - Nickel - Molybdenum - Manganese
Nitinol	Titanium - Nickel
Titanium alloy 1	Titanium - Vanadium - Aluminum - Nickel (traces)
Titanium alloy 2	Titanium - Aluminum - Niobium - Tantalum
Gold	Nickel - Gold (Gold coated stents)

Table 2: Main metal alloys used in medical devices

For instance, atrial septal occluder devices for the treatment of interatrial shunts are made of nitinol which is a nickel and titanium alloy. Some patients with pre-procedural known nickel allergy developed chest pain, palpitations, atrial fibrillation and late pericardial effusion following such devices implantation [54].

Alternatively, patient may develop systemic symptoms only as hypotension, malaise, nausea, and vomiting, fevers and rigors without any cutaneous involvement [55].

In other case reports allergy and inflammatory reactions have occurred in patients with prosthetic valves and other endovascular prostheses leading to postoperative complications as loosening tissue with failure of the implant or an production of hyperplastic scar

around the metal device [52,54,56]. Previously, aseptic bone necrosis with loss of hip prostheses due to Ni and metal hypersensitivity has been reported [57], sometimes presenting with local pain, swelling, cutaneous erythema, joint and muscle pain, implant failure or delay in reparation of the surgical wound, mimicking a recurrent infection around the operation site. The latter manifestations may be observed following pacemaker implantation in Ni and metal sensitive patients, too [58].

Actually, SNAS is still a controversial disease [3] and not all the clinicians are completely convinced about its existence and the correct criteria to identify it, because only a little percentage of patients with Ni contact allergy show a worsening of dermatitis following an increased oral intake of Ni rich foods, although the relationship between dietary Ni and cutaneous symptoms relapse has been confirmed [59,60]. Interestingly, statistical reviews of cases involving adverse reactions after implantation of metal hardware demonstrate that metal sensitivity can be proven causative in fewer than 0.1-1% of cases in which sensitivity reactions exist [53,61]. In the light of this short review, 5 main patterns of Ni sensitization can be identified where hypersensitivity symptoms are connected to the source of exposure to Ni:

A sensitization due to a domestic contact with every-day and domestic items, responsible for an allergic contact dermatitis;

A respiratory exposure, mainly occupational, with clinical manifestations as airborne induced dermatitis or metal induced allergic asthma or rhinitis;

A sensitization through the gastrointestinal route with cutaneous and intestinal symptoms due to foods containing Ni (SNAS 1° type)

A sensitization related to an endogenous implantation of a Ni containing medical devices (coronary stents, pacemaker, dental material and alloys, knee or hip prostheses, needles for infusion, etc.), occurring in the organ interested by the prosthesis and with systemic and/or cutaneous clinical aspects (SNAS 2° type)

An overlap SNAS, where the aforementioned sources and mechanisms are associated.

## Potential Associated Inflammatory and Autoimmune Diseases

Some researchers have investigated the association of Ni allergy with other immune, metabolic and inflammatory diseases. It has been postulated the continuous exposure to Ni or its assumption in low doses may contribute to maintain a chronic inflammatory status in the body.

Lusi et al. observed an unusually high prevalence of Nickel allergy in overweight subjects, especially women with metabolic syndrome in the perimenopause age [62], thus they enrolled 87 (15 males, 72 females) with high Body Mass Index (BMI >26 Kg/m<sup>2</sup> patients to be patch-tested with Ni sulphate 5% plus other antropometric measurements as height, weight, BMI, waist circumference, blood pressure and laboratory tests (liver function, total cholesterol, triglycerides, serum glucose). The patch test revealed a considerable higher prevalence of Ni allergy in overweight patients compared to the general population (59% in overweight female subjects versus 9-15% of female general population) [62]. Interestingly, 43 overweight female patients started a low Ni diet, but only 24 of them completed the diet and the follow up.

At the 24th week, patients showed a BMI decrease and the mean decline in waist circumference [62].

The authors proposed that obesity and Ni allergy were linked to an overproduction of a proinflammatory cytokine, IL-17, whose serum level has been found elevated in obese patients [63] and in subjects with Ni contact dermatitis [64].

Previously other researchers had investigated the potential association between Ni allergy and chronic fatigue syndrome [65], seronegative arthritis [66] and autoimmune thyroiditis [67], but it is unclear as such manifestations should be considered extra-cutaneous aspects of SNAS or contemporary co-morbidities related to a common immune dysregulation.

Pacor et al. reported that in few selected cases of seronegative arthritis, articular symptoms may be triggered by food antigens, including Ni sulphate. In a study on 88 patients they identified 54 patients with chronic urticaria affected by seronegative arthritis and a suspected food additive intolerance on the basis of an improvement of symptoms after a food additives-free diet [66].

After an additive-and nickel-free diet for 4 weeks, the patients underwent double blind, placebo-controlled challenges (DBPC) with Ni sulphate and food additives as tartrazine, erythrosine, sodium benzoate, p-hydroxybenzoate, sodium meta-bisulfite and monosodium glutamate. The DBPC test resulted positive in 13 patients and Ni resulted the most offending hapten responsible for the worsening of arthralgia and urticaria, because only two patients resulted positive to DBPC with eritrosine and monosodium glutamate and to sodium metabisulfite [66].

Moreover, it has been suggested many heavy metals, beside Ni, are intrinsically able to promote inflammatory and autoimmune phenomenon in humans with different mechanisms as for instance a direct immune-toxic effect inducing a selection of autoreactive T-cell clones [68,69].

## Conclusion

Ni allergy may induce different clinical and morphological patterns, including SNAS. However that kind of systemic disease is more likely to be elicited in a minority of patients and there could be various types of SNAS, linked to patient environmental exposure to different nickel sources.

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