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# Serum levels of sICAM-1 in subjects affected by systemic nickel allergy syndrome

## *Livelli sierici di sICAM-1 in soggetti affetti da sindrome da allergia sistemica al nichel*

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Key words

Allergic contact dermatitis • ICAM-1 • Nickel • Systemic nickel allergy syndrome

Parole chiave

*Dermatite allergica da contatto • ICAM-1 • Nichel • Sindrome da allergia sistemica al nichel*

## Summary

The Systemic Nickel Allergy Syndrome (SNAS) is characterized by cutaneous reactions and/or gastrointestinal symptoms due to the intake of nickel in food, in patients affected by allergic contact dermatitis to nickel. Its pathogenesis is still unknown. It has been demonstrated that nickel-sensitive individuals whose dermatitis flares up after oral challenge with nickel, show significant decreases in fractions of CD3+ CD45RO+ CLA+ and CD8+ CD45RO+ CLA+ blood lymphocytes, suggesting migration of CD8+ "memory" CLA+ T lymphocytes from the blood to peripheral tissues. Intracellular adhesion molecule-1 (ICAM-1) is a membrane glycoprotein that plays a central role in cell-to-cell-mediated immune responses. It is expressed on lymphocytes, endothelial cells, and keratinocytes of skin biopsies in patients affected by allergic contact dermatitis to nickel.

**Objective**

The aim of this study was to evaluate serum levels of soluble ICAM-1 (sICAM-1) in a group of patients affected by SNAS in a phase of non activity of the disease.

**Methods**

Two groups of subjects were included in the study: 10 patients affected by SNAS and 7 healthy controls.

**Results**

Patients with SNAS showed higher sICAM levels than control subjects (301.82 ± 72.23 *vs.* 230.9 ± 43.92 ng/mL; $p < 0.05$).

**Conclusions**

The high levels of serum sICAM-1 found in SNAS patients in stable conditions let us hypothesize the presence of a minimal persistent inflammation such as in patients with allergic inflammatory diseases to mites during an asymptomatic period.

## *Riassunto*

*La sindrome da allergia sistemica al nichel (SNAS) è caratterizzata da reazioni cutanee e/o sintomi gastrointestinali dovuti all'ingestione di nichel contenuto negli alimenti, in pazienti già affetti da dermatite allergica da contatto. La sua patogenesi non è ancora del tutto nota. È stato dimostrato che soggetti sensibili al nichel con riattivazione delle manifestazioni dopo test di scatenamento orale con nichel, mostrano una significativa riduzione dei linfociti CD3+ CD45RO+ CLA+ e CD8+ CD45RO+ CLA+. Ciò suggerisce la migrazione dei linfociti T "memoria" CD8+ CLA+ dal sangue ai tessuti periferici.* Intracellular adhesion molecule-1 *(ICAM-1) è una glicoproteina di membrana che gioca un ruolo centrale nelle risposte immuni cellulo-mediate. Essa è espressa su linfociti, cellule endoteliali e cheratinociti di biopsie cutanee in pazienti affetti da dermatite allergica da contatto.*

***Obiettivo***

*Scopo di questo studio è valutare i livelli sierici della forma solubile di ICAM-1 (sICAM-1) in un gruppo di pazienti affetti da SNAS, in una fase di non attività della patologia.*

***Metodi***

*Due gruppi di soggetti sono stati inclusi nello studio, il primo composto da 10 pazienti affette da SNAS, il secondo da 7 soggetti sani di controllo.*

***Risultati***

*Le pazienti affette da SNAS hanno mostrato livelli sierici di sICAM-1 più alti rispetto ai controlli (301,82 ± 72,23* vs. *230,9 ± 43,92 ng/mL; $p < 0,05$).*

***Conclusioni***

*I più alti livelli di sICAM-1 trovati nelle pazienti con SNAS in condizioni di stabilità della patologia, ci fanno ipotizzare la presenza di una flogosi minima persistente, così come avviene nei pazienti con patologie allergiche infiammatorie da acari durante i periodi asintomatici.*

## Introduction

Nickel is an ubiquitous metal used in many objects of common use. It is considered the major contact allergen, responsible of occupational (metalworkers, hairdressers, dental technicians, shoemakers, etc.) and non-occupational contact dermatitis. Because of the large use of jewellery and other personal objects that contain this metal, nickel allergy mainly affects women. Epidemiological studies show that the prevalence of nickel allergy in industrial countries is about 20-25% in females and 4-7% in males [1-4].

In 1970s some Authors noted that a considerable number of nickel-sensitive patients have dermatitis at sites other than those in direct contact with nickel-plated items [5]. This type of eruptions, called "secondary eruptions" affects, usually, the elbow flexures, the neck, the inner thighs. Sometimes are present a vescicular dermatitis of the palm, side of the finger and/or soles of the feet, or a symmetrical nummular eczema or keratotic eczema of the elbows [6].

Now it is known that nickel can be responsible, also, of respiratory symptoms (rhinitis, asthma) and/or systemic reactions, as urticaria, angioedema and gastrointestinal symptoms (nausea, meteorism, abdominal pain, diarrhoea) appearing after ingestion of foods and beverages containing nickel. In fact this metal is pratically ubiquitous and is present, with variable concentration, in almost all the components of our daily diet [4]. The average human daily intake of nickel is approximately 200 micrograms in Europe, while in USA is about 300-600 micrograms [4]. The ubiquitous nature of nickel intake makes it difficult to establish its essentiality in the human diet; nevertheless it has been proposed a nickel dietary requirement for humans of 50 micrograms per day [6]. One to 10% of ingested nickel only is absorbed within the gastrointestinal tract. Nickel concentration in sweat is high: sweating thus may provide an important route for excretion of nickel from the body. Serum nickel concentration vary from 1.6 to 7 micrograms/L and urinary nickel concentration from 2 to 5 micrograms/L per day [7]. The feature due to the intake of nickel in food, clinically expressed as cutaneous reactions and/or gastrointestinal symptoms, is defined Systemic Nickel Allergy Syndrome (SNAS).

The immune pathogenesis of SNAS seems to differ partially from that of allergic contact dermatitis since it involves immune components not included in the plain cutaneous syndrome.

Few studies have attempted to describe the immunological mechanisms underlying the cutaneous nickel-allergic reactions elicited by systemic oral nickel exposure. The histopathology of the flare-up reactions in nickel-sensitive patients reacting to oral nickel challenge was found to be similar to the reactions in allergic contact dermatitits [8]; but because SNAS starts after a few hours or up to 1-2 days following experimental challenge with nickel, more than one type of immunological reaction may be involved [9].

Oral challenge experimental trials have been used to show that oral intake of nickel can elicit systemic contac dermatitis in nickel-sensitive individuals. These experimental trials have aimed to establish SNAS symptoms, to verify whether this syndrome may be the result of an imbalanced nickel metabolism, to study serum and mucosal immunologic components [10].

In particular, Di Gioacchino et al. have examined blood and intestinal mucosa lymphocyte subpopulations, as well as cytokine production in SNAS patients compared to healthy controls and patients affected by allergic contact dermatitis only. The study demonstrated a reduced NK cell activity in sensitised patients in respect to the normal subjects and the addition of nickel to the PBMC cultures induces a significant decrease of NK cell activity greater in cell populations derived from allergic subjects than non allergic. Moreover, they observed a significant decrease in CD4+ CD45RO- in blood 24 hours after oral nickel challenge. Likely, "virgin" cells decrease as a consequence of their maturation into cells with a "primed memory marker" (CD45RO+) in response to antigen stimulation [11].

A study of Jensen et al. described some of the immunological mechanisms underlying nickel-allergic reactions elicited by oral exposure to nickel. T-cell subtypes (CD3+, CD4+, CD8+ and CD45RO+), expression of skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA) were investigated. Nickel-sensitive individuals whose dermatitis flared up after oral challenge with nickel showed significant decreases in fractions of CD3+ CD45RO+ CLA+ and CD8+ CD45RO+ CLA+ blood lymphocytes, suggesting migration of CD8+ "memory" CLA+ T lymphocytes from the blood to peripheral tissues [9].

The histological and immunohistochemical exams of the gastrointestinal mucosa of SNAS patients, showed an inflammatory infiltrate of lymphocytes and plasma cells with edema, vasodilatation, slight flattening of the villi and elongation of the crypts in the lamina propria [12] and an increase of CD45RO+ "memory" lymphocytes in the lamina propria and in the epithelium and lower levels of epithelial CD8+ lymphocytes [11].

The expressions of CLA and CD45RO on the lymphocytes cannot be considered specific markers of nickel sensitivity, because recurrent contact with any antigen can induce an increase in "memory" T cells with skin-homing ability. However, not only results from patch test and *in vitro* stimulation studies indicate that nickel-reactive cells are T cells expressing CLA and CD45RO [13-16], but in SNAS patients also are reported similar data, as previous showed [9].

Therefore, these studies confirm that ingested nickel may induce flare-up of cutaneous reactions in some nickel-allergic patients, independently of the degree of sensitization and the intake of metal. In these patients, oral nickel stimulates the immune system, inducing maturation of T lymphocytes from virgin into memory cells; these latter cells seem to accumulate in both the gastrointestinal mucosa and the skin [11].
To better clarify the immunological mechanisms of SNAS, some studies tried to find differences in serum cytokine levels. It was found that nickel-allergic women who reacted to oral nickel had higher serum IL-2 and lower serum IL-5 before challenge than the non-reacting nickel-sensitive women and the healthy controls. 24 h after nickel ingestion, nickel-sensitive women who reacted to the challenge showed a significant increase in serum IL-5 [11 17]. These data were confirmed by Jensen et al., that found that only the nickel-sensitive individuals who reacted to the challenge with the highest nickel dose (4.0 mg) had significantly increased levels of IL-5 and to a lesser extent IL-6 and IL-10 24 h after challenge. These findings could indicate that the activation of type 2 lymphocyte subsets in the peripheral blood requires a high nickel exposure dose. No differences in the levels of serum IL-2, IL-4, IFN-γ and TNF-α were seen before or after challenge in any of the groups. However, the levels of IFN-γ and TNF-α, both before and after challenge, were below detection levels for most of the participants [9].
It is known that in allergic contact dermatitis induced by nickel, adhesion molecules are expressed on lymphocytes, endothelial cells, and keratinocytes of skin biopsies [18]. Moreover, nickel is known to induce gene transcription of adhesion molecules ICAM-1, VCAM-1, and E-selectin in endothelial cells activating nuclear factor (NF)-kappa B, a transcription factor involved in inducible expression of adhesion molecules [19].
Intracellular adhesion molecule-1 (ICAM-1) (CD54) is a glycoprotein membrane and a member of the immunoglobulin superfamily. It plays a central role in cell-to-cell-mediated immune responses and is a ligand for leukocyte function-associated antigen-1 (LFA-1) [20].
The aim of this study was to evaluate serum levels of soluble ICAM-1 (sICAM-1) in a group of patients affected by SNAS in a phase of non activity of the disease.

## Methods

### Subjects

Two groups of subjects were included in the study. Group A was composed by 10 patients affected by SNAS, group B by 7 healthy controls. All patients were females with a range of age of 27-51 years. The patients presented apart from an allergic contact dermatitis to nickel, a chronic urticaria and/or angioedema, and gastrointestinal symptoms, as abdominal pain, diarrhoea, meteorism, vomiting. SNAS was diagnosticated by patch test with nickel sulphate and oral nickel challenge with a dose of 2.5 mg of nickel. All healthy controls were negative to patch test to nickel sulphate.
All subjects had signed an informed consent form.

### Sera

Serum obtained from peripheral blood was allowed to clot at room temperature for two hours, separated by centrifugation at 1200 x g for 15 min in a 4235 A centrifuge (ALC Int. S.r.L., Milan, Italy) and stored at -80 °C until use. Serum was collected in a period of non activity of the disease, that is during a low nickel diet begun at least a month before.

*Cytokine detection*

Soluble ICAM-1 levels were analysed in duplicate serum samples by immunoenzymatic methods (sICAM-1 ELISA-Kit, Diaclone Research, Unimed-Scientifica, Milan, Italy). The detection limit was < 0.35 ng/mL.

*Statistical analysis*

Differences in serum levels were assessed by one way analysis of variance (ANOVA) and the Student-Newman-Keults test. Data were expressed as mean ± standard deviation. P-values $< 0.05$ were considered significant.

*Results*

Patients with SNAS showed higher sICAM levels than control subjects (301.82 ± 72.23 *vs.* 230.9 ± 43.92 ng/mL; $p < 0.05$).

## Discussion

It is well known that adhesion molecules play a crucial role in recruiting and activating inflammatory cells during allergic reactions. The expression of these molecules is important for the regulation of the leukocyte traffic in inflammatory skin diseases also, and in particular in allergic contact dermatitis [21]. Several studies, in fact, demonstrated the expression of ICAM-1 and other adhesion molecules on lymphocytes, endothelial cells, and keratinocytes of biopsies from skin lesions of patients affected by allergic contact dermatitis [18].
Moreover, ICAM-1 has been shown to play important roles in the production of other allergic inflammations. In fact, it is also known that high serum lev-

els of sICAM-1 are present in allergic rhinitis and asthma, and correlate with the severity of the disease. Thus, the soluble form of this adhesion molecule may be a useful marker for the presence of allergic inflammation [22]. In the present study we found higher serum levels of sICAM-1 in patients affected by SNAS, than in healthy controls. It is important to underline that the sICAM-1 values showed were obtained in stable conditions (during a low nickel diet) and not during an attack or immediatly after the oral nickel challenge. A possible explanation of this result is the presence of a minimal persistent inflammation. It is known, in fact, that in allergic rhinitis and asthma, even when symptoms are absent, a minimal level of persistent inflammation may persist [23]. It has been demonstrated that patients with mite allergy (i.e., continuously exposed to allergen) present a minimal persistent inflammation both at nasal and conjunctival levels. This inflammation is characterized by the presence of leukocyte infiltration and ICAM-1 expression on epithelial cells and by a relationship between specific and nonspecific hyperreactivity in the absence of clinical symptoms [24].
As in house dust mite allergy the natural exposure to allergen is continuous and its avoidance is almost impossible, in SNAS patients the absence of nickel contact is very difficult, in particular, a free nickel diet is impossible to set up, and a low nickel diet is hard because the most common foodstuff used in the Italian diet contain large amounts of nickel. Therefore, we hypothesize that little continuous exposure to nickel, in SNAS patiens may result in a minimal persistent inflammation, present even when patients are asymptomatic. This thesis is supported by the presence of high levels of serum sICAM-1 in SNAS patients in stable conditions, such as ICAM-1 is expressed on epithelial cells in patients with mucosal allergic inflammation during an asymptomatic period.
In conclusion, the pathogenesis of SNAS is still unknown and further investigations are needed to better clarify the immunological mechanisms of this disease. However, in light of a possible minimal persistent inflammation in SNAS, it is important to consider a prophylactic approach to treating the disease to prevent or reduce exacerbations during an acute increase in allergen. In this point of view, it seems to be useful to keep under control the symptoms of SNAS, a hyposensitizing treatment consisting in the administration by oral route of minute amounts of nickel sulphate.

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