OPEN ACCESS

GAVIN PUBLISHERS

Journal of Community Medicine & Public Health

Review Article

Conti MV, et al. J Community Med Public Health 5: 225.
DOI: 10.29011/2577-2228.100225

Systemic Nickel Allergy Syndrome (SNAS): Taking Stock of Medical Nutrition Therapy SNAS and Nutrition

Maria Vittoria Conti[1*], Giulia Bissacco[1], Rachele De Giuseppe[1], M Gabriella Calcagno[2], Giuseppe D'Antona[3], Hellas Cena[1,4]

[1]Dietetics and Clinical Nutrition Laboratory, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Italy

[2]Allergy and Immunology Unit, ICS Maugeri, Institute of Care and Research, Scientific Institute of Pavia, Italy

[3]CRIAMS-Sport Medicine Centre, University of Pavia, Voghera, Italy

[4]Clinical Nutrition and Dietetics Service, Unit of Internal Medicine and Endocrinology, ICS Maugeri IRCCS, Pavia, Italy

[*]**Corresponding author:** Maria Vittoria Conti, Dietetics and Clinical Nutrition Laboratory, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, via Bassi 21, 27100 Pavia, Italy.

Citation: Conti MV, Bissacco G, De Giuseppe R, Calcagno MG, D'Antona G, et al. (2021) Systemic Nickel Allergy Syndrome (SNAS): Taking Stock of Medical Nutrition Therapy SNAS and Nutrition. J Community Med Public Health 5: 225. DOI: 10.29011/2577-2228.100225

Received Date: 25 October, 2021; **Accepted Date:** 01 November, 2021; **Published Date:** 05 November, 2021

Abstract

Nickel is a ubiquitous metal present in different products such as soil, food, and water. Being ubiquitous, it is difficult to avoid contact in everyday life. Moreover, it could be the cause for Nickel allergy, Allergic Contact Dermatitis, and Systemic Nickel Allergy Syndrome. The treatment of patients affected by Systemic Nickel Allergy Syndrome does not yet have a standard protocol. This narrative review proposes an overview of the current knowledge of Systemic Nickel Allergy Syndrome associated with symptomatology, diagnosis, and medical nutrition treatment-related care practices. The authors focus on the studies published in the last ten years with a focus on the Systemic Nickel Allergy Syndrome, its diagnosis, treatment, and the possible solutions. Despite the extensive research in this field, many questions remain regarding the medical treatment of patients with SNAS. Nickel free diets have been highly criticized because of low compliance. At the same time, SNAS remains common and continues to be a health problem in the general population. Clinicians should be aware of the potential chronicity of the disease, resulting in a decreased quality of life and societal and economic impacts. The authors conclude that further and broader studies, more rigorously conducted, are needed to address this issue.

Keywords: Nickel; Allergy; Clinical treatment; Systemic syndrome

Introduction

Nickel (Ni) is a heavy hard metal identified by the atomic number 28. It is the fifth most common element on earth, and it occurs in nature mostly as oxides, sulphides, and silicates [1]. It can be defined as ubiquitous since it is found in soil (5-500 mg/kg), vegetables (0.5-5 mg/kg), animals (0.1-5 mg/kg), fresh water (5-100 mg/L), in industrial by-products, as well as in fertilizers, cigarettes, and in car exhaust gases [1]. Nickel concentration in soil and in plant products vary from area to area depending on the soil type, on the use of synthetic fertilizers or pesticides, and/or contamination from industrial discharges [2]. Nickel is also present in many metal alloys (costume jewellery, dishes, keys, coins, and various metal tools) and in cosmetic products [1].

In living organisms, Nickel plays a key role in a wide variety of biological processes: it acts as a coenzyme for the metabolism of glucose and is involved in some hormonal activities, including prolactin, and in lipid metabolism and nucleic acid synthesis

(DNA, RNA) [3]. The human body contains approximately 1 mg Ni, especially in bones, the pancreas, and saliva [3].

Being ubiquitous, it is difficult to avoid contact with Ni in everyday life1. This represents a limit for subjects with Nickel allergy and Allergic Contact Dermatitis (ACD), an eczematous skin reaction to direct exposure to chemicals, who are continuously exposed to Ni, even in minimal amounts [2].

Furthermore, Nickel may induce other clinical manifestations besides ACD, like Systemic Contact Dermatitis (SCD) and Systemic Nickel Allergy Syndrome (SNAS), which have to be considered and are required to be addressed for best care [4]. All in all, sensitization to Nickel may occur by means of different mechanisms:

i. skin contact with Nickel, inducing Allergic Contact Dermatitis (ACD);

ii. Nickel ingested from food, provoking Systemic Nickel Allergy Syndrome (SNAS) and

Systemic Contact Dermatitis (SCD), with gastrointestinal symptoms and/or chronic dermatopathy [5].

SCD develops when Nickel-sensitized individuals are exposed via a systemic route, such as dietary Nickel ingestion, with flare-ups of earlier eczema lesions caused by previous exposure to the metal [1], or with signs of pompholyx, vesicular hand eczema, baboon syndrome, papular macular exanthema, flexural eczema, itching, and skin rash [1].

SNAS manifestation is instead characterized by gastrointestinal symptoms including bloating, diarrhea or constipation, vomiting, nausea, abdominal pain, and cutaneous signs [5,6]. SNAS prevalence in patients with ACD is largely unknown [6]. In one recent study, up to 6% of patients in Europe were identified as being allergic to Nickel while diagnosed with SNAS, implying that it may be under-identified in the population affected by dermatitis2,7.

On the contrary, a high prevalence of Nickel Allergy has been observed globally [7]. The highest number of cases has been registered in Asia and in North America, underlying an increasing trend from 15.5% in 2009-2010 to 18.5% in 2011-2012 [8]. In Europe, the prevalence has declined in some countries, thanks to the implementation of the EU Nickel Directive [9].

Nickel allergy mainly affects adults (approximately 8% to 19% of the general population) and children and adolescents (8% to 10%) [1]. According to data published by the European Contact Allergy Surveillance System (ESSCA) [10], Italy is the first country in Europe regarding the prevalence of Nickel allergy (32.1%), while Denmark is the last, with a 9.7% prevalence rate [10]. In Italy, as well as in other European countries, gender difference in the prevalence rate is confirmed: Nickel allergy is more common among females than males, 22% vs 5.3%, respectively [11]. This difference may be due to diverse rates of skin exposure to Nickel due to a higher use of cosmetics, jewellery, leather, etc., which is more frequent among women [11]. Nickel allergy has also been observed more in professionals, such as hairdressers, domestic cleaners, metalworkers, and caterers, owing to their repeated exposure to this metal [11].

Since patch test positivity represents an effective first step tool for SNAS diagnosis (the patch test is necessary but not sufficient for diagnosis), the rise in ACD prevalence may imply an increased number of patients suffering from SNAS, who often are underdiagnosed due to undefined symptoms [11].

Until now, knowledge about the treatment of SNAS remains unclear; therefore, this narrative review proposes an overview of the current knowledge of Systemic Nickel Allergy Syndrome (SNAS) associated with symptomatology, diagnosis, and with medical nutrition treatment-related care practices [11].

Systemic Nickel Allergy Syndrome

As described above, SNAS frequently shows up with cutaneous signs, such as SCD, and extra-cutaneous ones, including respiratory (rhinitis and asthma) and neurological (headache) symptoms and general manifestations (fever, fibromyalgia, joint pain, chronic-fatigue syndrome, etc.), along with gastrointestinal signs [11,12].

However, some authors suggest that symptoms such as headache, dizziness, chronic fatigue, cough, and dyspnea, frequently attributed by patients to Nickel ingestion, may not be due to SNAS, since no Nickel Oral Challenge (NOC) induction was done [7].

It is well documented that Nickel is a strong hapten with a good chemical reactivity and a high molecular weight and hydrophobicity, which facilitates its penetration through the skin and mucous membranes [13]. Nickel combines with some skin proteins of the skin and establishes an antigenic complex, which is recognized as non-self by the immune system triggering an immune response [13].

In the specific case of SNAS, dietary Nickel ingestion causes Nickel conjugation to intestinal proteins [13]. Nickel's ability to induce an allergic reaction is due to the presence of two unpaired electrons in its peripheral orbit, which allow an organic bond with peptides or proteins leading to antigenic complexes responsible for allergic reactions [13].

Even though the specific SNAS immune-reaction is still unclear; some Immunological studies have demonstrated that SNAS is characterized by the involvement of a complex cytokine

network with production and release Th2 other than Th1 cytokines, typical of a type IV immune reaction, besides IFN-γ, IL-2, and TNF-α increase [12].

Immunohistochemistry of intestinal biopsies, taken after 10 mg Nickel oral challenges in SNAS patients, demonstrated an infiltration of CD4+ cells in the duodenal lamina propria and in the epithelium with a strong reduction of epithelial CD8+ lymphocytes, due to apoptosis induced by the strong antigen challenge [13].

The histopathology of the flare-up eczema in patients with SNAS after oral Nickel challenge is similar to the reactions caused by allergic contact dermatitis, but because SCD starts from few hours up to 1-2 days after Nickel ingestion, more than one type of hypersensitivity mechanism may be involved [5].

Diagnosis and Treatment of SNAS

Individuals are clinically assessed for SNAS and confirmed by a positive patch test, which is a fundamental requirement to prove SNAS existence, although Ricciardi, et al. stated that reactivity grade to Nickel patch test is not directly correlated to symptoms intensity [6].

Gold standard for SNAS diagnosis is based on an Oral Provocation Test (OPT), called also Nickel "Oral Challenge" (NOC) that can be performed only after 4-6 weeks of a Nickel-free diet [6].

OPT consists in gradually increasing doses of Nickel, tablets/capsules, starting from 1.25 mg dose [13]. In absence of symptoms, this dose is doubled after 24 hrs. and symptoms are then evaluated. The maximum dose administered is 3.75 mg, representing 10 times the physiological dietary Nickel intake [11-13]. Nickel OPT is considered positive if cutaneous systemic symptoms occur with or without gastrointestinal symptoms as bloating and diarrhea and/or typical cutaneous manifestations as flare-up reactions in patch test sites, itching or generalized erythema [11].

An observed rapid cutaneous response following oral Nickel provocation suggests a complex interplay within SNAS between Type IV (cellular) and III (humoral) hypersensitivity reactions. Jensen, et al. demonstrated a statistically significant rise in IL-5, a Th2 response, within 24 hours after oral challenge, highlighting the role of the Th2 Response in the initial elicitation phase of SNAS [2,7]. Different is the procedure described by Falagiani P, et al. suggesting diagnosing SNAS if symptoms are consistent with the findings of a thorough clinical evaluation. If these symptoms improve a month post Nickel free diet, clinical assumption is confirmed [5]. Nickel patch test is then performed and, if positive, a provocation test with Nickel sulphate is carried out after 3-4 weeks interval [5].

The provocation test consists of administering a capsule containing talc as placebo, followed by a capsule containing 0.6 mg of Nickel sulphate, 1 hour later [5]. The oral challenge is tested in the morning, in individuals who have fasted for 12 hours. If the test is still negative, a further dose of 1.25 mg Nickel is administered after a 1-hour interval from the last dose; skin status and systemic symptoms are evaluated and recorded 24 hours after the challenge [5].

As far as "Nickel Free diet" (N-F diet) concerns, the practical limitation is that there's no standard dietetic protocol universally accepted and recommended [11]. Since Nickel is a ubiquitous trace metal, it's very hard to provide a complete N-F diet, therefore usually N-F diet ends up to be a low Nickel diet [11].

Many authors recommend the BraMaNi diet by Braga and Maccarinelli, developed to minimize additive content and vasoactive amines in foods [11]. This protocol applies to adult men and women with normal weight, with the following energy and dietary macronutrient composition: 1932 Kcal, 16.28% protein, 27.71 % lipids (5.66% saturated fatty acids) and 55.89% Carbohydrate for males and 1733 Kcal, 15.83% protein, 26.22% lipids (8.33% saturated fatty acids), 57.84 % carbohydrates for females, with about 50 μg /day Nickel [13].

Results have shown an improvement of gastrointestinal and cutaneous symptoms following this "restriction" period [12]. Anyhow, adherence to a Nickel free diet is essential during the oral provocation test period to avoid false positive results [13].

Possible Solutions

As described previously, the quantity of Nickel contained in food depends on many factors, therefore precise estimation is difficult and it varies sensibly, being strongly influenced by seasonality and Ni concentration in the soil [14,15].

This has an impact on estimated daily intake which is consequently approximate according to different studies; average daily intake of Nickel ranges from 200 μg to 350 μg/day16, while the recommended daily intake is about 50 μg [10-13]. As with most minerals, only a small percentage of the quantity ingested with food is absorbed [11].

The factors influencing bioavailability are many, including diet composition and interaction with other dietary nutrients or medications. Its absorption may be suppressed by binding, chelating substances, competitive inhibitors or redox reagents 6 [6,11].

Complexing agents, as ethylenediaminotetraacetic (EDTA) reduce plasma-Nickel levels, while ascorbic acid, citric acid and pectin affect nickel absorption [17]. Also tannins influence nickel absorption by inhibiting iron and zinc one [17]. On the other hand, Nickel absorption is often enhanced by substances which increase pH, solubility, oxidation or by chelating agents that are actively absorbed like organic molecules [11].

However, human body's retention of dietary Nickel is low: it is estimated to be around 3-6% of total Nickel absorbed, while serum concentrations vary from 1.6 to 7 μg/L and urinary Nickel concentration from 2 to 5 μg/L [16]. Until now, protocols proposed to counteract Nickel related symptoms and signs, referring mainly to SNAS, are various but not fully proven to be a valid solution so far [7]. The main protocols suggested in literature are hereby reported and discussed.

Iron Supplementation

It has been observed that Nickel absorption can be enhanced by iron deficiency and thus individuals with iron deficiency and/or sideropenic anemia (IDA) tend to retain more Nickel from the diet [18]. This is due to the Divalent Metal Transporter (DMT) protein up-regulation in the intestinal mucosa of IDA patients [18]. DMT protein is present on the enterocytes luminal surfaces in the intestinal epithelium, with the role of transporting iron (Fe^{++}) into the enterocyte. In absence or inadequacy of dietary iron intake, DMT protein tends to immediately bind and transport other available divalent cation(s), including Nickel, across the membrane [18]. This is important for those suffering from Nickel allergy since this metal is an ubiquitous trace element and is present in most foods [18]. Conversely, it has also been found that both adequate iron intake and status can limit Nickel absorption due to the down regulation of DMT protein in the luminal surfaces of enterocytes [17]. Few clinical trials observed benefits from oral iron supplementation in addition to a Nickel free Diet in women with Iron Deficiency Anaemia (IDA) [17].

Regarding the amount of iron to be administered, Sharma, et al. conducted two studies in which individuals with chronic urticaria and hand eczema were treated with oral iron supplementation [18]. The authors prescribed respectively 30 mg of iron (divided in two doses of 15 mg per day) for 12 weeks and 150 mg of iron (into 3 daily administrations) for 6 weeks along with a Nickel free diet [17-19]. Even if both studies reported a reduction in symptoms severity, the authors concluded that a further multicenter study, including a larger sample size with longer follow-up, was recommended [19]. Besides, it is necessary to acknowledge that all the results previously described were relative to patients with ACD and not to those specifically affected by SNAS. Therefore, to date, there are no results proving that iron supplementation successfully improves the symptoms of patients with SNAS [19].

Vitamin C Supplementation

The role of Vitamin C promoting redox of trivalent iron (non-eme iron) into divalent iron (eme-iron), necessary for intestinal absorption, is well documented. Therefore, Vitamin C increases iron bioavailability, reducing Nickel absorption [20].

According to the American Academy of Dermatology the daily recommended dosage of vitamin C for optimal result is 500-1000 mg at every meal (before, during or right after meals) [8,16], confirmed by others showing a subsequent significant decrease in Nickel plasma levels [16].

Treatment with Chelate Agents

The use of chelates is considered another aid to reduce Nickel bioavailability and enhance the effect of a Nickel free diet [21]. Disulfiram, known as an effective treatment for chronic alcoholism, has been used as an oral chelator since 1979 despite the side hepatotoxic effects [22]. Once absorbed in the gut, it oxidizes into two molecules of sodium diethyldithiocarbamate, able to bind Nickel and subsequently excreted in the urine [23]. Results suggest that calcium sodium EDTA (Ethylenediaminetetraacetic acid), a synthetic compound able to coat metal molecules and stop their reactivity, could be used to bind metals including Nickel [23].

Calcium sodium EDTA is poorly absorbed in the gastrointestinal tract: only a percentage ranging from 5 to 15% enters the bloodstream where it can chelate and remove toxins from the blood [21]. Even if FAO/WHO Expert Committee on Food Additives (JECFA) Committee stated that no adverse health effects have been reported for sodium calcium EDTA intake, the frequent consumption under the recommended upper levels of foods high in this additive is not recommended, since it could bind other minerals such as iron, causing a consequent deficit [21,22].

Nickel Free Diet

Up until now, a Nickel free diet is the most used treatment for SCD and SNAS, even if it is difficult for patients to adhere to since it is very selective and restrictive, affecting food choices and the long term quality of life of patients [24], as well as exposing patients to risk from many nutrients and micronutrient inadequacies4, including dietary fibres, with consequent dysbiosis [25].

At present, nearly all of the Nickel free diet prescriptions, other than BraMa-Ni diet, consists of a long food restriction list with no dietary indications [11].

Most of the nutritional protocols are very restrictive, and only a few SNAS patients are allowed to reintroduce the forbidden foods after a long period, whereas the majority of them have to maintain a lifelong Nickel free diet. Adherence to this type of very restrictive diet, with low food variety, may affect the overall nutritional status of patients [25]. Since plant food is the main dietary source of Nickel, avoiding foods rich in Nickel for a long period is equivalent to adopting a fruit-and-vegetable-poor dietary pattern, which is likely to lead to inadequate micronutrient intake, thus increasing the risk of developing nutrient deficiencies, including Magnesium, Potassium, Vitamin C, and Folic Acid [26].

Moreover, national and international differences in the nickel content of food should be acknowledged. Pizzutelli, et al.

compared different foods with high Nickel content, showing big discrepancies according to the different composition tables [4]. Excluding peanuts, beans, lentils, peas, soybeans, oats, cocoa, chocolate, nuts, and whole wheat, which are uniformly considered high in Nickel, other data are discordant [4], thereby impacting on the prescription of a Nickel free diet. Until now, there has been no ascertained data even on the minimum quantity of Nickel that triggers symptoms. Tammaro, et al. suggested that a range between 0.6 and 5.6 mg causes flare ups, thus making it difficult to identify a "safe level" [25].

Among the various solutions reported in the literature, Mislanker, et al. proposed a scoring system that assigned a score from 0 to 10 for each food item depending on the Nickel content per serving [16]. Therefore, patients were advised to manage their meals by combining foods without exceeding a score of 15 points, corresponding to a maximum nickel content of 150 μg, which would help avoid clinical manifestation. To those more sensitive, a score below 5 was recommended [16].

Some recent results also took into consideration the possibility of combining a nickel-free diet with simultaneous probiotics supplementation [27]. Randazzo, et al. evaluated the effects of probiotic *Lactobacillus reuteri* DSM 17938 strain supplementation in patients suffering from SNAS, in terms of the modulation of the fecal LAB population linked to a reduction in Gastro Intestinal and cutaneous symptoms and to an increase the quality of life of patients [27].

Their results suggested that probiotic *Lactobacillus reuteri* could be a useful supplementation during a Nickel-free diet, increasing gut population diversity, which could contribute to restoring the intestinal homoeostasis conditions [27]. These results were confirmed by Francesca Lombardi, et al. who described the effects of a Nickel-free diet alone or in combination with the oral consumption of appropriate probiotics in SNAS patients [28].

According to their urinary indican/skatole levels, patients were assigned to a dysbiosis type/grade and followed a Nickel-free diet for three months [28]. Overall, after three months of treatment in general (diet alone with or without probiotics), Ni-sensitivity and dysbiosis levels greatly improved. The association of a Nickel-free diet with a specific probiotic oral supplementation (Lactobacilli- or Bifidobacteri) was significantly more effective in decreasing dysbiosis or achieving eubiosis than was the case through diet alone [28]. Even though, a Nickel-free diet followed for a long time could lead to an increased risk of micronutrient inadequacy, there is evidence showing that a diet high in Nickel could have a negative impact on human health [17].

According to Lusi E, et al. a general excess of dietary Nickel is comparable to an excessive dietary intake of heavy metals [26]. The authors reported that a high dietary intake of Nickel is associated with an increased risk of weight gain, especially in premenopausal women [26]. The prevalence rate of Nickel allergy in overweight women is 63%, compared to 12% in the general population, and a physiological diet formulated to be low only in Nickel intake has been effective in reducing BMI and waist circumference in overweight females [26].

These findings have been recently confirmed in a larger cohort of 1,128 individuals with obesity, showing that Nickel allergy was more frequent in the presence of excessive weight [29]. The results in the literature report that excessive dietary intake of Nickel also causes a profound imbalance in the commensal gut flora [26]. In fact, potentially pathogenic Nickel resistant bacteria have been recently identified in the human gut of obese people [26].

Hyposensitization to Nickel

Nickel oral hyposensitization is a mechanism of immune tolerance in a Nickel-sensitized patient through the ingestion of low Nickel doses. This practice has been known for a long time. Initially, Sjovall, et al. performed two controlled studies, each including 24 patients with Nickel allergic contact dermatitis, with an oral administration of 5.0 mg Nickel sulphate once a week for six weeks [30]. The symptom severity, as measured by a patch test before and after Nickel administration, was significantly reduced [30]. Nevertheless, over the years different studies investigating Nickel oral hyposensitization to treat SNAS have not yet provided sufficient results to consider this technique as a definitive solution for treating patients affected by this syndrome [30].

Nickel and Gut Microbioma: Preliminary Results from the Literature

According to preliminary results from the literature, a correlation between Nickel sensitive patients, gut microbiota composition, and obesity was identified [29]. A clinical trial conducted in a small-sized sample investigated the presence of nickel resistant bacteria in the human gut, studying the correlation of this bacteria with nickel sensitive severity and overweightness in women [28]. The authors collected stool samples from 28 females with Nickel hypersensitivity diagnosis (divided into two subgroups according to their BMI; BMI>25 and <25) and from 11 patients without Nickel hypersensitivity (control group) [28]. To verify gut sensitization to Nickel, the stool samples were inoculated with Nickel Sulphate 250 mM ($NiSO_4$), using a series of liquid cultures with increasing concentrations of $NiSO_4$ [28]. An analysis of the microbial composition, revealed that levels of Enterobacteriaceae tended to decrease progressively with increasing $NiSO_4$ concentrations, while Lactic Acid Bacteria (Enterococcaceae, Streptococcaceae and Lactobacillaceae) increased [28].

Lactobacillales were found in higher amounts in patients with increased BMI and higher degrees of Nickel allergy severity [28]. In fact, it is well documented that some strains of Lactobacillales (e.g., *Lactobacillus fermantum*) use Nickel ingested in the diet to protect the body from potential Nickel toxicity [31].

Lactic acid bacteria bind to toxic substances, such as aflatoxin B1 and food-borne mutagen Trp-P-2 within the gastro-intestinal tract, thereby reducing their uptake [28]. This might support the hypothesis that Lactic acid bacteria are involved in Nickel detoxification [31].

Recent findings have fueled the controversy about the role of Lactobacillales in obesity: subjects with obesity are likely populated by particular strains of Lactobacillales compared to non-obese subjects, including some strains of Nickel resistant Lactobacillae that could be actually responsible for shaping the obese phenotype [31]. To date, data present in the literature related to this issue is still limited and controversial, and thus the role of gut microbiota related to SNAS patients must be further examined [26].

Conclusion

At present, it is impossible to draw definite evidence-based recommendations about the nutritional support and management of SNAS. Nickel-free diets have been highly criticized for non-compliance and the inadequate intake of micronutrients. At the same time, SNAS is fairly common and remains quite relevant in the general population, and it

needs to be diagnosed and treated early before it becomes chronic, thereby impairing the quality of life and negatively impacting the socio-economic status of both individuals and the health care system. Despite the extensive research in this field, many questions remain regarding the medical nutrition treatment of patients with SNAS. Uncertainties, contradictions, and inconsistencies appear to be numerous and repeated. Finally, there are doubts about the composition and the therapeutic value of a Nickel-free diet itself. Further and broader studies, more rigorously conducted, are needed to address this issue in order to draft evidence-based recommendations with a personalized nutritional approach.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Author's Contributions

Conti MV, Bissacco G equally contributed to the conception and design of the research; Conti MV, Bissacco G and De Giuseppe R contributed to the interpretation of the data; Conti MV, Bissacco G, De Giuseppe R and Cena H drafted the manuscript. Conti MV, Bissacco G, De Giuseppe R, Cena H, Calcagno MG and D'antona G critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Ahlström MG, Thyssen JP, Wennervaldt M, Menné T, Johansen JD (2019) Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis 81: 227-241.
2. Jensen CS, Menné T, Johansen JD (2006) Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta□analysis. Contact Dermatitis 54: 79-86.
3. Kumar S, Trivedi AV (2006) A review on role of nickel in the biological system. Int J Curr Microbiol App Sci 5: 719-727.
4. Pizzutelli S (2011) Systemic nickel hypersensitivity and diet: myth or reality? Eur Ann Allergy Clin Immunol 43: 5-18.
5. Falagiani P, Di Gioacchino M, Ricciardi L, Minciullo PL, Saitta S, et al. (2008) Systemic nickel allergy syndrome (SNAS): A review. Rev Port Imunoalergologia 16: 135-147.
6. Ricciardi L, Arena A, Arena E, Zambito M, Ingrassia A, et al. (2014) Systemic nickel allergy syndrome: epidemiological data from four Italian allergy units. Int J Immunopathol Pharmacol 27: 131-136.
7. Bergman D, Goldenberg A, Rundle C, Jacob SE (2016) Low Nickel Diet: A Patient-Centered Review. J Clin Exp Dermatol Res 7: 355.
8. American Academy of Dermatology Association (2015) Position statement on nickel sensitivity.
9. Schuttelaar MLA, Ofenloch RF, Bruze M, Cazzaniga S, Elsner P, et al. (2018) Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: The EDEN Fragrance Study. Contact Dermatitis 79: 1-9.
10. Manam S, Tsakok T, Till S, Flohr C (2014) The association between atopic dermatitis and food allergy in adults. Curr Opin Allergy Clin Immunol 14: 423-429.
11. Ricciardi L, Furci F, Isola S, Minciullo PL, Saitta S, et al. (2019) Systemic nickel allergy syndrome: tips and tricks on how to be suspected and treated. J Biol Regul Homeost Agents 33: 1289-1292.
12. Pizzutelli S (2015) Reply to: Update on systemic nickel allergy syndrome and diet. Eur Ann Allergy Clin Immunol 47: 27.
13. Braga M, Quecchia C, Perotta C, Timpini A, Maccarinelli K, et al. (2013) Systemic nickel allergy syndrome: nosologic framework and usefulness of diet regimen for diagnosis. Int J Immunopathol Pharmacol 26: 707-716.
14. Kageyama Y, Aida K, Kawauchi K, Morimoto M, Akiyama T, et al. (2019) Higher incidence of zinc and nickel hypersensitivity in patients with irritable bowel syndrome. Immun Inflamm Dis 7: 304-307.

15. Rizzi A, Nucera E, Laterza L, Gaetani E, Valenza V, et al. (2017) Irritable bowel syndrome and nickel allergy: what is the role of the low nickel diet? J Neurogastroenterol Motil 23: 101-108.

16. Mislankar M, Zirwas MJ (2013) Low-nickel diet scoring system for systemic nickel allergy. Dermatitis 24: 190-195.

17. Sharma AD (2013) Low nickel diet in dermatology. Indian J Dermatol 58: 240.

18. Sharma AD (2010) Benefit of iron therapy in the management of chronic urticaria due to nickel sensitivity. Indian J Dermatol 55: 407-408.

19. Sharma AD (2011) Iron therapy in hand eczema: a new approach for management. Indian J Dermatol 56: 295.

20. Das S, Reddy RC, Chadchan KS, Patil AJ, Biradar MS, et al. (2019) Nickel and Oxidative stress: Cell Signaling Mechanisms and Protective Role of Vitamin C. Endocr Metab Immune Disord Drug Targets. 20: 1024-1031.

21. Chen JK, Thyssen JP (2018) Metal Allergy: From Dermatitis to Implant and Device Failure. Springer.

22. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

23. Rundle C, Jacob SE (2017) Chelation Therapy for Nickel Allergy. Journal of the Dermatology Nurses Association 9: 46-49.

24. Cunningham E (2017) What Role Does Diet Play in the Management of Nickel Allergy? J Acad Nutr Diet 117: 500.

25. Tammaro A, Narcisi A, Persechino S, Caperchi C, Gaspari A (2011) Topical and systemic therapies for nickel allergy. Dermatitis 22: 251-255.

26. Lusi EA, Santino I, Petrucca A, Zollo V, Magri F, et al. (2019) The Human Nickel Microbiome and its relationship to Allergy and Overweight in Women. BioRxiv 546739.

27. Randazzo CL, Pino A, Ricciardi L, Romano C, Comito D, et al. (2015) Probiotic supplementation in systemic nickel allergy syndrome patients: study of its effects on lactic acid bacteria population and on clinical symptoms. J Appl Microbiol 118: 202-211.

28. Lombardi F, Fiasca F, Minelli M, Maio D, Mattei A, et al. (2020) The Effects of Low-Nickel Diet Combined with Oral Administration of Selected Probiotics on Patients with Systemic Nickel Allergy Syndrome (SNAS) and Gut Dysbiosis. Nutrients 12: 1040.

29. Watanabe M, Masieri S, Costantini D, Tozzi R, De Giorgi F, et al. (2018) Overweight and obese patients with nickel allergy have a worse metabolic profile compared to weight matched non-allergic individuals. PLoS One 13: e0202683.

30. Di Gioacchino M, Ricciardi L, De Pità O, Minelli M, Patella V, et al. (2014) Nickel oral hyposensitization in patients with systemic nickel allergy syndrome. Ann Med 46: 31-37.

31. Armougom F, Henry M, Vialettes B, Raccah D, Raoult D (2009) Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. PLoS One 4: e7125.