

Annotated Bibliography of Research Related to Systemic Nickel Allergy Syndrome (SNAS)

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5 March 2019

In this SNAS bibliography, my annotations highlight what I found relevant. I encourage you to read the original works and form your own interpretations. If a reference says "Abstract only", it means I could not find an open source version (which also means I may be missing relevant details in my interpretation). Otherwise, you should be able to find them on the Internet.

If you use this bibliography for academic purposes, please acknowledge the work in any publication to which it contributed.

1. SNAS and Nickel SCD Review Articles

Bergman, D. et al., 2016. Low nickel diet: A patient-centered review. *Journal of Clinical and Experimental Dermatology Research*, 7(355), p.2.

- Review article, defines SNAS, SCD and ACD, describes a low nickel diet, reviews the literature regarding underlying immunology and hyposensitization treatment.

Pizzutelli, S., 2015. Reply to: Update on systemic nickel allergy syndrome and diet. *European Annals of Allergy and Clinical Immunology*, 47(1), p.27.

- Rebuttal letter to Goldenberg's 2015 letter, restating his position without offering new evidence.

Goldenberg, A. and Jacob, S.E., 2015. Update on systemic nickel allergy syndrome and diet. *European Annals of Allergy and Clinical Immunology*, 47(1), pp.25-26.

- Letter to the editor regarding Pizzutelli's 2011 paper, disputing its claim that SNAS is "controversial".
- Provides a good definition of SNAS and a summary of its pathophysiology.

Calogiuri, G.F. et al., 2014. Nickel hypersensitivity: A general review on clinical aspects and potential co-morbidities. *Journal of Allergy and Therapy*, 7, p.243.

- A review of SNAS research dating back to 1975. Discusses symptoms, implants, food, dental materials.
- Defines 5 patterns of nickel sensitization:
 1. Prolonged contact/ACD
 2. Occupational respiratory exposure
 3. Gastrointestinal route (foods containing Ni): SNAS 1° type
 4. Implants containing Ni, including stents, pacemakers, dental materials, prostheses, needles: SNAS 2° type
 5. A combination of the above routes.

Lampel, H.P. and Silvestri, D.L., 2014. Systemic contact dermatitis: current challenges and emerging treatments. *Current Treatment Options in Allergy*, 1(4), pp.348-357.

- Review article on SCD that includes SNAS.

Fabbro, S.K. and Zirwas, M.J., 2014. Systemic contact dermatitis to foods: nickel, BOP, and more. *Current Allergy and Asthma Reports*, 14(10), p.463.

- A review of SCD to several food-borne allergens: nickel, cobalt, chromium, BoP, PG, urushiol, sesquiterpene lactones, formaldehyde, garlic, propolis and sorbic acid.
- Says SCD is completely unrelated to type I (IgE) allergies, contrary to some other work.
- Classic presentation of SCD to nickel is hand dermatitis, itchy papules on the elbows and/or knees, and “widespread symmetric macropapular eruptions”. Reappearance of prior sites of ACD in the absence of cutaneous exposure should strongly suggest SCD.
- Includes a table of common presentations for each allergen.

Katta, R. and Schlichte, M., 2014. Diet and dermatitis: food triggers. *The Journal of Clinical and Aesthetic Dermatology*, 7(3), p.30.

- A review article on ACD and SCD that includes nickel.
- Lists treatments including diet and lifestyle changes to reduce nickel exposure, along with the other top contact allergens.

Sharma, A.D., 2013. Low nickel diet in dermatology. *Indian Journal of Dermatology*, 58(3), p.240.

- A review of nickel allergy as a cause of dermatitis and its treatment via a low nickel diet.
- Covers food and non-food sources of nickel and non-dietary treatments.

Yoshihisa, Y. and Shimizu, T., 2012. Metal allergy and systemic contact dermatitis: an overview. *Dermatology Research and Practice*, 2012.

- A review of metal SCD with a section on nickel.
- Proposes using a blood test that measures Th1 and Th2 cytokine production to confirm the diagnosis of metal allergies.

Tamaro, A. et al., 2011. Topical and systemic therapies for nickel allergy. *Dermatitis*, 22(5), pp.251-255.

- A review article of treatments for SNAS, including topical, UVB, systemic immunosuppressive, zinc, low nickel diet, disulfiram, and hyposensitization therapies.

Pizzutelli, S., 2011. Systemic nickel hypersensitivity and diet: myth or reality? *European Annals of Allergy and Clinical Immunology*, 43(1), p.5.

- A very critical review of the SNAS literature up to 2011 that questions studies that support food-borne nickel as a symptom source and the low nickel diet as a treatment.
- Has a table demonstrating how variable the advice is from 11 different sources.
- Provides a good description of SNAS and SCD.
- Discusses how difficult it is to rigorously test for SNAS because nickel is ubiquitous, which makes double-blind testing difficult as consumed nickel is uncontrolled, and scoring is subjective.
- Concludes that more rigorous studies need to be done to establish that nickel allergy is indeed responsible for SNAS symptoms.
- Claims there is a “strong psychosomatic effect”, with no citations to support the statement.

Petrucci, F., Bocca, B., Forte, G., Caimi, S. and Cristaudo, A., 2009. Role of diet in nickel dermatitis. *The Open Chemical and Biomedical Methods Journal*, 2, pp.55-7.

- A review of SCD and nickel sources, including dietary, and treatments.

Thyssen, J.P. and Maibach, H.I., 2008. Drug-elicited systemic allergic (contact) dermatitis—update and possible pathomechanisms. *Contact Dermatitis*, 59(4), pp.195-202.

- A review of SCD to metals and drugs.
- Lists 10 different terms used in the literature for SCD, not including SNAS.
- SCD is a type 3 and 4 allergy, and the initial immune reactions may take place in both the skin and gastrointestinal mucosa. Metal allergies are Th1 and Th2 driven.
- Recommends using the term Systemic Allergic Dermatitis (SAD) instead of SCD since contact is not a requirement. [I would propose Systemic Allergy Syndrome (SAS) since dermatitis isn't always a symptom either!]
- Systemic symptoms of SAD include headaches, fever, malaise, arthralgia, vomiting and diarrhea.
- Patch testing should not be done prior to 6 weeks of an adverse reaction. Negative patch testing should be followed up with intradermal testing. The LTT is a useful adjunct test.

Jensen, C.S., Menné, T. and Duus Johansen, J., 2006. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis*, 54(2), pp.79-86.

- Meta-analysis of 9 studies finding that for patients with SCD or chronic eczema, 1% will react to oral nickel doses less than 0.22mg using the more "sensitive" findings, which is a normal dietary exposure rate.

2. Low Nickel Diets and Dietary Treatment Studies

Rizzi, A. et al., 2017. Irritable Bowel Syndrome and nickel allergy: What is the role of the low nickel diet? *Journal of Neurogastroenterology and Motility*, 23(1), p.101.

- Patients with IBS and all other causes ruled out and a positive nickel patch test (20 of them) were put on the BraMa-Ni low nickel diet for 3 months.
- There was significant improvement in all subjective GI symptoms, but the overall health survey didn't differ significantly.
- The intestinal permeability improved more for patients with moderate to severe skin reactions, and worsened for half of the patients.
- Confirms the high prevalence of anxiety and other psychological symptoms.

Antico, A. and Soana, R., 2015. Nickel sensitization and dietary nickel are a substantial cause of symptoms provocation in patients with chronic allergic-like dermatitis syndromes. *Allergy & Rhinology*, 6(1), p.e56.

- Of 1726 patients with chronic allergic-like skin diseases, none had extracutaneous (SNAS) symptoms. This may be because any patient with an IgE allergy to anything was excluded.
- 339 (20%) tested nickel positive, and 52 recovered by avoiding contact with nickel.
- 207 achieved complete or near complete recovery by following their low-nickel diet (list included). The diet was ineffective for 51.
- 185 had a positive oral challenge (on an empty stomach); in 26 the response was severe. Average time of reaction to challenge was 5.3 ± 2.5 hours, ranging from 3 to 12 hours.

Perez, L.D.M., França, A.T. and Zimmerman, J.R., 2015. Systemic nickel allergy syndrome, *World Allergy Organization Journal*, 8(S1), p.A89.

- Very brief overview of a Brazilian SNAS study with some language clarity issues.
- 331 patients with SNAS symptoms improved after 60 days on a low nickel diet; for those who went back to their regular diet, symptoms returned between 7 and 20 days.

Ricciardi, L. et al., 2014. Systemic nickel allergy syndrome: Epidemiological data from four Italian allergy units. *International Journal of Immunopathology and Pharmacology*, 27(1), pp.131-136.

- A statistical analysis of SNAS prevalence in an Italian allergy clinic. SNAS was confirmed in 98 patients (5.78%) of the 1,696 referred to an allergy clinic for a variety of symptoms (the reasons for referral are not well defined), having a positive patch test and responding to one month on a low nickel diet.
- The most common symptoms were cutaneous (51 patients), gastrointestinal (87 patients) and other systemic clinical manifestations (37 patients). The unexpected result is that cutaneous symptoms are not as common as gastrointestinal.
- An IgE-mediated food allergy was found in 16 out of the 98 SNAS patients (16.3%), and the authors propose that the higher incidence is caused by damage to the intestinal mucosa.

Mislankar, M. and Zirwas, M.J., 2013. Low-nickel diet scoring system for systemic nickel allergy. *Dermatitis*, 24(4), pp.190-195.

- Provides a points-based scoring system for a low nickel diet, based on data on the nickel content of food from the FDA's Total Diet Study. [The basis of the Rebelytics LND]

Braga, M. et al., 2013. Systemic nickel allergy syndrome: nosologic framework and usefulness of diet regimen for diagnosis. *International Journal of Immunopathology and Pharmacology*, 26(3), pp.707-716.

- Describes SNAS and presents the BraMa-Ni low nickel diet, a meal plan with specific foods [that also happen to be low histamine].
- Oral nickel challenge elicited skin and GI symptoms, and that's all. [This may be because they did the oral challenge after a month on the diet, which could prevent a nickel-provoked histamine overflow reaction.]
- 8 patients of 98 experienced GI symptoms with no skin symptoms.
- High rate of lactose intolerance in the SNAS population.
- Acceptance and adherence to the BraMa-Ni meal plan was much better than for the forbidden food list.
- Reference related to histamine amounts does not exist (the journal's website redirects to a shopping site), and the website that has "appropriate recipes" does not resolve. Their source of nickel food measurements is not cited.

Picarelli, A. et al., 2011. Oral mucosa patch test: a new tool to recognize and study the adverse effects of dietary nickel exposure. *Biological Trace Element Research*, 139(2), pp.151-159.

- 86 patients with at least one intestinal symptom related to nickel ingestion were tested with an oral mucosa patch test (omPT) and patch tests (5% NiSO₄).
- Not everyone had extra-intestinal symptoms.
- 38.4% had a positive patch test while 61.6% had a positive omPT. Of the 53 patients with a positive omPT, 6 showed a lesion within 30 minutes, indicating a Th2 or immediate-type (IgE) response. All omPT-positive patients had a relapse in their symptoms after the omPT.
- After 2 months on a low nickel diet (restricting certain "high-nickel" foods, as per Sharma 2007) 52 of the 53 omPT-positive had improved symptoms.
- Discusses the variable responses and the combination of Th1 and Th2 cytokines involved in nickel allergy and ACD.

Sharma, A.D., 2011. Iron therapy in hand eczema: a new approach for management. *Indian Journal of Dermatology*, 56(3), p.295.

- Twelve patients prescribed a low nickel diet plus an iron supplement (15 mg twice daily before meals) fared better than a control group of 11 on the low nickel diet alone. After 12 weeks, 5/11 patients in the

control group had complete whereas the iron group had complete recovery in 10/12. Patients with anemia were excluded, i.e. the patients were not iron deficient.

- If a person has low iron, the body produces more divalent metal transporter (DMT) in order to absorb more of it. But it transports other metals as well, as they are available, including nickel. The DMT's preference in order of affinity is Fe >Zn >Mn >Co >Cd >Cu >Ni >Pb.

Zirwas, M.J. and Molenda, M.A., 2009. Dietary nickel as a cause of systemic contact dermatitis. *The Journal of Clinical and Aesthetic Dermatology*, 2(6), p.39.

- Presents 3 case studies where patients' dermatitis cleared upon following a low nickel diet.
- Prior to the eruption two of the three had increased their intake of high nickel foods: whole grains, soy beans.
- "It should be noted that it has been the lead author's experience that there is not a correlation between a history of typical nickel contact dermatitis (earring dermatitis or infraumbilical dermatitis) and the likelihood of dietary nickel playing a role in a patient with widespread dermatitis or itch. The lack of a history of typical nickel reactions, in the authors' opinion, does not rule out nickel as a cause of widespread dermatitis or pruritus."
- Makes the valid point that a low nickel diet is harmless and inexpensive and so should be considered in patch-test positive cases.

Kaaber, K., Veien, N.K. and Tjell, J.C., 1978. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *British Journal of Dermatology*, 98(2), pp.197-201. (Abstract only)

- Patients with chronic nickel dermatitis who reacted to an oral challenge were put on a low nickel diet for 6 weeks.
- 9 of the 17 improved, and 2 of those 9 were able to resume a normal diet without symptoms.
- There was a drop in nickel excretion while on the low nickel diet, with no difference between those who improved and those who did not.

3. Non-Dietary Treatments

Medications

Pigatto, P.D. et al. 1990. Disodium cromoglycate versus diet in the treatment and prevention of nickel-positive pompholyx. *Contact Dermatitis*, 22(1), pp.27-31. (Abstract only)

- In 24 cases of dishydrotic eczema caused by nickel that did not respond to a low nickel diet, disodium cromoglycate (a mast cell stabilizer) improved objective and subjective symptoms, coinciding with a reduction in intestinal permeability.

Supplements

Onodera, R., et al., 2018. Zinc ions have a potential to attenuate both Ni ion uptake and Ni ion-induced inflammation. *Nature Scientific Reports*, 8(1), p.2911.

- An in vitro study (not directly in humans) showing that zinc, cobalt and manganese inhibit the uptake of nickel into cells, that Zn inhibits IL-8 production whereas Mn and Co enter cells and increase it, and that a zinc deficiency enhances nickel uptake into cells surrounding implants. A zinc deficient state might therefore increase sensitivity to nickel.

Magrone, T. et al., 2017. In vitro effects of nickel on healthy non-allergic peripheral blood mononuclear cells. The role of red grape polyphenols. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, 17(2), pp.166-173. (Abstract only)

- In human blood cells, exposure to nickel results in a decrease of IL-17 and an increase in nitric oxide. Supplementation of polyphenols increased IL-17 and reduced NO.

Quirk, S.K. et al., D.K., 2016. Vitamin D in atopic dermatitis, chronic urticaria and allergic contact dermatitis. *Expert Review of Clinical Immunology*, 12(8), pp.839-847.

- A review of vitamin D's role in AD, urticaria and ACD.
- Vitamin D enhances defences against microbes and inhibits excessive inflammation.
- There are no human studies of vitamin D in humans with ACD, only mice. The authors do not recommend supplementation for the purpose of suppressing ACD.

Patlar, S. et al., 2011. The effect of vitamin A supplementation on various elements in elite taekwondo players. *Biological Trace Element Research*, 139(3), pp.296-300. (Abstract only)

- Athletes given 100 mg Vitamin A daily for 6 weeks had "significantly reduced" blood levels of nickel relative to values before supplementation.

Solomons, N.W. et al., 1982. Bioavailability of nickel in man: Effects of foods and chemically-defined dietary constituents on the absorption of inorganic nickel. *The Journal of Nutrition*, 112(1), pp.39-50.

- [This is the primary reference supporting vitamin C supplementation.]
- When 5 mg of nickel was added to milk (whole), black coffee (with sugar), tea (with lemon and sugar), orange juice or Coca-Cola, serum nickel was significantly lower than control (water) in all cases except cola. Serum nickel was also lower when taken with 1 g ascorbic acid.
- Comparing nickel absorption when taken with meals, a North American breakfast of eggs, toast, bacon and coffee suppressed nickel significantly more than a Guatemalan breakfast of beans, corn tortillas and coffee.

Probiotics

Randazzo, C.L. et al., 2015. Probiotic supplementation in systemic nickel allergy syndrome patients: Study of its effects on lactic acid bacteria population and on clinical symptoms. *Journal of Applied Microbiology*, 118(1), pp.202-211.

- Patients had a positive patch test, GI reactions, recurrent abdominal pain and cutaneous reactions such as urticaria, itching and eczema after ingestion of nickel-containing food. There were 9 in the experiment and 7 placebo; both followed a low nickel diet.
- The experimental group was given 1 tablet BioGaia L. reuteri for 2 weeks. Symptoms were measured at baseline, 2 weeks and 4 weeks.
- There was significant improvement of all cutaneous symptoms after 2 weeks of probiotic treatment.
- GI symptoms took longer to improve, but decreased by 4 weeks.

Rosenfeldt, V. et al., 2003. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology*, 111(2), pp.389-395.

- Concluded that L rhamnosus 19070-2 and L reuteri DSM 122460 was beneficial in the management of atopic dermatitis in 43 children aged 1-13, with the effect more pronounced when the child had a positive IgE skin prick test.
- A small proportion worsened with treatment.

Oral Hyposensitization

Di Gioacchino, M. et al., 2014. Nickel oral hyposensitization in patients with systemic nickel allergy syndrome. *Annals of Medicine*, 46(1), pp.31-37.

- A double-blind placebo-controlled trial of oral nickel hyposensitisation.
- Patients began hyposensitization after a month on the BraMa-Ni diet, which is low nickel and low histamine.
- 141 patients met inclusion criteria, split into 4 groups with different final levels of oral nickel in the hyposensitization process.
- The group taking the highest dose, 1.5 µg, fared the best with reintroduction of high nickel foods, with the lower doses not differing significantly from placebo.

Ricciardi, L. et al., 2012. Systemic nickel allergy: Oral desensitization and possible role of cytokines interleukins 2 and 10. *International Journal of Immunopathology and Pharmacology*, 26(1), pp.251-257.

- 22 women diagnosed with SNAS via oral exposure to nickel sulfate underwent oral hyposensitization, increasing in dose over two years. Higher-nickel foods were reintroduced gradually after 9 weeks on a low nickel diet.
- After 2 years there was a significant improvement in VAS scores and the oral challenge was negative in 18 patients. There was a statistically significant decrease in the levels of the IL-2 cytokine.

Minelli, M. et al., 2010. Oral hyposensitization to nickel induces clinical improvement and a decrease in TH1 and TH2 cytokines in patients with systemic nickel allergy syndrome. *International Journal of Immunopathology and Pharmacology*, 23(1), pp.193-201.

- 23 SNAS patients on a low nickel diet and receiving NiOH (gradually increasing over 10 weeks and maintaining for 12 months) had a greater success rate of nickel-rich food re-introduction, decreased drug use, improved visual analog score, and decreased cytokines after treatment, compared to 12 controls on a low nickel diet alone.
- All SNAS patients (confirmed by oral challenge) were given NiOH capsules 3 times a week at increasing doses from 0.1 ng to 3 µg in 10 weeks with a maintenance phase of 1.5 µg a week for a period of 12 months. Two could not tolerate the highest dose. All 35 participants continued a low nickel diet.
- The tested cytokines were lower in the treated group than in the diet alone group on average, but it should be noted that the standard deviations of these measurements are very large.
- Nickel-containing foods were re-introduced gradually, starting at 4 months. The controls were not able to reintroduce nickel-rich foods.

Tammaro, A. et al., 2009. Allergy to nickel: First results on patients administered with an oral hyposensitization therapy. *International Journal of Immunopathology and Pharmacology*, 22(3), pp.837-840.

- 67 patients followed a low nickel diet for 10 weeks while also doing slowly increasing hyposensitization.
- After a year at the maintenance dose, 67% reported full remission, and 27% reported improvement in symptoms.

Schiavino, D. et al., 2006. A clinical trial of oral hyposensitization in systemic allergy to nickel. *International Journal of Immunopathology and Pharmacology*, 19(3), pp.593-600.

- 290 patients were selected (mostly female) with systemic cutaneous symptoms and/or digestive symptoms.
- Patients were given standard prick and patch tests to identify allergens.

- Patients followed a low nickel diet and avoided stainless steel utensils for 4 weeks, and patients who improved at least 80% did an oral challenge test, increasing dose until symptoms appeared.
- 136 patients participated in hyposensitization over 315 days, 95 in a control group that did a low nickel diet alone.
- Ninety-four patients (69.1%) completed the protocol, and after returning to a free dietary regimen, 64 (47.0%) reported a complete remission of symptoms, 23 (16.9%) had symptom improvement higher than 80%, rarely presenting mild cutaneous and/or digestive symptoms and 7 (5.2%) had a partial benefit, reintroducing only some of these foods (limited diet).
- In the control group, after 1 year on a low nickel diet alone, 78 patients (82.1%) presented a relapse of pre-existing systemic symptoms when nickel-containing foods were reintroduced.

Sauna

Hohnadel, D.C. et al., 1973. Atomic absorption spectrometry of nickel, copper, zinc, and lead in sweat collected from healthy subjects during sauna bathing. *Clinical Chemistry*, 19(11), pp.1288-1292.

- Nickel concentration in sweat was found to be 52 ± 36 (range 7-180) $\mu\text{g/L}$ for men and 131 ± 65 (range 39-270) $\mu\text{g/L}$ for women.

Chelation

Aaseth, J., Crisponi, G. and Anderson, O., 2016. *Chelation therapy in the treatment of metal intoxication*. Academic Press.

- A textbook on the state of metal chelation as of 2016.
- Also covers metal allergies, listed as an effect of toxic exposure to a metal.

Giampreti, A. et al., 2016. N-acetyl-cysteine as effective and safe chelating agent in metal-on-metal hip-implanted patients: Two cases. *Case Reports in Orthopedics*, 2016.

- In two elderly patients with hip implants that gave them cobalt and chromium toxicity, NAC was a safe and effective chelation agent. [One would think it would work for nickel as well.]

Sears, M.E., 2013. Chelation: harnessing and enhancing heavy metal detoxification - A review. *The Scientific World Journal*, 2013.

- Natural substances that have been shown to prevent uptake of heavy metals include: dietary fibres such as grains and fruit; natural polymers such as citrus pectin, alginate and chlorella; sulphur-containing foods such as allium or brassica; supplements including taurine, methionine, alpha lipoic acid, N-acetyl cysteine (NAC), selenium, and minerals such as calcium, zinc, iron and magnesium. Results are mixed for cilantro.
- Nickel is not included in this review, so other reviews are more appropriate for the pharmaceutical chelators. However it does cover combination therapies using two chelators with different strengths.
- Blood, urine and hair measurements only indicate exposures in recent days or months.
- Chelation should be titrated up slowly since aggressive treatment causes too fast a shift in both essential and toxic elements. There is a rebound of levels in the blood following discontinuation, as the elements migrate from tissue and bone back into the bloodstream where they have greater effect (redistribution). [This may explain why symptoms sometimes worsen in the first few months of a low nickel diet.]
- Adequate hydration and bowel regularity are essential so that mobilization equals excretion.
- Products that stop metals from being reabsorbed in the intestines include cholestyramine, psyllium, charcoal, and thiolized silica.

- Mineral status must be monitored.
- Allergic reactions have been reported with DMSA, DMPS and CaNa₂EDTA.

Flora, S.J. and Pachauri, V., 2010. Chelation in metal intoxication. *International Journal of Environmental Research and Public Health*, 7(7), pp.2745-2788.

- Nitrilotriacetic acid (NTA) has been shown to possess the ability to mobilize nickel from brain, heart, kidney and liver of nickel poisoned rats.
- Most chelating agents have serious side effects.

Smolik, S. et al., 2008. Characteristics of chelation ability of chosen metal ions by protective ointments containing Na₂H₂EDTA. *Acta Polonae Pharmaceutica*, 65(1), pp.125-128.

- In an *in vitro* study, a barrier cream containing 10% EDTA at pH 7.0-7.4 was found to be effective for binding nickel and cobalt, for prevention of nickel and cobalt dermatitis due to occupational exposure.
- Barrier creams alone do not affect allergic reaction.

Sharma, A.D., 2006. Disulfiram and low nickel diet in the management of hand eczema: A clinical study. *Indian Journal of Dermatology, Venereology, and Leprology*, 72(2), p.113.

- Study comparing a low nickel diet with disulfiram to a control group on a normal diet with placebo found that 10/11 patients with chronic vesicular hand dermatitis and nickel allergy improved on the diet with medication, versus 1/10 in the control group. All patients reacted to oral nickel sulfate challenge (showing systemic dermatitis).
- The study does not compare the diet alone to the medication alone.

Blanuša, M. et al., 2005. Chelators as antidotes of metal toxicity: therapeutic and experimental aspects. *Current Medicinal Chemistry*, 12(23), pp.2771-2794.

- The recommended treatments for nickel *toxicity* are sodium diethylcarbodiithioate (DDTC) and disulfiram, based on very limited human data. Disulfiram has been observed to cause hepatotoxicity and possible redistribution of nickel in the brain.
- BDCG and 2,3-dimercaptosuccinic acid (DMSA) have been used in experiments on animals.
- Refers to a case where British-Anti-Lewisite (BAL), a chelator that can get into cells, was used for nickel poisoning (Sunderman1981), but that reference says it is relatively ineffective.

Grandjean, P. et al., 1997. Placebo response in environmental disease: chelation therapy of patients with symptoms attributed to amalgam fillings. *Journal of Occupational and Environmental Medicine*, 39(8), pp.707-714. (Abstract only)

- In patients who attribute their illness to mercury from amalgam fillings, chelation with oral Succimer (a mercury chelating agent) or placebo gave the same amount of symptom improvement, immediately after and 5 to 6 weeks after treatment.

Neuvonen, P.J. and Olkkola, K.T., 1988. Oral activated charcoal in the treatment of intoxications. *Medical Toxicology and Adverse Drug Experience*, 3(1), pp.33-58.

- Most metals are not efficiently adsorbed to activated charcoal. Nickel is not specifically mentioned, however.
- Large doses may cause vomiting. Constipation and diarrhea have occurred. Be wary of fillers such as sorbitol and sodium bicarbonate.

Christensen, O.B. and Kristensen, M., 1982. Treatment with disulfiram in chronic nickel hand dermatitis. *Contact Dermatitis*, 8(1), pp.59-63. (Abstract only)

- In 11 patients with nickel allergy and hand eczema, 2 patients healed and 8 improved with disulfiram treatment. Mild relapses occurred in all patients within 2-16 weeks of discontinuation.
- Liver enzymes should be monitored during treatment.

Sunderman, F.W., 1981. Chelation therapy in nickel poisoning. *Annals of Clinical and Laboratory Science*, 11(1), pp.1-8.

- In 1911 nickel was used to treat epilepsy, chorea, migraine and neuralgia, and it was reported to have "peculiar and elective power in controlling the damaging effects of sexual vice on the nervous system."
- Discusses allergic dermatitis and exposure via diet and cooking equipment.
- A review that recommends a low nickel diet, Dithiocarb (DDC) or antabuse (possibly on a week-on/week-off schedule) and topical steroids with or without DDC for nickel dermatitis.
- Noted that DDC was did not have significant side effects or lower essential mineral levels in rat and dog experiments.

Kaaber, K. et al., 1979. Antabuse treatment of nickel dermatitis. Chelation—A new principle in the treatment of nickel dermatitis. *Contact Dermatitis*, 5(4), pp.221-228.

- In 11 patients with nickel allergy and hand eczema, 7 patients healed, 2 improved, and 2 were unchanged with Antabuse treatment. Relapses occurred in 6 patients on discontinuation.
- 9 of 11 had a flare at the beginning of treatment.
- 7 experienced side effects including fatigue, headaches and dizziness. The treatment was discontinued in 4 because of side effects.

4. Bioavailability

Peeters, K. et al., 2017. Nickel speciation in cocoa infusions using monolithic chromatography—Post-column ID-ICP-MS and Q-TOF-MS. *Food Chemistry*, 230, pp.327-335.

- Three forms of nickel were found in cocoa through mass spectrometry: nickel gluconate (40%), Ni²⁺, and nickel citrate, in descending order.
- States that Ni²⁺ is the most bioavailable species.

Bartos, A., Majak, I. and Leszczyńska, J., 2014. Uptake and assimilability of nickel in the course of systemic allergy: Implications for elimination diet. *Food Research International*, 55, pp.412-417.

- Nickel exposure largely depends on the food matrix that either favors or confines its availability for human digestive enzymes.
- Average daily consumption found to be 227 ± 70 µg/day for students (20) and 161 ± 60 µg/day for senior staff (9).
- Nickel uptake is an aggregate of individual, geographical, seasonal and cultural dietary factors.
- Food samples were dissolved in 36% HCl and porcine pepsin added to simulate digestion.
- A variety of foods were tested to determine their release rate (nickel compared before and after digestion). Baguette and caraway seeds had the highest nickel release rate. Corn, red bean, basil, nutmeg, paprika, clove, walnut and roasted peanuts all had below 50% release rate. Nuts and cocoa are all around 50%.
- In the blood of 15 male and 15 female healthy students, there was a higher baseline amount of nickel in the women. They assume the difference is from cutaneous exposure, i.e. jewelry. When comparing the men's intake to blood sera they estimate a total 16% nickel uptake, in agreement with WHO findings.

Nielsen, G.D. et al., 1999. Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity. *Toxicology and Applied Pharmacology*, 154(1), pp.67-75.

- Serum levels of nickel increase 13-fold when nickel is taken on an empty stomach compared to taken with scrambled eggs. Clearance rates increase when nickel is taken after eggs. 9/20 patients with pompholyx hand eczema experienced aggravation of eczema during the study.

Sunderman Jr, F.W. et al., 1989. Nickel absorption and kinetics in human volunteers. *Proceedings of the Society for Experimental Biology and Medicine*, 191(1), pp.5-11. (Abstract only)

- Nickel was given to human volunteers with food and on an empty stomach. It was found that 20%-40% of the nickel was ingested from the water dose, whereas only 1% was ingested from the food dose.

5. IBS and GI Symptoms

Limone, B.A. et al., 2017. Complementary intradermal and patch testing for increased diagnostic accuracy of nickel allergy in non-celiac wheat insensitivity. *Nutrients*, 9(6), p.536.

- A letter to the editor in support of testing patients with non-celiac wheat sensitivity for nickel allergy, as proposed in D'Alcama's 2017 paper.

Borghini, R. et al., 2017. New insights in IBS-like disorders: Pandora's box has been opened. *Gastroenterology and Hepatology from Bed to Bench*, 10(2), pp.79-89.

- A review of IBS and its possible causes, including Nickel Allergic Contact Mucositis.
- Also lists some treatments, surprisingly including iron supplementation without a deficiency diagnosis.

D'Alcama, A. et al., 2017. Contact dermatitis due to nickel allergy in patients suffering from non-celiac wheat sensitivity. *Nutrients*, 9(2), p.103.

- In 60 patients diagnosed with non-celiac wheat sensitivity, 10% also had a positive nickel patch test, double that of the control group.

Borghini, R. et al., 2017. Nickel allergic contact mucositis: Duodenal histological, immunohistochemical and cultural characterization of an emerging clinicopathologic entity. *Gastroenterology*, 152(5), p.S813. (Abstract only)

- In samples of the duodenum taken from patients with a positive nickel oral mucosa patch test, higher levels of IFN- γ and decreased IL-10 were found after exposure to nickel.

Borghini, R. et al., 2016. Nickel-related intestinal mucositis in IBS-like patients: Laser doppler perfusion imaging and oral mucosa patch test in use. *Biological Trace Element Research*, 173(1), pp.55-61.

- Oral mucosa patch testing (omPT) requires qualitative evaluation and is subject to error. The authors propose the use of laser Doppler perfusion imaging (LDPI) to augment omPT to diagnose intestinal mucositis caused by nickel allergy. LDPI uses a laser to detect increased blood flow to tissues, and gives a quantitative result.
- In their test group, all patients with nickel allergy and GI symptoms showed an increase mean perfusion value pre- and post-omPT. There was no increase in the control group.

Pasqui, F. et al., 2015. Adverse food reaction and functional gastrointestinal disorders: Role of the dietetic approach. *Journal of Gastrointestinal and Liver Diseases*, 24(3), pp.319-327.

- A review of GI disorders that briefly includes SNAS, its diagnosis and treatment.

Cazzato, I.A. et al., 2011. Fecal calprotectin in Systemic Nickel Allergy Syndrome (SNAS). *Gastroenterology*, 140(5), p.S-283.

- Elevated concentrations of calprotectin, a calcium and zinc binding protein, are found in the feces of 20 SNAS patients.
- The levels decreased drastically after weeks on a low nickel diet, along with significant symptom improvement.

Cazzato, I.A. et al., 2011. Lactose intolerance in systemic nickel allergy syndrome. *International Journal of Immunopathology and Pharmacology*, 24(2), pp.535-537.

- In 178 SNAS patients and 60 healthy controls, a lactose breath test was positive in 74.7% of the SNAS group compared to 6.6% of the control group.
- The authors hypothesize that in SNAS patients, the nickel-induced pro-inflammatory status could temporarily impair the brush border enzymatic functions, resulting in hypolactasia.

Schoelmerich, J. and Rogler, G, 2000. Correlation between nickel allergy towards dentures and Crohn's disease: A case report. *Gastroenterology*, 118(4), p. A1135.

- The authors report a case of a woman who had severe Crohn's disease that began after she started using dentures that contained nickel. There were obvious signs of oxidation in the mouth. After not using the dentures, the patient fully recovered.

Dormer, R.L. et al., 1974. The effect of nickel on secretory systems. Studies on the release of amylase, insulin and growth hormone. *Biochemical Journal*, 140(2), pp.135-142.

- In rats, Ni inhibits the release of amylase by about 20%, almost completely inhibits insulin under certain conditions, and inhibits growth hormone under certain conditions.

6. Links to Other Conditions

GERD

Stanghellini, V. et al., 2016. Nickel sensitization in patients with gastro-esophageal reflux disease. *United European Gastroenterology Journal*, 4(2), pp.184-190.

- Patients with GERD but no neoplastic diseases, relevant skin lesions, dermatitis, known autoimmune diseases or previously diagnosed nickel allergy, or current treatment with steroidal or antihistaminergic therapies were included in the study. These were split into erosive vs. non-erosive groups. The control group did not have GERD.
- All patients were patch tested for nickel allergy. All GERD patients were instructed to follow a standard GERD diet, and the nickel allergic patients also a low-nickel diet, for 6 months.
- Nickel sensitization was significantly more common among patients with GERD than patients without GERD (39.5% vs. 16.4%, respectively). Asthma was also more frequent in the nickel allergic group.

Campanale, M. et al., 2014. Nickel free-diet enhances the *Helicobacter pylori* eradication rate: a pilot study. *Digestive Diseases and Sciences*, 59(8), pp.1851-1855.

- Since *H. Pylori* requires a nickel-containing enzyme, patients diagnosed with *H. Pylori* infection but without SNAS, food allergies, drug allergies, liver disease, neoplasms, kidney failure or who had recently used antimicrobial agents, bismuth compounds, proton pump inhibitors (PPI) or H2 receptor antagonists, were studied for the effect of a low nickel diet on treatment.
- Those who added a low nickel diet to a round of two antibiotics had a significantly higher eradication rate (22 out of 26 for the diet plus antibiotics vs. 12 out of 26 for the antibiotics alone).

Metabolic Conditions

Watanabe, M. 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(8), p.e0202683.

- In 1128 obese and overweight patients, 666 displayed symptoms and were tested for nickel allergy, 463 of those patch-tested positive for nickel.
- The nickel-allergic were found to have lower insulin-like growth factor 1 (IGF-1) and a higher rate of growth hormone deficiency.
- [It is not clear to me why they excluded almost 500 obese patients who did not show symptoms of nickel allergy from their sample. This biases the result to have a higher rate of nickel allergy, although it does ensure that the non-nickel-allergic in the sample probably have something else wrong with them.]

Lusi, E.A. et al., 2015. High prevalence of nickel allergy in an overweight female population: a pilot observational analysis. *PloS One*, 10(3), p.e0123265.

- In an overweight population, nearly 60% were nickel allergic. Of the 24 overweight females who completed the trial, the average waist circumference decreased by almost 12 cm.
- There was no control group for the low nickel diet without nickel allergy. Since the diet was calorie controlled as well as low nickel, the caloric restriction alone may be responsible for the weight loss.

Endometriosis

Borghini, R. et al., 2018. Relationship between nickel allergic contact mucositis and nickel-rich diet in symptomatic women suffering from endometriosis. *Digestive and Liver Disease*, 50(2), p. e234.

- 14 out of 16 symptomatic women with endometriosis tested positive for nickel allergy. After 3 months on a low nickel diet, all showed statistically significant improvement.

Thyroid

Takir, M., Turkoglu, O. and Turkoglu, Z., 2017. Thyroid hormone and ultrasonographical analyses in patients with nickel allergy. *Eurasian Journal of Medicine and Oncology*, 1(3), pp.145-148.

- 79 patients and 43 controls were studied for a relationship between thyroid conditions and nickel allergy.
- Mean platelet volume and total IgE levels were significantly high in the patient group, and monocyte and eosinophil levels were low.
- Thyroid function was the same in both groups, but the incidence of thyroid cysts and thyroiditis was significantly higher in patients with nickel allergy.

Andrioli, M., et al., 2015. Systemic nickel allergic syndrome as an immune-mediated disease with an increased risk for thyroid autoimmunity. *Endocrine*, 50(3), pp.807-810.

- To study the risk of chronic autoimmune thyroiditis (CAT) in SNAS patients, 239 subjects with some form of immune-mediated inflammatory disorder were recruited. 136 were diagnosed with SNAS.
- All of the subjects had normal thyroid function, but 26.5% of the subjects with SNAS versus 12.7% of those without SNAS were diagnosed with CAT based on antibodies (TGAAb or TPOAb) or ultrasound.
- CAT is twice as prevalent in patients with SNAS than in patients with other immune-mediated disorders.

Respiratory Conditions

Gelardi, M. et al., 2017. Allergic and nonallergic rhinitis and skin sensitization to metals: Is there a link? *European Annals of Allergy and Clinical Immunology*, 49(3), pp.106-109.

- Investigates the relationship between rhinitis and metal hypersensitivity by separating rhinitis into groups: allergic rhinitis, non-allergic rhinitis, and overlapping. Compared to a control group, non-allergic rhinitis and overlapping had a higher incidence of metal allergy.
- Concludes that "it is conceivable that the association of metal sensitisation and nonallergic rhinitis is not simply "by chance", and would deserve further investigations."

Brera, S. and Nicolini, A., 2005. Respiratory manifestations due to nickel. *Acta Otorhinolaryngologica Italica*, 25(2), p.113.

- In 20 patients with a positive nickel patch test and rhinitis, 7 also had a positive prick test to nickel (35%).
- Nickel allergy was confirmed to be the cause of rhinitis via a provocation test.
- Those who maintained a low nickel diet for 2-4 months experienced a reduction in symptoms.

Skin Conditions

Nakayama, H. and Chen, K., 2018. How to treat metal hypersensitive alopecia areata and atopic alopecia. *Clinical Dermatology Research Journal*, 2018.

- Metal allergy was found with severe types of alopecia areata (AA) at the rate of 69.9% and the elimination of metal allergens from dental metals and cooking instruments leads to satisfactory hair regrowth and long-term prevention of severe relapse of AA at the rate of 75.5%.
- Has a good description of how a metal becomes an allergen, by binding with keratin, and a possible explanation of why Ni/Co and Ag/Hg tend to appear together.
- The authors recommend against oral nickel challenge because of the illness it can cause, calling it unethical. In one case of alopecia, the hair loss was worsened by an oral challenge to NiSO₄.
- Provides a review of 8 case studies where alopecia was cured by removing the allergenic dental metals and/or avoiding stainless steel pots and pans and instead using ceramics, enamel-coated or glassware.
- Gives patch-testing statistics for 104 alopecia cases, 229 AD cases, and 336 contact dermatitis cases.
- Type IV mite allergy is also a common cause of alopecia; treatment is environmental remediation.
- Treatment must be done quickly (less than 6 years) before dermal fibrosis destroys the hair follicles.

Burning Mouth Syndrome

Lynde, C.B., Grushka, M. and Walsh, S.R., 2014. Burning mouth syndrome: Patch test results from a large case series. *Journal of Cutaneous Medicine and Surgery*, 18(3), pp.174-179.

- Of 132 patients with burning mouth syndrome, 66 had possibly relevant positive patch test results, of which nickel and the gallates were the most prevalent.

7. Other Nickel Sources

See also the annotated bibliography of nickel in dental restorations.

Darsow, U. et al., 2012. Influence of dietary factors, age and nickel contact dermatitis on nickel excretion. *Contact Dermatitis*, 67(6), pp.351-358.

- Using urinary excretion, and foods logs, determined that nickel-rich food correlates with renal nickel excretion, and that frequent ingestion of supplements and stagnant tap water increases renal nickel excretion.
- A higher mean was seen in older women (in contrast to Bartos) and cookware containing nickel.
- The range of Ni concentration in urine went very high for smokers, even though the average was the same.

Supplements

Schwalfenberg, G., Rodushkin, I. and Genuis, S.J., 2018. Heavy metal contamination of prenatal vitamins. *Toxicology Reports*, 5, pp.390-395.

- In 26 brands of prenatal vitamins collected in Edmonton: "All 51 samples contained Ni. The upper limit of exposure for Ni according to the USP guidelines is 60 µgm/day and the maximum found in any sample was 34 µgm/day. The average was about 5 µgm/day."
- More than half of the brands tested were above the acceptable limits for lead.

Cardoso, P. et al., 2017. Determination of nickel and manganese contaminants in pharmaceutical iron supplements using energy dispersive x-ray fluorescence. *Applied Spectroscopy*, 71(3), pp.432-437. (Abstract only)

- Found iron supplements contained 36 µg/dose.

Adolfo, F.R. et al., 2016. Simultaneous determination of cobalt and nickel in vitamin B12 samples using high-resolution continuum source atomic absorption spectrometry. *Talanta*, 147, pp.241-245. (Abstract only)

- Nickel in B12 supplements was found to range from 9.48 to 26.20 µg/L. Not sure how this translates to a dose.

Wollein, U. et al., 2015. Potential metal impurities in active pharmaceutical substances and finished medicinal products—A market surveillance study. *European Journal of Pharmaceutical Sciences*, 77, pp.100-105.

- Report on metal content in pharmaceuticals. Waiting for response from author regarding supplementary tables, which contain the results for nickel.

Li, G. et al., 2015. Elemental impurities in pharmaceutical excipients. *Journal of Pharmaceutical Sciences*, 104(12), pp.4197-4206.

- Shows iron-based excipients (fillers) are highest in nickel (up to 154 µg/g).

Patlar, S. et al., 2011. Elements in sera of elite taekwondo athletes: Effects of vitamin E supplementation. *Biological Trace Element Research*, 139(2), pp.119-125. (Abstract only)

- Athletes given 300 mg Vitamin E for 6 weeks had “significant increases” in blood levels of nickel relative to values before supplementation.

Avula, B. et al., 2010. Quantitative determination of multiple elements in botanicals and dietary supplements using ICP-MS. *Journal of Agricultural and Food Chemistry*, 58(16), pp. 8887-8894. (Abstract only)

- A variety of supplements were tested (21 in total). Nickel was found in “low concentrations in most of the samples” they tested.

van der Voet, G.B. et al., 2008. Clinical and analytical toxicology of dietary supplements: A case study and a review of the literature. *Biological Trace Element Research*, 125(1), pp.1-12.

- Shows some herbal supplements having relatively high nickel content (up to 1.6 µg/g). Vitamin A has .055 µg/g.

Ponce de León, C.A., Bayón, M.M. and Caruso, J.A., 2002. Trace element determination in vitamin E using ICP-MS. *Analytical and Bioanalytical Chemistry*, 374(2), pp.230-234. (Abstract only)

- Found nickel in Vitamin E at 0.060 µg/g.

Pesticides

Defarge, N., de Vendômois, J.S. and Séralini, G.E., 2017. Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides. *Toxicology Reports* 5, pp. 156-163

- Pesticides and herbicides were examined for their heavy metal content, and nickel was found in most of the samples.
- Nickel was most significant in fungicides and insecticides, but nearly all of them exceeded the EU admissible level of 20 ppb. However, at their recommended dilutions it appears that only 4 of the 23 samples exceeded this limit.

Needles

Mehta, V., Vasanth, V. and Balachandran, C., 2011. Nickel contact dermatitis from hypodermic needles. *Indian Journal of Dermatology*, 56(2), p.237.

- Two case studies are presented, patients with a 1+ and 2+ nickel allergy having dermatitis to needles in a hospital setting.
- The DMG test was negative but the needles sampled had 8% nickel.
- Concludes with a time limit for infusions while using steel needles based on the EU Nickel Directive.

Cooking equipment

Papuc, C. et al., 2017. The influence of cookware on the concentration of trace metals and lipid peroxidation in pork muscle. *Revista de Chimie*, 68(7), pp.1476-1480.

- Pork was used to determine the nickel leached from aluminum, ceramic coated aluminum, brass and stainless steel pans, with acid.
- After 50 minutes at 200°C, aluminum < stainless steel < brass < ceramic.

Lomolino, G., Crapisi, A. and Cagnin, M., 2016. Study of elements concentrations of European seabass (*Dicentrarchus labrax*) fillets after cooking on steel, cast iron, teflon, aluminum and ceramic pots. *International Journal of Gastronomy and Food Science*, 5, pp.1-9.

- In this study, fish was cooked in several types of pan, all from the same brand (Ballarini), and the nickel was measured raw and after cooking, and with acid. The result: cast iron < steel < teflon < ceramic < aluminum. This will depend highly on the composition of the materials used in this brand (since steel can be many different metal mixtures, and the aluminum pan must also be a nickel-containing alloy).

Kamerud, K.L., Hobbie, K.A. and Anderson, K.A., 2013. Stainless steel leaches nickel and chromium into foods during cooking. *Journal of Agricultural and Food Chemistry*, 61(39), pp.9495-9501.

- Used tomato sauce to determine that nickel contribution is dependent on stainless steel grade, cooking time, and how new the cookware is.

Santonen, T, Stockmann-Juvala, H. and Zitting, A., 2010. *Review on toxicity of stainless steel*. Finnish Institute of Occupational Health, Helsinki.

- A review of how stainless steel is made, its designations (alloy compositions), and release of metals, including nickel, from cooking equipment and articles in contact with skin.
- A review of articles to date on nickel released from steel cookware concludes that the nickel released is “inconsistent”. The report sometimes uses the term “negligible” but does not define what that means.
- Although carried out independently by the Finnish Institute of Occupational Health, the study was commissioned by the International Stainless Steel Forum (ISSF) and the European Confederation of Iron and Steel Producers (EUROFER), which may introduce a bias. The individual papers should be consulted.

Pollution

Mann, E. et al., 2010. Does airborne nickel exposure induce nickel sensitization? *Contact Dermatitis*, 62(6), pp.355-362.

- In 309 school-age children, statistically significant associations were shown between exposure to nickel in ambient air and urinary nickel concentration as well as between urinary nickel concentration and nickel sensitization.
- Higher sensitization rates were associated with higher airborne nickel levels.

Tattoos

Laux, P. et al., 2016. A medical-toxicological view of tattooing. *The Lancet*, 387(10016), pp.395-402.

- “Reactions [of an allergic nature] can appear months or years after the tattoo was done. This is a remarkably long period of sensitisation induction and, although the exact reasons have not yet been elucidated, this delayed complication is an example of the much wider problem—intradermal deposit of tattoo pigments results in lifelong exposure.”

Jacobsen, E. et al., Eds., 2012. Chemical substances in tattoo ink. *Survey of chemical substances in consumer products no. 116*, Miljøstyrelsen.

- 61 samples of 10 different colour series of tattoo ink were tested. All 61 inks had a nickel concentration that exceeded the limit set by the Council of Europe’s ResAP(2008) Table 3. Actual values ranged from 0.03-18 µg/g, with no colour a clear winner.

Bocca, B., 2013. Heavy metals in tattoo inks. *First International Conference on Tattoo Safety*, Berlin.

- 56 inks from 4 suppliers were tested. Median nickel content ranged from 0.14-0.45 µg/g for each supplier, with a maximum of 9.6 µg/g.
- Anything above 1 µg/g should not be in contact with skin. 9 of the 56 samples were above that limit.

Implants

Frigerio, E. et al., 2011. Metal sensitivity in patients with orthopaedic implants: A prospective study. *Contact Dermatitis*, 64(5), pp.273-279.

- One year post-implantation (72 patients), 5 patients who had initially tested negative for a metal allergy became positive for at least one or more metal constituents of the prosthesis on at least one or the other test.
- Suggests that exposure to the metals in the prostheses led to sensitization.
- Some patients tested positive when they had no history of allergic reaction. Authors conclude that testing prior to choosing an implant is important.
- Most of the patients tested positive for nickel (21%), followed by cobalt (8%), palladium (3%), chromium (2%), and molybdenum (2%). Positivity for cobalt, chromium and palladium was always associated with a positive reaction to nickel, probably because of cross-reactivity. There were no positive results for titanium or vanadium before or after, due to lower sensitization rates.

Sunderman, F.W., 1990. Use of sodium diethyldithiocarbamate in the treatment of nickel carbonyl poisoning. *Annals of Clinical and Laboratory Science*, 20(1), pp.12-21.

- "It is recognized that patients with implanted prostheses may on occasion develop malignant tumors. It seems probable that their development is related to the presence of nickel."

8. Accumulation and Elimination

Schaller, K.H. et al., 2007. Elimination kinetics of metals after an accidental exposure to welding fumes. *International Archives of Occupational and Environmental Health*, 80(7), pp.635-641. (Abstract only)

- The elimination of nickel was found to be biphasic in an accidentally exposed welder. The half-life for nickel was 25 and 610 days (in urine) and 30 and 240 days (in blood).
- This means that we can expect an initially faster drop-off of nickel levels, getting down to 50% of the initial level in about 3 months. Then the elimination slows down and takes about 2 years to get down to about 20% of what it was at the start in urine, or about 5% in blood. By 4 years, the nickel in blood was eliminated.

Calamari, D. et al., 1994. Nickel and freshwater fish. *Water Quality for Freshwater Fish*, pp. 31-53.

- The half-life of nickel in trout muscle is 71 days.

Tossavainen, A. et al., 1980. Application of mathematical modelling for assessing the biological half-times of chromium and nickel in field studies. *Occupational and Environmental Medicine*, 37(3), pp.285-291.

- The elimination half-life was found to be 17-39 hours for nickel in urine, and 20-34 hours for nickel in plasma.

Torjussen, W. and Andersen, I., 1979. Nickel concentrations in nasal mucosa, plasma, and urine in active and retired nickel workers. *Annals of Clinical & Laboratory Science*, 9(4), pp. 289-298.

- In retired nickel plant workers, the elimination half-life of nickel from nasal mucosa was found to be 3.5 years.

Bergman, B. et al., 1980. The distribution of nickel in mice. *Journal of Oral Rehabilitation*, 7(4), pp. 319-324.

- In mice, 3 weeks after implantation of a nickel isotope, the distribution pattern of nickel was dominated by high uptake in the lung tissues, central nervous system, kidneys, hard tissues and skin. (Abstract only)

Oskarsson, A. and Tjalve, H., 1979. An autoradiographic study on the distribution of $^{63}\text{NiCl}_2$ in mice. *Annals of Clinical & Laboratory Science*, 9(1), pp. 47-59.

- In mice injected intravenously with a nickel isotope, after 3 weeks radioactivity could be seen in the kidneys, cartilage, connective tissues, skin, lung, brain and spinal cord.

9. Histamine

Hagel, A.F. et al., 2013. Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 386(9), pp.789-793. (Abstract only)

- IV ascorbic acid decreased histamine in the blood, with more of an effect on allergic patients than patients with infections.

Kehoe, C.A. et al., 2000. Plasma diamine oxidase activity is greater in copper-adequate than copper-marginal or copper-deficient rats. *The Journal of nutrition*, 130(1), pp.30-33.

- In rats fed a diet that was either deficient, marginal or adequate in its copper content, it was found that plasma DAO activity was significantly lower in both copper-deficient and copper-marginal groups when compared to the copper-adequate group.

Förström, L., Goldyne, M.E. and Winkelmann, R.K., 1975. IgE in human eccrine sweat. *Journal of Investigative Dermatology*, 64(3), pp.156-157.

- States that histamine and other inflammatory agents are present in sweat, provides references.
- Shows the presence of IgE in sweat, and says the other immunoglobulins are there.

10. Testing

Zhu, T.H. et al., 2018. The medical necessity of comprehensive patch testing. *Dermatitis*, 29(3), pp.107-111.

- The T.R.U.E. patch test has a 66% detection rate at best. Testing with supplemental allergens beyond a screening series, depending on the individual patient's history and findings, is needed to increase diagnostic accuracy.
- In some cases it is more appropriate to forgo limited and standard patch testing and go straight to a comprehensive test in order to provide a cure for the patient.

Fonacier, L. and Noor, I., 2018. Contact dermatitis and patch testing for the allergist. *Annals of Allergy, Asthma and Immunology*.

- Review article of diagnosis, patch testing and treatments that includes systemic dermatitis to nickel.
- Acrylates, fragrances, and volatile allergens should be used immediately, however some allergens in a petrolatum base may be prepared 24 to 48 hours before application.
- Patch tests should be removed and read at 48 hours, read again at 3-7 days (96 hours optimally), and finally at 7-10 days for late bloomers such as metals (nickel sulfate, gold sodium thiosulfate, palladium chloride, potassium dichromate, cobalt chloride), some antibiotics (neomycin), topical corticosteroids, and dyes (paraphenylenediamine).

Ständer, S. et al., 2017. Evaluation of lymphocyte transformation tests as compared with patch tests in nickel allergy diagnosis. *Contact Dermatitis*, 76(4), pp.228-234.

- In a study of 100 subjects, 50 with suspected nickel allergy and 50 with no skin symptoms on metal contact, patch test results and patient history were compared to LTT blood tests.
- The LTT had 96% specificity (2/50 false positives) and 88% sensitivity (2/18 false negatives).
- The LTT response was positive in 13 of the 32 patch test-negative/ history-positive patients.
- A considerable discussion is had about the errors possible in patch testing. In particular, nickel is known for its ability to give late patch test reactions, which may account for some of the patch test-negative/ history-positive differences.
- Concludes that LTT is an important additional tool for determining nickel allergy, particularly in people who cannot have patch testing, to confirm a negative patch test result, and in patients sensitized to nickel by internal exposure, for example patients with metal implants.
- The study excluded patients who had implants or piercings containing nickel as this may result in nickel allergy without cutaneous manifestations.

Schaeffer, A.C. et al., 2016. The reproducibility of nickel, cobalt and chromate sensitization in patients tested at least twice in the period 1992–2014 with TRUE Test. *Contact Dermatitis*, 75(2), pp.111-113.

- Of 115 subjects who patch tested positive for nickel allergy, 107 were positive on the second test (67%).
- The persistence of weak, positive reactions to nickel tended to decrease as the time interval between testing increased, whereas the reproducibility of strong, positive reactions was stable over time.
- Errors in patch testing were not discussed.

11. Polysensitization

Limone, B.A. and Jacob, S.E., 2017. Insights into the global effect of nickel dermatitis on polysensitization. *Annals of Allergy, Asthma & Immunology*, 118(6), p.749.

- A letter stressing the importance of early diagnosis of nickel allergy due to the high prevalence (>50%) of polysensitization with nickel, which happens because the weakening of the skin's barrier enables sensitization to other allergens.
- Four statistically significant pairings with nickel are fragrance mix 1, chrome, cobalt and balsam of peru.

Hegewald, J. et al., 2005. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. *Allergy*, 60(3), pp.372-378.

- Out of 7232 who tested positive to nickel, 1437 were also allergic to cobalt, or about 20%, and 697 were also allergic to chromate, or about 10%.

- The authors state that the results strongly suggest that some people are more susceptible to contact sensitizations in general, and these people are also more likely to test positive to nickel, cobalt, and chromate.

12. Surveillance and Legislation

Schuttelaar, M.L., Ofenloch, R.F., Bruze, M., Cazzaniga, S., Elsner, P., Gonçalo, M., Naldi, L., Svensson, Å. and Diepgen, T.L., 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), pp.1-9.

- In 5 European countries, the age-standardized prevalences of sensitization to nickel, cobalt and chromium were, respectively, 14.5%, 2.1%, and 0.8%. The highest prevalence of nickel sensitization was seen in Portugal (18.5%) and the lowest (8.3%) in Sweden.
- Significant associations were observed between nickel allergy and being female and having piercings (currently or in the past). More piercings correlate with a higher sensitization rate.

Ahlström, M.G. et al., 2017. Prevalence of nickel allergy in Europe following the EU Nickel Directive – A review. *Contact Dermatitis*, 77, pp.193–200.

- Nickel allergy remains a substantial problem in the population despite the EU Nickel Directive. Steps should be taken for better prevention of nickel allergy, as the prevalence remains unacceptably high in EU countries.

Schnuch, A. et al., 2012. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy*, 67(7), pp.847-857.

- German ACD surveillance showing prevalence of nickel sulphate sensitization at 13-15% of patients who saw a dermatologist for standard patch testing (the highest rate of all).
- Statistics show that reduction of exposure via the EU directive reduces the sensitization rate for nickel, particularly dramatically in children. Other substances show similar trends.
- Notes a plateau in the rate decrease due to a failure of the EU directive to regulate imported costume jewelry. The problem persists.

Jacob, S.E. et al., 2009. Nickel allergy in the United States: A public health issue in need of a “nickel directive”. *Journal of the American Academy of Dermatology*, 60(6), pp.1067-1069.

- Letter to the editor advocating for a US nickel directive, based on the EU directive, and for a public awareness campaign to prevent nickel sensitization in children.

Rietschel, R.L. et al., 2008. Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis*, 19(1), pp. 16-19.

- In North America, nickel sensitivity has increased over the last 12 years and most of this increase is due to the prevalence in women.
- The data show a steady increase in nickel sensitivity from 14.5% in 1992 to 18.8% in 2004.

13. Immunology of SNAS

Bechara, R. et al., 2017. Nickel sulfate promotes IL-17A producing CD4+ T cells by an IL-23-dependent mechanism regulated by TLR4 and Jak-STAT pathways. *Journal of Investigative Dermatology*, 137(10), pp.2140-2148. (Abstract only)

- "Ni-ACD is a complex immunologic disease involving not only a cell-mediated Th1 response but also Th17 cell development with alterations in IFN- γ levels and TLR4, Jak-STAT, p38MAPK, and NF- κ B immunologic pathways." - <https://www.dermatitisacademy.com/nickel-allergy-pathways/>

Saluja, S.S. et al., 2016. Contact urticaria to nickel: A series of 11 patients who were prick test positive and patch test negative to nickel sulfate 2.5% and 5.0%. *Dermatitis*, 27(5), pp.282-287. (Abstract only)

- Presents a series of 11 patients who tested positive to a nickel prick test but negative to a patch. The authors suggest that IgE allergy to nickel may be far more common than once thought.

Büyüköztürk, S. et al., 2015. Oral nickel exposure may induce Type I hypersensitivity reaction in nickel-sensitized subjects. *International Immunopharmacology*, 26(1), pp.92-96.

- This study finds the presence of Type I hypersensitivity in addition to a Type IV immune reaction in patients with chronic systemic symptoms related to nickel. Nickel containing dental alloys and oral nickel intake seem to trigger systemic symptoms in previously nickel sensitized patients.
- Of 39 patients with a positive patch test, 27 had a positive skin prick test (70%).

de Mello, L.M. et al., 2009. TH1/TH2 balance in concomitant immediate and delayed-type hypersensitivity diseases. *Immunology Letters*, 124(2), pp.88-94.

- Nickel allergy involves TH1 cells. Dust mite allergy involves TH2 cells. However, the Th1-derived cytokine IFN-gamma inhibits the proliferation of Th2 lymphocytes, so how can the two types of allergy coexist?
- Patients presenting with IgE and cell-mediated allergies were analyzed for cytokine production. The level of IFN-gamma was lower in the group that had both types of allergy.

Sosroseno, W., 1995. The immunology of nickel-induced allergic contact dermatitis. *Asian Pacific Journal of Allergy and Immunology*, 13(2), p.173.

- A discussion of the mechanisms behind nickel ACD, which includes mast cell involvement.