Nickel
March 2013

Introduction

Nickel, while being an essential trace element, can also be toxic. It was first identified in plant and animal tissue in the 1920's, but efforts to identify a specific physiological role for this metal in man were for many years unsuccessful [1]. The toxic effects of nickel (which does not accumulate in the tissues during lifetime exposure) were found to be largely a result of the gastric irritation provoked by nickel salts, rather than inherent toxicity, and a mechanism was identified in mammals for limiting gastrointestinal absorption of nickel [2] – which strongly suggests a physiological role for the metal. However, the prevalence of nickel dermatitis in modern society has been well recognised, along with the fact that it has a higher incidence in women rather than men [2]. Today there are eight known nickel-dependent enzyme systems [3]; in particular, it is required for the action of hydrogenases, in which nickel is found together with iron-sulphur clusters. There is also a nickel-based superoxide dismutase. Nickel has also been found to be greatly elevated in the serum of patients after myocardial infarction [4].

Environmental exposure to nickel

Nickel is one of the five ferromagnetic elements; on account of its inertness to oxidation it is valued for the alloys it forms. It is used in coins and also for plating iron and brass, and is thus present in many industrial and consumer products, especially those made of stainless steel. It is also used to give a green tint to glass. The commonest source of environmental nickel exposure is from jewellery, dental crowns and also cooking pots. A small amount of nickel is added to lower carat gold to harden it (pure 24 carat gold is very soft). There is a high percentage of nickel in costume jewellery and these levels are regulated in the UK by the Trading Standards Institute Enforcement Regulations (2008) which follows the EU Nickel Directive [94/27/EC] [5]. These regulations require that the rate of nickel release from jewellery which comes into direct contact with skin should not exceed 0.5 micrograms per square centimetre per week. Note that the nickel migration rate is regulated, rather than the nickel content.

Nickel excreted through the skin gives rise to cutaneous hypersensitivity, which is reported as affecting females more commonly than males, with an incidence of up to 23% of the female population [6]. Nickel triggers more hypersensitivity reactions than any other metal partly because it is so widely used; it is present in cigarettes, jewellery, buttons and coins [7]. It may be found in dental restorations, and is the most common orthodontic metal to cause dermatitis [8].

Food can be a major source of nickel and nutritionists have developed special "low-nickel" diets, cutting out foods such as cocoa, chocolate, broccoli and nuts. Drinking water can also be a significant source of nickel where there is industrial or agricultural run-off into the supply. In general, diets based on plant foods deliver a greater nickel load than those with a high protein content, and this can result in food being a significant source of exposure to sensitised patients [9]. Patients with diffuse manifestations of nickel allergy can thus reduce both their cutaneous and gastrointestinal symptoms by following a low nickel diet. However, nickel frequently contaminates food and so its avoidance may be very difficult. The daily intake of this metal with food has been estimated to be about 300 milligrams, with the highest content in oatmeal, nuts, cocoa, chocolate and soybeans; a daily dietary requirement of 25 – 35 micrograms has been suggested (i.e. 1/1000th of the estimated intake) [10,11]. In sensitized patients, nickel ingestion can not only cause a recurrence of chronic contact dermatitis, but also provoke other dermatopathies, such as those triggered

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by immunoglobulin E (IgE)–mediated allergy. Such evidence suggests that nickel allergy may be not only mediated by type I and type IV Coombs reactions. Activation of T cells by nickel may result in a mixed immune response, causing both IgE antibody production (from type 1 T helper cells) and the development of contact dermatitis (from type 2 T helper cells) [12].

Nickel sensitivity

Sensitised individuals may show an allergy to nickel affecting their skin, which can result in both cutaneous and systemic manifestations. A severe form of this allergy (systemic nickel allergy syndrome) is characterized by dermatitis, pompholyx and urticaria (cutaneous manifestions) with headache, asthenia, itching, and gastrointestinal disorders borderline on coeliac disease (systemic symptoms). Allergic contact dermatitis from nickel, which is less severe but may progress, is an inflammatory skin condition caused by a type IV hypersensitivity response, which manifests after recurrent contact with the metal. The actual clinical symptoms observed are related to the phase of the dermatitis: the acute phase can be characterized by itching, erythema, oedema, vesicles, and scaling with visible borders, while the chronic phase is characterized by lichenification and itching. As well as the sensitizing potential of the nickel allergen, mutations in the *filaggrin* gene complex and an alteration of *toll-like receptor 4* (TLR4) in allergic patients have been recently identified as additional risk factors for nickel contact dermatitis to [9,13,14].

Oral zinc therapy

Nickel can interact with essential divalent metal ions at the active sites of important biomolecules and, based on animal studies, some of the effects of nickel may be eliminated or reduced by administration of zinc sulphate ($ZnSO_4$). One clinical study in humans has shown that the administration of $ZnSO_4$ can improve the symptoms of nickel contact dermatitis and eliminate or reduce the majority of patch-test reactions; intolerance to $ZnSO_4$ was not observed. This study showed that $ZnSO_4$ therapy is both effective and safe [15,16].

Hyposensitization with nickel

The concept of hyposensitisation suggests that the induction of tolerance to a specific antigen may be obtained either by a mechanism of active suppression or by the induction of a clonal allergy [17,18]. A double-blind-versus-placebo study has demonstrated that oral nickel administration in humans may reduce the number of circulating T-cell lymphocytes activated against nickel [19]. It has also been shown that that complete tolerance to nickel can be maintained for 2 years as long as oral contact with the allergen is avoided. [20]. The first oral hyposensitization therapy was based on the administration of non-toxic nickel doses to sensitized mice for 3 weeks [21] However, the first successful result with humans was obtained in 1987 [22] when less-intense patch test reactions were observed after the administration of oral capsules containing different nickel concentrations to a group of patients for 6 weeks. Since then clinical trials of oral hyposensitization therapy have confirmed these results [23,24,25].

Nickel allergy remains highly prevalent, and knowledge of its pathology has led to increased occupational and environmental hygiene. The low-nickel diet plus hyposensitization with oral nickel is at present the only therapy that acts on the pathogenic mechanisms of this condition, so it could be considered the only effective "therapy" for nickel sensitivity [26]. Nutritional treatments to promote nickel excretion, however, include administration of methionine (500 mg twice a day between meals), zinc and selenium supplementation, together with N-acetyl cysteine or glutathione complex last thing at night. This regime should be followed for a limited period of time, and methionine should only be given if the subject can adequately catabolise homocysteine to cysteine (which is a vitamin B6-dependent step).

Lymphocyte transformation (MELISA) testing for nickel allergy

Metal sensitisation, including nickel allergy, has historically been diagnosed using epicutaneous patch testing [27]. Patch testing may, however, yield false positive or false negative results, and, as an *in vivo* test, may exacerbate symptoms in a sensitised subject. An alternative is an *in vitro* lymphocyte transformation test, optimised as MELISA (an acronym for memory lymphocyte immunostimulation assay) [28]. This test was originally used in the pharmaceutical industry to detect allergy to drugs and has been validated over a number of years for the detection and monitoring of metal sensitivity [29].

Specimen requirements

Blood for nickel analysis should be collected into a trace element-free (dark blue top) BDH venoject tube. For urine determinations a sample from a 24-hour or 6-hour urine collection should be submitted. Hair samples for nickel analysis should be cut from the back of the head, or nape of the neck, as close to the scalp as possible. At least 0.5gm of hair is required, which is about one heaped tablespoonful. Only hair up to 1½" (4cm) from scalp should be used.

Blood for MELISA testing should be taken into sodium citrate tubes (two 9 ml venoject tubes provide sufficient blood for testing up to 3 metals).

Methodology

Nickel determinations are carried out by inductively coupled plasma-mass spectrometry (ICPMS).

Interpretation of results

Hair analysis (for 18 elements, including nickel) is the most sensitive method for assessing excess exposure to nickel, since, along with other potentially toxic metals, it is sequestered into the hair as a de-toxification mechanism, thus initially avoiding its health-deleterious effects.

Nickel is primarily excreted via the urine, with a biological half life of two to three days. Both blood and urine measurements can be used to monitor nickel exposure and absorption. Blood levels in nickel-allergic individuals may, however, be lower than in non-allergic control subjects due to the avoidance of nickel-rich foods by sensitised individuals.

The best test for nickel sensitivity per se is the MELISA stimulation index.

The reference interval for whole blood Ni is 5.0 – 13.0 nmol/L.

The reference interval for urine Ni is ≤ 27.2 umol/mol creatinine .

The reference interval for hair Ni is ≤1.40 μg of nickel per gram of hair.

The permitted level for Ni in drinking water is ≤ 20 μg/L.

Results for the in vitro lymphocyte transformation test (MELISA) are expressed as a stimulation index for lymphocyte proliferation on exposure to nickel; a value for this index of less than 2 is negative, while a value between 2 and 3 suggests a borderline sensitisation to nickel. A sensitisation index of between 3 and 10 is a positive response, while a value of greater than 10 is a strong positive response. Nickel reactivity is the most frequent positive response recorded in subjects undertaking MELISA testing.

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