

Biosensors in Detection of Nickel Hypersensitivity

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ABSTRACT

Usage of numerous dental materials, starting from diagnosis to rehabilitation for the management of oral diseases are not devoid of posing a potential risk of inducing allergic reactions to the patient, technician and dentist. The materials used for dental restorations, orthodontic instruments etc must satisfy the biocompatibility specifications since they are indicated for a long time in the oral cavity. Popular usage of nickel in dentistry has brought about an unpopular trend in allergic reactions. The wave of metal allergies that are the result of nickel usage in orthodontics, are more prevalent in dentistry. Metallic taste, angular cheilitis, and periodontitis may be associated with release of nickel from orthodontic appliances. It is manifested as Nickel Allergic Contact Stomatitis (NiACS). A burning sensation is the most frequent symptom. A systematic approach for the selection and monitoring of dental materials used in orthodontics thereby giving an insight to predict their risk of inducing allergic reactions. The scope of detection of dental materials related allergies can be used chairside before introducing the material to the oral cavity. Use of detection may not be used only for diagnostic method but also a therapeutic method. Hence, dental materials related allergen detection, and management have become significant priorities within the healthcare fraternity, and there is an urgent requirement for reliable, sensitive, and user-friendly technologies to trace allergens in dental materials.

KEYWORDS: Nickel hypersensitivity, Contact dermatitis, Biosensor, Patch test

INTRODUCTION

Nickel allergy is a type of contact dermatitis caused by direct contact with nickel. It is the most common cause of metal-related contact dermatitis and may be seen in healthcare. In orthodontic treatments we use brackets, bands, wires etc. which contain nickel 8%. Absorption of Nickel into the system is quick, and it causes delayed hypersensitivity reaction. Nickel Allergic Contact Stomatitis (NiACS) a burning sensation is the most frequent symptom. Metallic taste, angular cheilitis, and periodontitis may be associated with release of nickel from orthodontic appliances. Patch testing represents the gold standard for the diagnosis of ACD from nickel.

METAL ALLERGY

Metals are pervasive in our environment and are frequently utilized in costume jewelry, coins, mobile phones, and dental materials. These metals include gold (Au), silver (Ag), mercury (Hg), nickel (Ni), titanium (Ti), chromium (Cr), copper (Cu), and cobalt (Co). Contact hypersensitivity to metals affects roughly 10%–15% of the population of humans.^[1,2] With an estimated population frequency of 10% in

women vs. 2% in males, this allergy is significantly more prevalent in women than in men.^[3,4] Clinically, metal allergy is connected to the root of contact dermatitis, pustulosis palmoplantaris, lichen planus, dyshidrotic eczema, and burning mouth syndrome^[5-8]. Additionally, metal allergies are more common in people with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome.^[9] According to a prior study, nickel (II) sulfate causes sensitization in about 15% of people, followed by cobalt chloride and potassium dichromate, which affect about 5% and 3% of people, respectively^[10] Nickel allergy is the most common^[2,11], and clinically important condition that is becoming a threat to public health^[12,13] The use of nickel alloys is common in dentistry, and high concentrations of nickel can be found in food. Metal allergy is mainly diagnosed by patch testing. Several reports have demonstrated that the removal of causal metal can successfully improve allergic symptoms. Therefore, in addition to the metal concentration, a special quality of metal seems to be important for the pathogenesis of metal allergy^[14-16] Nickel ions released from various alloys are potent allergens or haptens that can trigger skin inflammation^[17-19] They penetrate the skin and activate epithelial cells that produce various cytokines or chemokines. The reaction follows complex immune responses that involve the activation of antigen-presenting cells (APCs) and T cells^[20-22] Some cytokines activate APCs, such as Langerhans cells (LCs) or dendritic cells (DCs). Activated APCs migrate to the draining lymph nodes where they present the allergens or haptens to naive CD4-positive T cells. Subsequent re-exposure to the same allergen or hapten would lead to the activation of hapten-specific T-cells, which subsequently enter the bloodstream and produce visible signs of hypersensitivity at 48 to 72 h after allergen or hapten exposure^[23] However, the precise molecular mechanisms that mediate the interactions between epithelial and immune cells in nickel allergy remain unknown.

RELEASE OF NICKEL IONS FROM STAINLESS STEEL ALLOYS USED IN DENTAL BRACES

Nickel ions leached in sufficient quantities from nickel-containing alloys may induce nickel sensitization or elicit allergic contact dermatitis. Nickel-containing stainless-steel alloys are generally considered safe for nickel-sensitive individuals to use. Stainless steel alloys used in the metallic parts of orthodontic braces contain 3– 155 mg% nickel^[24]. The amounts of nickel ions released in vitro from dental braces depend upon the alloys and the test system employed^[25-31]. In vitro nickel ion release from nickel-chromium dental casting alloys (not stainless steel) has been reported as 42 mg/cm² /D in pooled human saliva and in vitro release rate of full-mouth orthodontic appliances has been estimated to be in the range from 26 mg nickel/D immersed in 0.05% sodium chloride to 40 mg nickel/D immersed in artificial saliva^[25,27] Studies have found nickel ion release from low-sulfur stainless steel alloys in artificial sweat to be less than 0.03 mg/cm² /week. Most stainless-steel alloys release less than 0.05 mg/cm² /week, but high sulfur stainless steel may release as much as 15 mg/cm² / week into artificial sweat^[30,31]. Saliva may potentially corrode the different alloys and thereby release nickel ions into the adjacent oral mucosa, but the quantity of the corrosive products that may be absorbed by dental patients is unknown

CLINICAL SIGNS

Localized primary eruptions or generalized secondary eruptions, which may or may not be eczematous, are examples of clinical characteristics. Recurrent eczematous lesions on the areas in direct contact with nickel-releasing objects, such as the umbilical region (button on trousers), earlobes, wrists, and neck, are the hallmark of primary eruptions.^[32] As a result of contact with cell phones, piercings, and hair clasps,

the face and scalp may become affected.^[33-36] Transcutaneous, inhalatory, intravenous, or oral exposure to nickel can result in exposed people developing a systemic allergic contact dermatitis. Involvement of previously exposed areas (flare-up of dermatitis and/or patch test sites), as well as previously unexposed areas (maculopapular exanthema, pompholyx, flexural eczema, "baboon syndrome," and lesions that resemble vasculitis), are among the clinical features. The maculopapular exanthema with flexural involvement manifests as a symmetrical eruption on the inner thighs, anogenital regions, neck, face, eyelids, elbow flexures, and forearms.^[37]

Pompholyx has been linked to nickel allergy in women, teenagers, and twins, however there is ongoing debate over this connection.^[38-40] Nickel can cause a special type of systemic allergic contact dermatitis that has a distinct dose-response connection. Researchers found that CD8+ "memory" CLA+ T cells and T lymphocytes with a type 2-cytokine profile are implicated in nickel sensitivity in people whose dermatitis worsened following oral nickel provocation.^[41] Nickel can occasionally produce non-eczematous dermatitis, including contact urticaria, papular lichenoid eruptions, and lesions that resemble vasculitis.^[42-45]

TESTS TO DETERMINE NICKEL HYPERSENSITIVITY

Patch testing

Contact allergy is diagnosed by patch testing. As this test measures only whether the individual is sensitized or not, a positive test reaction is not necessarily an indicator of clinical disease. Clinical relevance of patch test results should always be established. There is a high degree of concordance between history of nickel exposure and outcome of patching testing.^[46,47]

Nickel is the most common positive patch test allergen. It has been estimated that nickel-positive tests are seen in 10% to 30% of female patients, 2% to 8% of male patients, 15.9% of children and 13.7% of patients older than 65, but it varies greatly, depending on the selected population.^[48,49,50]

Although sensitivity and sensibility of patch testing is not exactly known, reproducibility is generally high, even though results may vary in the same patient at different times.^[51-53]

The standard patch test concentration of nickel sulfate is 5% pet in Europe and 2.5% pet in the USA. Positive reactions are usually strong. False-positive reactions may occur in atopics, where follicular irritative reactions are common. Weak true-positive reactions can also show a follicular pattern.

False-negative reactions can also occur. In case of strong clinical suspicion, the test can be repeated with nickel chloride 5%, which increases nickel concentration, by using penetration enhancers such as dimethyl sulfoxide (DMSO) or scratching the skin before patch test application.

Since patch tests are often performed by different specialists including allergologists, dermatologists, pediatricians, and general physicians, special training is essential to correctly judge and interpret the test in order to distinguish allergic from irritative reactions and establish patch test relevance.

Patch testing is considered safe in children, but positive reactions should be assessed with caution. Some limitations include the small patch test surface, hyper mobility (which may result in loss of patch test materials), particularly in younger children, and the hesitation of some parents to allow patch testing. Some authors recommend the same patch test concentration as in adults, but others recommend lower allergen concentration.^[54] In case of doubtful reactions it is advisable to retest with a lower concentration.

Dimethylglyoxime (DMG) spot-test

This test identifies metallic objects that contain high nickel concentrations (at least 1:10,000) and can be useful to screen personal items in individuals allergic to nickel. An object that gives a negative result is unlikely to induce the dermatitis. Dermatology staff may test a patient's metal alloys in the office or nickel-sensitive patients can purchase a test kit and be taught how to use it at home to screen jewelry, metallic surfaces or any other metal object.

The spot-test kit contains 1% dimethylglyoxime in alcohol solution (30 mL) and 10% ammonium hydroxide solution (30 mL). There are two methods to perform the test. Fisher's original method consists in putting a few drops of each solution on the metallic object; a positive reaction is denoted by a pink-red precipitate.^[55] Most metal alloys give a positive reaction, except stainless steel.

A modification of this technique was proposed by Shore who suggests applying a few drops of DMG and then a few drops of ammonium hydroxide on a cotton-tipped applicator that is then rubbed against the object. A pink-red precipitate on the applicator tip detects a positive reaction.^[56]

The test can roughly quantify the nickel content as the precipitate color can vary between pale pink to red.

Experimental oral provocation

This technique is not routinely recommended, but it is a possibility in patients with pompholyx when a possible role of nickel is suspected.

Nickel dietary intake varies from 0.1 mg to 0.5 mg, and thus the induction of systemic dermatitis by foods remains controversial, as experimental doses are usually higher than those introduced with foods.^[57-60]

Several studies had been performed in order to induce flare-ups of nickel dermatitis by oral challenge, particularly in patients with pompholyx.^[61-67] It was shown that flare-up occurs in a dose-response way.^[68]

Finger immersion test

The patient is asked to put one or more fingers in a solution containing nickel to see which concentrations in consumer products can cause a flare-up of hand eczema.^[69] It might be indicated in selected cases of hand eczema, particularly in an occupational subset.

The lymphocyte proliferation test

This test can be useful in the diagnosis of nickel sensitivity. Duarte showed that lymphocyte proliferation was higher in patients allergic to nickel (17 patients) than in controls (25 patients) for all the nickel concentrations tested.^[70]

Prick test

This may be indicated in cases of contact urticaria due to nickel. Intradermic test Intradermic test is almost never used on clinical practice, but it may be utilized in case of doubtful patch test reactions, either to identify false-positive reactions or to confirm a clinical suspicion of nickel dermatitis in patients with negative patch tests.^[71] It can also reveal the degree of sensitivity with different titrations, which can't be done with standard patch tests.^[72]

Biosensors

The novelty of this work is the potential adoption of biosensors for detecting metal allergies, which have immense applicative value in health fraternity and public health. Ideally, we take 48-72 hours to diagnose allergy but here we are trying to detect nickel allergen chairside using biosensors so that we have immediate results.

A biosensor is a device that uses the biological sensing component to react with the target analyte and generate a signal that can be quantified concerning the concentration of the target analyte. The primary component of the biosensor is the biological sensing component, which is in charge of detecting the analyte and producing a response signal. The transducer, the second element, transforms the signal generated by the biological sensing element into a measurable output. The third element of the biosensor is the amplifier, which amplifies and the processor analyses the signal and gives out the quantitative information for displaying them on an electronic display system. Biosensing has been developed for the determination of protein concentration because of its extreme sensitivity to species, including food allergens, toxic proteins, marker proteins, antibodies, and pharmaceutical proteins^[73] (Singh, 2016; Xia et al., 2010). SPR biosensors have been widely applied to the measurement of the

After the patch results, we use ELISA for confirmatory testing and to detect the protein binding substance. We'll find out the protein binding substance which binds to the antibody causing the reaction. Using this protein binding substance, we will develop a biosensor which will detect the allergen chairside.

CONCLUSION

Nickel is the most common sensitizing agent worldwide. Allergic contact dermatitis due to this metal represents great morbidity, as well as cases of systemic allergic contact dermatitis, which can be misdiagnosed as adverse drug reactions, delaying the correct diagnosis and leading to inappropriate treatment. Normally, it takes 48–72 hours to diagnose an allergy, but in this case, we're aiming to use biosensors to quickly find nickel allergen at the chairside. Biosensors enable quicker results, which decrease chairside time and visit frequency.

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