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## ALLERGIC REACTIONS TO NICKEL-CONTAINING ORTHODONTIC APPLIANCES: CLINICAL SIGNS AND TREATMENT ALTERNATIVES

*Nickel is the most common contact allergen. Nickel-containing orthodontic appliances are implicated in allergic reactions, which represent a type IV delayed hypersensitivity immune response. Nickel hypersensitivity is diagnosed through the patient's history, clinical findings, and biocompatibility testing (patch skin tests). While testing the level of nickel in mucosa and blood does not have diagnostic value, the in vitro cell proliferation assays could be an important diagnostic tool. Allergic hypersensitivity reactions may involve intra- and extra-oral clinical signs, comprising diffuse erythema, edema, eczema, fissuring, desquamation, and symptoms such as itching and soreness. Caution and close monitoring should be exercised when placing nickel-containing orthodontic appliances in patients with known histories of nickel contact dermatitis, as the original treatment approach might need modification. The aim of this article is to provide orthodontists with the necessary knowledge about the biologic mechanisms, diagnostic tools, and clinical signs, as well as the treatment alternatives to nickel-induced allergic reactions. World J Orthod 2008; 9:399–406.*

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In modern orthodontics, a wide variety of appliances and devices containing nickel is used. Nickel content ranges from 8% (in stainless steel) to more than 50% (nickel-titanium alloys).<sup>1–3</sup> Nickel has been correlated with carcinogenic,<sup>4</sup> mutagenic,<sup>5</sup> cytotoxic,<sup>6</sup> and allergenic<sup>7–12</sup> activity.

Nickel is the most common allergenic element<sup>13</sup> and triggers more allergic reactions than all other metals combined.<sup>14</sup> It is estimated that 2% to 27.5% of the general population has hypersensitivity to nickel, with females being affected more than males.<sup>15–23</sup> The higher prevalence in females is related to environmental exposure (con-

tact with detergents, jewelry, wrist-watches, metal buttons, and buckles); in males, occupational exposure is more frequent (in industries that use nickel as a raw material).<sup>16,24,25</sup> Most recently, in a population-based study from northern Norway, 27.5% of women patch-tested positive for nickel compared to only 5.1% of men.<sup>21</sup>

Despite the high prevalence of nickel allergy in the general population, especially among females, adverse reactions associated with nickel-containing orthodontic appliances are not frequently reported. Little epidemiologic data exist on nickel hypersensitivity in relation to fixed orthodontic appliances. In Norway,

the incidence of adverse patient reactions in orthodontic practice is approximately 0.4%.<sup>26</sup> In a survey of 68 orthodontic offices in the German state of Hesse, less than 0.2% of the patients exhibited an allergic skin reaction in the course of their orthodontic therapy.<sup>27</sup> No statistical significant differences were observed between the reactions to patch tests before and after the placement of fixed appliances in orthodontic patients in Brazil.<sup>28,29</sup> In 2007, in Wisconsin (USA), an analysis of 43 surveys including more than 33,000 orthodontic patients suggested that prevalence of adverse reactions to nickel was 0.03%.<sup>30</sup> Also, a questionnaire study in Norway and Finland concluded that nearly half of the respondents reported at least 1 adverse patient reaction to nickel during orthodontic treatment with fixed appliances.<sup>31</sup>

The purpose of this article is to provide orthodontists with knowledge about the biologic mechanisms of this phenomenon, diagnostic tools, and clinical signs, as well as treatment alternatives that can prevent nickel-induced allergic reactions. With this information in mind, clinicians will be able to recognize signs of nickel sensitization and adjust their treatment approach to meet the best interest of the patient.

## BIOLOGY OF THE ALLERGIC REACTION

Hypersensitivity is when an adverse reaction follows contact with subtoxic doses of foreign substances. Three mechanisms comprise hypersensitivity reactions: allergy, intolerance, and hyperreactivity. While intolerance is usually related to foodstuffs and inborn errors of metabolism, hyperreactivity is connected to volatile irritants. An allergy, on the other hand, is an acquired condition resulting in an overreaction upon contact and arises from a genetic predisposition and previous sensitization from exposure to the allergen.<sup>19</sup>

The hypersensitivity reaction to nickel is a type IV delayed reaction, due to the direct relationship with the presence of this metal in the environment, and may be induced with ingestion or direct contact with the skin and/or mucosa.<sup>24</sup> The term “delayed” refers to the fact that the reaction occurs 24 to 48 hours after exposure.<sup>32,33</sup> Once the nickel is absorbed by the skin or mucosa, it binds to certain proteins associated with Langerhans cells to form a complete antigen. By means of the Langerhans cells, this antigen is brought into contact with the T lymphocytes of the regional lymph nodes, and results in the formation of specialized T cells at the initial sensitization phase. Upon subsequent exposure with the allergen, the contact of nickel with these specialized T cells releases inflammatory mediators, resulting in further attraction of T cells and causing tissue damage at the elicitation phase.<sup>19</sup>

## ALLERGEN DETERMINATION

When there is suspicion of an allergic reaction, the allergen must be determined. Nickel sensitivity is usually diagnosed through patient history, clinical findings, and biocompatibility testing,<sup>34,35</sup> including cutaneous sensitivity tests (patch skin tests).<sup>36</sup> A skin test is more discriminating than a mucosal membrane test because greater concentrations of a potential allergen are required in the latter.<sup>37,38</sup>

### Patch skin test

The diagnosis of a nickel allergy is confirmed by the results of patch skin testing,<sup>39</sup> which, when properly interpreted, are acceptable as evidence of sensitivity. In this procedure, epicutaneous tests are performed by applying small amounts of an allergen that has been dissolved in a medium such as petroleum to the skin. The use of alcohol, acetone, or water as a vehicle may result in false-negative

results due to the potential interaction of dissolved salt in these vehicles with the adhesive tape or in false-positive test results due to the increase in the salt concentration after evaporation of the vehicle. The use of white petrolatum as a vehicle is safer, prevents possible oxidation, does not evaporate, and rarely causes an allergic reaction.<sup>24</sup> After 48 hours, the clinician evaluates the patient's reaction according to the intensity of the erythematous reactions. The ranking is from negative to extremely strong or irritative.<sup>19</sup> According to International Research Contact Dermatitis Group guidelines, scores 0 (absent reaction) and 1 (light erythema) are considered negative, while scores 2 (erythema), 3 (erythema, edema, papules), and 4 (erythema, edema, papules, vesicles) are considered positive.

The most clinically relevant method to estimate the release of nickel leaching from orthodontic alloys would be to measure it in biological fluids (saliva, serum, and urine). Urine and serum metal concentrations, however, are dependent on the excretory rate of nickel, which is a highly individualized parameter and species-specific.<sup>3</sup> Nickel in the plasma of healthy subjects averages 2.1 µg/L, with a range of 1.4 to 3.4 µg/L. More than 90% of the nickel ingested in the diet is excreted in feces. Absorbed nickel tends to localize in connective tissues, kidneys, and lungs. Most absorbed nickel is believed to be excreted in urine, with an average of 4.5 µg/L (range 1.9 to 9.6 µg/L).<sup>40</sup> Thus, the amount of nickel in the diet could affect the levels of nickel in biological fluids.

### Mucosa and saliva

With saliva being the first diluting pool of nickel, the measurements of metal concentration from oral mucosa or saliva would have a direct association with the amount of the metal leached from orthodontic appliances. To assess the release of nickel in patients wearing orthodontic appliances while simulating oral condi-

tions as carefully as possible, a full-mouth orthodontic appliance consisting of brackets, bands, and wires was incubated in a 0.05% sodium chloride solution.<sup>1</sup> The amount of nickel released in vitro by this simulated orthodontic appliance was about 40 µg per day. Because human dietary intake of nickel is reported to be 300 to 500 µg per day,<sup>41</sup> the release of 40 µg of nickel per day is well below the normal daily intake and may not be of clinical significance.<sup>1</sup> In vivo investigations have shown a variance in nickel concentration with an increase at insertion of fixed orthodontic appliances, dependent on the number of bands and brackets used at each participant,<sup>42</sup> or no increase 1 month after the insertion of appliances.<sup>43</sup> In a study, in order to evaluate the absorption of nickel by the oral mucosa, mucosa cells were harvested from areas adjacent to patients' braces before and after attachment. The nickel content was measured with electrothermal atomic absorption spectrometry. No measurable amounts of nickel were found in any of the samples before or after attachment.<sup>44</sup> In contrast, an in vivo investigation evaluating the presence of metal ions in oral mucosa cells with comet assay indicated that nickel concentrations were higher in orthodontic patients than in controls and that nickel released from fixed orthodontic appliances can induce DNA damage in buccal cells.<sup>45</sup>

### Changes in the blood level

To determine whether any changes occur in the nickel levels in blood in orthodontics patients, blood samples were collected from orthodontic patients with no reported allergy before the placement of orthodontic appliances and 2 months and 4 to 5 months afterward.<sup>46</sup> While normal whole blood concentrations for nickel have been reported to be between  $2.4 \pm 0.5$  ng/mL and  $30 \pm 19$  ng/mL,<sup>47-50</sup> no significant or consistent increase in the blood level of nickel was recorded using atomic absorption spectrophotom-

etry from the biodegradation of orthodontic appliances during the initial 5 months of treatment.<sup>46</sup> Consequently, the amount of nickel in the blood cannot be used as a diagnostic tool to determine any sensitivity to the specific allergen.

## Urinary levels

Only 1 study compared pretreatment and treatment levels of nickel in the urine of orthodontic patients wearing fixed appliances. Urine samples have been monitored by atomic absorption spectrophotometry before and after fixed orthodontic appliance placement to detect their systematic response to potentially corrosive materials. The findings of the study indicate that nickel increases significantly in patients' urine 2 months after the placement of the appliances. However, the biologic effect of the increased nickel concentration in the urine is unknown. More studies are needed to validate these results.<sup>51</sup>

## In vitro cell-proliferation assays

In an effort to evaluate the immunologic profile of nickel antigens in patients undergoing orthodontic treatment, an in vitro cell-proliferation assay was used. This technique tests the effect of nickel antigens on the lymphoproliferative response in vitro by using peripheral blood mononuclear cells from patients with orthodontic appliances. By assessing the nickel-induced cell proliferation index, this approach is able to distinguish nickel-sensitive from nonnickel-sensitive patients and also discriminate those with positive skin tests. A positive skin test is associated with a higher proliferation index. A study using a cell-proliferation assay as the basic methodology to assess nickel sensitivity among orthodontic patients suggests that continuous exposure to nickel casting alloys might lead to oral tolerance mechanisms that modulate nickel sensitivity, as evidenced by the lower cell proliferation index over

24 months. Although this optimized methodology for assessing cellular immune status could enable diagnostic testing of nickel sensitivity and thus, improving the specificity and minimizing the false-positive results, more studies are needed to clarify the major cell phenotype associated with nickel-sensitive individuals.<sup>52</sup>

Nickel is an allergen eliciting false-positive reactions in patch skin testing due to the irritancy of test materials; it is sometimes difficult to distinguish an irritant reaction from a true allergic response, and patients may need to be tested more than once. Due to varying sensitivity of the patient, false-negative reactions can occur. It therefore appears reasonable to search for a more objective in vitro alternative. The cell-proliferation assay appears to be 1 procedure that could be used with relatively reliable results. At this point, this method can be used only in association with patch testing and has often given results inconsistent with the patch test.<sup>53</sup>

## CLINICAL SIGNS OF NICKEL ALLERGY

Nickel allergies may comprise intraoral red zones, blisters, and ulcerations, extending to the perioral area, and are referred to as allergic contact mucositis or dermatitis.<sup>19</sup> These reactions are not necessarily limited to the exposure site. Eczematic and urticarial reactions of the face or more distant skin areas can occur with redness, irritation, itching, eczema, soreness, fissuring, and desquamation.<sup>19</sup> Urticarial reactions are generally associated with type I immediate IgE mediated allergic reactions and would be atypical for allergic contact dermatitis. Mucosal and gingival reactions, as well as potential general dermal and systemic reactions, can appear in unusual circumstances.<sup>54</sup>

In cases of known nickel allergies, the sensitization process may have taken place weeks or years before the hypersensitive reaction from orthodontics. The presence of nickel in everyday objects

that are in contact with the skin, such as metal suspenders, clothing buckles, wristwatches, appliances, eyeglasses, jewelry, or piercing devices, may have attributed to the development of nickel allergy.<sup>19</sup> Documented factors influencing this sensitization include mechanical irritation, skin maceration, increased environmental temperatures, increased intensity, and duration of exposure.<sup>55</sup>

In the literature, there have been reports of localized allergic responses attributed to the nickel-containing orthodontic appliances.<sup>7,8,10-12,56-60</sup> Extraoral allergic reactions have been observed more frequently than intraoral ones,<sup>27,61</sup> including redness, itching, eczema, dryness, pain, and wrinkling and exfoliation of the skin, all of which have been largely attributed to the metal parts of headgear.<sup>58,59</sup> Intraoral allergic reactions include redness, edema, itching and dryness of the lips and oral mucosa, burning sensations, as well as gingival inflammation. Occasionally, fever has been reported as systemic reaction.<sup>7,56</sup>

Most intraoral allergic reactions are related to the use of nickel-containing orthodontic appliances. Despite these reports, safe conclusions for the general population cannot be extrapolated because there is a lack of data directly linking the prevalence of nickel-induced effects in nonsensitized individuals with the insertion of nickel-containing orthodontic appliances.<sup>3</sup> Studies have shown that orthodontic therapy with conventional stainless steel appliances does not initiate or aggravate a nickel hypersensitivity reaction.<sup>28,29</sup> Even for nickel-sensitive patients, no greater risk of developing discomfort in the oral cavity during orthodontic treatment has been found than for nonsensitive patients.<sup>20,30,63</sup> Rather, data suggest that treatment with nickel-containing orthodontic appliances before sensitization to nickel (such as ear piercing) may reduce the frequency of nickel hypersensitivity due to the slow, long-term release of nickel from orthodontic appliances (nickel tolerance).<sup>19,20,61</sup> On the other hand, tolerance does not exclude the possible development of

allergic reactions after orthodontic treatment once a previous sensitizing exposure to nickel occurs.<sup>3</sup>

## TREATMENT ALTERNATIVES FOR PATIENTS ALLERGIC TO NICKEL

In cases where sensitivity to nickel is confirmed through a patch test, alternative treatment modalities should be employed to eliminate the risk of allergic reactions due to the specific allergen.

As known, the general composition of the metal components of the orthodontic appliances is 18/8 stainless steel (18% chromium and 8% nickel). Leaching of these elements may induce an allergic reaction after sensitization, more commonly with nickel.<sup>54</sup> However, most of the investigations have concluded that stainless steel is safe in all intraoral orthodontic components in nickel-sensitive patients, since the crystal lattice of the alloys binds the nickel, thus preventing it from reacting.<sup>63</sup> The only reports of allergic reactions to stainless steel wires are those in which the stainless steel used for intermaxillary or internal fixation had increased nickel content and were not tested for corrosion.<sup>56,64</sup>

The nickel content of nickel-titanium wire alloys may exceed 45%,<sup>2</sup> although the risk of nickel release from these alloys is not proportional to their nickel content.<sup>65</sup> In case of an allergy to nickel-titanium archwires, alternatives include twistflex stainless steel wires, titanium molybdenum alloy, and pure titanium wires.<sup>66</sup> Additionally, gold-plated wires can be safely used. Also, coated wires, such as the plastic/resin-coated, and ion-implanted nickel-titanium archwires reportedly exhibit less corrosion than stainless steel or noncoated nickel-titanium wires, which result in a lesser release of nickel.<sup>67</sup>

As for the brackets, nickel-free brackets, such as ceramic (produced using polycrystalline alumina, single-crystal sapphire, and zirconia), polycarbonate (made from plastic polymers), titanium,

or gold-plated brackets, may be used.<sup>3,66</sup> Furthermore, companies offer many nickel-free products as auxiliaries to the regular orthodontic appliances for use in patients with nickel sensitivity. For these patients, plastic-coated headgear, glass-fiber buccal tubes, titanium buccal tubes, epoxy-coated quick-tie ligatures, titanium molybdenum alloy expansion screws, and nickel-free stainless steel wires for removable appliances are recommended.<sup>66</sup> Also, a hypoallergenic version of a rapid palatal expander (RPE) and Frankel appliance have been constructed, successfully used, and reported in the literature.<sup>69</sup>

In cases where no history of nickel allergy is reported but allergic reactions do appear shortly after the attachment of fixed orthodontic appliances, treatment must be discontinued and any intra- or extraoral appliances containing nickel removed.<sup>3</sup> After healing, treatment should resume using alternative alloys, whether they be gold, platinum, nickel-free stainless steel, or titanium-molybdenum alloys.<sup>69</sup>

Regarding the cost implications of treating a nickel-sensitive patient with the suggested alternative materials, these could range from an increase of 30% for nickel-free brackets and archwires to in excess of 3 times the average cost of esthetic brackets and archwires.<sup>67</sup>

## CONCLUSION

Nickel produces more allergic reactions than any other metal used in orthodontics. The diagnosis of a nickel allergy is confirmed by the results of patch testing. Exposure to nickel-containing orthodontic appliances may cause allergic reactions intraorally, extraorally, or both. Extraoral allergic reactions have been observed more frequently than intraoral ones. Even when there is no previous sensitization to the specific allergen, clinical signs of an allergic reaction should make the clinician suspicious and reluctant to use nickel-containing orthodontic appliances. Instead, nickel-free treatment alternatives are recommended for the benefit of the patient.

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