CLINICAL PREDICTORS OF METAL ALLERGIC SENSITIZATION IN ORTHODONTIC PATIENTS

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SUMMARY

Objectives: This study aimed to assess the predictors of allergic sensitisation to titanium and nickel in patients undergoing orthodontic treatment.

Methods: A total of 250 patients undergoing orthodontic treatment were invited to participate, and 235 were analysed (67% females). A patch test was performed using nickel sulphate, titanium, titanium dioxide, titanium oxalate, titanium nitride, and petrolatum as control. In addition, clinical signs of the oral mucosa, gingiva, tongue, lips, and allergological history were assessed.

Results: The predictors of metal allergic sensitisation in patients undergoing orthodontic treatment were adult age (OR = 2.6; 95% CI: 1.2–5.5; p = 0.016), female sex (OR = 3.0; 95% CI: 1.1–7.9; p = 0.025), exfoliative cheilitis (OR = 4.8; 95% CI: 1.9–12.4; p = 0.001), history of contact hypersensitivity (OR = 7.0; 95% CI: 1.3–35.4; p = 0.025), history of contact hypersensitivity to metals (OR = 8.3; 95% CI: 1.4–50.2; p = 0.021), and piercings (OR = 5.4; 95% CI: 2.1–13.9; p = 0.001). When predictors were analysed separately for these two metals, titanium sensitisation predictors were contact hypersensitivity to metals and piercing, whereas nickel sensitisation predictors were age and piercing.

Conclusion: A positive patch test alone cannot draw definite conclusions regarding allergy. However, metal allergies in patients with orthodontic appliances could be considered in cases of previous contact hypersensitivity, previous reactions to metals, exfoliative cheilitis, and piercing.

Key words: allergic sensitization, titanium; nickel, orthodontics

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INTRODUCTION

Hypersensitivity reactions are harmful immune responses that lead to tissue damage and can cause serious medical conditions and diseases. Hypersensitivity reactions usually do not lead to symptomatic reactions during the first encounter but after re-exposure to the antigen. Despite positive allergological testing, if there is no allergic reaction, allergy is defined as a concomitant disease after an immune reaction to a foreign antigen. The definition of an allergy may be inapplicable; however, it can be considered an allergic sensitisation. Sensitisation is the process in which the body becomes abnormally sensitive and/or allergic to a certain substance. During this process, the immune system produces defence proteins such as antibodies or allergen-specific defence T lymphocytes (1). Interacting intrinsic properties of exogenous proteins, environmental and other factors play a role, however, the immune characteristics of the host and the tissue exposed are crucial in explaining why not every sensitised host develops a true allergy (2).

Although the literature supports the opinion that oral allergic reactions are uncommon, some research suggests that they may be more prevalent. Most allergic reactions in the oral cavity are caused by contact allergic reactions according to a pathophysiological mechanism (3). Clinical signs of allergic reactions depend on the nature and efficacy of the allergen, specific variants of the generated response mediated by T lymphocytes, and the degree of dysregulation of the genetically programmed immune-inflammatory response (4).

When performing allergy testing, a thorough medical history, with special attention to personal and family allergology history, experience with diseases and clinical examination should be considered. Although the patch test is regarded as the gold standard and a key component in diagnosing contact hypersensitivity, cutaneous and mucosal hypersensitivity reactions do not always coincide. The identification of patch test hypersensitivity does not necessarily mean that an individual will experience oral signs and symptoms of the allergy, which is why it is called allergic sensitisation.

Nickel is found in the baseline series of patch tests in the form of nickel sulphate but titanium allergens for patch tests are not standardised. The most commonly used allergen in patch tests for titanium is titanium dioxide, however, it rarely confirms the clinical suspicion of an allergy. Titanium dioxide is poorly soluble owing to its poor skin penetration ability, which may explain the controversial negative patch test results despite the established clinical suspicion of an allergy (5). Nevertheless, it appears that titanium dioxide, unlike the skin, penetrates the oral mucosa well (6). Therefore, the use of other titanium salts has been suggested, even though only a few studies have used them in their methodology.

Numerous possible sources of nickel sensitisation are found in the proximate vicinity as an integral part of different items for everyday use (small household appliances and tools, coins, imitation jewellery, clothing clasps, metal parts of musical instruments, and mobile phones) (7). Furthermore, hypersensitivity to nickel is more common in women than in men and is more common in patients with asthma (8).

This study aimed to assess the clinical signs and allergological history as predictors of allergic sensitisation to titanium and nickel in patients undergoing orthodontic treatment. We hypothesised that the most expected clinical manifestations of allergic sensitisation to metals are lip changes and gingival hyperplasia.

MATERIALS AND METHODS

A total of 250 participants undergoing orthodontic treatment for a minimum of 6 weeks and a maximum of 1 year, adolescents and adults aged 11–45 years were invited to participate in the study. Finally, the total sample consisted of 235 participants with complete documentation.

All participants had an orthodontic appliance with the same chemical composition and titanium and nickel contents (brackets manufactured by Ortho Classic, USA, and wires by GAC International, Japan). The relative exclusion criterion was the practice of water sports such as swimming and water polo if the participant did not want to miss his/her sports commitment. Exclusion criteria included diabetes, endocrine, autoimmune diseases, and immunosuppressive therapy.

Personal and family allergological history were assessed (atopy, exposure to metals professionally and through hobbies, previous sensitisation and skin reactions, skin diseases, other diseases and conditions, and medications).

Allergological testing included an epicutaneous patch test for nickel (II) sulphate hexahydrate 5%, titanium 10%, titanium dioxide 10%, titanium (IV) oxalate hydrate 5%, titanium (III) nitride 5%, and petrolatum 100% as a control (Chemotechnique Diagnostics, Sweden). The epicutaneous test was performed on the upper arm, which had previously been degreased with medical benzine (Medimon, Split, Croatia). Allergens were in contact with the skin for 2 days, and the participants were instructed not to wet the area during those days. The skin reactions were read according to the manufacturer's instructions on three occasions: 2, 4 and 7 days after the patch test application. Data on prevalence have been reported previously (9).

The intraoral examination included detection of changes in the oral mucosa with emphasis on parts of the oral mucosa that were in direct contact with the orthodontic appliance (erythema, hyperkeratosis, erosion, ulceration, reticular changes, papules, or plaque), gingiva (hyperplasia, hyperkeratosis), tongue (exfoliative glossitis, atrophy, coated tongue), and lips (cheilitis, exfoliative cheilitis, angular cheilitis).

Statistical Analysis

Predictors of allergic sensitisation were analysed using Fisher's exact test, logistic regression, and odds ratio (OR) with a 95% confidence interval. The effect size for Fisher's test was quantified using Cramer's V. Cohen criteria used in the interpretation: $r=0.1$–0.3 (small effect size), $r=0.3$–0.5 (medium), $r=0.5$–0.7 (large), and $r>0.7$ (very large effect size). In addition, in the interpretation of OR, 1.5 was considered mild, moderate >3, and large >9. All statistical analyses were performed using IBM SPSS 22 software (IBM Corp., Armonk, NY, USA).

RESULTS

In univariate analyses, allergic sensitisation to nickel and/or titanium was related to age, sex, changes in the lips, exfoliative cheilitis, contact hypersensitivity, and contact hypersensitivity to metals, imitation jewellery, and piercing (Tables 1 and 2). In addition, the highest odds of allergic sensitisation to titanium and/or nickel were observed in those with a history of reactions to metals (22.9 ×).

When considering all predictors in the logistic regression model, for hypersensitivity to titanium and/or nickel, age, sex, exfoliative cheilitis, history of contact hypersensitivity, history of contact hypersensitivity to metals, and piercings remained significant (Table 3).

Predictor changes in the lips were not included in the logistic regression model because exfoliative cheilitis is a type of change in the lips and represents a more precise predictor.

Table 1. *Association of clinical signs with titanium and/or nickel sensitisation (N = 235)*

Variable	Category	Sensitisation No n (%)	Sensitisation Yes n (%)	p-value*	Effect size	OR (95% CI)
Sex	Female	132 (81.0)	31 (19.0)	0.038	0.135	2.6 (1.0–6.5)
	Male	66 (91.7)	6 (8.3)			
Age	Adolescents	110 (89.4)	13 (10.6)	0.031	0.149	5.8 (1.1–4.8)
	Adults	88 (83.3)	24 (16.7)			
Changes in the lips	No	162 (87.1)	24 (12.9)	0.027	0.152	2.4 (1.1–5.2)
	Yes	36 (73.5)	13 (26.5)			
Exfoliative cheilitis	No	181 (87.0)	27 (13.0)	0.003	0.211	3.9 (1.6–9.5)
	Yes	17 (63.0)	10 (37.0)			

*Fisher's exact test; OR – odds ratio

Table 2. *Association of allergological history data with titanium and/or nickel sensitisation (N = 235)*

Variable	Category	Sensitisation		p-value*	Effect size	OR (95% CI)
		No n (%)	Yes n (%)			
Contact hypersensitivity	No	167 (90.8)	17 (9.2)	< 0.001	0.339	6.3 (3.0–13.4)
	Yes	31 (60.8)	20 (39.2)			
Reaction to metals	No	196 (86.7)	30 (13.3)	< 0.001	0.340	22.9 (4.5–115.3)
	Yes	2 (22.2)	7 (77.8)			
Reaction to imitation jewellery	No	171 (88.6)	22 (11.4)	< 0.001	0.256	4.3 (2.0–9.3)
	Yes	27 (64.3)	15 (35.7)			
Piercing	No	182 (87.5)	26 (12.5)	0.001	0.247	4.8 (2.0–11.5)
	Yes	16 (59.3)	11 (40.7)			

*Fisher's exact test; OR – odds ratio

Table 3. *Clinical signs and allergological history data as predictors of allergic sensitisation to nickel and/or titanium*

Variable	B*	SE	p-value	OR (95% CI)
Sex (female)	1.1	0.5	0.025	3.0 (1.1–7.9)
Age (adult)	0.9	0.4	0.016	2.6 (1.2–5.5)
Exfoliative cheilitis	1.6	0.5	0.001	4.8 (1.9–12.4)
Contact hypersensitivity	1.9	0.9	0.025	7.0 (1.3–38.4)
History of contact hypersensitivity to metals	2.1	0.9	0.021	8.3 (1.4–50.2)
Piercing	1.7	0.5	0.001	5.4 (2.1–13.9)
Constant	−2.6	0.3		

*Logistic coefficient; SE – standard error; OR – odds ratio

Table 4. *Association of age and clinical signs with nickel sensitisation (N = 235)*

Variable	Category	Sensitisation		p-value*	Effect size	OR (95% CI)
		No n (%)	Yes n (%)			
Age	Adolescent	113 (91.9)	10 (8.1)	0.013	0.168	2.8 (1.2–6.1)
	Adult	90 (80.4)	22 (19.6)			
Changes in the lips	No	165 (88.7)	21 (11.3)	0.041	0.132	2.3 (1.0–5.1)
	Yes	38 (77.6)	11 (22.4)			
Exfoliative cheilitis	No	184 (88.5)	24 (11.5)	0.017	0.168	3.2 (1.3–8.2)
	Yes	19 (70.4)	8 (29.6)			
Changes in the tongue	No	193 (87.7)	27 (12.3)	0.038	0.150	3.6 (1.1–11.2)
	Yes	10 (66.7)	5 (33.3)			
Exfoliative glossitis	No	199 (87.3)	29 (12.7)	0.022	0.149	5.1 (1.1–24.2)
	Yes	4 (57.1)	3 (42.9)			

*Fisher's exact test; OR – odds ratio

In the univariate analyses, allergic sensitisation to titanium was related to contact hypersensitivity to metals and piercing. Participants with a history of contact hypersensitivity to metals had 7.8 × higher odds (95% CI: 1.4–43.6; p = 0.005, V = 0.178), while those with piercing had 5.9 × higher odds for titanium allergic sensitisation (95% CI: 1.5–22.3; p = 0.018, V = 0.188). When these predictors were included in the logistic regression model, both contact hypersensitivity to metals (OR = 9.2; 95% CI: 1.5–57.1; p = 0.017) and piercing (OR = 6.5; 95% CI: 1.6–25.9; p = 0.009) remained significant; furthermore, their significance increased.

In the univariate analyses, allergic sensitisation to nickel was related to age, changes in the lips, exfoliative cheilitis, changes in the tongue, and exfoliative glossitis (Table 4). From the medical history, allergic sensitisation to nickel was related to contact hypersensitivity in general, contact hypersensitivity to metals, cosmetics, imitation jewellery, and piercings (Table 5).

A history of contact hypersensitivity and contact hypersensitivity to metals had moderate effect size, while all other factors

Table 5. Association of allergological history data with nickel sensitisation (N = 235)

Variable	Category	Sensitisation		p-value*	Effect size	OR (95% CI)
		No n (%)	Yes n (%)			
Contact hypersensitivity	No	171 (92.9)	13 (7.1)	< 0.001	0.363	7.8 (3.5–17.4)
	Yes	32 (62.7)	19 (37.3)			
Contact hypersensitivity to metals	No	200 (88.5)	26 (11.5)	< 0.001	0.309	15.4 (3.6–65.3)
	Yes	3 (33.3)	6 (66.7)			
Contact hypersensitivity to imitation jewellery	No	175 (90.7)	18 (9.3)	< 0.001	0.268	4.9 (2.2–10.9)
	Yes	28 (66.7)	14 (33.3)			
Piercing	No	184 (88.5)	24 (11.5)	0.017	0.168	4.9 (1.3–8.2)
	Yes	19 (70.4)	8 (29.6)			

*Fisher's exact test; OR – odds ratio

had small effect size. History of contact reaction with metals was related to higher odd, age and changes on the lips were related to mild odds while all other factors were related to moderate odds.

When all predictors were included in the logistic regression model, only age and piercing remained significant predictors of allergic sensitisation to nickel. Age remained equally significant (OR = 2.8; 95% CI: 1.2–6.5; p = 0.014), while the significance of piercing mildly increased (OR = 3.5; 95% CI: 1.2–9.8; p = 0.019).

DISCUSSION

This study suggests that several clinical signs and allergological history data could be associated with allergic sensitisation to metals, primarily prior contact hypersensitivity reactions, previous reactions to metals, and changes in the lips. However, clinical reactions are rare and quite imperceptible, possibly due to the differential susceptibility of the oral mucosa to allergic reactions when compared to the skin. The number of antigen-presenting Langerhans cells is lower in the oral mucosa than in the skin (10). It seems that the expression of allergic contact reactions in the oral mucosa requires 5–12x antigen exposure than skin (10).

Previously, it was reported that the prevalence of allergic sensitisation to titanium and/or nickel in patients undergoing fixed orthodontic treatment was 15.5%, less frequently to titanium at 4.5% than to nickel at 13.5% (9).

The higher prevalence of metal hypersensitivity was predominantly related to the female sex in most studies (11, 12), which is concurrent with our study. More than half of nickel-sensitised patients are sensitive to at least one more metal, and the predictors of polysensitisation to metals are female sex and older age (13). The higher prevalence of nickel hypersensitivity in females is likely related to environmental exposure due to more frequent and earlier contact with jewellery, earrings, and other metal objects. Our univariate analysis of isolated allergic sensitisation to nickel did not show the female sex as a predictor of sensitisation; however, some studies reported sexual dimorphism, with women being 4.3 times more likely to be hypersensitive to nickel (14). The risk of titanium allergy is higher in patients who are sensitive to other metals (15). These results also suggest that older or adult patients are at a higher risk of allergic sensitisation to nickel and/or titanium than other younger persons. Older age is probably associated with more frequent sensitisation to metals owing to a longer period of exposure. However, new generations may be equally exposed to nickel due to trends, regardless of gender, since many boys pierce their ears or wear a wristwatch during adolescence, which may also be a variant of nickel exposure. North American studies on the prevalence of nickel allergic sensitisation in the paediatric population suggest very high results, with a prevalence of 22.4% in adolescents (16). In contrast, European studies have reported a lower prevalence rate of 11.8% in adolescents (17). The prevalence of nickel allergy is 14–18% in adults of both sexes in European Union countries (18). The low prevalence at a younger age of European adolescents is probably due to the European Union's implementation of restrictions regarding the acceptable nickel content in products contacting the skin. History of contact hypersensitivity has also been associated with allergic sensitisation to metals (11–14). The association between the history of contact hypersensitivity, history of reaction to metals, and the reaction to imitation jewellery is probably due to cross-allergies, that is a higher chance of polysensitization to various allergens in people who already have a contact allergy (13). This study identified piercing as a predictor of allergy to one or both study metals. A North American study with a large sample size found that piercing was linked to nickel hypersensitivity (19). Interestingly, a study of polysensitization to metal allergens did not find an association between metal allergies and jewellery in general (13).

Reactions to imitation jewellery are also predictors of sensitisation to at least one of these metals. An earlier meta-analysis found that orthodontic treatment was not related to the frequency of nickel sensitisation unless patients had previously been exposed to jewelleries (20). If orthodontic treatment is completed before exposure to earrings and imitation jewellery, it is considered to have a protective effect, i.e., it reduces the risk of developing a nickel allergy (21, 22).

Metals are allergens frequently associated with lip changes. This study also found that changes in the lips were predictors of nickel and/or titanium sensitisation, with exfoliative cheilitis being the most significant lip change associated with allergic sensitisation. Exfoliative cheilitis was previously reported as a characteristic contact allergy, although these studies generally evaluated only allergic reactions to nickel in patients with orthodontic appliances (23, 24).

Although univariate analyses indicated that age, lip changes, exfoliative cheilitis, tongue changes, and exfoliative glossitis were related to allergic nickel sensitisation, multiple logistic regression revealed that medical history was a more powerful predictor. Previous studies have reported that lip changes and exfoliative cheilitis are associated with nickel allergy in orthodontic patients (23, 24). Interestingly, this study did not find any of the clinical signs as statistically significant predictors of nickel allergic sensitisation. This may be because it was only a sensitisation, i.e., several sensitised patients have a positive epicutaneous test, but they do not develop an allergic reaction. For nickel sensitization, only adult age is a statistically significant predictor, while from allergological anamnestic data, only piercing, which coincides with the previous study reporting piercing as a predictor of nickel sensitization (19). The onset of allergic reactions in patients undergoing orthodontic treatment seems much less frequent than the frequency of allergies in the population, with a prevalence of 0.1–0.2% (25). A much higher dose of nickel is required to elicit reactions in the oral mucosa than that required for the skin (26). Recent epidemiological studies indicate that a reduction in the risk of developing nickel hypersensitivity is associated with the estimated release of nickel from the orthodontic appliance and the duration of orthodontic treatment provided that orthodontic treatment precedes the wearing of earrings. Sex, age at the time of ear piercing, and the number of earrings are important risk predictors for the development of nickel hypersensitivity (21). The most important risk factors for nickel allergy are the number of earrings and the duration of exposure to imitation jewellery. Orthodontic treatment before wearing earrings reduces the risk of nickel allergies (22, 27).

In univariate analyses, titanium allergy was associated with metal hypersensitivity and piercing. In the logistic regression model, the contact reaction to metals and piercing remained significant and consistently significant. Some previous research suggests that hypersensitivity to titanium has not been associated with jewellery, although in this study, piercing was found to be a significant predictor of titanium sensitisation. Piercing was a significant predictor of allergy to both metals, probably because some piercing materials contain some form of titanium or titanium oxide that prevents corrosion, while others do not. The same study reported cheilitis as one of the common signs of a clinical manifestation of an allergic reaction to titanium (28). Titanium allergic sensitisation does not appear to be related to age or female sex, probably because of early exposure to titanium through sunscreens, cosmetics, paints, and food.

Increased acidity of saliva, the use of fluoride, and harder brushes in the maintenance of oral hygiene as well as an individual's dietary habits may contribute to the increased release of nickel into the oral cavity (25, 29). However, clinically, determining the exact amount of released ions is not entirely possible because many distinct factors contribute to the same process at different magnitudes (oral temperature, saliva composition, saliva acidity, eating habits, oral hygiene products, wire structure, and bacteria). An analysis of different juices showed that carbonated drinks like Coca-Cola had the greatest effect on increasing nickel release. Interestingly, orange juice, which has a low pH, does not increase the release of nickel from orthodontic appliances (30). In addition, research has shown that vegetarians are exposed to higher daily average doses of nickel intake in food. Some foods, such as cocoa and its products, nuts, soy, oats, and seed oil also contain a high proportion of nickel. However, it is believed that eating habits do not significantly affect the development of nickel allergy (22, 27).

A limitation of this study is the difficulty in capturing the onset of allergic reactions. It is possible that at the time of the check-up, some of the participants did not exhibit clinical manifestations. However, we managed to thoroughly cover the medical and allergological history of the participants. Our results can be generalised to the population of orthodontic patients treated with fixed appliances because the same alloys are used everywhere. In addition, this is one of the rare studies investigating titanium allergies in orthodontic patients. Future studies should concentrate on the immunohistochemical analyses of gingival tissue, especially the investigation of T helper-17 cells, and research on gingival crevicular fluid.

CONCLUSION

A positive patch test alone cannot lead to a definite conclusion regarding oral contact allergy. The onset of hypersensitivity reactions in patients undergoing orthodontic treatment is rare and imperceptible. However, previous contact hypersensitivity, previous reactions to metals, exfoliative cheilitis, and piercing could indicate metal allergy in orthodontic patients.

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Conflict of Interests

None declared

Adherence to Ethical Standards

The study was performed according to the Declaration of Helsinki 1964 and its later amendments. All participants signed a written informed consent and the institutional Ethics Committee approved the study (No. 003-05/15-1119 and 003-08/15-01/24).

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