Smell and taste in titanium and nickel allergic sensitization in orthodontic patients

Žigante, Martina; Peternel, Sandra; Muhvić Urek, Miranda; Rinčić Mlinaric, Marijana; Pop Acev, Darko; Špalj, Stjepan

Received: 24 February 2020 | Revised: 4 April 2020 | Accepted: 10 April 2020

DOI: 10.1111/ocr.12379

SHORT COMMUNICATION

Orthodontics & Craniofacial Research | WILEY

Smell and taste in titanium and nickel allergic sensitization in orthodontic patients

Martina Zigante[1] | Sandra Peternel[2] | Miranda Muhvic Urek[3] | Marijana Rincic Mlinaric[4] | Darko Pop Acev[5] | Stjepan Spalj[1]

[1]Department of Orthodontics, Faculty of Dental Medicine, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

[2]Department of Dermatovenereology, Faculty of Medicine, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

[3]Department of Oral Medicine and Periodontology, Faculty of Dental Medicine, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

[4]Orthodontic Office Rincic Mlinaric, Zadar, Croatia

[5]Dental Office Pop-Acevi, Skopje, North Macedonia

Correspondence
Martina Zigante, Department of Orthodontics, University of Rijeka, Faculty of Dental Medicine, address: Kresimirova 40, 51000 Rijeka, Croatia.
Email: martina.zigante@uniri.hr

Funding information
Hrvatska Zaklada za Znanost, Grant/Award Number: DOK-09-2018 and IMUNODENT IP-7500-09-2014

Abstract

Objective: To assess the prevalence of allergic sensitization to titanium and nickel in orthodontic patients and to evaluate alterations of smell and taste.

Subjects and Methods: A total of 250 subjects were invited to participate, 245 accepted. The age range was 11-45 years, 68% were females and 52% adolescents. An epicutaneous patch test was performed. Of the positive subjects in the patch test, 26 participated in the taste and smell testing and were matched by age and sex with 26 negative subjects.

Results: The prevalence of hypersensitivity to titanium and/or nickel in orthodontic patients was 15.5%. Taste and smell were more impaired in sensitized subjects ($P \leq .025$), taste was more affected than smell and the tastes most affected were sour and bitter tastes, while the sweet taste was least impaired.

Conclusion: The allergic sensitization to titanium is more uncommon than to nickel, with altered smell and taste related to those hypersensitivities.

KEYWORDS

nickel, orthodontics, smell, taste, titanium

1 | INTRODUCTION

Dental treatment introduces titanium- and nickel-containing biomaterials (implants, crowns, bridges and orthodontic appliances) which can induce a late hypersensitivity reaction.[1]

A nickel allergy occurs more frequently than allergies to other metals altogether.[2] Due to its high biocompatibility, titanium was previously considered to have no allergic potential; however, titanium can erode when it co-exists with other metals or is exposed to fluoride ions in the acidic environment, such as in the oral cavity.[3,4]

The aims of this study were to assess the prevalence of the allergic sensitization to titanium and nickel in patients undergoing orthodontic treatment with fixed appliances containing titanium and nickel and to evaluate whether subjects experiencing hypersensitivity have an altered sense of smell and taste.

2 | MATERIALS AND METHODS

A total of 250 subjects undergoing orthodontic treatment in three orthodontic offices in Croatia were invited to participate and 245 accepted. Assuming a prevalence of hypersensitivity of 15%-20% (95% confidence intervals 10%-25%) and precision of 5%, the estimated sample size was calculated to be 196-246. The inclusion criterion

was treatment with a fixed orthodontic appliance, while exclusion criteria were subjects affected by diabetes, endocrine and autoimmune diseases, and subjects practising water sports. All three orthodontic offices used the same kind of orthodontic brackets (Ortho Classic) and nickel-titanium wires (GAC International). The age range was 11-45 years (median 18, interquartile range 16-22), 68% were females and 52% adolescents.

The allergy testing included an epicutaneous patch test to nickel sulphate, titanium, titanium dioxide, titanium oxalate, titanium nitride and petrolatum as a control (Chemotechnique Diagnostics). Testing was performed on average 4 months after bonding the fixed appliance. The upper arm skin was cleaned by medical petrol, and the patch test was applied for two days. For confirmation of any allergic reaction, skin reactions were evaluated and documented on the second, fourth and seventh day after applying patch tests. If the skin reactions together with itching were exacerbated during the period of evaluation, this was considered as an allergic reaction, otherwise, reactions which lessened over time were regarded as irritations.

Of the preliminary 38 patch test positive subjects, 26 subjects (68.4%) were non-smokers and consented to participating in further testing of taste and smell. They were matched by age and sex with 26 patch test negative subjects, also non-smokers. Therefore, the sample included 52 subjects (75% female, 39% adolescents) within the age range of 15-46 years (median 20, interquartile range 18-24). Testing of the sense of taste was performed using the Taste Strips (Burghart Messtechnik, Wedel, Germany). Testing was performed on average 6 months after bonding of the fixed appliance. Subjects did not eat or chew chewing gum one hour before testing. The testing consisted of 18 flavoured strips (16 with taste and two tasteless controls). Before each new flavour strip, the subjects rinsed their mouth with water. The taste strips were applied to the middle of the anterior third of the tongue. Subjects chose between sweet, salty, sour, bitter and tasteless strips. The result of the test was the sum of the correct answers; each correct answer was awarded one point, while the tasteless strips were not graded.

The Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany) was used for examination of odour disorders. The test consisted of 12 containers with individual odours and associated answer cards representing four possible answers for each container, and the subjects had to choose the card they believed was correct. The subjects did not consume food or drink for a period of 15 minutes before testing. The result of the test was the sum of the correct answers.

The prevalence of allergic sensitization was estimated with 95% confidence intervals (CI). To compare differences in the sense of taste and smell between sensitized and non-sensitized subjects, the Mann-Whitney test was used. The effect size was calculated by the formula $r = Z/\sqrt{N}$. For interpretation, the following criteria were used as follows: 0.1-0.3 = small effect size, 0.3-0.5 = medium, 0.5-0.7 = large and >0.7 very large.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The local Ethics Committee also approved the study (No. 003-05/15-1119 and 003-08/15-01/24), and informed consent was obtained from all individual participants included in the study.

3 | RESULTS

The prevalence of allergic sensitization to titanium and/or nickel in patients undergoing orthodontic treatment was 15.5% (95% CI 11.5%-20.6%). The prevalence of allergic sensitization to nickel was 13.5% (95% CI 9.8%-18.3%) and to titanium compounds was 4.5% (95% CI 2.5%-7.9%). The frequency of hypersensitivity to particular compounds is listed in Table 1.

The sense of taste and smell was more impaired in subjects experiencing hypersensitivity to titanium and/or nickel, sense of taste was more affected than sense of smell, and the most affected tastes were sour and bitter tastes, while the sweet taste was least impaired (Table 2).

In order to control the homogeneity of the sensitized group, sub-analyses of subjects tested for taste and smell were carried out. The subgroup of subjects sensitized only to nickel without titanium

TABLE 1 Results of patch test in preliminary study assessing prevalence of hypersensitivity to titanium and nickel

Allergic sensitization	N	%	95% CI
nickel and/or titanium	38	15.5	11.5%-20.6%
nickel	33	13.5	9.8%-18.3%
only nickel without titanium compounds	27	11	7.7%-15.6%
titanium compounds	11	4.5	2.5%-7.9%
pure titanium	1	0.4	0.1%-2.3%
titanium dioxide	2	0.8	0.2%-2.9%
titanium nitride	3	1.2	0.4%-3.5%
titanium oxalate	7	2.7	1.4%-5.8%
only titanium compounds without nickel	5	2	0.9%-4.7%
both nickel and titanium	6	2.5	1.1%-5.2%

compounds comprised 18 persons. They were matched in terms of age and sex with same number of subjects from the control group. Of the total of N = 36 (69% females and 53% adolescents), the age range was 15-46 years (median 20, interquartile range 18-23.75). The senses of taste and smell were more impaired in subjects experiencing hypersensitivity to nickel while the sense of bitterness was most impaired, followed by sourness (Table 3).

The subgroup with sensitization to titanium had eight subjects and half of them were sensitized to both titanium and nickel. When matched with eight subjects from the control group by age and sex, the age range was 15-23 (median 19, interquartile range 16.5-21.75), 87.5% were females and 56% were adolescents. There was evidence of impairment in both cases, with regard to the sense of taste and smell in subjects sensitized to titanium; however, of the total score of taste, only the sweet and bitter tastes indicated statistical significance, the salty taste being mostly impaired (Table 3).

Lastly, the subgroup of subjects with hypersensitivity to titanium compounds only, without nickel (N = 4), was matched by age and sex with the control group and analysed. The age range of those eight subjects was 15-23 (median 19, interquartile range 15.5-21.75), all of them were females and 50% were adolescents. Taste was significantly impaired in subjects sensitized only to titanium, primarily salty tastes, followed by sour tastes (Table 3).

4 | DISCUSSION

Allergic sensitizations to titanium and nickel in patients undergoing orthodontic treatment are not very frequent; titanium hypersensitivity is more uncommon than that of nickel, and alterations of the senses of taste and smell accompany them.

A recent meta-analysis reports an average prevalence of nickel hypersensitivity of 19% in orthodontic patients,[5] while our study found a somewhat lower prevalence. On the other hand, a low incidence of allergic reactions during orthodontic treatment is reported, ranging between 0.03% and 0.3%.[6,7] This implies that the majority of subjects were sensitized to nickel before starting orthodontic treatment. Nickel allergy is frequently associated with reactivity to other metals, as a result of cross-reactivity or multiple sensitizations.[8] Present research demonstrated that 18% of subjects experiencing nickel hypersensitivity also had titanium hypersensitivity, while 55% of those sensitized to titanium were sensitized to nickel at the same time. Titanium hypersensitivity prevalence ranges from 0.6% up to 4%, and our estimate is similar.[9,10]

Previous data also suggest that gustatory impairment and other sensatory dysfunctions may be the symptoms of oral contact allergy.[11] Sense of taste was more impaired than sense of smell in subjects sensitized to nickel and titanium in this research, probably due to the anatomical seating of the receptors. Since taste buds are located mostly on the tongue, the pathological mechanism of oral contact allergy could affect them directly, leading to destruction.[12] Certain areas on the tongue are more sensitive than others to specific tastes[13,14] which may explain why the sour and bitter tastes seem to be the most frequently affected, while the sweet taste was the least affected. Sub-analyses indicate that nickel could be more responsible for reducing the bitter taste, titanium for reducing the salty taste, while both nickel and titanium are equally responsible for the deterioration of a sour taste. Titanium also affects the sense of smell less than nickel. However, because of the small titanium

TABLE 2 Comparison of sense of taste and smell between sensitized to nickel and/or titanium and non-sensitized subjects

	Mean ± SD	Median (IQR)	95% CI	min-max	*P*	*r*
Sweet score (range 0 (low)-4 (high))						
Sensitized	3.2 ± 0.8	3 (2-4)	2.9-3.5	2-4		
Non-sensitized	3.5 ± 0.6	3.5 (3-4)	3.2-3.7	2-4	.202	−0.177
Sour score (range 0 (low)-4 (high))						
Sensitized	2.0 ± 0.9	2 (1-2)	1.6-2.3	1-4		
Non-sensitized	2.9 ± 1.0	3 (2-4)	2.5-3.3	0-4	.001	−0.480
Salty score (range 0 (low)-4 (high))						
Sensitized	2.8 ± 1.1	3 (2-4)	2.3-3.2	0-4		
Non-sensitized	3.5 ± 0.7	4 (3-4)	3.3-3.8	1-4	.006	−0.378
Bitter score (range 0 (low)-4 (high))						
Sensitized	2.5 ± 1.1	2.5 (2-3.25)	2.1-3.0	1-4		
Non-sensitized	3.5 ± 0.6	4 (3-4)	3.2-3.8	2-4	.001	−0.465
Taste score (range 0 (low)-16 (high))						
Sensitized	10.4 ± 2.4	11 (8.75-12.25)	9.5-11.4	6-14		
Non-sensitized	13.5 ± 1.7	14 (13-14)	12.8-14.1	7-16	<.001	−0.655
Smell score (range 0 (low)-12 (high))						
Sensitized	9.7 ± 1.4	10 (9-11)	9.1-10.2	7-12		
Non-sensitized	10.4 ± 0.8	10 (10-11)	10.1-10.7	9-12	.025	−0.310

TABLE 3 Comparison of sense of taste and smell between subgroups

	Mean ± SD	Median (IQR)	95% CI	min-max	*P*	*r*
Sweet score (range 0 (low)-4 (high))						
Sensitized only to Ni	2.9 ± 0.8	3 (2-4)	2.6-3.3	2-4		
Non-sensitized	3.5 ± 0.5	3.5 (3-4)	3.2-3.8	3-4	.031	−0.361
Sour score (range 0 (low)-4 (high))						
Sensitized only to Ni	2.0 ± 0.8	2 (1-2.25)	1.6-2.4	1-4		
Non-sensitized	2.7 ± 1.0	3 (2-3.25)	2.2-3.2	0-4	.024	−0.377
Salty score (range 0 (low)-4 (high))						
Sensitized only to Ni	2.9 ± 1.2	3 (2-4)	2.3-3.5	0-4		
Non-sensitized	3.4 ± 0.8	4 (3-4)	3.1-3.8	1-4	.159	−0.235
Bitter score (range 0 (low)-4 (high))						
Sensitized only to Ni	2.4 ± 1.1	2 (1.75-3.25)	1.9-2.9	1-4		
Non-sensitized	3.6 ± 0.6	4 (3-4)	3.3-3.9	2-4	.001	−0.536
Taste score (range 0 (low)-16 (high))						
Sensitized only to Ni	10.2 ± 2.7	11 (8-13)	8.9-11.6	6-14		
Non-sensitized	13.3 ± 1.9	14 (12.75-14)	12.3-14.2	7-16	<.001	−0.607
Smell score (range 0 (low)-12 (high))						
Sensitized only to Ni	9.7 ± 1.4	9.5 (9-11)	9-10.4	7-12		
Non-sensitized	10.6 ± 0.7	10.5 (10-11)	10.3-11	10-12	.034	−0.353
Sweet score (range 0 (low)-4 (high))						
Sensitized to Ti	3.6 ± 0.7	4 (3.25-4)	3-4.3	2-4		
Non-sensitized	4.0 ± 0.0	4	4	4	.144	−0.365
Sour score (range 0 (low)-4 (high))						
Sensitized to Ti	1.9 ± 1.0	2 (1-2)	1-2.7	1-4		
Non-sensitized	2.6 ± 0.7	2.5 (2-3)	2-3.3	2-4	.062	−0.466
Salty score (range 0 (low)-4 (high))						
Sensitized to Ti	2.5 ± 0.9	2.5(2-3)	2.3-3.5	0-4		
Non-sensitized	4.0 ± 0.0	4	4	4	.001	−0.816
Bitter score (range 0 (low)-4 (high))						
Sensitized to Ti	2.9 ± 1.0	3 (2.25-3.75)	2-3.7	1-4		
Non-sensitized	3.8 ± 0.5	4 (3.25-4)	3.4-4.1	3-4	.037	−0.520
Taste score (range 0 (low)-16 (high))						
Sensitized to Ti	10.9 ± 1.9	11 (9.5-11.75)	9.4-12.4	8-14		
Non-sensitized	14.4 ± 0.9	14 (14-15)	13.6-15.1	13-16	.002	−0.779
Smell score (range 0 (low)-12 (high))						
Sensitized to Ti	9.5 ± 1.3	10 (8.5-10)	8.4-10.6	7-11		
Non-sensitized	10.1 ± 0.6	10 (10-10.75)	9.6-10.7	7-11	.364	−0.227
Sweet score (range 0 (low)-4 (high))						
Sensitized only to Ti	3.5 ± 1.0	4 (2.5-4)	1.9-5.1	2-4		
Non-sensitized	4.0 ± 0.0	4	4	4	.317	−0.354
Sour score (range 0 (low)-4 (high))						
Sensitized only to Ti	1.5 ± 0.6	1.5(1-2)	0.6-2.4	1-2		
Non-sensitized	3.0 ± 0.8	3 (2.25-3.75)	1.7-4.3	2-4	.036	−0.741
Salty score (range 0 (low)-4 (high))						
Sensitized only to Ti	2.3 ± 0.5	2 (2-2.75)	1.5-3.1	2-3		

(Continues)

TABLE 3 (Continued)

	Mean ± SD	Median (IQR)	95% CI	min-max	*P*	*r*
Non-sensitized	4.0 ± 0.0	4	4	4	.011	−0.894
Bitter score (range 0 (low)-4 (high))						
Sensitized only to Ti	2.5 ± 1.0	3 (1.5-3)	0.9-4.1	1-3		
Non-sensitized	3.8 ± 0.5	4 (3.25-4)	3-4.6	3-4	.040	−0.727
Taste score (range 0 (low)-16 (high))						
Sensitized only Ti	9.8 ± 1.5	10 (8.25-11)	7.4-12.1	8-11		
Non-sensitized	14.8 ± 1.0	14.5 (14-15.75)	13.2-16.3	14-16	.019	−0.826
Smell score (range 0 (low)-12 (high))						
Sensitized only to Ti	9.5 ± 1.0	10 (8.5-10)	7.9-11.1	8-10		
Non-sensitized	10.3 ± 0.5	10(10-10.75)	9.5-11.1	10-11	.186	−0.468

hypersensitivity sample, the allergic sensitization to the metals may in fact be manifested by the same disruption of smell and taste, regardless of the type of metal. Even though the majority of orthodontic patients show no clinical signs of allergy to nickel and titanium, perhaps an impaired sense of taste may be worthy of note.

Smell receptors are located away from the oral cavity and, therefore, are not directly affected by an oral contact allergy. Given the multisensory nature of flavour perception,[15] it is possible that the common pathological mechanism underlies both smell and taste disorders. Since the gustatory and olfactory systems are considered phylogenetically among the oldest in the encephalon, they react together in processing chemical substances in the oral and nasal cavities. Therefore, smell and taste impairments occur simultaneously when a chemical substance is present in the oral and nasal cavities.[16] Some studies consider atopic diseases and allergic contact dermatitis to be closely related[17,18] due to environmental or hereditary predispositions, or because of the intersection of pathophysiological mechanisms underlying type I and type IV hypersensitivity.[19] Therefore, people with an atopic disease are more prone to contact allergies. Their allergic rhinitis and chronic nasal congestion can also cause smell and taste disorders.[16] Some nickel allergies can also be directly associated with rhinitis and nasal obstruction, inducing or contributing to an alteration in smell.[20]

5 | CONCLUSION

Allergic sensitization to titanium is more uncommon than sensitization to nickel with an altered sense of smell and taste related to those sensitizations. These findings could shed some light on a potential clinical manifestation of titanium and nickel hypersensitivity in orthodontics, since the majority of patients show no clear clinical signs of allergy to nickel and titanium.

ACKNOWLEDGEMENTS

This study was supported by the Croatian Science Foundation under the Grants HRZZ IMUNODENT IP-7500-09-2014 and DOK-09-2018.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

ORCID

Martina Zigante https://orcid.org/0000-0002-8357-4047
Sandra Peternel https://orcid.org/0000-0001-8590-0451
Stjepan Spalj https://orcid.org/0000-0003-4836-3903

REFERENCES

1. Syed M, Chopra R, Sachdev V. Allergic reactions to dental materials – a systematic review. *J Clin Diagn Res*. 2015;9:4-9.
2. Hostynek JJ, Maibach HI (eds). *Nickel and the Skin: Absorption, Immunology, Epidemiology, and Metallurgy*. Bosa Raton, FL: CRC Press; 2002.
3. Koike M, Fujii H. In vitro assessment of corrosive properties of titanium as a biomaterial. *J Oral Rehabil*. 2001;28:540-548.
4. Fragou S, Eliades T. Effect of topical fluoride application on titanium alloys: a review of effects and clinical implications. *Pediatr Dent*. 2010;32:99-105.
5. Gölz L, Papageorgiou SN, Jäger A. Nickel hypersensitivity and orthodontic treatment: a systematic review and meta-analysis. *Contact Dermatitis*. 2015;73:1-14.
6. Schuster G, Reichle R, Bauer RR, Schopf PM. Allergies induced by orthodontic alloys: incidence and impact on treatment. Results of a survey in private orthodontic offices in the Federal State of Hesse, Germany. *J Orofac Orthop*. 2004;65:48-59.
7. Volkman KK, Inda MJ, Reichl PG, Zacharisen MC. Adverse reactions to orthodontic appliances in nickel-allergic patients. *Allergy Asthma Proc*. 2007;28:480-484.
8. Torres F, das Graças M, Melo M, Tosti A. Management of contact dermatitis due to nickel allergy: an update. *Clin Cosmet Investig Dermatol*. 2009;2:39-48.
9. Sicilia A, Cuesta S, Coma G, et al. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res*. 2008;19:823-835.
10. Lhotka CG, Szekeres T, Fritzer-Szekeres M, et al. Are allergic reactions to skin clips associated with delayed wound healing? *Am J Surg*. 1998;176:320-323.
11. Raap U, Stiesch M, Kapp A. Clinical symptoms and diagnostic workup of allergic reactions on the oral mucosa. *Hautarzt*. 2012;63:687-692.
12. Bromley SM. Smell and taste disorders: a primary care approach. *Am Fam Physician*. 2000;61:427-436.

13. Boring E. *Sensation and perception in the history of experimental psychology*. New York, NY: Academic Press; 1942.
14. Bartoshuk LM. The biological basis of food perception and acceptance. *Food Quality Prefer*. 1993;4:21-32.
15. Spence C. Multisensory flavor perception. *Cell*. 2015;161:24-35.
16. Neto FXP, Targino MN, Peixoto VS, et al. Sensorial abnormalities: smell and taste. *Int Arch Otorhinolaryngol*. 2011;15:350-358.
17. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on atopic diseases and dermatitis. *Br J Dermatol*. 2001;144:523-532.
18. Netterlid E, Hindsén M, Ekqvist S, Henricson KA, Bruze M. Young individuals with atopic disease and asthma or rhinoconjunctivitis may have clinically relevant contact allergies. *Dermatitis*. 2014;25:115-119.
19. Kolberg L, Forster F, Gerlich J, et al. Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study. *ERJ Open Res*. 2020;6:00178-2019.
20. Brera S, Nicolini A. Respiratory manifestations due to nickel. *Acta Otorhinolaryngol Ital*. 2005;25:113-115.

How to cite this article: Zigante M, Peternel S, Muhvic Urek M, Rincic Mlinaric M, Pop Acev D, Spalj S. Smell and taste in titanium and nickel allergic sensitization in orthodontic patients. *Orthod Craniofac Res*. 2020;23:517–522. https://doi.org/10.1111/ocr.12379