

Nickel allergy in relation to piercing and orthodontic appliances – a population study

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Summary

Background. Studies have shown conflicting results on the association between nickel exposure from orthodontic appliances and nickel sensitization.

Objectives & Method. In a cross-sectional study, we investigated the association between nickel sensitization and exposure to orthodontic appliances and piercings. 4376 adolescents were patch tested following a questionnaire asking for earlier piercing and orthodontic treatment. Exposure to orthodontic appliances was verified in dental records.

Results. Questionnaire data demonstrated a reduced risk of nickel sensitization when orthodontic treatment preceded piercing (OR 0.46; CI 0.27–0.78). Data from dental records demonstrated similar results (OR 0.61, CI 0.36–1.02), but statistical significance was lost when adjusting for background factors. Exposure to full, fixed appliances with NiTi-containing alloys (OR 0.31, CI 0.10–0.98) as well as a pooled 'high nickel-releasing' appliance group (OR 0.56, CI 0.32–0.97) prior to piercing was associated with a significantly reduced risk of nickel sensitization.

Conclusion. High nickel-containing orthodontic appliances preceding piercing reduces the risk of nickel sensitization by a factor 1.5–2. The risk reduction is associated with estimated nickel release of the appliance and length of treatment. Sex, age at piercing and number of piercings are also important risk indicators. Research on the role of dental materials in the development of immunological tolerance is needed.

Key words: cross-sectional; dental braces; patch test; questionnaire; tolerance.

Nickel is the most common contact allergen in Europe and the United States (1, 2). Many children and adolescents are exposed to nickel intra-orally from orthodontic appliances (dental braces) with alloys containing up to 50% nickel (3). There is public concern about the release of nickel and sensitization from such appliances. In an

earlier study, we found orthodontic appliances in 45% of adolescents (4).

The level of *in vitro* release of nickel from orthodontic appliances has been reported to be 22–40 µg of nickel per day, which is low in comparison with the estimated dietary intake of 100–800 µg per day (5–9). The release of nickel varies with the composition and manufacture of the appliance components, and between archwire alloys and mechanical straining, but not with actual nickel content (6–8).

The results from studies *in vivo* on nickel content in saliva and other body fluids as a result of insertion of orthodontic components are inconsistent (10–13). No differences have been demonstrated between individuals with or without orthodontic appliances, or between saliva

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collected before and after appliance insertion (14–17). We have recently found significantly higher nickel contents in dental plaque in patients with orthodontic appliances than in non-orthodontic patients (17).

The diverse findings regarding nickel release between *in vitro* and *in vivo* studies are probably attributable to the lack of comparable micro-environmental conditions in relation to pH, temperature, stress simulation, presence of microbes, and properties of the saliva. The methodological reliability and the clinical relevance of the *in vitro* models used have been questioned, as they differ from the conditions in the oral cavity (3).

Clinical studies indicate an insignificant risk of sensitization to nickel from orthodontic appliances or elicitation of reactions in sensitized persons (18–27). Rather, a reduced risk of nickel allergy, owing to oral tolerance, has been suggested in some clinical and experimental studies (23, 28–31).

Piercing, in particular, seems to trigger nickel sensitization (32). Intra-oral release of nickel from orthodontic appliances may act synergistically or antagonistically in the development of nickel allergy (23).

The purpose of this study was to investigate the association between nickel allergy, exposure to intra-oral orthodontic appliances, and piercings. We aimed to secure high quality exposure data on orthodontic appliance treatment by analysing dental records and obtaining valid health data from test-verified cases of nickel allergy.

Hypothesis

We hypothesize that oral exposure to nickel in orthodontic appliances prior to a piercing event may have a protective effect against nickel sensitization. Age at piercing, atopy and sex were considered to be potential confounding factors.

Subjects and Methods

Study design

The study was a cross-sectional survey on nickel allergy in upper secondary schools in the cities of Umeå and Örebro, Sweden. The study period extended from September 2000 to May 2004. Nickel allergy was verified by a positive patch test reaction. Exposure to piercing was reported by questionnaire [age at piercing, and number and localization of piercing(s)]. Exposure to intra-oral orthodontic appliances was recorded with a questionnaire (age at start of orthodontic appliance treatment) and verified from dental records. For all participants who reported having received orthodontic treatment, dental records were examined.

Sampling and calculation of sample size

Of 7543 adolescents (4409 girls and 3134 boys) in the visited school classes, 6095 (81%) answered a questionnaire following a briefing session. The median age of respondents was 17.1 years (range 14.0–23.4 years). Among pupils present at the briefing sessions (6364), nearly 96% answered the questionnaire, and 70% (4439) of those consented to patch testing. Sixty-three patch tests fell off and could not be evaluated. Of the 4376 adolescents who answered the questionnaire and performed the patch test, 2976 (68%) were girls and 1400 (32%) boys (Fig. 1). The population and study design, as well as the statistical management of dropout/non-participation, have been described previously (33).

The sample size was chosen to achieve a sufficient number of adolescents for a case–referent analysis on exposure to nickel and nickel allergy by investigating orthodontic appliance treatment preceding (non-exposed/reference exposure) and following (exposed/risk exposure) piercing. Thirty per cent of the adolescents were estimated to have received orthodontic appliance treatment, 90% of the schoolgirls were estimated to have pierced their ears at 15 years of age, and the prevalence of nickel allergy was estimated to be 12–15%. The power was set to 80%, the significance level to 0.05, the smallest detectable odds ratio (OR) to 2.0, and the case–referent ratio to 1:4. A minimum of 184 'cases' (with nickel allergy and exposed to both orthodontic appliances and piercing in varying order) were needed. On the basis of these assumptions, it was determined that the analysis would require 3700 girls, and the total sample size would need to be 7400 male and female students. After testing 4376 pupils, we had retrieved 197 'cases', and the data collection was stopped (Fig. 1).

Questionnaire

A questionnaire was administered during visits to classes, at which point the patch test was also offered. The pupils were asked whether they had received orthodontic appliance treatment, and, when there were affirmative answers, their age when the appliance was placed and a description of their first appliance were recorded. In addition, the questionnaire included questions on age at (ear) piercing, number of piercings, eczema caused by metal contact, tattooing, diet, smoking habits, atopy, and hand eczema (33).

Patch test method

We used ready-to-use TRUE Test® panels 1 and 2 (Mekos Laboratories A/S, Hillerød, Denmark) containing 24 of the

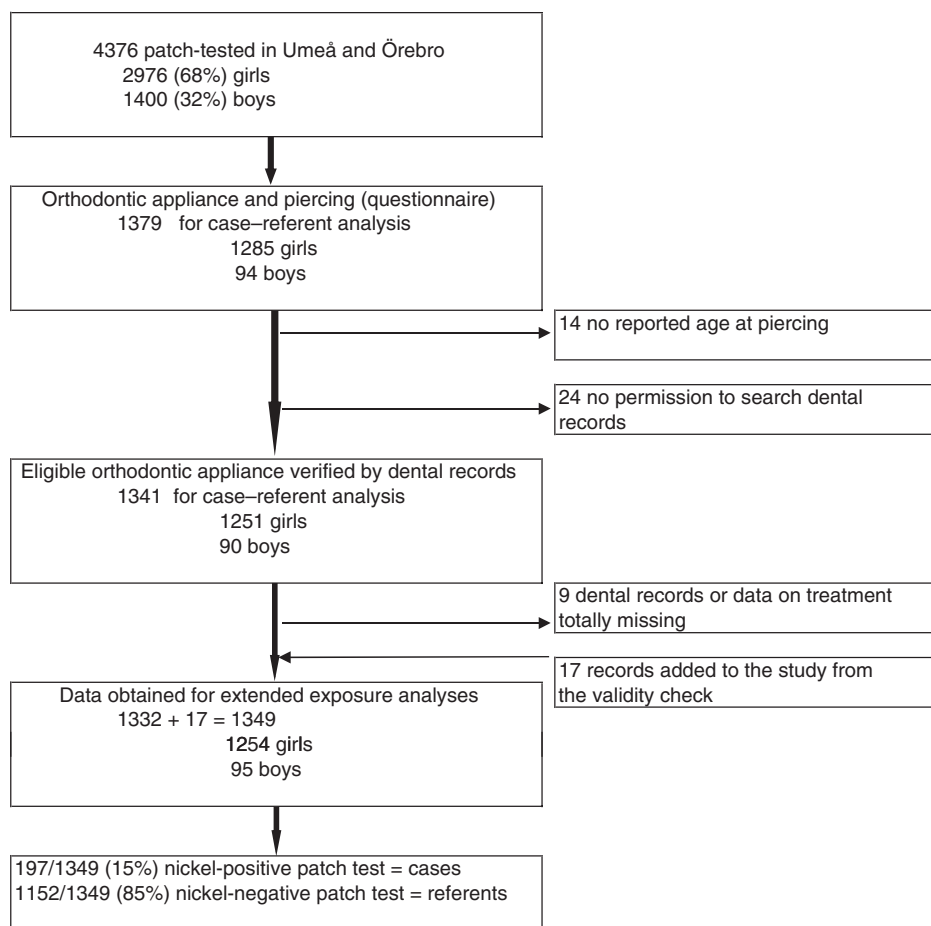


Fig. 1. Retrieval of cases and referents for statistical analyses in the cross-sectional study.

most common allergens. No patch tests were performed during the summer months (June–August) (33). Nickel allergy was defined as a positive test (+, ++, or ++++) at day 4 and read according to international guidelines (34).

Verification of intra-oral exposure to orthodontic appliances from dental records

Of 4376 (2976 girls and 1400 boys; Fig. 1) successfully patch-tested students, 4161 (95.1%) [2871 (96.5%) girls and 1290 (92.1%) boys] gave permission for data to be collected on exposure to orthodontic treatment from their dental records. Among the 1379 students with reported exposure to both orthodontic treatment and piercing, we traced all dental records from general and specialist dental clinics for 1341 (97.5%) individuals. Data were obtained from 1332 dental records. In addition, 17 records from a validity test among a random sample ($n = 330$) of students reporting non-exposure to orthodontic appliances were added to the dataset.

The following data were collected from dental records: (i) date(s) at placement of appliance(s); (ii) type of appliance; and (iii) duration of appliance treatment. The orthodontic appliances were categorized into groups, on the basis of an estimated rate of exposure to nickel (Table 1) (5–6, 8, 35–39).

Data handling and statistical analysis

The χ^2 -test was used for comparison of proportions. Statistical significance was defined as $p < 0.05$. Associations between the dependent variable (positive nickel patch test reaction) and independent variables were analysed as ORs with 95% confidence intervals (CIs) with logistic regression.

Age at piercing was converted into a piercing date by adding 6 months to individual dates of birth (mid-year method). The estimated difference in exposure to nickel from intra-oral orthodontic appliances was expressed by the following variables: (i) total time spent undergoing

Table 1. Classification of recorded types of appliance based on their estimated intra-oral nickel release

Group	Type of appliance	Metal exposure	Estimated intra-oral nickel release
1	Appliances with no metal components; acrylic or resilient splints without clasps	None	None
2	Plates, activators with and without extra-oral traction, bonded buttons	Few stainless steel components, no solders i.o.	Probably low ^a
3	One or two molar bands, lingual arches, extra-oral traction, sectional fixed appliance in one jaw	Stainless steel components, solders (intra-oral or extra-oral)	Moderate ^b
4	Full fixed appliance unimaxillary or bimaxillary, rapid maxillary expansion-appliances or similar	Stainless steel components; extensive exposure	Probably high ^c
5	Same as group 4, but with NiTi-containing alloys	Stainless steel components; high Ni content verified	High ^d
6	All types of retention appliance, etched or enamel retained bridges, brass ligatures	Mainly stainless steel; long-term; unknown	Unknown; probably low
7	Ag-/Au-chains applied to surgically uncovered teeth	Alloys contacting open wounds	Unknown

^aToms (35), Jones et al. (36).^bGrimsdottir et al. (6), Gjerdet & Hero (37).^cPark & Shearer (5), Maijer & Smith (38).^dJia et al. (8), von Fraunhofer (39).

appliance treatment (in days); and (ii) different types of appliance groups, including a ('pooled') variable expressing appliances with estimated low or high nickel release. In case-referent analyses, exposure to appliances placed before piercing (reference category) was compared with exposure to appliances following piercing (risk category).

The statistical software package SPSS™ (version 12.0.1) was used.

Ethical considerations

The study was approved by the Ethics Committee of the Faculty of Medicine and Odontology, Umeå University (§491/98, dnr 98-390). Participation in the study was based on written consent from the pupils following parental approval.

Results

General characteristics

Reliability of self-reported data. Among 330 randomly selected students reporting no orthodontic appliance treatment, dental records from 30 (9.1%) verified exposure to some type of intra-oral appliance. After examination of 1341 dental records for those adolescents who reported exposure to orthodontic appliances, 5 (0.4%) were identified as having received no treatment with orthodontic appliances.

The median age, according to the questionnaire, when orthodontic appliances were first placed was ~1 year higher than the median age verified from dental records (11.4 years for girls and 11.7 years for boys).

Self-reported prevalence of orthodontic treatment and piercing. Among the 4376 patch tested students, orthodontic appliance treatment was reported in 51.7% of females and in 38.5% of males (Table 2). From the questionnaire data, the median age when orthodontic appliances were first placed was 12 years (range 5–20 years; girls 12 years and boys 13 years). Piercing was reported for 83.8% of the girls and 19.5% of the boys. The self-reported median age at piercing was 10 years (range 1–19 years; girls 10 years and boys 11 years).

Distribution of nickel allergy (patch test-positive) for self-reported orthodontic appliance treatment and piercing (Table 3). The overall prevalence of nickel allergy among 4376 patch-tested students was 9.9% (girls 13.3% and boys 2.5%). For girls reporting exposure to piercing with or without orthodontic treatment, higher prevalences of nickel allergy (up to 18.7%) were found. A low prevalence of nickel allergy was found for students who had not had orthodontic appliance treatment or piercing, as well as for those exposed exclusively to orthodontic appliances, with similar occurrence in boys and girls. A lower prevalence of nickel allergy was observed in total and among girls ($p < 0.0001$) when orthodontic treatment preceded piercing.

Table 2. Characteristics of patch tested students (from questionnaire)

Variable	Females, n = 2976		Males, n = 1400		Total, n = 4376	
	n	%	n	%	n	%
Orthodontic appliance	1531	51.7	540	38.5	2071	47.4
Orthodontic appliance and piercing	1285	43.2	94	6.7	1379	31.5
Piercing	2494	83.8	272	19.5	2766	63.3
Piercing ^a						
Single	1824	73.1	235	86.4	2059	74.4
Multiple, ≥ 2	670	26.9	37	13.6	707	25.6
Age at piercing ^b						
1–8 years	908	36.8	49	18.8	957	35.0
9–11 years	850	34.4	95	36.4	945	34.6
12–19 years	713	28.8	117	44.8	830	30.4
Atopy	1532	52.4	565	40.9	2097	48.7

^aRefers to percentage among pierced subjects.^bNo age reported (n = 23).**Table 3.** Nickel allergy in relation to reported use and sequence of orthodontic appliances and piercing

Orthodontic appliance	Piercing	Total (n = 4376) (%)	Nickel patch test-positive (%) Girls (n = 2976)	Nickel patch test-positive (%) Boys (n = 1400)
No	No	24/912 (2.6)	6/235 (2.6)	18/677 (2.7)
Yes	No	17/692 (2.5)	8/246 (3.3)	9/446 (2.0)
Yes, first	Yes	28/353 (7.9)	28/324 (8.6)	0/29 (0.0)
No	Yes	185/1382 (13.4)	180/1198 (15.0)	5/184 (2.7)
Yes ^a	Yes ^a	204/1379 (14.8)	201/1285 (15.6)	3/94 (3.2)
Yes	Yes, first	156/875 (17.8)	153/819 (18.7)	3/56 (5.4)

^aWithout the sequence of orthodontic appliance and piercing being taken into account.**Case–referent analysis based on reported exposure to orthodontic appliances**

No difference in the prevalence of nickel sensitivity was observed between adolescents reporting exposure (10.7%) and those reporting non-exposure (9.1%) to orthodontic appliances.

The association between nickel sensitivity and exposure to orthodontic appliances preceding and following piercing was evaluated with multivariate logistic regression analysis. In the final multivariate model, adjustments were made for other significant variables (sex, piercing age, and number of piercings). Atopy was not found to be a significant risk indicator. There was a significant association between nickel sensitivity and sequence of orthodontic appliance treatment and piercing, with a reduced risk of having a positive patch test reaction if orthodontic treatment preceded piercing (n = 1334, OR 0.46, 95% CI 0.27–0.78). There was also a significant association between nickel sensitivity and sex, suggesting a five-fold increased risk of nickel allergy among girls as compared with boys (OR 5.10, 95% CI 1.59–16.40). Multiple piercing increased the risk of a positive patch test reaction to nickel by almost 50% as compared with single piercing (OR 1.48, 95% CI 1.06–2.06).

Case–referent analysis based on exposure to orthodontic appliances verified by dental records (Table 4)

Association between nickel sensitivity and sequence of orthodontic appliance treatment and piercing. As with the case–referent analysis based on questionnaire data, a comparable variable based on the sequence of orthodontic appliance treatment and piercing was created, and included three categories: (i) placement of an orthodontic appliance 1 year or more before the reported age at first piercing; (ii) orthodontic appliance treatment placement and piercing within the same year; and (iii) first piercing performed 1 year or more before placement of an orthodontic appliance. The results were similar to those from the questionnaire data when this variable was incorporated into the multivariate model (Table 4). Although statistical significance was lost, the same trend of a reduced risk of nickel sensitivity (OR 0.61) was seen in the multivariate analysis adjusting for sex, piercing age and number of piercings when an appliance was placed 1 year or more before piercing (Table 4).

Nickel sensitivity in relation to type of orthodontic appliance. Of the orthodontically treated students, 62% had worn two

Table 4. Risk [odds ratios (ORs) with 95% confidence intervals (CIs)] of nickel sensitivity based on dental records in a multivariate logistic regression model with the dependent variable 'positive patch test reaction to nickel' and independent variables (sex, timing of orthodontic treatment, and piercing, age at time of piercing, and number of piercings); ref., reference category

Variable	No of students	OR	Multivariate analysis 95% CI	p-value
Orthodontic appliance				
Before piercing	406	0.61	0.36–1.02	0.06
Within the same year	267	0.85	0.55–1.31	0.47
After piercing (ref.)	676	1.00		
Sex				
Female	1254	5.00	1.56–16.05	<0.01
Male (ref.)	95	1.00		
Age at time of piercing				
1–8 years	472	1.32	0.76–2.29	0.32
9–11 years	459	1.64	1.02–2.62	0.04
12–19 years (ref.)	418	1.00		
Piercing				
Multiple	360	1.54	1.11–2.15	0.01
Single (ref.)	989	1.00		

Table 5. Risk [odds ratios (ORs) with 95% confidence intervals (CIs)] of nickel sensitivity in students exposed to orthodontic appliances before piercing. Univariate and multivariate logistic regression analyses are based on data verified from dental records. Exposure to nickel from appliances is given for (a) each group of appliance(s) before versus after piercing, and similarly, for (b) pooled groups with nickel-releasing appliances (low/high exposure to nickel) before versus after piercing. The reference category is appliances or groups of appliances placed after piercing

	Number (n) in analysis	Univariate analysis			Multivariate analysis ^a		
		OR	95% CI	p-value	OR	95% CI	p-value
(a) Group of appliance(s)							
Group 1 ^b	61	0.79	0.18–3.42	0.75	0.63	0.12–3.33	0.59
Group 2 ^b	662	0.58	0.37–0.92	0.02	1.30	0.67–2.50	0.44
Group 3 ^b	318	0.60	0.30–1.20	0.15	0.93	0.36–2.39	0.88
Group 4 ^b	275	0.52	0.23–1.17	0.11	0.54	0.20–1.48	0.23
Group 5 ^b	324	0.40	0.18–0.92	0.03	0.31	0.10–0.98	0.04
Group 6 ^b	445	0.46	0.20–1.05	0.06	0.80	0.26–2.50	0.70
Group 7 ^b	34	0.32	0.03–3.06	0.32	^c	^c	^c
(b) Pooled groups with Ni-releasing appliances							
Low exposure (groups 1 + 2)	418	0.43	0.24–0.79	<0.01	1.23	0.66–2.29	0.52
Low exposure (groups 1 + 2 + 3)	564	0.52	0.32–0.84	<0.01	1.32	0.66–2.61	0.19
High exposure (groups 4 + 5)	785	0.57	0.36–0.89	0.01	0.56	0.32–0.97	0.04
High exposure (groups 3 + 4 + 5)	931	0.61	0.41–0.91	0.02	0.66	0.40–1.08	0.10

^aAdjusted for sex, age at time of piercing, and number of piercings.^bAppliance group as a singular variable or combined with other appliance groups regardless of grading.^cNo data available, owing to an insufficient number of cases.

or more orthodontic devices. Multivariate analyses of exposure to each appliance group (1–7), exclusively or in combination with other groups of appliances, before and after piercing, are shown in Table 5. Exposure to group 5 in combination with other appliances showed a reduced risk of nickel allergy when it preceded piercing (OR 0.31, 95% CI 0.10–0.98) as compared with exposure to the same types of appliance after piercing. Similarly, the 'high Ni-release' group (groups 4 and 5) showed a reduced risk of nickel allergy when exposure to the appliance

preceded piercing (OR 0.56, 95% CI 0.32–0.97). All other groups did not differ significantly from the corresponding reference categories in multivariate analysis.

Non-pierced students exposed to orthodontic appliances showed no enhanced risk of nickel allergy (OR 0.85, 95% CI 0.43–1.70) as compared with the reference category without any exposure.

Nickel sensitivity in relation to length of exposure to an orthodontic appliance. The risk of nickel allergy decreased with

duration of orthodontic treatment. Exposure to an orthodontic appliance (before piercing) for a period of >6 months indicated a reduced risk of nickel allergy (OR 0.62, 95% CI 0.38–1.02). Extending the treatment to 1–2.5 years lowered the risk even further (OR 0.53, 95% CI 0.27–1.00).

Discussion

Reliability of data

The strengths of our study are the use of test-verified nickel allergy, the collection of data on exposure to orthodontic appliances from dental records, a large sample size, and the use of multivariate logistic regression models.

The risk of recall bias in data from our questionnaire was partly confirmed by a tendency to report the onset of orthodontic treatment as being approximately 1 year later than was noted in dental records. The time of first piercing, which we could not verify, may be biased in a similar way. However, it has been suggested that piercing, as a singular event, is easier to recall than extended periods of orthodontic treatment (23).

Selection bias was minimized as dental records for almost 96% of those included in the case-referent study were traced. In the questionnaire-based data there was a small proportion of misclassification regarding earlier orthodontic treatment. This did not induce any bias other than dilution of the risk estimates as these adolescents did not differ from others with respect to nickel allergy.

Risk of nickel allergy in relation to orthodontic treatment and piercing

In line with observations by Kerosuo et al. (23), the present study did not find any increased risk of nickel sensitization following orthodontic appliance treatment. Recently, Johansson et al. (21) drew similar conclusions, although their study was not designed to answer the present research question. The five-fold increase in risk of nickel allergy in girls as compared with boys, which was also apparent in the multivariate analyses where piercing was adjusted for, is likely to reflect a difference in nickel exposure between the sexes, which can be hypothetically explained by boys being pierced at an older age and using less nickel-containing jewellery than girls (40).

Sequence of piercing and orthodontic treatment

The risk of nickel sensitivity almost halved (OR 0.46) when orthodontic appliance treatment preceded exposure to piercing. This supports conclusions drawn in other studies (23, 28, 29, 41–43).

Association between nickel allergy and type of orthodontic appliance

The majority of students reporting appliance treatment had been exposed to multiple orthodontic devices, each of which is likely to vary in its release of nickel, owing to composition, corrosion resistance, and mechanical straining (6–8, 44). We introduced a detailed and graded classification based on estimated nickel release in our analyses (Table 1). There is, however, uncertainty regarding the factors influencing this release (3, 44, 45). There is a lack of studies on the role of galvanic coupling between dissimilar metal components of the appliances, which may promote corrosion and subsequent ionic release from the alloys. Various combinations of appliances were therefore analysed. The multivariate analyses showed a reduced risk among students exposed to full fixed appliances with NiTi-containing alloys (before piercing). Fixed appliances, used before the piercing event, were also shown by Kerosuo et al. (23) to significantly lower the risk of nickel sensitivity.

Extra-oral traction devices would theoretically increase the risk of nickel sensitization, owing to skin exposure. We did not see such an effect. This may be explained by an increased awareness of the risk of nickel sensitization, which has led to measures aimed at minimizing skin exposure (46).

Association between nickel allergy and duration of appliance treatment

A trend towards more allergic response with time was found by Feasby et al. (47). In contrast to this, our results indicate a reduced risk when the duration of appliance treatment (before piercing) is increased to up to 2.5 years, which corresponds with the treatment periods that are common in orthodontics. Our data support the hypothesis that oral nickel exposure from appliances, when exceeding a threshold level, induces a state of tolerance rather than sensitization (23).

Possible nickel-specific immunological tolerance induction

The term 'oral tolerance' is used to describe a state of immunological unresponsiveness to an antigen presented via the oral route. Our results indicate such a supportive effect of nickel exposure from orthodontic appliances prior to piercing, as suggested by the results of other experimental and epidemiological studies (23, 24, 28–31, 42, 43, 48–51). Furthermore, our observations show a time-dependent and dose-dependent immune response. Such an immunological response is also supported by recent studies that have demonstrated the pivotal role

in immunosuppression played by the oral mucosa and regional lymph nodes (52–54). The critical Langerhans cells have been found in larger numbers in early gingivitis, which is frequently observed in orthodontic patients, and nickel has been found in the dental plaque as well as in the oral mucosa of orthodontic patients (17, 55, 56). Specifically in relation to nickel-specific oral tolerance in orthodontic patients, Rustemeyer et al. (51) found that 'successfully tolerized' individuals may be immunologically characterized by nickel-specific T cell release of a downregulatory cytokine, interleukin-10, and thus suggest that long-lasting oral exposure to nickel may induce an active immunological tolerance mediated by regulatory T cells, preventing subsequent sensitization.

Conclusions

The following conclusions may be drawn from our study.

There was no increase in the risk of sensitizing adolescents to nickel by the use of oral orthodontic appliances.

When orthodontic appliance use preceded exposure to piercing, there was a reduced risk of nickel sensitivity. Furthermore, there was a reduced risk with the use of full fixed appliances with an assumed high release of nickel as compared with appliances including alloys with a lower nickel release. The risk reduction was most prominent when the duration of orthodontic treatment (before piercing) was 1–2.5 years.

These results should thus reduce parental and patient concerns about sensitization from orthodontic appliances. The results support the concept of induction of immunological tolerance via oral administration of nickel.

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