

Prevalence of nickel hypersensitivity in orthodontic patients: A meta-analysis

Olga-Elpis Kolokitha,^a Eleftherios G. Kaklamanos,^b and Moschos A. Papadopoulos^c

Thessaloniki, Greece

Introduction: In spite of growing concern of routine mechanotherapy modalities in patients' health and recent regulations on nickel exposure, there has been no relevant meta-analysis. The aim of this study, therefore, was to investigate the effect of orthodontic therapy on the prevalence of nickel hypersensitivity and compare it with the prevalence in the general population. **Methods:** Several electronic databases were searched. Hand-searching was also performed to identify additional relevant studies. Initially, 324 articles were retrieved. After applying specific inclusion criteria, 8 studies were eligible for the meta-analysis. Meta-analysis was performed with Comprehensive Meta-Analysis software (version 2.2.046, Biostat, Englewood, NJ). Evaluations of the validity of the included articles and of publication bias were also performed. **Results:** A lack of high-validity longitudinal studies of the prevalence of nickel hypersensitivity in patients before and after orthodontic treatment and in appropriate controls was noted. From the studies retrieved, no statistically significant difference between the odds for a positive patch-test result before orthodontic treatment and after the placement of the appliances was observed. Orthodontic patients with no cutaneous piercing or with skin pierced have no statistically significant differences of nickel hypersensitivity after treatment compared with the general population. **Conclusions:** Orthodontic treatment is not associated with an increase in the prevalence of nickel hypersensitivity unless subjects have a history of cutaneous piercing. High-validity studies are needed to produce strong evidence to further support the results of this meta-analysis. (Am J Orthod Dentofacial Orthop 2008;134:722.e1-722.e12)

Although nickel (Ni) is the most prevalent allergen causing allergic contact dermatitis, appliances containing Ni still are a major part of the orthodontic armamentarium.^{1,2} In the light of the growing concern of routine mechanotherapy modalities in patients' health³ and recent regulations on the evaluation and control of the risks of Ni exposure,⁴ contemporary information on Ni-induced sensitization in orthodontic patients would be of particular interest.

There is a lack of data in the literature directly linking the prevalence of Ni-induced side effects in nonsensitized people with orthodontic materials. It has also been suggested that the risk of sensitization from orthodontically derived Ni in these patients is extremely low.⁵ It is possible that an increased risk of Ni sensitization of potential orthodontic patients can be induced by wearing Ni-containing jewelry at an early

age.⁶ Moreover, it has been suggested that oral exposure with Ni-containing orthodontic appliances before cutaneous Ni exposure might actually reduce Ni hypersensitivity.⁷ To critically evaluate the prevalence of Ni hypersensitivity after the placement of orthodontic appliances, we conducted a systematic review and a meta-analysis of the available literature.

MATERIAL AND METHODS

The first phase of this meta-analysis involved the development of a specific protocol.^{8,9} The MOOSE guidelines in reporting meta-analyses formed the basis of data presentation.¹⁰

We conducted 2 separate searches because of the scarcity of studies investigating simultaneously Ni hypersensitivity in orthodontic patients and the general population matched by characteristics such as age, nationality, race, sex, etc. The first search aimed to identify potentially relevant studies concerning the prevalence of Ni hypersensitivity in patients having orthodontic therapy. The second search focused on potentially relevant studies on Ni hypersensitivity in a general unselected population.

Citations to potentially relevant studies published in journals, dissertations, and conference proceedings were located by searching the appropriate electronic databases. In addition, efforts to identify potentially

From the Department of Orthodontics, School of Dentistry, Aristotle University of Thessaloniki, Thessaloniki, Greece.

^aLecturer.

^bResident.

^cAssociate professor and program coordinator.

Reprint requests to: Olga-Elpis Kolokitha, Department of Orthodontics, School of Dentistry, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Greece; e-mail, okolok@dent.auth.gr.

Submitted, November 2007; revised and accepted, January 2008.

0889-5406/\$34.00

Copyright © 2008 by the American Association of Orthodontists.

doi:10.1016/j.ajodo.2008.01.013

relevant unpublished or ongoing studies were made by searching the databases of research registers. Table I presents the databases searched and outlines the search strategy used. In addition to the electronic searches, hand searching was also performed by checking the references of the retrieved articles. No restrictions were applied during the identification procedure for publication time, status, or language of the studies.

Studies of risk factors generally cannot be randomized because exposing subjects to harmful risks is unethical.¹¹ Studies appropriate to be included in the review fulfilled specific criteria concerning study design, participants' characteristics, intervention characteristics, and principal outcome measures; these are shown in detail in Table II.

Initially, the titles and abstracts, if available, of the articles identified were reviewed. Each article was checked for whether it presented data on the prevalence of positive patch-test scores after the placement or removal of orthodontic appliances and/or the prevalence in the general population. Any study not fulfilling this criterion was excluded from further evaluation. If the reviewer could not decide on the eligibility of a study from the title and the abstract, the full text was retrieved. Duplicate citations, such as dissertations that formed the basis of published trials, conference abstracts of published trials, case reports, case series, and review articles were discarded. For the remaining articles, the corresponding full texts were retrieved for further evaluation.

These were evaluated in duplicate by 2 reviewers working independently. Data abstraction was performed by using specially designed forms and involved bibliographic details, details on study design, participants' characteristics, and results about positive Ni patch-test scores before orthodontic treatment or after the placement or removal of orthodontic appliances, or in the general population. The studies were divided into 3 categories: (1) longitudinal data before orthodontic treatment and after the placement of orthodontic appliances, (2) only cross-sectional data after the placement or removal of orthodontic appliances, and (3) data regarding the general population. Any differences were resolved through mutual agreement.

These processes were not performed blinded, since scientific evidence does not strongly recommend masked assessment.¹² Interreviewer agreement on study eligibility during the screening was assessed by calculating the kappa score with SPSS statistical software (version 12.0.0, SPSS, Chicago, Ill).

The quality of nonrandomized trials cannot be evaluated in the same way as has been proposed for randomized controlled trials.^{13,14} In the case of the

former, various criteria have been suggested to critically appraise their validity.⁸ The same 4 sources of bias noted in randomized controlled trials (selection, performance, attrition, and detection biases) can be applied to other types of studies; however, good judgment is necessary.⁸

The possible sources of bias in nonrandomized trials according to Higgins and Green⁸ and the parameters to consider for the trials included in this meta-analysis are shown in Table III.

The retrieved data were analyzed with specially designed software, Comprehensive Meta-Analysis (version 2.2.046, Biostat, Englewood, NJ).

For the studies on the prevalence of Ni hypersensitivity before orthodontic treatment and after the placement of orthodontic appliances, the odds ratio (OR) of a positive Ni patch test before orthodontic treatment to a positive Ni patch test after the placement of orthodontic appliances and the respective 95% CI were calculated. For the studies reporting the prevalence of Ni hypersensitivity only after placement or removal of orthodontic appliances, and in the general population, the relevant event rates were computed.

The random-effects method for meta-analysis was used to combine the OR of a positive Ni patch test before orthodontic treatment to the odds of a positive Ni patch test after the placement of orthodontic appliances, for the studies of Ni hypersensitivity before orthodontic treatment and after the placement of orthodontic appliances. Moreover, the random-effects method was used to summarize Ni sensitivity data among studies presenting information only after the placement or the removal of orthodontic appliances. The latter group of studies was compared with the summary measure of Ni patch-test positivity in the general population. The choice of the random-effects model was based on the assumption that the variability in the studies retrieved could influence the effects under investigation, according to the approach of Borenstein et al.¹⁵

To identify heterogeneity, the Cochran test for homogeneity and the I^2 test were calculated to check for heterogeneity and inconsistency, respectively. Subgroup analyses were performed with the approach according to Deeks et al.¹⁶ Because it was suggested that piercing or other forms of cutaneous exposure might increase the risk of Ni sensitization, the prevalence of Ni hypersensitivity was calculated in subgroups.^{6,17} The subgroups were formed according to the presence or absence of cutaneous piercing, and the sequence of piercing relative to orthodontic treatment.

Publication bias was assessed by preparing a funnel plot. Funnel plot asymmetry was inspected graphically

Table I. The databases searched in the meta-analysis

<i>Databases of published trials</i>	<i>Studies on orthodontic patients (number of hits)</i>	<i>Studies on the general population (number of hits)</i>
MEDLINE searched via PubMed (1950 to week 1, November 2007)	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) Limited to humans (168)	nickel AND (random OR general) Limited to humans (384)
EMBASE searched via ScienceDirect (1974 to November 2007)	(atopy OR allergy OR hypersensitivity) AND (orthodontic OR braces) Limited to humans (180)	nickel AND (random OR general) Limited to humans (586)
Cochrane Database of Systematic Reviews searched via the Cochrane Library (2007, Issue 4)	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) in all fields (28)	nickel AND (random OR general) in all fields (19)
Cochrane Central Register of Controlled Trials searched via the Cochrane Library (2007, Issue 4)	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) in all fields (5)	nickel AND (random OR general) in all fields (37)
Google Scholar Beta searched on November 2, 2007	Orthodontic AND nickel AND (atopy OR al- lergy OR hypersensitivity) Limited to medicine, pharmacology and veteri- nary science (324)	nickel allergy AND (random population OR general population) Limited to medicine, pharmacology and veterinary science (881)
Web of Science searched on November 2, 2007	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A & HCI; Timespan=1970-2007 DocType=ARTICLE > SubjCat=DENTISTRY, ORAL SURGERY & MEDICINE (55)	nickel AND (random OR general) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1970-2007 DocType=ARTICLE > SubjCat=ALLERGY (22)
Evidence-Based Medicine searched on November 2, 2007	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) (1)	nickel random general (525)
Scopus searched on November 2, 2007	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) AND (LIMIT- TO(DOCTYPE, "ar")) AND (LIMIT- TO(SUBJAREA, "DENT") OR LIMIT- TO(SUBJAREA, "MULT")) (65)	nickel AND (random OR general) AND (LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(SUBJAREA, "DENT") OR LIMIT-TO(SUBJAREA, "MULT")) (303)
Windows Live Academic searched on November 2, 2007	Orthodontic AND nickel AND (atopy OR allergy OR hypersensitivity) (1)	nickel AND (random OR general) AND population (247)
LILACS database searched on November 2, 2007	(atopy OR allergy OR hypersensitivity) AND (orthodontic OR braces) (7)	nickel AND (random OR general) (4)
Bibliografia Brasileira de Odontologia searched on November 2, 2007	(atopy OR allergy OR hypersensitivity) AND (orthodontic OR braces) (5)	nickel AND (random OR general) (0)
<i>Databases of dissertations and conference proceedings</i>		
Digital dissertations searched via UMI ProQuest on November 2, 2007	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) (5)	nickel AND (random OR general) (507)
Conference Paper Index searched via Cambridge Scientific Abstracts (1982 to November 2, 2007)	(atop* OR allerg* OR hypersensitivity) AND (orthodont* OR braces) (1)	nickel AND (random OR general) (0)
<i>Databases of research registers</i>		
MetaRegister of Controlled Trials (all registers active and archived) searched via www.controlled-trials.com , November 2, 2007	(atopy OR allergy OR hypersensitivity) AND (orthodontic OR braces) (11)	nickel AND (random OR general) (14)

Table II. Criteria for selecting studies to be included in the meta-analysis

Criteria category	Definition			
	Studies on orthodontic patients		Studies on the general population	
	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
Study design	The studies included should investigate the prevalence of Ni hypersensitivity before orthodontic therapy and after the placement or the removal of orthodontic appliances. Studies reporting the prevalence of Ni hypersensitivity only after the placement or the removal of orthodontic appliances were eligible for inclusion.	Studies only on other potential allergens were excluded.	The studies included should investigate the prevalence of Ni hypersensitivity.	Studies only on other potential allergens were excluded.
Participants' characteristics	Studies included could involve subjects of any age. Studies included should involve assessment of Ni hypersensitivity in both male and female patients.	Studies of less than 10 participants, case reports, case series, and review articles were excluded. Studies only on males or on females were excluded.	Studies included could involve subjects from the general, unselected population. Studies included should involve subjects of comparable age to those who usually have orthodontic treatment.	Studies of less than 10 participants, case reports, case series, and review articles were excluded.
Intervention characteristics	Studies included could involve any kind of fixed or removable orthodontic appliances.			
Principal outcome measures	The studies included should provide measurements of Ni sensitization prevalence in the form of positive patch-test scores with the ICDRG scale. ²⁹	Studies that used other methods of investigating Ni sensitivity were excluded.	The studies included should provide measurements of Ni sensitization prevalence in the form of positive patch-test scores with the ICDRG scale. ²⁹	Studies that used other methods of investigating Ni sensitivity were excluded.

and measured numerically by using the approach according to Egger et al.¹⁸ and Sterne et al.^{19,20} Evidence of asymmetry was based on $P < 0.10$.

RESULTS

In the present study, the summary prevalence of Ni hypersensitivity of patients subjected to orthodontic treatment is presented and compared to the prevalence observed in the general population. Details on the performed meta-analysis concerning the prevalence of Ni hypersensitivity in the general population will be published elsewhere. The main characteristics of the studies concerning the general population are presented in Table IV.

The flow diagram of the retrieved studies through the selection process is presented in Figure 1. Initially, 324 articles were identified. After applying the inclusion and exclusion criteria, 8 studies were considered appropriate for the meta-analysis. Two trials presented data on positive Ni patch tests before orthodontic

treatment and after the placement of orthodontic appliances,^{21,22} and 6 studies contained data only after the placement or removal of the appliances.²³⁻²⁸

The kappa score for interreviewer agreement on trial eligibility during screening was 0.985, indicating high interreviewer agreement.

The characteristics of the 8 studies are shown in Tables V and VI. The subjects' ages were 9 to 48 years. The subjects in 5 studies were patients in clinics providing orthodontic therapy; the other studies were conducted in other settings (schools, dermatology clinics, and student health services). The subjects were treated with fixed orthodontic appliances in 6 studies, removable appliances in 1 study, and both fixed and removable appliances in 1 study.

In these studies, patch-test evaluations were performed at various intervals after placement, and the International Contact Dermatitis Research Group scale was used for the interpretation of the results.²⁹

Table III. Possible sources of bias according to Higgins and Green⁸ and parameters to consider for this meta-analysis

Sources of bias		Parameters to consider
Selection bias	Need to control for confounders	1. Study population: selected or unselected 2. Homogeneity of the population 3. A control group 4. Controlling for cutaneous piercing exposure to Ni: Ni exposure through piercing might cause increased risk of Ni sensitization.⁶ Some countries have implemented regulations for Ni exposure (ie, Denmark after 1992 and European Union countries after 2000).¹⁷ Thus, the place and the time of the study could have influenced the results.
Performance bias	Need to evaluate the validity of the measurement of the exposure to the intervention of interest	Data collected retrospectively might not be valid in measuring exposure to Ni from orthodontic appliances.
Attrition bias (applicable to longitudinal studies)	Need to present data on possible losses and analyses for the losses	1. Statement about the participants in the study, statement (or inferred from the tables) about those who violated the study protocol, dropped out, or were withdrawn from each group, and the respective reasons for each group. 2. Use of analyses to include all participants entering a trial irrespective of what happened subsequently.
Detection bias	Need for the assessor to be unaware or unaware of the subjects' exposure to the intervention of interest (blinding)	1. In studies of orthodontic patients, the assessor was aware of the subject's exposure to Ni from the orthodontic appliances. 2. In studies of the general population, the assessor could be informed beforehand whether the subject was exposed to Ni from orthodontic appliances.

Table IV. Main characteristics of the general-population studies included in the meta-analysis

Study and location	Participants		Positive reaction to Ni (%)
	n	Age (y)	
Barros et al ³⁷	M, 376	5-14	0.9
Portugal	F, 186		
Dotterud and Falk ³⁸	M, 223	7-12	8.5
Norway	F, 201		21.9
Kerosuo et al ²⁴	M, 283	14-18	3
Finland	F, 417		30
Mortz et al ²⁶	M, 526	12-16	2.5
Denmark	F, 620		13.7

M, Males; F, females.

In 4 trials, the history of cutaneous piercing was evaluated, and the relative data could be deduced.^{23,24,26,27} Piercing prevalences were 56.3% to 74.3% for the total sample examined (males, 0.0%-26.0%; females, 81.3%-94.5%).

Only 2 studies provided data for the prevalence of Ni hypersensitivity in patients before orthodontic treatment and after the placement of orthodontic appliances.^{21,22} These would have been evaluated as having higher validity than the remaining 6 that evaluated Ni hypersensitivity only after treatment, if they had included an appropriate control group.²³⁻²⁸ However, neither longitudinal evaluation of an appropriate control group was made, nor researchers

considered possible confounders such as cutaneous piercing.

From the studies that evaluated Ni hypersensitivity after treatment, only that by Mortz et al²⁶ investigated an unselected and relatively homogeneous group.

A detailed evaluation of the studies in the meta-analysis regarding the various sources of bias is given in Table VII.

The effect of orthodontic treatment on the prevalence of positive Ni patch tests before orthodontic treatment and after the placement of the appliances is shown in Figure 2. In addition to basic statistical data, OR, and 95% CI, the forest plots are shown. The forest plots depict graphically the OR for a positive patch test before and after treatment in each trial, represented by the center of a circle, with the respective 95% CI, represented by a horizontal line. The vertical axis that passes through number 1 of the horizontal axis depicts the point of no difference in the odds of positive Ni patch-test scores before orthodontic treatment and after the placement of the appliances. If the CI line intersects the vertical axis, there is no difference in the respective odds. Therefore, no statistically significant difference in the odds for a positive patch test before orthodontic treatment and after the placement of the appliances was observed. In addition, no evidence of heterogeneity was seen.

The prevalence of Ni hypersensitivity in patients having orthodontic treatment and the general popula-

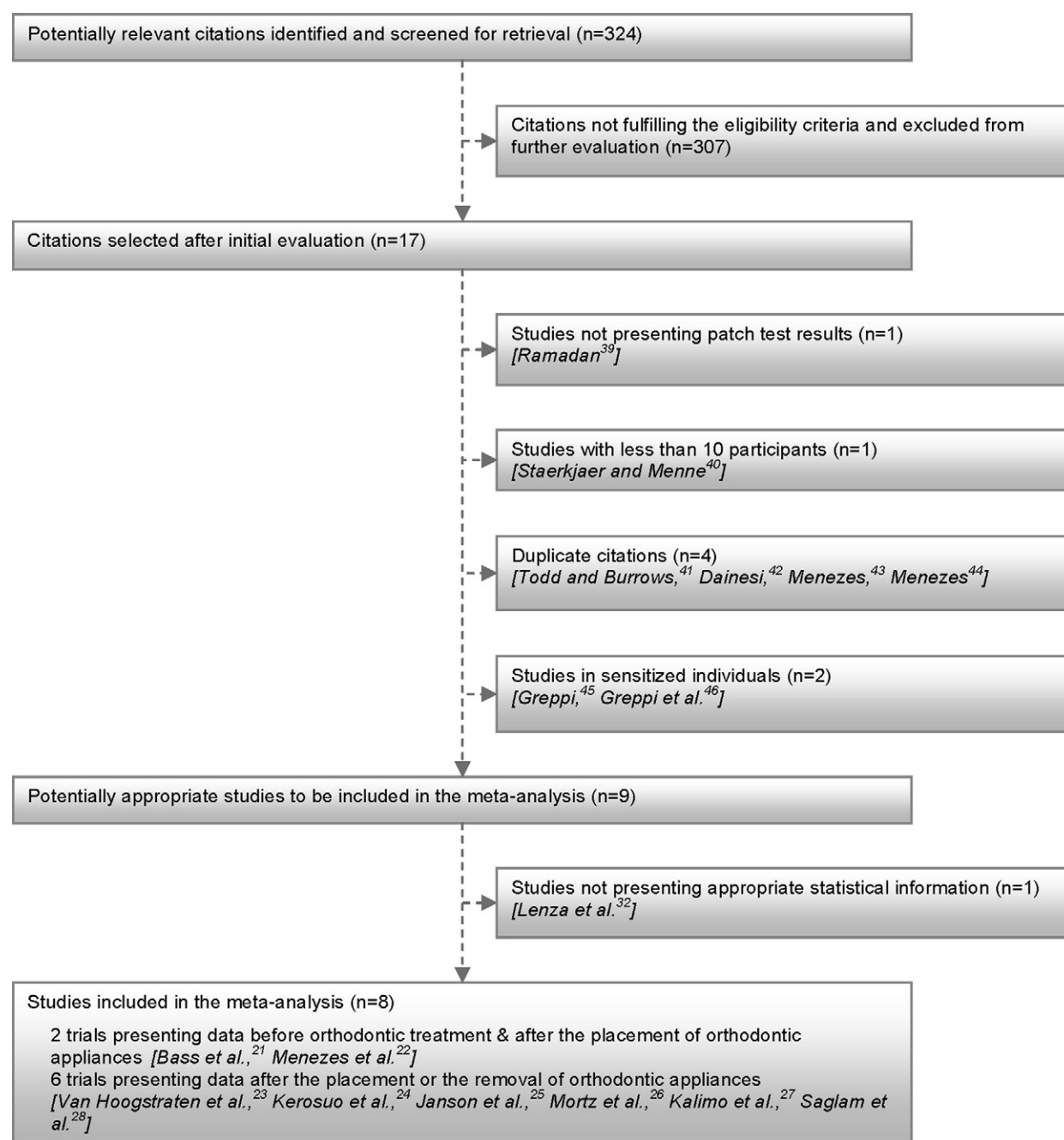


Fig 1. Flow diagram of the retrieved studies through the selection process.³⁹⁻⁴⁶

tion is shown in Table VIII. The total sample of patients having orthodontic treatment had a higher prevalence of Ni hypersensitivity than did the general population. Orthodontic patients without cutaneous piercing had no statically significant difference in Ni hypersensitivity prevalence; this was also true for patients who had orthodontic treatment before piercing. Patients who had cutaneous piercing before orthodontic treatment had a

statistically significant increase in the prevalence of Ni hypersensitivity.

Data analysis showed no statistically significant difference in the prevalence of Ni hypersensitivity when all samples were compared regarding the timing of orthodontic treatment in relation to cutaneous piercing ($P = 0.177$).

The Cochran test for homogeneity and the I^2 test showed heterogeneity in the source studies. However,

Table V. Characteristics of the studies on orthodontic patients included in the meta-analysis: characteristics of the participants

Study and location	Participants		Selection	Type of treatment
	n	Age (y) (mean and range)		
Bass et al ²¹	M, 11	14.6 (12-17)	Patients of an orthodontic department	Fixed appliances
United States	F, 17	23.9 (13-48)		
Menezes et al ²²	M, 17	9-25	Patients of an orthodontic department	Fixed appliances
Brazil	F, 21			
Van Hoogstraten et al ²³	M, 73	10-35	Patients at 9 dermatology clinics	Removable appliances
European countries	F, 209			
Kerosuo et al ²⁴	M, 198	13-18	Patients who received orthodontic treatment with metallic appliances at a municipal dental clinic	Fixed appliances
Finland	F, 279			
Janson et al ²⁵	M, 21	12.9-31.5	Patients of an orthodontic department	Fixed appliances
Brazil (evaluated during treatment)	F, 45			
Janson et al ²⁵	M, 17	12.5-28.6	Patients of an orthodontic department	Fixed appliances
Brazil (evaluated after treatment)	F, 27			
Mortz et al ²⁶	M, 134	12-16	Epidemiologic study in schools	"Dental braces"
Denmark	F, 246			
Kalimo et al ²⁷	M, 15	nm for the orthodontically treated group	Randomly selected university students attending student health service	Fixed and removable appliances
Finland	F, 55			
Saglam et al ²⁸	74	nm for the group tested after therapy	Patients of an orthodontic department	Fixed appliances
Turkey				

M, Males; F, females; nm, not mentioned.

this was taken a priori into consideration when performing the meta-analysis by choosing the random-effects model.

Publication bias was first assessed visually with a funnel plot analysis (Fig 3). Since studies of varying sample sizes were included in meta-analysis, the Egger linear regression method was also used (intercept, 0.554; 95% CI, -4.02 to 5.79; *t*, 0.427; df, 7; 2-tailed *P* = 0.682). Although an indication of asymmetry was observed in the funnel plot toward small studies, no evidence of publication bias was found according to the Egger linear regression method.¹⁹

DISCUSSION

Meta-analysis is a research study design that aims to summarize the findings from many studies and indicate where the weight of the evidence lies, thus producing evidence that is more powerful than the primary studies included in the analysis. Furthermore, the possibility of a subgroup analysis is 1, if not the main, advantage of the meta-analytic approach. However, meta-analysis, like other methods of scientific research, is subject to biases that should be routinely examined in sensitivity analyses and funnel plots.^{30,31} In our study, every effort to minimize possible bias in the location of studies was made by searching many databases, checking the reference lists, and placing no

restrictions for year of publication, publication status, or language of the articles retrieved. Potential bias in the inclusion of studies was addressed by setting specific criteria and checking for interreviewer agreement during the selection process. Moreover, the likely presence or absence of publication bias was assessed by the Egger linear regression method and the funnel plot analysis. No evidence of publication bias was found.

By means of electronic and hand searching, 324 articles were identified, from which only 8 fulfilled the inclusion criteria for this meta-analysis. The fact that only 8 studies in the current literature met the inclusion criteria reflects the scarcity of relevant research and the lack of data. This is in spite of growing concern on the potential risks of Ni in many orthodontic biomechanical modalities. It also indicates that some trials did not meet the criteria. One could not expect to retrieve randomized controlled trials on the effect of orthodontic treatment on the prevalence of Ni hypersensitivity, since studies of risk factors generally cannot be randomized because exposing subjects to harmful risks is unethical.¹¹ However, the lack of high-validity longitudinal studies of Ni hypersensitivity in patients before and after orthodontic treatment and in appropriate controls should be mentioned. The only such trial retrieved lasted only 4 months and did not have adequate statistical information to be included in the meta-analysis.³² The

Table VI. Characteristics of the studies on orthodontic patients included in the meta-analysis: Ni patch testing and Ni cutaneous piercing exposure characteristics

Study	Ni patch-test timing			Patch-test evaluation	Controlling for Ni cutaneous exposure		
	Before OT	During OT	After OT		Control	Prevalence	
Bass et al ²¹ (longitudinal trial)	✓	✓		After 48 or 72 hours, ICDRG scale	No control for Ni cutaneous exposure		
Menezes et al ²² (longitudinal trial)	✓	✓		After 48 and 72 hours, ICDRG scale	No control for Ni cutaneous exposure		
Van Hoogstraten et al ²³			✓	After 72, 96, or 120 hours, ICDRG scale	Yes, piercing	M	26.0%
						F	86.6%
						M+F	70.9%
Kerosuo et al ²⁴			✓	After 72, 96, or 120 hours, ICDRG scale	Yes, piercing	M	nm
						F	nm
						M+F	56.3%
Janson et al ²⁵ (cross-sectional trial)		✓	✓	After 48 and 96 hours, ICDRG scale	Yes, but cannot be deduced for the group during or after OT		
Mortz et al ²⁶			✓	After 120 hours, ICDRG scale	Yes, piercing	M	22.3%
						F	81.3%
						M+F	60.5%
Kalimo et al ²⁷			✓	After 72 and 96 hours, ICDRG scale	Yes, piercing	M	0%
						F	94.5%
						M+F	74.3%
Saglam et al ²⁸			✓	After 48, 96, or 120 hours, ICDRG scale	Yes, but cannot be deduced for the group after OT		

OT, Orthodontic treatment; ICDRG, International Contact Dermatitis Research Group; M, male; F, female.

other longitudinal studies retrieved did not include comparisons to control groups.^{21,22} In addition, more studies of lower validity were found that investigated the prevalence of Ni hypersensitivity only after placement or removal of orthodontic appliances.²³⁻²⁸ Even if these studies included a control group, the population under investigation was selected and heterogeneous. Only 1 study involved an unselected and relatively homogeneous population, but no comparison between the orthodontically treated and the untreated groups was made.²⁶

In addition, research effort was spent on studies that did not include an adequate number of participants or did not use appropriate and common outcome measures. Patch testing is an excellent evidence-based method for identifying contact allergens, and the absence of appropriate reporting excluded many studies from this meta-analysis.³³

To compare the prevalence of Ni hypersensitivity to the prevalence in the general population, a separate search was performed for studies with unselected samples. This could involve some biases, since it is not possible for samples of the general population to be matched exactly to those of orthodontic patients in general characteristics, such as age, nationality, race, sex, etc. To control as much as possible for the effect of age, only studies with

subjects of comparable ages to those having orthodontic treatment were included.

Analysis of the studies evaluating Ni hypersensitivity after the placement or the removal of orthodontic appliances showed that patients in the total sample having orthodontic treatment had a higher prevalence of Ni hypersensitivity. However, when people with cutaneous piercing, considered a significant risk factor for Ni allergy,³⁴ were omitted from the sample, patients having orthodontic treatment did not have a statistically significant difference in Ni hypersensitivity than did the general population. Furthermore, orthodontic patients who had skin piercing exposure to Ni had a statistically significant difference than did the general population. This difference was more pronounced when piercing preceded orthodontic treatment. However, in patients who had orthodontic treatment before piercing, no statistically significant difference was observed. Based on these findings, scientific evidence suggests that orthodontic treatment is not associated with an increase of Ni hypersensitivity, unless patients have a history of previous cutaneous piercing exposure to Ni. Moreover, in the 2 longitudinal studies, no statistically significant difference between the odds for a positive patch-test result before orthodontic treatment and after the placement of the appliances was observed.

This finding could be of particular interest re-

Table VII. Analysis of the various sources of bias in the studies in the meta-analysis

Study	Sources of bias
Van Hoostraten et al ²³	1. Selected and heterogeneous population. Control group. Control for cutaneous piercing exposure to Ni. Performed in European Union countries before the Ni exposure regulation. 2. Retrospective collection of data from interviews. Patients were asked whether they wore removable appliances and the age they had their ears pierced. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.
Bass et al ²¹	1. Selected and heterogeneous population. No control group. No control for cutaneous piercing exposure to Ni. Performed in the United States. 2. Prospective evaluation of oral exposure to Ni. 3. Losses described but not explained. 4. The assessor was aware of the subject's exposure to Ni from orthodontic appliances.
Kerosuo et al ²⁴	1. Selected and heterogeneous population. No control group. Control for cutaneous piercing exposure to Ni. Performed in Finland before European Union regulations. 2. Retrospective collection of data from questionnaires and patients' orthodontic records. Patients were asked whether they had received orthodontic treatment and the age they had their ears pierced. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.
Janson et al ²⁵	1. Selected and heterogeneous population. No control group. Control for cutaneous piercing exposure to Ni, but piercing prevalence cannot be deduced for the group after orthodontic treatment. Performed in Brazil. 2. Retrospective collection of data from interviews. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.
Mortz et al ²⁶	1. Unselected and more homogeneous population. Control group but no comparison with the orthodontically treated group. Control for cutaneous piercing exposure to Ni. Performed in Denmark after Danish regulations. It is unclear whether the subjects had pierced their ears before or after the Ni exposure regulation. 2. Retrospective collection of data from questionnaires and interviews. Patients were asked whether they wore dental braces and whether they had their ears or any other part of their skin pierced. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.
Kalimo et al ²⁷	1. Selected and heterogeneous population. Control group but no comparison with the orthodontically treated group. Control for cutaneous piercing exposure to Ni. Performed in Finland before European Union regulations. 2. Retrospective collection of data from interviews. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.
Menezes et al ²²	1. Selected and heterogeneous population. No control group. No control for cutaneous piercing exposure to Ni. Performed in Brazil 2. Prospective evaluation of oral exposure to Ni. 3. No losses occurred. 4. The assessor was aware of the subjects' exposure to Ni from orthodontic appliances.
Saglam et al ²⁸	1. Selected and heterogeneous population. No control group. Control for cutaneous piercing exposure to Ni, but piercing prevalence cannot be deduced for the group tested after orthodontic treatment. Performed in Turkey. 2. Retrospective collection of data from a questionnaire. 4. No statement that the assessor was blinded. No information on whether the assessor was informed beforehand on the subjects' exposure to Ni from orthodontic appliances.

1, Selection bias; 2, performance bias; 3, attrition bias; 4, detection bias.

garding both general policies on limiting human exposure to Ni and risk management in orthodontic daily practice.

Current concerns on possible adverse sequelae from Ni exposure in orthodontic practices,³ combined with increased reporting of allergic reactions attributed to orthodontic treatment,³⁵ might extend the limitations on Ni content in items regularly used in orthodontic treatment (brackets, bands, archwires) and raise liability issues for orthodontic practitioners. It is also

possible that future legislation will affect everyday orthodontic practice by influencing the choice of mechanotherapy and modifying the financial dimension of orthodontic treatment. In contrast to these concerns, the data from this meta-analysis suggest that contact sensitization to Ni is not increased by oral exposure from orthodontic appliances but is mainly affected by previous cutaneous exposure, usually ear piercing. In addition, our results show that the tolerance concept, suggesting that orthodontic treatment with appliances

Studies included in the meta-analysis

Bass *et al.*, 1994²¹
Menezes *et al.*, 1996²²

Total (95% CI)

Test for heterogeneity: Q-value = 0.148, df = 1 ($p = 0.701$), $I^2 = 0\%$

Test for overall effect: Z = 1.345 ($p = 0.178$)

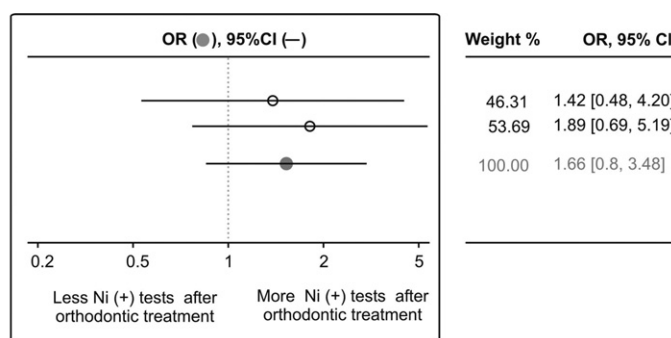


Fig 2. OR and 95% CI of a positive Ni patch-test score before orthodontic treatment and after the placement of orthodontic appliances. Statistical data and forest plots are presented. The forest plot is composed of a vertical axis that passes through number 1 of the horizontal axis and depicts the point of no difference in the odds of positive Ni patch-test scores before orthodontic treatment and after the placement of orthodontic appliances.

Table VIII. Prevalence of Ni hypersensitivity in patients having orthodontic treatment: comparisons with the general population

Study group	Ni hypersensitivity		Heterogeneity				Comparisons with general population (P)
	n	Summary prevalence (%)	Q value	df (Q)	Significance (P)	I ²	
Total sample of OT	1459	21.4	55.016	8	0.000	85	0.037
OT without cutaneous piercing	250	6.1	10.551	2	0.005	81	0.127
OT with cutaneous piercing	751	30.3	30.843	3	0.000	90	0.002
OT before cutaneous piercing	267	21.7	20.561	3	0.000	85	0.086
Cutaneous piercing before OT	466	35.9	18.873	3	0.000	84	0.000
General population	2832	12.3	50.734	3	0.000	94	

OT, Orthodontic treatment; I², inconsistency.

containing Ni before cutaneous exposure to Ni might actually lower the incidence of Ni hypersensitivity,²³ should be substantiated. Consequently, efforts to control the risks from Ni should be directed to the regulation of Ni exposure on the skin. Such attempts have already been effective in reducing Ni sensitization.¹⁷

These results are also of interest to orthodontists from a risk-management perspective. Ni hypersensitivity, although probably not influenced by orthodontic treatment, is present in considerable percentages in both the general population and orthodontic patients. Thus, the possibility for orthodontic appliances to elicit contact hypersensitivity reactions during treatment is not negligible. Moreover, the importance of contact allergic reactions in patients with atopic diseases is still being debated, and increased frequencies of contact allergy have been reported in such patients.³⁶ Consequently, the orthodontist should be aware that patients with Ni hypersensitivity might have a greater chance of a contact or an atopic hypersensitivity reaction and

should be prepared to modify the treatment accordingly.

Alternative treatment modalities can be used so that the patients with Ni hypersensitivity can benefit from orthodontic treatment. Instead of metallic brackets, alternatives include ceramic, polycarbonate (plastic), titanium, and gold-plated brackets.⁵ Stainless steel and gold-plated archwires are safe for Ni-sensitive orthodontic patients. Coated wire and beta-titanium wires are also alternatives.⁵

CONCLUSIONS

Based on the results of this meta-analysis, it seems that orthodontic treatment is not associated with an increase in the prevalence of Ni hypersensitivity, unless subjects have a history of Ni exposure from cutaneous piercing. However, many orthodontic patients have Ni hypersensitivity, and the clinician should be prepared to manage a possible reaction. The lack of high-validity primary studies about Ni hypersensitivity in orthodontic patients should be considered, and consequently,

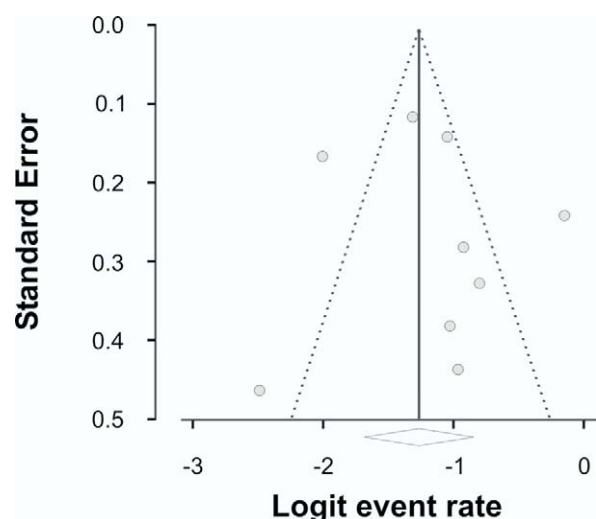


Fig 3. Funnel plot analysis for the evaluation of publication bias.

high-validity studies are needed to produce strong evidence to further support these results.

REFERENCES

1. Krob HA, Fleischer AB Jr, D'Agostino R Jr, Haverstock CL, Feldman S. Prevalence and relevance of contact dermatitis allergens: a meta-analysis of 15 years of published T.R.U.E. test data. *J Am Acad Dermatol* 2004;51:349-53.
2. Marks JG, Belsito DV, DeLeo VA, Fowler JF Jr, Fransway AF, Maibach HI, et al. North American Contact Dermatitis Group patch-test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998;38:911-8.
3. Turpin DL. California proposition may help patients in search of better oral health. *Am J Orthod Dentofacial Orthop* 2001;120:97.
4. European Union. Commission Regulation (EC) No 565/2006: Imposing testing and information requirements on the importers or manufacturers of certain priority substances in accordance with Council Regulation (EEC) No 793/93 on the evaluation and control of the risks of existing substances. *Official Journal of the European Union* 2006;L99:3.
5. Eliades T, Athanasiou AE. In vivo aging of orthodontic alloys: implications for corrosion potential, nickel release, and biocompatibility. *Angle Orthod* 2002;72:222-37.
6. McDonagh AJ, Wright AL, Cork MJ, Gawkrödger DJ. Nickel sensitivity: the influence of ear piercing and atopy. *Br J Dermatol* 1992;126:16-8.
7. White JM, Goon AT, Jowsey IR, Basketter DA, Mak RK, Kimber I, et al. Oral tolerance to contact allergens: a common occurrence? A review *Contact Dermatitis* 2007;56:247-54.
8. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*, Version 5.0.0. (updated February 2008), The Cochrane Collaboration, 2008. Available at: www.cochrane-handbook.org. Accessed March 30, 2008.
9. Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J, editors. *Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. CRD report number 4*. 2nd ed. York, United Kingdom: NHS Centre for Reviews and Dissemination; University of York; 2001.
10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
11. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. *Am J Public Health* 1999;89:1009-17.
12. Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, et al. Assessing the quality of reports of randomized trials: implication for the conduct of meta-analyses. *Health Technol Assess* 1999;3:1-98.
13. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
14. Pildal J, Chan AW, Hróbjartsson A, Forfang E, Altman DG, Gøtzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *BMJ* 2005;330:1049.
15. Borenstein M, Hedges L, Rothstein H. *Meta-analysis: fixed effect vs. random effects*. Available at: www.meta-analysis.com. Accessed November 2, 2007.
16. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in health care: meta-analysis in context*. 2nd ed. London: BMJ Publication Group; 2001.
17. Jensen CS, Lisby S, Baadsgaard O, Volund A, Menne T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002;146:636-42.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
19. Sterne JA, Egger M, Davey Smith G. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101-5.
20. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119-29.
21. Bass JK, Fine H, Cisneros GJ. Nickel hypersensitivity in the orthodontic patient. *Am J Orthod Dentofacial Orthop* 1993;103:280-5.
22. Menezes LM, Campos LC, Quintao CC, Bolognese AM. Hypersensitivity to metals in orthodontics. *Am J Orthod Dentofacial Orthop* 2004;126:58-64.
23. Van Hoogstraten IM, Andersen KE, Von Blomberg BM, Boden D, Bruynzeel DP, Burrows D, et al. Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin Exp Immunol* 1991;85:441-5.
24. Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, Hensten-Pettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop* 1996;109:148-54.
25. Janson GR, Dainesi EA, Consolaro A, Woodside DG, de Freitas MR. Nickel hypersensitivity reaction before, during, and after orthodontic therapy. *Am J Orthod Dentofacial Orthop* 1998;113:655-60.
26. Mortz CG, Lauritsen JM, Bindlev-Jensen C, Andersen KE. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense

- adolescence cohort study on atopic diseases and dermatitis (TOACS). *Acta Derm Venereol* 2002;82:359-64.
27. Kalimo K, Mattila L, Kautiainen H. Nickel allergy and orthodontic treatment. *J Eur Acad Dermatol Venereol* 2004;18:543-5.
 28. Saglam AM, Baysal V, Ceylan AM. Nickel and cobalt hypersensitivity reaction before and after orthodontic therapy in children. *J Contemp Dent Pract* 2004;5:79-90.
 29. International Contact Dermatitis Research Group. European Standard Series (ICDRG 1984). *Contact Dermatitis* 1984;11:63-4.
 30. Egger M, Smith GD. Meta-analysis: bias in location and selection of studies. *BMJ* 1998;316:61-6.
 31. Papadopoulos MA. Meta-analysis in evidence-based orthodontics. *Orthod Craniofac Res* 2003;6:12-26.
 32. Lenza MA, Moore RN, Cohen DM, Hoffman M. Nickel sensitivity to orthodontic archwires [abstract 2115]. *J Dent Res* 1993;72:368.
 33. Vender RB. The utility of patch testing children with atopic dermatitis. *Skin Ther Lett* 2002;7:4-6.
 34. Thyssen JP, Linneberg A, Menne T, Johansen JD. The epidemiology of contact allergy in the general population—prevalence and main findings. *Contact Dermatitis* 2007;57:287-99.
 35. 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.
 36. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from northern Norway. *Contact Dermatitis* 2007;56:10-5.
 37. Barros MA, Baptista A, Correia TM, Azevedo F. Patch testing in children: a study of 562 schoolchildren. *Contact Dermatitis* 1991;25:156-9.
 38. Dotterud LK, Falk ES. Metal allergy in north Norwegian schoolchildren and its relationship with ear piercing and atopy. *Contact Dermatitis* 1994;31:308-13.
 39. Ramadan AA. Effect of nickel and chromium on gingival tissues during orthodontic treatment: a longitudinal study. *World J Orthod* 2004;5:230-4.
 40. Staerkjaer L, Menne T. Nickel allergy and orthodontic treatment. *Eur J Orthod* 1990;12:284-9.
 41. Todd DJ, Burrows D. Nickel allergy in relationship to previous oral and cutaneous nickel contact. *Ulster Med J* 1989;58:168-71.
 42. Dainesi EA. Study of nickel hypersensitivity reaction, before, during and after fixed corrective orthodontic therapy [thesis]. Bauru, Brazil: University of Sao Paulo; 1995.
 43. Menezes LM. Hypersensitivity to metals in orthodontic appliances [thesis]. Rio de Janeiro, Brazil: University of Rio de Janeiro; 2000.
 44. Menezes LM. Orthodontic appliances do not sensitize patients to metals. *Dental Abstracts* 2005;50:116.
 45. Greppi AL. A prospective case-control study of nickel hypersensitivity reactions in orthodontic patients [thesis]. Toronto, Ontario, Canada: University of Toronto; 1991.
 46. Greppi L, Smith DC, Woodside DG, Varrela T. Nickel hypersensitivity reactions in orthodontic patients [abstract 768]. *J Dent Res* 1991;91:70.