

Nickel-free vs conventional braces for patients allergic to nickel: Gingival and blood parameters during and after treatment

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Introduction: Allergic and inflammatory reactions have commonly been associated with the release of metal ions during orthodontic treatment. Our objective was to evaluate prospectively gingival and blood status in patients allergic to nickel. **Methods:** Allergy to nickel was diagnosed using a patch test. Two groups were established: conventional braces ($n = 21$) and nickel-free braces ($n = 21$). The gingival index was used to determine gingival status before treatment, periodically for 12 months (evaluations every 3 months), and 1 month after the removal of the braces. Blood status was evaluated with a complete blood count, including the quantification of nickel and immunoglobulin E before treatment, during treatment, and 1 month after removal of the braces. The data were analyzed using Mann-Whitney, Student t , Wilcoxon, repeated measures analysis of variance, Friedman, and chi-square tests. Either the Pearson or the Spearman correlation coefficients were calculated, when appropriate. **Results:** The number of basophils increased significantly among the evaluations in both groups (conventional, $P = 0.002$; nickel-free, $P = 0.001$), whereas the number of eosinophils and the immunoglobulin E levels decreased significantly in the conventional group ($P = 0.004$). Plasma nickel levels were increased before and during treatment, and decreased 1 month after removing the braces in both groups, but the differences were significant only in the nickel-free group ($P = 0.002$). No correlations were found between the concentrations of nickel and immunoglobulin E, basophils, or eosinophils, or between the gingival index and either bands or segmented neutrophils ($P \geq 0.05$). **Conclusions:** Patients treated with nickel-free braces had better gingival health and smaller blood changes than did those treated with conventional braces. All abnormalities tended to be eliminated after the removal of the braces. (Am J Orthod Dentofacial Orthop 2016;150:1014-9)

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Alloys containing nickel are widely used in orthodontic appliances and can account for up to 55% of the weight of such devices.¹ However, nickel is considered one of the most common allergens,² with up to a 30% prevalence rate of contact allergy, depending on age, sex, and ethnicity.³

In general, orthodontic materials are considered highly biocompatible.⁴ However, side effects have been reported in the literature, including allergic and inflammatory reactions, cytotoxicity, and mutagenicity.⁵ Inflammation seems to play a pivotal role in the initiation of nickel-induced hypersensitivity, promoting the activation and recruitment of immune cells to the exposure area.⁶ Thus, studies have indicated nickel to be a cause of changes in periodontal and immunologic statuses in allergic patients.⁷⁻⁹

Previous studies by our research group involving patients allergic to nickel and treated with conventional

braces demonstrated that periodontal status was particularly harmed, including a change in the number of neutrophils, but remission occurred with the removal of the braces.^{7,10} As a result of these findings, we initiated a new set of experiments involving allergic patients who received nickel-free braces compared with those who received conventional braces, in which the former group demonstrated better periodontal status during treatment.¹¹ Thus, studies involving a periodontal evaluation in relation to blood parameters in this group were needed for comparisons with previous trials.

Nickel-free devices are reported to release low amounts of nickel ions, which could diminish hypersensitivity among allergic patients.^{7,12} Therefore, studies involving nickel-free braces may provide important information by first determining whether nickel is truly responsible for triggering responses of an inflammatory or allergic nature.

The aim of this study was to perform a longitudinal evaluation of gingival and blood statuses among patients allergic to nickel, by comparing conventional and nickel-free braces.

MATERIAL AND METHODS

A study was conducted with a sample of patients ranging in age from 10 to 45 years. The sample size was calculated using the formula for the comparison of 2 means,¹³ and the parameters used were determined in a previous study.⁷ Considering a standard deviation of 0.10 plasm levels of nickel in allergic patients, since this is an important variable and patients were allergic to this metal, and a 0.10 difference to be detected between the groups (conventional and nickel-free braces) with 80% statistical power and 5% standard error, we determined that a minimum of 16 subjects were needed in each group. We added 5 subjects in each group to compensate for possible losses. A total of 42 allergic subjects were recruited for this study. After enrollment, we had 28 female and 14 male subjects. Thus, we formed 14 pairs of female and 7 pairs of male subjects. Subsequently, a random allocation was performed in each pair, so that 1 subject received nickel-free braces, and the other received conventional braces.

All patients began treatment at the same time. Before placement of the braces, all participants received prophylaxis with bicarbonate spray and counseling with regard to oral hygiene. Oral hygiene measures consisted of brushing the teeth at least 4 times a day and using dental floss with the help of a needle and mouthwash to facilitate the removal of plaque. Conventional and nickel-free Roth Monobloc Morelli braces (Dental Morelli,

Sorocaba, São Paulo, Brazil) were used. The conventional braces contained 16% to 20% chrome, 8% to 13% nickel, and 2% to 3% molybdenum. The nickel-free braces contained up to 18% chrome, 0.2% to 4% nickel, and 3.5% molybdenum.

Data were collected based on a study by Pazzini et al¹¹ that involved the same sample and is described briefly below.

Before treatment, a skin patch test was used to identify patients with a nickel allergy. According to the allergy evaluation standards of the Brazilian Medical Association and the Federal Medicine Council (Brazilian Study Group on Contact Dermatitis, 2000), this is the most efficient method for confirming the etiologic diagnosis of allergic contact eczema. After 48 hours, the patches were removed, and 1 reading was performed in compliance with the norms of the International Contact Dermatitis Research Group.¹⁴

Clinical gingival characteristics (color, volume, and bleeding) were assessed. A standardized probe with a millimeter ruler was used to determine the presence or absence of gingival bleeding around the maxillary and mandibular first premolars at 4 points on the vestibular, palatine/lingual, and mesial and distal faces. These teeth were selected because of their locations at the halfway point of each quadrant of the oral cavity. The gingival index was used for this evaluation, with qualitative changes in the gingival tissues taken into consideration.^{15,16} Gingival assessments were conducted by a blinded, duly calibrated examiner (R.J.J.) ($\kappa > 0.90$) before the start of treatment (T0) and at regular 3-month intervals for 12 months with the braces in place (T1, T2, T3, and T4) as well as 1 month after removal of the braces (T5). After the periodontal evaluation, prophylaxis was performed at each session with a bicarbonate spray.

All participants underwent a full blood test, with the determination of the total immunoglobulin E (IgE) and the amount of circulating nickel in the blood before treatment (examination 1), 9 months into orthodontic treatment (examination 2), and 1 month after removal of the braces (examination 3).⁷ The examination before treatment had not been performed in the previous studies.

For the blood count, analyses were performed of leukocytes, basophils, eosinophils, bands, segmented neutrophils, platelets, lymphocytes, and monocytes. Fecal examinations were performed on all participants to determine parasitic infestations (helminth eggs and larvae or protozoan cysts), since parasitic infections can affect the IgE and white blood cell count, especially the number of eosinophils. All laboratory examinations were performed by a duly trained pharmacist-biochemist, and no patient exhibited parasitosis.

Statistical analysis

All data were analyzed using SPSS for Windows (version 22.0; IBM, Armonk, NY). The frequencies of the variables studied were first determined. The Shapiro-Wilk test was used to determine the normality of the distribution of the quantitative variables. Repeated measures analysis of variance (ANOVA) or the Friedman test was used to determine intergroup and intragroup differences regarding blood components. Either the nonpaired *t* test or the Mann-Whitney test was used to determine differences in blood components between the conventional and nickel-free groups during examinations 1, 2, and 3. Either the paired *t* test or the Wilcoxon test was used to determine these differences within the same group. Intergroup and intragroup comparisons of the gingival index among the 6 evaluation sessions were performed using the chi-square and Friedman tests, respectively. The Dunn correction was used to adjust the *P* values for multiple testing. Nonparametric tests were applied because the gingival index is a qualitative method. Thus, the values for the 0, 1, 2, and 3 scores cannot be used as ordinary variables and were dichotomized as presence (1, 2, or 3) or absence (0) of gingival inflammation for statistical purposes. A *P* value of 0.05 or less was considered to have statistical significance.

All aspects of this study, including the methods to obtain informed consent and agreement from the participants (parents or caregivers of adolescents), were independently reviewed and approved by the Human Research Ethics Committee of the Centro Universitário of Lavras (Brazil) under process number 0015.0189.000-10. This study was conducted in compliance with the principles for medical research involving human subjects in the Declaration of Helsinki. All data remained anonymous and confidential.

RESULTS

Forty-two patients proved to be allergic to nickel (28 female [67%], 14 male [33%]). The study began with 21 patients in each group. However, only 20 in the conventional group and 17 in the nickel-free group completed all treatment sessions.

With regard to blood components, a statistically significant difference in segmented neutrophils was found between the groups only during treatment. The number of basophils increased significantly between examination 1 (before treatment), examination 2 (9 months into treatment), and examination 3 (1 month after removal of the braces) in both groups, whereas the number of eosinophils decreased among the evaluation periods in the conventional group. Moreover, a decrease in IgE levels

occurred among the evaluations in the conventional group. Plasma nickel levels were increased before and during treatment and decreased 1 month after removing the braces in both groups, but the differences were significant only in the nickel-free group (Table I).

Table II shows the intragroup and intergroup findings with regard to the gingival index, demonstrating significant differences among the different evaluation times ($P \leq 0.05$), with higher values in the conventional group than in the nickel-free group. Significant differences between the groups were detected at T3 and T4.

Correlations were tested between nickel concentration and IgE, basophils, and eosinophils, as well as between IgE and the numbers of both bands and segmented neutrophils before (examination 1), 9 months after the placement of the braces (examination 2), and 1 month after the removal of the braces (examination 3). However, no significant correlations were found in either group among the 3 examinations (data not shown in Table II).

DISCUSSION

In this study, the relationship between gingival status and blood parameters was evaluated in allergic patients treated with either conventional or nickel-free braces. Examinations were made on the sample before orthodontic treatment, which was not performed in previous studies and therefore limits comparisons of the data.^{7,10,17}

European regulations on the amount of nickel that may be released from objects with direct and prolonged skin contact, such as items inserted into pierced body parts, significantly reduced the incidence of nickel allergy among young Danish women from 27.6% in 1985 to 16.8% in 2007.¹⁸

Nickel is known for its potential to cause allergic reactions in the oral cavity.¹⁹ In this study, however, no correlation was found between circulating nickel levels and IgE quantification in either the conventional or the nickel-free group, although IgE plays an important role in the pathogenesis of allergic as well as inflammatory reactions and is generally increased in patients who suffer from allergies.²⁰ This indicates that nickel may not influence the peak production of IgE.²¹ Hypersensitive reactions to nickel over a long time are likely to occur only with prior sensitization from nondental contact, which is rare, and small doses of nickel may induce tolerance to this allergen.²² With orthodontic braces, continuous exposure in the oral cavity may be a pivotal factor supporting tolerance among persons who have not been previously sensitized.²³

Some studies have suggested an immediate reaction to nickel. Di Tola et al²⁴ found that despite the moderately increased number of circulating B lymphocytes

Table I. Comparative analysis of blood components in conventional and nickel-free groups before (exam 1), during (exam 2), and after (exam 3) orthodontic treatment

Component	Conventional group				Nickel-free group			
	Exam 1 (mean ± sd)	Exam 2 (mean ± sd)	Exam 3 (mean ± sd)	P value	Exam 1 (mean ± sd)	Exam 2 (mean ± sd)	Exam 3 (mean ± sd)	P value
Leukocytes (mm ³)	5989.47 ± 1771.37	5920.00 ± 2244.34	6789.45 ± 1865.45	0.142A	5450.58 ± 1948.46	5900.00 ± 1947.11	6823.52 ± 1751.95	0.066A
Basophils (mm ³)	10.00 ± 0.73 ^a	26.84 ± 17.65 ^b	44.20 ± 41.65 ^b	0.002F	6.47 ± 9.31 ^a	26.47 ± 23.16 ^b	37.05 ± 36.55 ^b	0.001F
Eosinophils (mm ³)	380.52 ± 270.53 ^a	271.94 ± 191.36 ^b	298.68 ± 241.50 ^{a,b}	0.040F	381.82 ± 209.51	294.35 ± 185.80	307.65 ± 238.02	0.824F
Bands (mm ³)	37.27 ± 100.53	31.57 ± 115.72	21.05 ± 53.53	0.867F	29.41 ± 98.51	0.00 ± 0.00	1.76 ± 5.30	0.368F
Segments (mm ³)	5358.50 ± 913.24	5297.89 ± 982.18 [*]	5129.15 ± 919.60	0.674A	4910.58 ± 1032.80	4668.82 ± 756.39 [*]	4980.60 ± 1123.90	0.191A
Lymphocytes (mm ³)	3528.50 ± 846.24	3552.10 ± 906.21	3544.75 ± 841.52	0.998A	3897.05 ± 968.00	4102.35 ± 937.08	3775.30 ± 1024.65	0.184A
Monocytes (mm ³)	652.50 ± 224.82	659.47 ± 262.98	728.95 ± 248.05	0.297B	599.41 ± 236.18	547.88 ± 342.48	643.52 ± 219.20	0.740F
Platelets (mil/mm ³)	240.00 ± 57.10	229.05 ± 54.28	247.20 ± 66.60	0.099A	225.35 ± 47.92 ^a	231.05 ± 43.97 ^b	234.10 ± 40.35 ^{a,b}	0.012A
IgE (UI/mL)	479.55 ± 773.79 ^a	370.74 ± 646.59 ^b	335.60 ± 560.75 ^b	0.040F	469.56 ± 545.75	414.99 ± 531.85	523.92 ± 844.65	0.790F
Nicke 1 (mcg/L)	1.24 ± 1.26	2.05 ± 0.79	1.60 ± 0.80	0.079A	0.80 ± 0.82 ^a	1.77 ± 0.78 ^b	1.40 ± 0.60 ^{a,b}	0.016A

Different superscript lowercase letters indicate significant intragroup differences (same person during experiments 1, 2, and 3).

Exam, Examination; sd, standard deviation; A, repeated measures ANOVA; F, Friedman test; P ≤ 0.05.

*Indicates significant differences between groups (conventional and nickel-free).

Table II. Comparison of mean gingival index scores over time in the conventional and nickel-free groups

	Conventional (n = 20)	Nickel-free (n = 17)	P value
T0	0.30 ^a	0.53	0.286
T1	0.45 ^{a,b}	0.53	0.457
T2	0.60 ^{a,b}	0.47	0.368
T3	0.75 ^b	0.23	0.026*
T4	0.75 ^b	0.29	0.031*
T5	0.25 ^a	0.35	0.761
Pvalue	0.014	0.426	

Friedman test (intragroup) and chi-square test (intergroup); P ≤ 0.05.

Different superscript letters indicate significant differences between lines in the same column.

*Significant differences between groups.

after the oral mucosal nickel patch test in nickel-sensitive patients, total IgE serum concentrations were not increased; this agrees with our findings. We believe that this finding may exclude the possibility of an IgE-dependent immediate hypersensitivity reaction and indicate that nickel may act as a mast cell discharger. Although this hypothesis could be in the realm of possibilities, the existence of an IgE-mediated immune mechanism cannot be ruled out. Nickel was formerly postulated to induce only a Th1 cell response and a related cytokine pattern. Researchers later demonstrated that nickel is also able to stimulate Th2 cells.²⁵

The continuous low-level stimulus of antigens, such as nickel, raises the level of interleukin-4 produced by T cells, regardless of whether a person is allergic; this favors a polarized immune response for a Th2 profile, with a characteristic cell and molecule population through a pathway dependent on STAT-6 and GATA-3.²⁶ In this study, increases in basophils and nickel were found in both groups, and a reduction in IgE was found in the conventional group; this indicates a Th2 immune response. These findings agree with data described by Niiyama et al,²⁷ who assessed the systemic response produced by nickel. Studies have also reported a nickel-produced response with a predominance of Th1 CD4+ T cells because of the presence of interferon-γ, but the balance generally tends to favor the expression of Th2 cells and inhibit other subpopulations, thereby playing a suppressive role in the immune response.^{28,29} After activation, T lymphocytes proliferate and differentiate into Th1 or Th2 effector cells. A similar result occurred regarding the number of lymphocytes, which also increased between evaluation times, but this increase did not achieve statistical significance. This may be

explained by the fact that people allergic to nickel have few T cells, or lack specific suppressor T cells, which regulate the number of leukocyte populations.³⁰

More than a direct sensitizing agent of skin and mucosa, nickel appears to alter gingival status, acting as a modifying factor of periodontal disease in sensitive patients. In our study, gingival abnormalities differed between the groups only after 9 months (T3), demonstrating that the reaction depends on exposure time.^{7,10} The increase in the gingival index over time in the conventional group and the decrease in the nickel-free group suggest that chemicals with a low molecular weight, such as nickel, may irritate tissues by inducing the production of various proinflammatory and chemotactic molecules and are potentially allergenic when able to bind to proteins, such as immune response molecules.³¹ Furthermore, nickel induces T lymphocytes to produce cytokines, thereby stimulating tissue proliferation, which may favor gingival hyperplasia and blood changes.³² The pattern and level of cytokines secreted are critical to triggering differential immune responses that can lead to different degrees of tissue damage. Temperature, microorganisms, enzymatic compounds, and ions normally present in the oral cavity particularly favor the breakdown and release of metallic elements from dental casting alloys.³¹ It would therefore be plausible to suppose that the continuous release of small amounts of nickel together with poor hygiene to the epithelium could be an initiating factor of gingival overgrowth induced by orthodontic braces.³³

The gingival epithelium is the first barrier to come into contact with corrosive materials, such as nickel and bacteria. Human gingival fibroblasts are the major component of gingival tissues and are strongly affected by the release of interleukin-1 β , which is highly synthesized by gingival keratinocytes and monocytes/macrophages.³⁴ Human gingival fibroblasts express both interleukin-1Rs and toll-like receptors and function as nonprofessional inflammatory cells,³⁵ participating in inflammatory reactions such as gingivitis and periodontitis.^{36,37}

The number of bands is significantly higher in patients allergic to nickel than in nonallergic patients.⁷ Bands are stimulated in bacterial infections or inflammations. It has been suggested that nickel exerts an influence on local and systemic inflammatory reactions throughout orthodontic treatment.³¹ Although it was nonsignificant, the reduction in this study was greater in the nickel-free group than in the conventional group; this suggests less gingival inflammation with the use of nickel-free braces. Nickel-free stainless steel braces do not have a significant amount of nickel in their composition. This suggests that they may be a viable

alternative for allergic patients, despite their poorer mechanical properties, which are a limitation during orthodontic mechanics, since nickel considerably enhances resistance to oxidation and corrosion.³⁸ Moreover, nickel enhances the strength of the alloy in stainless steel.³⁹

Other studies have also reported the positive characteristics of nickel-free braces in terms of the release of nickel and allergic manifestations.^{12,40} Moreover, considerable differences in individual sensitivity to nickel as well as individual nickel absorption and excretion have been demonstrated.⁴¹ However, orthodontic treatment for nickel-sensitive patients may prove challenging. Further studies are needed to examine the cytotoxic effects of released nickel on in-vitro cell cultures and the extent to which corrosive products are actually absorbed by patients.² The increases in allergies to nickel and gingival diseases as well as the need for orthodontic treatment demonstrate the importance of our findings and the constant necessity with regard to future analyses.⁴²

CONCLUSIONS

1. Patients with nickel-free braces demonstrated better gingival health and fewer blood changes than did those treated with conventional braces.
2. Gingival and blood changes tend to disappear after removal of the braces.

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