Allergic reactions and nickel-free braces: A systematic review

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Abstract: Nickel-free braces have gained popularity as a viable alternative for patients who are allergic to nickel. The purpose of this systematic review was to determine whether evidence exists to justify the use of nickel-free brackets in orthodontic patients who are allergic to nickel. An electronic search was performed using 7 databases (MEDLINE, BBO, LILACS, Web of Science, EMBASE, BIREME and Cochrane Library), without restriction regarding year or language, with supplemental manual searching of the references of retrieved articles. The search strategy produced 89 papers. The data extraction and quality score of each paper were evaluated independently by two reviewers, once each. After selection based on the eligibility criteria, four papers, including 2 controlled clinical trials and 2 clinical trials, qualified for the final analysis. Quality assessment of the included articles was also performed. Nickel-free braces (Ni content - 2% max.) seem to represent a viable alternative for orthodontic patients who are allergic to nickel. However, further *in vivo* studies, considering the immunology characteristics of patients, are needed to determine the clinical implications of the findings of this study.

Descriptors: Orthodontic Brackets; Hypersensitivity; Nickel; Orthodontics.

Introduction

Austenitic stainless steel used in orthodontic braces contains 18% chrome, 0.15% carbon and 8% nickel.[1] The literature demonstrates that nickel is potentially allergenic and capable of causing a late-phase, type IV hypersensitivity reaction. Such a reaction will be characterized by signs such as gingival overgrowth, angular cheilitis and labial desquamation in the oral cavity.[2-4] Because orthodontic wires and brackets maintain proximity to the oral mucosa for long periods of time, they must be resistant to corrosion and ion release, and should not generate allergic responses. The material used should be well tolerated by oral tissues in the oral environment.[5]

There are a number of non-allergic braces for nickel-sensitive patients, such as titanium braces, which are more corrosion resistant and do not release nickel into the oral cavity.[5,6] Twenty-two zero five (2205) duplex stainless steel contains much less nickel, and could also be used to develop orthodontic appliances with less allergenic potential.[7] Other options include ceramic or plastic braces, as well as those with a low nickel concentration known as nickel-free braces.[1,8]

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However, there are reports in the literature that allergic reactions to nickel are frequently associated with reactions to other metals such as chrome and cobalt.[9-11] It is therefore difficult to assess the individual contribution of each component when considering the allergic reaction of patients. Thus, studies involving nickel-free braces may provide important information by first determining whether nickel is truly the agent responsible for triggering responses of an inflammatory and/or allergic nature. Moreover, such studies would determine whether nickel-free braces actually represent a viable alternative for patients who are allergic to nickel.

Discrepant outcomes have been produced by a considerable variety of diagnostic approaches, study designs, sample sizes and research approaches. Thus, the purpose of this systematic review was to determine whether evidence exists to justify the use of nickel-free brackets for orthodontic patients who are allergic to nickel. Moreover, a quality analysis of the methodological soundness of the studies used in this review is performed.

Materials and Methods

Research Strategies

To develop this study, we performed searches of relevant literature in electronic databases:

- Latin American and Caribbean Center on Health Sciences Information - BIREME (www.bireme.br): Lilacs database (Health Sciences Literature published in Latin America and the Caribbean since 1982) and Medline (International Literature, Medical and Biomedical areas, compiled since 1965);
- Web of Science (www.thomsonisi.com): Database of the sciences, social sciences, arts and humanities;
- Cochrane Library (http://cochrane.bvsalud.org): access to databases of Cochrane systematic reviews of controlled trials register of the Cochrane Collaboration, evaluation of health technologies, among others;
- BBO (Brazilian Bibliography of Dentistry).

Manual searches were also performed of reference lists of articles found in, and recovered from, the databases identified above. Screening of eligible studies and assessment of the methodological quality of the trials and data extraction were conducted. The following criteria guided the assessment of the quality of the papers selected:

1. study design (randomized clinical trials – RCT; Prospective – P; controlled clinical trials – CCT; Longitudinal – L: 3 points; clinical trials – CT: 1 point).
2. adequate sample size: 1 point.
3. adequate description of selection: 1 point.
4. valid measurement methods: 1 point.
5. use of method error analysis: 1 point.
6. blinding in measurements: 1 point.
7. adequate statistical methods: 1 point.
8. confounding factors included in the analysis: 1 point.

Sample sizes were considered adequate when presented with a sample calculation. Measurement methods were considered valid when a measurement error test was presented. Studies assessed from 0 to 5 points were considered of low methodological quality; those assessed from 6 to 8 points to be of medium quality; and those assessed from 9 to 10 points to be of high quality.

The data extraction and quality score of each paper were evaluated independently by two reviewers, once each. The reviewers selected the papers by reading the titles and abstracts. Full articles were obtained if there were insufficient data in the title and abstract to support a clear decision. There was very high agreement between the researchers in this phase.

The search was not limited by year, so the results include all articles that appeared in each of the databases, dating from the inceptions of the databases until August, 2010. The following keywords were used in the search: “nickel-free”, associated to “orthodontics”, “orthodontic brackets”, “nickel allergy and orthodontics”, “allergy”, “orthodontic appliances” and “hypersensitivity reaction”.

Selection Criteria

All randomized controlled trials comparing nickel-free braces with non-nickel-free braces were

considered. The outcomes were lack of allergic reactions. Studies *in vivo* were also included. Studies of case reports and review articles, abstracts and studies *in vitro* were not considered for this review.

Data Collection and Analysis

Data were collected considering the following items: author, year of publication, measures, study design, study groups, methods/measures and results. Differences were resolved by discussion to reach consensus between the two reviewers.

Results

The search strategy produced 89 papers. After selection, and based on the eligibility criteria, four papers qualified for the final analysis (Table 1). The complete texts of these papers were obtained for analysis.

Quality of the Studies

The quality of the investigation and methodological consistency were high in one study,[14] medium in one study[15] and low in two studies[8,12] (Table 2).

Table 1 - Retrieved studies.

Authors	Study Groups	Sample	Age (y)	Methods/ Measurements	Outcome Measurements
Tammaro *et al.*[12]	Patients affected by systemic allergy to nickel	67	ND	ND	Good results on consequent tolerance to nickel in treated patients
Pereira *et al.*[13]	This study was conducted in rats. A: A1: control, without brackets; A2: nickel-free brackets; A3: nickel brackets B: nickel brackets; sacrificed 2 days after appliance removal C: nickel brackets; sacrificed 7 days after bracket removal	21 7 7	-	Total and differential leukocyte numbers, IgA quantification and histopathologic analysis, and Histopathologic analysis of subcutaneous tissue	There were significant differences in the number of leukocytes between the nickel-implanted animals and the nickel-free and control groups after 14 days of implantation ($P < .05$). However, there were no significant differences among groups A1, A2, and A3 for the differential number of leukocytes and for the IgA quantification, except for the number of monocytes, which was three times higher in the nickel group (A3). The histopathologic findings did not show differences between groups
Pantuzo *et al.*[8]	I: test specimens with nickel II: test specimens without nickel	12 5	11 - 30	Patch Test McNemar test	The test specimens without nickel showed less allergic reaction when compared to those with the conventional alloy
Pacor *et al.*[14]	Patients with recurrent aphthous stomatitis (RAS)	380	ND	Patch Test	Seventy out of 380 patients (18.4%) presented a contact sensitization to nickel sulfate (positive patch test). In all of these, the orthodontic appliance was replaced with one made of nickel-free materials. All patients were re-examined by the dentist 6 months after the removal of the orthodontic appliance. The symptoms had completely remitted in 28/70 patients, had partially improved in 31/70 patients and had remained unchanged in 11/70 patients

ND: not declared.

Table 2 - Quality evaluation of the retrieved studies.

Articles	Study design	Sample size	Selection description	Valid measurement methods	Method error analysis	Blinding in measurement	Adequate statistics provided	Confounding factors considered	Judged quality standard
Tammaro *et al.* [12]	CT	Inadequate	Inadequate	No	ND	ND	No	ND	Low
Pereira *et al.* [13]	CCT	Adequate	Adequate	No*	Yes	ND	Yes	ND	Medium
Pantuzo *et al.* [8]	CT	Inadequate	Inadequate	Yes	Yes	ND	Yes	ND	Low
Pacor *et al.*[14]	CCT, L	Adequate	Adequate	Yes	Yes	Yes	Yes	ND	High

CCT: controlled clinical trial; CT: clinical trial; L: longitudinal; ND: not declared. *This measurement was considered not valid since it was conducted in rats, and the evidence level should be lower compared to that of human studies.

The most serious flaws were CT and CCT with small sample sizes, *in vitro* studies and inadequate description of the selection process. Problems regarding confounding variables, a lack of method error analysis and the absence of blinding in measurements are other examples of shortcomings. The choice of statistical method was not reported in one paper.[12]

Discussion

Only four studies fulfilled the inclusion criteria established for the present systematic review. This underlines the scarcity of consistent studies and a lack of scientific evidence to allow orthodontists to choose nickel-free braces safely. Only one study offered a high degree of evidence.[14] Thus, comparisons with other studies were performed in a limited manner due to differences in study designs, analysis methods, selection and sample size. Furthermore, meta-analysis and heterogeneity were not conducted due to the small number of studies with different methodologies that were found.

Nickel-free braces have been evaluated with regard to chemical composition and behavioral characteristics.[1,15] Nickel-free stainless steel braces produced by Morelli (Monobloc) proved not to have a significant amount of nickel in their composition.[1] This suggests that these braces may be a viable alternative for allergic patients.

Other studies also point to the positive characteristics of nickel-free braces in terms of the release of nickel and allergic manifestations.[8,16] Nickel is capable of influencing the periodontal condition of allergic orthodontic patients.[2] In a study by Pazzini *et al.*,[2] the patient's history of allergic reactions to nickel (reported in the patient history) and the patch test were conclusive for a diagnosis of nickel allergy. At the beginning of treatment, the patient's clinical condition progressed with the appearance of hyperplasic gingival areas associated with hyperemia and edema. Patients with a history of hypersensitivity often present these two symptoms, associated with appliances that contain nickel.[17,18] After seven months of treatment the appliances were removed, due to excessive areas of hyperplasia.[19] After the conventional appliance was removed the inflammatory condition improved significantly, demonstrating that nickel was possibly a modifying factor in allergic patients. One month after removal of the appliance and the subsequent reduction in inflammation, the decision was made to attach a nickel-free appliance. Treatment continued for another five months with hyperplasic areas remaining, but to a lesser degree. Although the study is a clinical case, it demonstrates a personal experience of the problem.

On the other hand, braces made from a Co-Cr wear-resistant alloy with the least Ni content (0.5%) did not release a lesser amount of Ni in comparison to conventional braces, not serving as an alternative to conventional braces. As a group, cobalt-based alloys may be generally divided into three categories: wear resistant, corrosion-resistant and heat-resistant materials. Wear-resistant cobalt-based alloys have the lowest Ni content (3% max.), 25% to 30% Cr, 0.25% to 3.3% carbon, as well as manganese, silicon, molybdenum, tungsten, iron and sodium. This alloy is used in bracket manufacturing. However, wear-resistant cobalt-based alloys (with low Ni content) exhibit limited resistance to aqueous corrosion.[15] The corrosion of brackets with the least Ni content (0.5%) may be explained by the characteristics exhibited by the Co-Cr wear-resistant alloy with low nickel content (3% max.) in an aqueous medium.

Nickel-free test specimens caused a significantly smaller allergic reaction in only 31% of patients sensitive to nickel.[8] One possible explanation for this is that the allergic reaction to nickel is often associated with allergies to chrome and cobalt, which are potent allergens found in the composition of the two specimens tested in the study cited. It is therefore valid to argue that the influence of nickel in the development of hypersensitivity reactions may be overestimated.

The study carried out by Pereira *et al.*[13] found no histopathological differences between groups with nickel-free and conventional braces. However, an increase was found in the total number of leukocytes in the nickel group with nickel brackets (A3), when compared with the nickel-free brackets (A2) and control (A1) groups. This is related to type IV immune response.[20,21] In this context, nickel binding

to endogenous macromolecules can stimulate macrophages and cytotoxic cells, up-regulating the expression of adhesion molecules.[22-24] The differential quantification of leukocytes in the current research shows that the difference in the total number of leukocytes was caused by an increase in the number of monocytes. It has been reported that low-dose exposure to nickel can alter the metabolism of monocytes.[25] Additionally, nickel induces T lymphocytes to produce several cytokines, including interferon IF-γ and interleukin IL-2, IL-5, and IL-10; and, it stimulates cellular proliferation.[19] However, this study evaluated histopathological features in rats, which make comparisons difficult when extrapolating to humans.

A retrospective data analysis of patch tests and oral nickel challenges in 380 patients (204 women and 176 men) affected by Recurrent Aphthous Stomatitis (RAS) was performed.[14] The symptoms of RAS had remitted completely in 28/70 patients, had partially improved in 31/70 patients and had remained unchanged in 11/70 patients when conventional nickel braces were replaced by nickel-free braces. This indicates that nickel-free brackets contributed to an improvement in approximately 85% of allergic patients. The results of this study demonstrate that, in some patients with a positive patch test to nickel sulfate, the perpetuation of RAS can be related to a hypersensitivity to ingested nickel salts, independently of local contact to nickel.

Conclusion

The results of the present study point to evidence in favor of the use of nickel-free braces (Ni content - 2% max.) as a viable alternative for orthodontic patients who are allergic to nickel. However, further *in vivo* studies, considering the immunology characteristics of patients, are needed to determine the clinical implications of the findings of this study. Moreover, high-validity studies are needed to produce strong evidence to further support the results of this systematic review.

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