applied sciences

MDPI

Review

The Changes in Nickel and Chromium Ion Levels in Saliva with Fixed Orthodontic Appliances: A Systematic Review

Klaudija Urbutytė *, Andrė Barčiūtė and Kristina Lopatienė

Department of Orthodontics, Faculty of Odontology, Lithuanian University of Health Sciences, J. Lukšos-Daumanto 6, 50106 Kaunas, Lithuania
* Correspondence: klaudija.urbutyte@stud.lsmu.lt

Abstract: Fixed orthodontic appliances (braces systems) contain variable amounts of nickel and chromium, which can lead to immune responses and allergic reactions. The objective of the present review was to evaluate the changes in the quantity of nickel and chromium in saliva among patients wearing braces systems. The electronic databases used to perform the search were Pubmed, ReasearchGate, and Google scholar. After an initial search of these electronic databases, 12 studies were included in the systematic literature review. Overall, 554 patients wearing non-removable orthodontic appliances participated in the research that we reviewed. The age of the subjects ranged from 11 to 35 years. The quantity of chromium and nickel ions in saliva was measured before the braces systems were placed and after some period of having them. After evaluating the changes in nickel and chromium levels in saliva during orthodontic treatment with fixed brackets, it can be concluded that there is an increase in the levels of nickel and chromium ions in saliva. There is a significant increase in these ions after placement of the orthodontic appliances, peaking from three to six months, but not reaching toxic levels. The levels then gradually decrease. A full and detailed examination of the patient before starting orthodontic treatment is important, and alternative orthodontic appliances for patients who are allergic to nickel and/or chromium should be recommended.

Keywords: nickel; chromium; saliva; fixed orthodontic appliances; dentistry; orthodontics

check for updates

Citation: Urbutytė, K.; Barčiūtė, A.; Lopatienė, K. The Changes in Nickel and Chromium Ion Levels in Saliva with Fixed Orthodontic Appliances: A Systematic Review. *Appl. Sci.* **2023**, *13*, 4739. https://doi.org/10.3390/app13084739

Academic Editors: Paola Gandini and Andrea Scribante

Received: 27 February 2023
Revised: 6 April 2023
Accepted: 7 April 2023
Published: 10 April 2023

1. Introduction

As the prevalence of orthodontic malocclusion and the need for treatment increases, more and more patients are indicated for orthodontic treatment with fixed orthodontic appliances (brackets). These appliances are composed of metal alloys of nickel (Ni), cobalt (Co), chromium (Cr), titanium (Ti), iron (Fe), and copper (Cu) [1]. During mastication, pressure and temperature fluctuations and electrochemical reactions with nutrients in the mouth cause the release of metal ions into saliva and, if these processes last for a longer time, they create a medium for long-term corrosion [2]. Research has shown that fixed orthodontic appliances release nickel and chromium ions into saliva through electrochemical decomposition, which leads to the production of free radicals and chemical changes in the DNA base [3]. Nickel and its compounds form arsenic and sulfide complexes, which are known allergens, mutagens, and carcinogens [4]. These ions can penetrate the mucous membrane and activate epithelial cells, which produce various cytokines or chemokines. An immune response is then triggered, during which antigen and T cells are activated. Some cytokines activate antigen-presenting cells, such as Langerhans cells or dendritic cells. The activated antigens migrate to the lymph nodes, where they release allergens to T cells. Subsequent re-exposure to the same allergen triggers the activation of specific T cells, which subsequently enter the bloodstream and cause visible signs of hypersensitivity after 48–72 h. However, the exact molecular mechanisms that mediate the interaction between epithelial and immune cells in nickel allergy are unknown [5,6].

Epidemiological studies have found hypersensitivity reactions to nickel and chromium, with 15.7% of the population being allergic to metal in general, 14.5% of the population being specifically allergic to nickel, and 0.8% being specifically allergic to chromium. Hypersensitivity to nickel is found in many countries around the world, with varying frequencies of sensitivity, but the risk of developing allergies remains high [6]. Allergic sensitivity to chromium is lower than that to nickel, but studies have shown that hypersensitivity reactions to chromium occur in about 10% of men and 3% of women [4,7]. The most common oral pathologies associated with nickel allergy are gingivitis and desquamative oral lesions, as well as complaints, such as a burning sensation, a metallic taste in the mouth, and pain, mostly related to the release of nickel and chromium ions from fixed orthodontic appliances [8–11].

In recent years, there has been a debate about the influence of metals in fixed orthodontic appliances (brackets) on allergic reactions. Clinical studies are being conducted in order to assess the release of nickel and chromium ions from fixed orthodontic appliances, the intensity of the release of the ions, the changes in the levels of the ions during orthodontic treatment, and the relationship between the levels of chromium and nickel ions and changes in the health status of patients [12]. The nickel and chromium content of saliva is usually measured using an atomic absorption spectrometer by taking saliva samples before orthodontic treatment and at specific time points during the treatment period (from 1 month to 1.5 years). Many studies have been conducted in the past, but not all researchers have agreed that nickel and chromium ions released from brackets have an effect on human health. However, the absence of summarized evidence in the literature concerning the effect of metal ions leaves considerable uncertainty. Hence, the present systematic literature review was conducted in order to evaluate and present the newest information about the influence of nickel and chromium ions in saliva in patients with fixed orthodontic appliances (brackets). Manufacturing and brand-related metallurgical features of the brackets are ignored.

2. Materials and Methods

2.1. Search Protocol

The review of the literature followed the PRISMA (Preferred Reporting Item for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered in the PROSPERO register of systematic literature reviews (CRD4202236140). Prior to the systematic review of literature, a preliminary literature search in databases was performed to assess the reliability of the idea of the study. A systematic literature review was conducted according to the study protocol. The aim of the study and the main question of the systematic review were formulated using the PECO (Population, Exposure, Comparison, and Outcomes) framework (Table 1).

Table 1. PECO.

Component	Description
Population (P)	Subjects included in the study were undergoing orthodontic treatment with brackets on both jaws; with permanent dentition; those without metal crowns or restorations containing nickel or chromium; no history of orthodontic treatment; and patients of both sexes.
Exposure (E)	Saliva samples of subjects undergoing orthodontic treatment with brackets were analyzed by using atomic absorption spectrometry.
Comparison (C)	Nickel and chromium levels in saliva before and during orthodontic treatment were compared.
Outcomes (O)	Nickel and chromium levels in the saliva of patients wearing fixed orthodontic appliances (brackets) on both jaws increased.
Study design	Cohort studies that assessed and compared nickel and chromium levels in saliva before and during orthodontic treatment.

The literature search was carried out by two independent researchers (K.U. and A.B.). The screening of scientific articles was carried out using electronic databases, including

Pubmed, ReasearchGate, and Google scholar; the most recent search was performed on 10 April 2022. The articles were selected using the following keywords: “nickel”, “chromium”, “saliva”, “brackets”, “atomic absorption spectrometer”, “in-vivo”, and “fixed orthodontic appliances”.

2.2. Article Screening

Upon conducting a search in each database (Pubmed, ReasearchGate, and Google scholar), a 10-year filter was activated. After the activation of the filter, 212 articles remained, of which 102 systematic reviews and meta-analyses were excluded, and 54 articles were excluded because the title did not meet the aim of the review, i.e., they were irrelevant articles. Detailed results of the article search, with reference to the electronic databases, are presented in the table below (Table 2).

Table 2. Results of the article search.

Keyword Combinations	Number of Articles		
	Pubmed	ReasearchGate	Google Scholar
nickel [MeSH Terms] OR nickel [All Fields] AND chromium [MeSH Terms] OR chromium [All Fields] AND saliva [MeSH Terms] OR saliva [All Fields])	159	36	26
saliva [All Fields] AND brackets [All Fields] AND atomic absorption spectrometer [All Fields]	5	5	0
nickel [All Fields] AND chromium [All Fields] AND saliva [All Fields] AND fixed orthodontic appliances [All Fields]	40	12	9
nickel [All Fields] AND chromium [All Fields] AND saliva [All Fields] AND in-vivo [All Fields]	26	3	1
nickel [All Fields] AND chromium [All Fields] AND brackets [All Fields]	79	9	9
Total	309	65	45
Final number of articles		419	

2.3. Criteria for the Inclusion of Articles in a Systematic Literature Review

1. Articles no older than 10 years (published between 11 September 2012 and 11 September 2022).
2. Clinical trials.
3. Articles published in English.
4. Articles published in peer-reviewed journals.
5. Research conducted on human subjects.

2.4. Criteria for the Exclusion of Articles

1. Systematic literature reviews and meta-analyses.
2. Studies conducted on animals.
3. In vitro studies.
4. Descriptions of one or more clinical cases.
5. Articles published in a language other than English.
6. Incomplete texts of articles.

2.5. Data Accumulation

Research data were collected according to the Cochrane methodology guidelines: authors, year of publication, type of study, sample of subjects, and the follow-up period.

After including articles that met the inclusion criteria in the further analysis, 56 articles were found; excluding duplicates and in vitro studies, 12 articles were included in this systematic review.

2.6. General Overview of the Articles

The screening of the articles was carried out according to the PRISMA literature screening guidelines (Figure 1). The initial search of the electronic databases retrieved 419 articles. After inclusion in the further analysis, 56 articles were found that met the inclusion criteria, and 12 articles were included in this systematic review. In order to ensure the objectivity of the literature review, the articles selected for full-text review were assessed by three independent researchers (K.U., A.B. and K.L.).

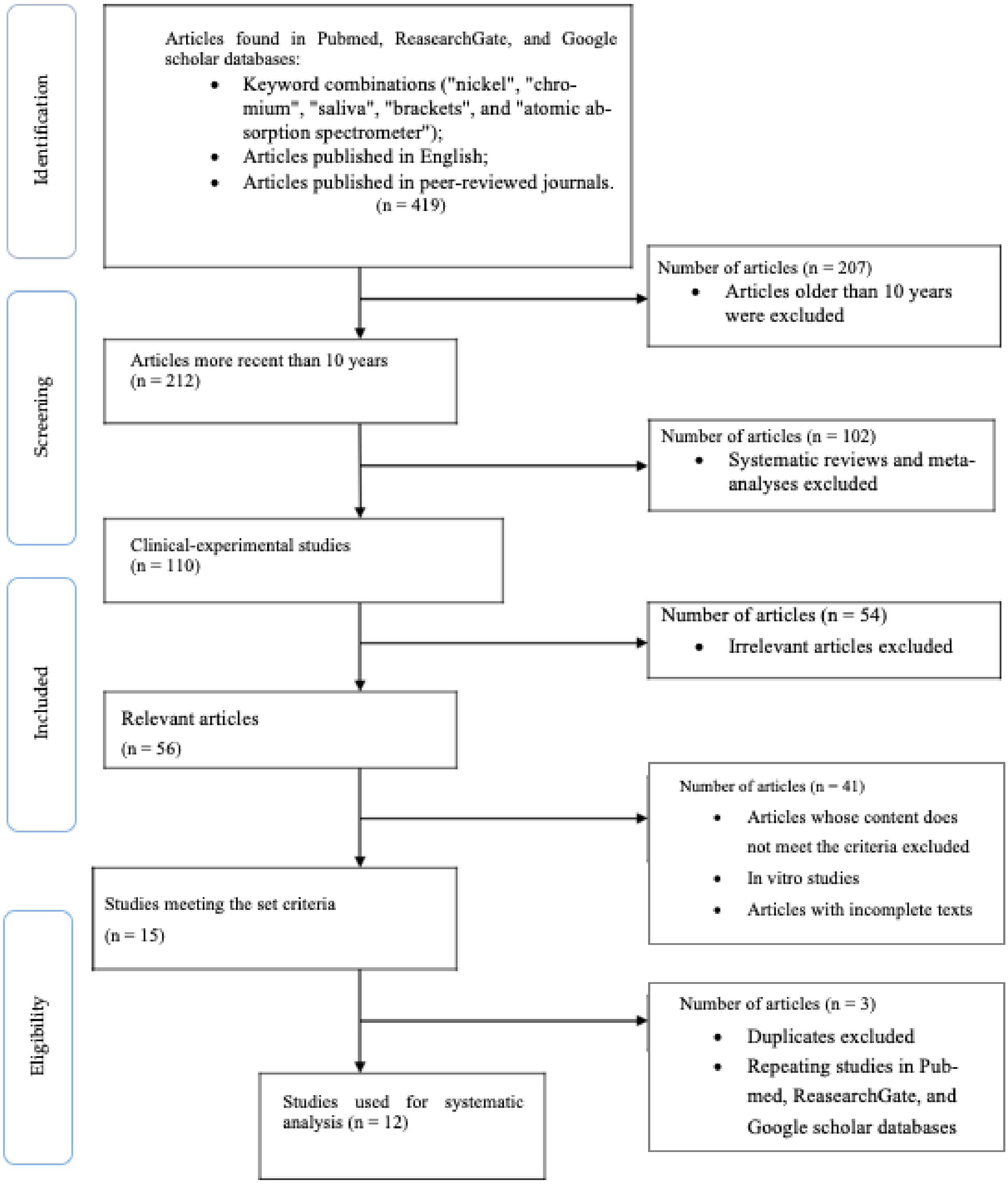

Figure 1. Risk and assessment of systematic errors.

Using the Cochrane questionnaire, the articles were assessed according to seven criteria of bias: selection bias and allocation bias, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other forms of bias associated with the study. A low risk of error, according to the above-mentioned criteria, was marked with a '+', a high risk of error was marked with a '-', and if the data were insufficient, a '?' was used. The publications that were included in the systematic literature review were subject to quality assessment. A detailed assessment of the randomized controlled trials is provided below (Table 3).

Table 3. Analysis and characteristics of the studies.

Author	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
A. Dwivedi et al. [2]	?	?	+	+	+	+
N. F. Talic et al. [13]	?	?	+	+	+	+
D. Quadras et al. [14]	?	?	+	+	+	+
B. Sunny et al. [15]	?	?	+	+	+	+
F. Amini et al. [16]	?	+	+	+	+	+
R. S. Nayak et al. [17]	?	+	+	+	+	+
A. Frois et al. [18]	?	?	+	+	+	+
S. Raina et al. [19]	?	+	?	+	+	+
L. Nanjanawar et al. [20]	?	+	?	+	+	+
M.S. Bengleil et al. [21]	+	+	+	+	+	+
D.P. Singhi et al. [22]	+	+	?	+	?	+
A. Jurela et al. [23]	?	+	?	+	?	+

3. Results

The studies involved 554 patients aged between 11 and 35 years. The sample size for the experimental groups (EGs) was 13–50 patients, whereas the sample size for the control groups (CGs) was 20–30 patients. In the selected studies, saliva samples were taken before orthodontic treatment in patients wearing a braces system for both jaws, and repeated samples were taken during the treatment. The subjects did not have any additional orthodontic appliances. The saliva samples were collected following the same protocol: the patients rinsed their mouths with distilled water for 30 s prior to the study, then saliva that was unstimulated for about 2 min was collected and placed in a plastic tube; the volume of the saliva collected was 2–5 mL. The collected samples were stored in a freezer (at −20 °C) and were subsequently analyzed by applying atomic absorption spectrometry, inductively coupled plasma/mass spectrometry, and inductively coupled plasma optical emission spectroscopy. The frequency of saliva sampling varied between studies. The results of the analyses are presented in Table 4.

Table 4. Results.

Author	Subject Groups (Number of Subjects)	Age of Subjects in Years	Time of Sampling	Results		Main Outcomes
N.F. Talic [13]	EG (40) CG (50)	EG—20.1 ± 3.4 CG—23.1 ± 4.2	After 1–32 months	After 1–32 months		Statistically significant differences were found in both nickel ($p < 0.05$) and chromium ($p < 0.05$) levels between EG and CG.
				Nickel level: EG—4.197 lg/L CG—2.3 lg/L	Chromium level: EG—2.9 lg/L CG—3.3 lg/L	
D. Quadras [14]	EG (50) CG (30)	EG—24 ± 1.2 CG—24 ± 1.2	Before the treatment;	Before the treatment		A significant increase in the metal ion levels were seen in participants before and after insertion of the appliance ($p < 0.001$).
				Nickel level: EG—4.24 ± 0.009 ng/mL CG—4.33 ± 0.002	Chromium level: EG—1.18 ± 0.01 ng/mL CG—1.13 ± 0.03	
			after 1 week;	After 1 week		
				Nickel level: EG—4.34 ± 0.008 ng/mL CG—4.33 ± 0.002 ng/mL	Chromium level: EG—0.59 ± 0.026 ng/mL CG—1.13 ± 0.03 ng/mL	
			after 3 months;	After 3 months		
				Nickel level: EG—11.1 ± 0.009 ng/mL CG—4.33 ± 0.002 ng/mL	Chromium level: EG—1.57 ± 0.08 ng/mL CG—1.13 ± 0.03 ng/mL	
			after 1 year;	After 1 year		
				Nickel level: EG—6.84 ± 0.005 ng/mL CG—4.73 ± 0.002 ng/mL	Chromium level: EG—0.94 ±0.069 ng/mL CG—1.18 ± 0.03 ng/mL	
			after 1.5 years.	After 1.5 years		
				Nickel level: EG—67 ± 10.08 ng/mL CG—5.02 ± 0.001 ng/mL	Chromium level: EG—30.8 ± 4.3 ng/mL CG—1.27 ± 0.9 ng/mL	
B. Sunny [15]	CG (30)	15–20		Before the treatment		A statistically significant difference ($p < 0.01$) was found in CG in nickel ion levels.
				Nickel level: CG—3.8 ng/mL	Chromium level: CG—13 ng/mL	
				After 1 month		
				Nickel level: CG—5 ng/mL	Chromium level: CG—14.9 ng/mL	

Table 4. *Cont.*

Author	Subject Groups (Number of Subjects)	Age of Subjects in Years	Time of Sampling	Results		Main Outcomes
F. Amini [16]	EG (28) CG (28)	16–19	After 12–18 months	After 12–18 months		A statistically significant difference ($p < 0.035$) was found between EG and CG in nickel levels. However, the difference in chromium levels between EG and CG was statistically insignificant.
				Nickel level: EG—18.5 ± 13.1 ng/mL CG—11.9 ± 11.4 ng/mL	Chromium level: EG—2.6 ± 1.6 ng/mL CG—2.2 ± 1.6 ng/mL	
A. Dwivedi [2]	EG (13)	15–33	Before the treatment;	Before the treatment		Statistically significant differences were found in both nickel ($p < 0.05$) and chromium ($p < 0.05$) levels between EG and CG before the treatment and after 1 week.
				Nickel level: EG—1.156 ± 0.675 ng/mL	Chromium level: EG—11.570 ± 2.145 ng/mL	
			after 1 week;	After 1 week		
				Nickel level: EG—6.841 ± 1.326 ng/mL	Chromium level: EG—70.386 ± 6.884 ng/mL	
			after 1 month;	After 1 month		
				Nickel level: EG—3.403 ± 1.631 ng/mL	Chromium level: EG—21.254 ± 5.099 ng/mL	
			after 3 months.	After 3 months		
				Nickel level: EG—3.124 ± 1.321 ng/mL	Chromium level: EG—20.002 ± 3.684 ng/mL	
R. S. Nayak [17]	EG (30)	10–25	Before the treatment;	Before the treatment		Statistically significant differences between EG and CG in nickel ($p < 0.05$) were found after 1 week and insignificant differences after 10–12 months. Statistically significant differences ($p < 0.05$) between EG and CG in chromium were found after 1 week and after 10–12 months.
				Nickel level: EG—48.78 ± 35.75 ng/mL	Chromium level: EG—69.74 ± 62.33 ng/mL	
			after 1 week;	After 1 week		
				Nickel level: EG—59.19 ± 32.82 ng/mL	Chromium level: EG—102.68 ± 68.65 ng/ml	
			after 10–12 months.	After 10–12 months		
				Nickel level: EG—46.33 ± 26.95 ng/mL	Chromium level: EG—87.07 ± 63.47 ng/mL	
A. Frois [18]	EG (17)	20 ± 8	Before the treatment;	Before the treatment		No statistically significant variations were observed between the different study times ($p > 0.05$).
				Nickel level: EG—153.7 µg/L	Chromium level: EG—174.0 µg/L	
			after 2 days;	After 2 days		
				Nickel level: EG—135.3 µg/L	Chromium level: EG—171.4 µg/L	

Table 4. *Cont.*

Author	Subject Groups (Number of Subjects)	Age of Subjects in Years	Time of Sampling	Results		Main Outcomes
A. Frois [18]	EG (17)	20 ± 8	after 1 week;	After 1 week		No statistically significant variations were observed between the different study times ($p > 0.05$).
				Nickel level: EG—145.1 µg/L	Chromium level: EG—180.4 µg/L	
			after 4 weeks;	After 4 weeks		
				Nickel level: EG—175.1 µg/L	Chromium level: EG—192.4 µg/L	
			after 12 weeks.	After 12 weeks		
				Nickel level: EG—131.5 µg/L	Chromium level: EG—173.3 µg/L	
S. Raina [19]	EG (20) CG (20)	16.5–17.5	During the treatment	During the treatment		Statistically significant differences were found between EG and CG in nickel levels ($p < 0.05$).
				Nickel level: EG—18.9 ng/mL CG -12.3 ng/mL		
L. Nanjannawar [20]	CG (21)	12–25	During the treatment	During the treatment		Statistically significant differences were not found in nickel levels ($p > 0.05$).
				Nickel level: CG—0.008		
Mudafara S. Bengleil [21]	EG (9) CG (9)	15–22	Before the treatment;	Before the treatment		Statistically significant differences were not found between EG and CG in nickel levels ($p > 0.05$) throughout the entire research period.
				Nickel level: EG—0.097 mg/L CG—0.066 mg/L		
			after braces placement;	After braces placement		
				Nickel level: EG—0.097 mg/L CG—0.074 mg/L		
			after 2 weeks;	After 2 weeks		
				Nickel level: EG—0.091 mg/L CG—0.079 mg/L		

Table 4. *Cont.*

Author	Subject Groups (Number of Subjects)	Age of Subjects in Years	Time of Sampling	Results		Main Outcomes
Mudafara S. Bengleil [21]	EG (9) CG (9)	15–22	after 4 weeks;	After 4 weeks		Statistically significant differences were not found between EG and CG in nickel levels ($p > 0.05$) throughout the entire research period.
				Nickel level: EG—0.208 mg/L CG—0.061 mg/L		
			after 8 weeks.	After 8 weeks		
				Nickel level: EG—0.071 mg/L CG—0.008 mg/L		
Depinder Pal Singh [22]	EG (32) CG (32)	12–33	During the treatment	During the treatment		Statistically significant differences were found between EG and CG in nickel levels ($p < 0.05$).
				Nickel level: EG—20.5 ng/mL CG—12.3 ng/mL		
Antonija Jurela [23]	EG (42) CG (42)	11–26	Before the treatment	Before the treatment		Statistically significant differences between EG and CG in nickel levels ($p < 0.05$) were found. Statistically significant differences ($p < 0.05$) between EG and CG in chromium were also found.
				Nickel level: EG—4.24 μg/L CG—5.53 μg/L	Chromium level: EG—1.95 μg/L CG—2.77 μg/L	
			After the treatment	After the treatment		
				Nickel level: EG—5.04 μg/L CG—4.39 μg/L	Chromium level: EG—0.01 ng/mL CG—1.00 ± 0.9 ng/mL	

4. Discussion

Nowadays, an increased prevalence of malocclusions and high demands for the use of brackets have prompted researchers to assess and develop new prevention protocols for metal ion absorption from saliva while using fixed appliances (brackets). The aim of this paper was to review and evaluate the effect of fixed orthodontic appliances (brackets) on the nickel and chromium ion levels in saliva. Twelve papers were included in the systematic literature review. Seven [15,18–23] were clinical studies, four [2,14,16,17] were in-vivo studies, and one [13] was a cross-sectional study. Synthesis of the data from the selected publications yielded controversial results. The studies summarized showed that fixed orthodontic appliances (brackets) had an impact on the levels of nickel and chromium ions in the subjects' saliva. However, the rate of increase in the ion content varied between the studies. After the placement of orthodontic appliances, the amount of nickel ions in saliva did not increase immediately in all the analyzed studies. In 2 [18,21] out of 12 studies, the nickel content decreased after the placement of orthodontic appliances and only increased later on. The authors stated that these inaccurate data could be due to the use of different brackets produced by different manufacturers. A. Frois et al. [18] observed that two days after the application of the brackets, nickel ion levels decreased from 153.7 μg/L to 135.3 μg/L, but started to increase a few days later; however, the nickel levels did not reach toxic levels. The WHO guideline values for drinking water currently accept a concentration of nickel of up to 70 μg/mL and a concentration of chromium of up to 50 μg/mL [14]. The authors of the paper discuss that this occurrence might be attributed to nickel binding to salivary proteins, thereby lowering its ionic form. Changes in individual salivary protein composition should therefore affect the concentration of nickel in the saliva and its absorption/distribution in the human body [7,24]. Three studies [20] reported that saliva samples were taken only once (during treatment), which leads to debate as to whether it is worthwhile assessing saliva only during treatment without measuring it before treatment. The synthesis of the data showed that nickel and chromium ion levels tended to peak between one and six months (but did not reach toxic levels) and then gradually decreased. It is interesting to note that the results of the present report are in agreement with a previous in vitro study [25]. However, it should be noted that all the analyzed studies used different measurement units, which might also lead to disagreements in the attempts to clarify the changes in metal ion levels in saliva whilst the brackets are worn. However, in a study by R.S. Nayak [17] and others, a decrease in nickel concentrations was only observed after 12 months. A systematic review based on two studies [15,20] found that mobile phone use increased the release of nickel and chromium ions and also found a positive correlation between the duration of mobile phone use and the release of nickel ions from fixed orthodontic appliances. The authors suggested that the anatomical position of the parotid salivary glands may have an influence on these changes in ion content [15].

The studies evaluated in the publications were carried out in a standardized way: saliva samples were collected using a standardized method, after rinsing the mouth with distilled water, and then the unstimulated saliva was placed in a saliva collection container. The saliva collection method can be stimulated or unstimulated. In all the studies, the saliva sample was collected without stimulation, as in this case, about two thirds of the total amount of the saliva is secreted by the sublingual salivary glands. In contrast, application of the stimulated method, in which saliva is stimulated with chewing gum or paraffin, results in a different salivary composition because all the salivary glands are stimulated and at least half of all the saliva is secreted by the parotid salivary glands. Therefore, stimulation may alter the protein composition of the saliva, and nickel has a high affinity for protein, thus affecting the nickel content of the saliva [26]. The movement and friction of the parts of the brackets can lead to corrosion and the release of metals into saliva [17].

In the oral cavity, the release of ions is influenced by many factors: saliva, which has a dynamic composition; physiological differences, such as diet, pH, physical condition, and the chemical properties of food; and the qualitative composition of the saliva and the rate of its release [27]. The daily intake of nickel and chromium ions is about 300–600 μg/day and

50–200 μg/day, respectively. The main sources of nickel and chromium ions are vegetables, cereals, and nuts [28]. The normal range of metal ions in the body is 300–600 μg for nickel and 50–200 μg for chromium [14], which is higher than the levels of these ions found in the saliva of the patients in this study. The age of the patient also has a significant influence on the qualitative and quantitative changes in the saliva. In adolescence, an increase in saliva can be observed due to hormonal changes during puberty. However, it has been shown that salivary secretion gradually decreases over time in adult patients, as age-related changes may inhibit the salivary glands. In all the studies, healthy patients with no dental or oral disease and no metal restorations were included in order to limit the effects of these variables [29]. In the study by F. Amini et al. [16], the aim was to completely eliminate environmental factors; therefore, a same-sex brother or sister was chosen in the treatment and control groups.

Chemical processes in the oral cavity can lead to a certain degree of corrosion and the release of metal ions [30] In ten studies, orthodontic treatment was followed by an increase in nickel and chromium ion levels, which could be due to corrosion on the surface of the brackets, metal archwires, and ligatures [31]. Nickel is a cathode and causes corrosion on the surface of stainless steel alloys during the first days of orthodontic treatment, after which these chemical reactions decrease. A chromium oxide layer is formed on the metal parts, and the chromium can be released into the oral cavity under the influence of physical and chemical factors [32].

A detailed medical and dental history is needed in order to create a personalized orthodontic treatment plan and to select the optimal appliances. For patients who are allergic to nickel, alternative orthodontic appliances are recommended, consisting of materials such as ceramics, polycarbonates, and metal alloys coated with epoxy resins, as well as brackets made of titanium, vanadium, cobalt-chrome, and aluminum [2].

In the event of even mild signs and symptoms of allergy during orthodontic treatment, it is necessary to carry out detailed examinations and to make a decision about modifying the orthodontic treatment and the continued use of the particular appliance [29]. However, in the future, our findings should be supported by more substantial research.

Limitations of the Review

The limitations include the wide range of sample sizes, variations in the timing of saliva sample collection, differences in the risk of bias and systematic errors, different units of measurement used, and differences in the measuring devices and their errors in the analyzed articles. The results of the studies may have also been influenced by the use of brackets produced by different companies. There is a need for more research with larger sample sizes and standardized protocols, and research that is conducted over a longer period of time in order to standardize the environmental factors that might influence the results of the study.

5. Conclusions

Changes in nickel and chromium levels in saliva occur during orthodontic treatment with fixed brackets. These levels tend to increase after the placement of orthodontic appliances, peak between three and six months without reaching toxic levels, and then gradually decrease.

A full and detailed examination of the patient and their medical history before starting orthodontic treatment is important, and alternative orthodontic appliances for patients who are allergic to nickel and/or chromium should be recommended.

Author Contributions: Conceptualization, K.U., A.B. and K.L.; methodology, A.B. and K.L.; validation, K.U. and K.L.; formal analysis, K.U., A.B. and K.L.; investigation, K.U. and A.B.; resources, K.U.; data, A.B. and K.L.; writing—original draft preparation, K.U. and A.B.; writing—review and editing, K.U., A.B. and K.L.; visualization, K.U.; supervision, K.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Velasco-Ibáñez, R.; Lara-Carrillo, E.; Morales-Luckie, R.A.; Romero-Guzmán, E.T.; Toral-Rizo, V.H.; Ramírez-Cardona, M.; García-Hernández, V.; Medina-Solís, C.E. Evaluation of the release of nickel and titanium under orthodontic treatment. *Sci. Rep.* **2020**, *10*, 1–10. [CrossRef] [PubMed]
2. Dwivedi, A.; Tikku, T.; Khanna, R.; Maurya, R.P.; Geeta Verma, R.C. Murthy Release of nickel and chromium ions in the saliva of patients with fixed orthodontic appliance: An in-vivo study. *Natl. J. Maxillofac. Surg.* **2015**, *6*, 62. [CrossRef] [PubMed]
3. Hafez, H.S.; Selim, E.M.N.; Eid, F.H.K.; Tawfik, W.A.; Al Ashkar, E.; Mostafa, Y.A. Cytotoxicity, genotoxicity, and metal release in patients with fixed orthodontic appliances: A longitudinal in-vivo study. *Am. J. Orthod. Dentofac. Orthop.* **2011**, *140*, 298–308. [CrossRef] [PubMed]
4. Hussain, H.D.; Ajith, S.D.; Goel, P. Nickel release from stainless steel and nickel titanium archwires—An in vitro study. *J. Oral Biol. Craniofacial Res.* **2016**, *6*, 213–218. [CrossRef]
5. Syed, M.; Chopra, R.; Sachdev, V. Allergic Reactions to Dental Materials—A Systematic Review. *JCDR* **2015**, *9*, ZE04. [CrossRef]
6. Schuttelaar, M.L.A.; Ofenloch, R.F.; Bruze, M.; Cazzaniga, S.; Elsner, P.; Gonçalo, M.; Naldi, L.; Svensson, Å.; Diepgen, T.L. Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: The EDEN Fragrance Study. *Contact Dermat.* **2018**, *79*, 1–9. [CrossRef]
7. Wang, Y.; Su, H.; Gu, Y.; Song, X.; Zhao, J. Carcinogenicity of chromium and chemoprevention: A brief update. *OncoTargets Ther.* **2017**, *16*, 4065–4079. [CrossRef]
8. Chakravarthi, S.; Chitharanjan, A.; Padmanabhan, S. Allergy and orthodontics. *J. Orthod. Sci.* **2012**, *1*, 83–87. [CrossRef]
9. Saito, M.; Arakaki, R.; Yamada, A.; Tsunematsu, T.; Kudo, Y.; Ishimaru, N. Molecular Mechanisms of Nickel Allergy. *Int. J. Mol. Sci.* **2016**, *17*, 202. [CrossRef]
10. Pazzini, C.A.; Pereira, L.J.; Marques, L.S.; Generoso, R.; de Oliveira, G., Jr. Allergy to nickel in orthodontic patients: Clinical and histopathologic evaluation. *Gen Dent.* **2010**, *58*, 58–61.
11. Pazzini, C.A.; Júnior, G.O.; Marques, L.S.; Pereira, C.V.; Pereira, L.J. Prevalence of Nickel Allergy and Longitudinal Evaluation of Periodontal Abnormalities in Orthodontic Allergic Patients. *Angle Orthod.* **2009**, *79*, 922–927. [CrossRef]
12. Martín-Cameán, A.; Jos, A.; Solano, E.; Iglesias-Linares, A. Genotoxic and cytotoxic effects and gene expression changes induced by fixed orthodontic appliances in oral mucosa cells of patients: A systematic review. *Toxicol. Mech. Methods* **2015**, *25*, 1–8. [CrossRef]
13. Talic, N.F.; Alnahwi, H.H.; Al-Faraj, A.S. Nickel and chromium levels in the saliva of a Saudi sample treated with fixed orthodontic appliances. *Saudi Dent. J.* **2013**, *25*, 129–133. [CrossRef]
14. Quadras, D.D.; Nayak, U.S.K.; Kumari, N.S.; Priyadarshini, H.; Gowda, S.; Fernandes, B. In vivo study on the release of nickel, chromium, and zinc in saliva and serum from patients treated with fixed orthodontic appliances. *Dent. Res. J.* **2019**, *16*, 209–215. [CrossRef]
15. Sunny, B.; Muddaiah, S.; Reddy, G.; Somaiah, S.; Shetty, B.; Akshatha, M.V. Comparative Evaluation Of Human Saliva For The Presence of Nickel And Chromium Released From Orthodontic Appliances Due To Radio Frequency Electromagnetic Radiation (Cell Phone Usage)—A Clinical Study. *IJDSIR* **2020**, *3*, 274–282.
16. Amini, F.; Jafari, A.; Amini, P.; Sepasi, S. Metal ion release from fixed orthodontic appliances—An in vivo study. *Eur. J. Orthod.* **2011**, *34*, 126–130. [CrossRef]
17. Nayak, R.S.; Khanna, B.; Pasha, A.; Vinay, K.; Narayan, A.; Chaitra, K. Evaluation of Nickel and Chromium Ion Release During Fixed Orthodontic Treatment Using Inductively Coupled Plasma-Mass Spectrometer: An In Vivo Study. *J. Int. Oral Health* **2015**, *7*, 14–20.
18. Fróis, A.; Mendes, A.R.; Pereira, S.A.; Louro, C.S. Metal Release and Surface Degradation of Fixed Orthodontic Appliances during the Dental Levelling and Aligning Phase: A 12-Week Study. *Coatings* **2022**, *12*, 554. [CrossRef]
19. Raina, S.; Adarshika; Raina, R.; Babbar, A.; Shriram, P. Assessment of salivary nickel levels in patients undergoing fixed orthodontic treatment. *J. Adv. Med. Dent. Sci. Res.* **2018**, *6*, 134–137.
20. Nanjannawar, L.G.; Girme, T.S.; Agrawal, J.M.; Agrawal, M.S.; Fulari, S.G.; Shetti, S.S.; Kagi, V.A. Effect of Mobile Phone Usage on Nickel Ions Release and pH of Saliva in Patients Undergoing Fixed Orthodontic Treatment. *J. Clin. Diagn. Res.* **2017**, *11*, ZC84–ZC87. [CrossRef]
21. Bengleil, M.S.; Orfi, J.M.; Abdelgader, I. Evaluation of Salivary Nickel Level During Orthodontic Treatment. *Int. J. Med. Health Sci.* **2013**, *8*, 12. [CrossRef]
22. Singh, D.P.; Thakur, S.; Abrol, T.; Vashisht, S.; Manhas, K.J. Assessment salivary nickel level in patients with fixed orthodontic treatment- A clinical study. *J. Adv. Med. Dent. Sci. Res* **2020**, *8*, 219–222.
23. Jurela, A.; Verzak, Ž.; Brailo, V.; Škrinjar, I.; Sudarević, K.; Janković, B. Salivary Electrolytes in Patients with Metallic and Ceramic Orthodontic Brackets. *Acta Stomatol. Croat.* **2018**, *52*, 32–36. [CrossRef] [PubMed]

24. Michalke, B.; Rossbach, B.; Göen, T.; Schäferhenrich, A.; Scherer, G. Saliva as a matrix for human biomonitoring in occupational and environmental medicine. *Int. Arch. Occup. Environ. Health* **2014**, *88*, 1–44. [CrossRef]
25. Sfondrini, M.F.; Cacciafesta, V.; Maffia, E.; Scribante, A.; Alberti, G.; Biesuz, R.; Klersy, C. Nickel release from new conventional stainless steel, recycled, and nickel-free orthodontic brackets: An in vitro study. *Am. J. Orthod. Dentofac. Orthop.* **2010**, *137*, 809–815. [CrossRef]
26. Petoumenou, E.; Arndt, M.; Keilig, L.; Reimann, S.; Hoederath, H.; Eliades, T.; Jäger, A.; Bourauel, C. Nickel concentration in the saliva of patients with nickel-titanium orthodontic appliances. *Am. J. Orthod. Dentofac. Orthop.* **2009**, *135*, 59–65. [CrossRef]
27. Crossner, C.G. Salivary flow rate in children and adolescents. *Swed. Dent. J.* **1984**, *8*, 271–276.
28. Baraceloux, D.G. Nickel. *J. Clin. Toxicol.* **1999**, *37*, 239–258. [CrossRef]
29. Friberg, L. *International Programme on Chemical Safety 1991 Environmental Health Criteria Nickel*; World Health Organization: Geneva, Switzerland, 1991; pp. 16–17.
30. Pillai, A.R.; Gangadharan, A.; Gangadharan, J.; Kumar, N.V. Cytotoxic effects of the nickel release from the stainless steel brackets: An in vitro study. *J. Pharm. Bioallied Sci.* **2013**, *5*, S1–S4. [CrossRef]
31. Bhaskar, V.; Reddy, V.V. Biodegradation of nickel and chromium from stainless steel crowns and space maintainers—An in vitro study. *Ann. Dent. Univ. Malaya* **1997**, *4*, 17–21. [CrossRef]
32. Barret, R.D.; Bishara, S.E.; Quinn, J.K. Biodegradation of nickel and chromium invitro. *Am. J. Orthod. Dentofac. Orthop.* **2015**, *8*, 37–41.