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Environmental and Occupational Exposure to Nickel in Iran: A Systematic Review

Leila Tavakkoli [1], *Abu-Bakr Jafarnejad* [2], *Narges Khanjani* [*3]

[1] *Department of Epidemiology and Biostatistics, School of Public Health, Kerman University of Medical Sciences, Kerman, Iran.*
[2] *Non-communicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran.*
[3] *Environmental Health Engineering Research Center, Kerman University of Medical Sciences, Kerman, Iran.*

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Corresponding Author:
Narges Khanjani
Email:
n_khanjani@kmu.ac.ir
Tel:
+983431325102

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ABSTRACT

Introduction: Nickel (Ni) is one of the toxic heavy metals that exposure to it has been connected with chronic respiratory complications such as asthma, chronic bronchitis, lung cancer and heart disease. In this research, original studies that investigated occupational or environmental exposure to Nickel and measured nickel levels in human tissues were reviewed.
Materials and Methods: In this study articles were reviewed systematically. National databases such as SID and Magiran as well as some international databases including PubMed, Web of Knowledge, Science Direct and Google Scholar were also searched; to extract studies conducted in Iran; until August 19, 2016.
Results: Based on the results, industrial professions such as welding and plating who dealt directly with nickel were at a higher risk of contamination. In overall, residents in large polluted cities or taking dental treatments, had more nickel concentrations in their body than others.
Conclusion: Considering the high nickel contamination in some industrial workers, it seems necessary to do regular surveillance in these occupational groups and avoid unnecessary exposure to nickel as much as possible. Also, safer dental material should be used in orthodontics.

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Introduction

Heavy metals such as Nickel are toxic and have negative effects on human health. These metals can be hazardous in even small amounts and endanger human health [1]. Nickel is a silvery-white metallic element that occurs naturally in the Earth`s crust [2-4]. Most of the refined nickel is used to manufacture stainless steels. In addition, it is used in aerospace and military applications, plating, coins, and batteries and in hybrid cars [2].

Inhalation is an important route for occupational exposure to nickel. The Occupational Safety and Health Administration (OSHA) reports the permitted amount of nickel exposure in occupations and workplaces to be 1.0 mg/m^3 [5]. The general population may get exposed to nickel through air,

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food and smoking [6, 7]. The Agency for Toxic Substances and Diseases Registry (ATSDR) has stated the reference values of nickel concentration in urine and serum for healthy adults are 1-3 µg/L and 0.2 µg/L, respectively [7]. According to ATSDR ToxGuide, the average concentration of nickel in ambient air is 2.22 ng/m^3, the typical concentration range in sediment and soil is 4-80 ppm, and the median nickel concentrations in water (rivers, lakes and ground waters) is 0.5-6 µg/L [7].

Nickel exposure can cause chronic respiratory complications such as asthma and chronic bronchitis, and also lung cancer and heart disease [8, 9]. The most common way of nickel exposure is skin contact and its complication is skin allergies [6, 9]. Nickel toxicity and carcinogenicity has been investigated in laboratory animals and workers exposed to nickel, and it seems that nickel is carcinogenic for humans [6, 10, 11]. A meta-analysis showed that occupational exposure, including exposure to nickel and its compounds increase the risk of pancreatic cancer [12]. The International Agency for Research on Cancer (IARC) has listed Nickel compounds as a group 1 human carcinogen [13].

The rational for doing this review is the need for having a review paper that summarizes the results of individual studies in this field. We need to know the range of Ni exposure in Iran. Several studies have been performed in Iran, in different groups and in different cities that reflect the level of exposure to nickle in Iranian people. The present paper attempted to summarize all of these studies and make a conclusion about the situation of this contaminant in humans, in Iran.

Materials and Methods

Databases and search strategy

Data was collected from national databases like SID and Magiran as well as some international databases including PubMed, Web of Knowledge, Science Direct and Google Scholar, until August 19, 2016. The following search terms were used “Exposure to Nickel", "Nickel measuring", "Nickel exposure", "Occupational exposure to Nickel", "Environmental exposure to Nickel", "Nickel toxicity" and "Nickel poisoning".

Inclusion criteria and Data extraction

Original articles about occupational or environmental exposure to Nickel that measured the level of nickle in human tissues such as blood serum, hair, saliva and urine; in Iran were included in this review article. Studies done outside Iran or on non-human samples were excluded.

All the retrieved articles were reviewed by two authors separately and the following data was extracted: first author, year of data collection, population, sample size, mean and standard deviation of nickel levels and location of sampling.

Results

As it is seen in figure 1, in total, from 305 retrieved articles, 18 articles were chosen. The population under study in the included articles and the method of reporting was very heterogeneous across the studies. Therefore it was decided to report the levels in each of the different populations separately and not to merge the data in a meta-analysis.

Most of the studies were performed in the general population (15 of 18 articles), especially among patients under treatment with orthodontic appliances (12 of 18) and also most of them were done in the capital city of Iran, Tehran (14 of 18).

Appendix 1 reports the possibility of selection bias, measurement or attrition bias in the included studies. A large number of these studies had selection bias (except one of them[14]) which means that the sample was not randomly selected from the population. The measurement methods were done for everyone enrolled in these studies identically by atomic absorption spectrophotometry, except in two of them [14, 15]. In all studies except one study [16], we could not tell if there was attrition bias, because there was no information about follow up.

In industrial jobs such as welding and plating, nickel concentrations were higher in workers who dealt directly with nickel than other people employed in the same industry [17, 18]. In the general population, people living in big polluted industrial cities [19] or those who had taken dental treatments,

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had more nickel concentrations in their body than others [20-28] (Table 1).

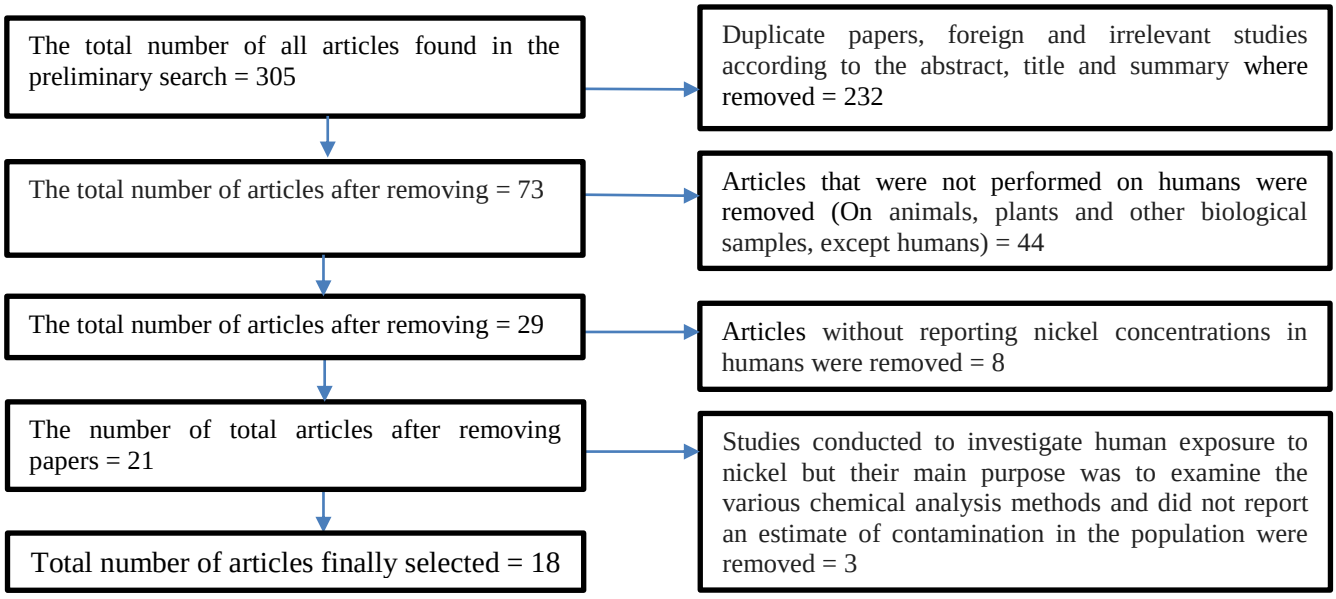

Figure 1: The flowchart of searching, excluding and selecting articles

Table 1: Summary of studies about human contamination with nickel in Iran

	First author and years of data collection (Ref)	Population	Sample	Mean ± SD of nickel levels	Location
1	Khadem, year not reported [14]	15 metal industrial workers	Hair, urine and nail	Hair = Not detected Urine = 5.31 ± 3.10 µg/L Nail = 57 ± 19 µg/g	Zanjan
2	Tadayon, 2009-2010[15]	250 women 33-35 years old: 142 controls and 108 diabetes type 2 patients	Hair	Patients = 2.023 ± 1.07 µg/g Controls = 1.851 ± 0.7 µg/g	Tehran
3	Amini, 2013-2014[16]	30 orthodontic patients 11-26 years old: The patients were divided into two groups of experimental (Metal-Injection Molding (MIM) brackets) and control (Conventional brackets), n=15 in each group.	Saliva	Brackets used: Baseline (pretreatment): -Controls = 7.12 ± 8.14 µg/l - Metal-Injection Molding (MIM) brackets = 8.62 ± 9.85 µg/l 60th day: Controls = 12.57 ± 9.96 µg/l Metal-Injection Molding (MIM) brackets = 8.86 ± 6.42 µg/l Regardless of the brackets used: Baseline (pretreatment) = 7.87 ± 8.91 µg/l 60th day = 10.71 ± 8.44 µg/l	Department of Orthodontics, Dental Branch, Islamic Azad University, Tehran
4	Soleimani, year not reported[17]	31 workers: - 24 cases (17 plating workers and 7 finishing workers) - 7 controls (3 quality control staff and 4 other	Urine	Plating workers = 77.45 µg/L or 56 µg/gr creatinine Finishing workers = 64.75 µg/L or 45 µg/gr creatinine Quality control staff = 20.27 µg/L or 24 µg/gr creatinine	A big plating workshop in West Tehran

		control staff, office workers without exposure to nickel)		Normal control staff = 19.91 µg/L or 21 µg/gr creatinine Smokers = 37.45 µg/gr creatinine Non-smokers = 60.15 µg/gr creatinine	
5	Golbabaei, 2011[18]	119 People (94 welders of natural gas pipes, 6 back welders, 29 assistants and 25 controls)	Urine	Welders = 4.75 ± 4.56 µg/L Back welders = 11.46 ± 6.64 µg/L Assistants = 1.39 ± 1.09 µg/L Control = 0.32 ± 0.29 µg/L	Brujen (Chaharmahal and Bakhtiari)
6	Tadayon , year not reported[19]	212 people (172 people from Tehran and 40 people from Tekab)	Hair	Tehran = 1.95 ± 1.27 µg/g Tekab = 0.35 ± 1.33 µg/g	Tehran and Tekab
7	Amini, year not reported (during 3 years)[20]	60 dental patients (30 cases with fixed orthodontic appliances and 30 controls without any type of orthodontic appliances or metal restoration in their mouth	Mucosa cell	Cases = 21.74 ± 11.41 ng/mg Controls = 12.26 ± 12.9 ng/mg	The Orthodontics Department of the Azad University, Tehran
8	Amini, year not reported[21]	20 patents with fixed orthodontics	Saliva	Baseline = 9.75 ± 5.02 µg/L 6 months after orthodontic treatment = 10.37 ± 6.94 µg/L 12 month later = 8.32 ± 4.36 µg/L	The Orthodontics Department of the Azad University, Tehran
9	Amini, year not reported[22]	60 dental patients (30 cases undergoing orthodontic therapy for a minimum period of 1 year and 30 controls)	Urine	Cases: 20 females = 9.9 ± 3.83 µg/L 10 males = 9.67 ± 3.25 µg/L Total = 9.81 ± 3.53 µg/L Controls: 20 females = 8.43 ± 2.94 µg/L 10 males = 6.65 ± 2.57 µg/L Total = 7.83 ± 2.87 µg/L	Tehran
10	Amini, 2012-2013[23]	10 patients with fixed orthodontics (6 females and 4 males)	Saliva	First time (before orthodontics) = 12.78 ± 5.26 µg/L Second time (3 months later and before stress) = 14.02 ± 5.14 µg/L Third time (after stress) = 14.90 ± 5.75 µg/L	The Orthodontics Department of the Azad University, Tehran
11	Amini, 2013-2014[24]	24 patients with orthodontics (12 males and 12 females)	Hair	Baseline: Females = 0.12 ± 0.05µg/g Males = 0.15 ± 0.06µg/g Total = 0.13 ± 0.05 µg/g 6 months later: Females = 0.67 ± 0.17µg/g Males = 0.66 ± 0.18 µg/g Total = 0.67 ± 0.17 µg/g Increase in Ni in all patients 6 months after orthodontic treatment = 0.53 ± 0.19 µg/g	The Orthodontics Department of the Azad University, Tehran
12	Saghiri, 2007-2012[25]	56 people (28 who did endodontic treatment and 28 controls)	Urine	Cases = 4.91 µg/L Controls = 4.34 µg/L	Tehran

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13	Amini, The sampling was performed 16±2 months after the start of treatment with fixed orthodontic appliances[26]	56 Subjects, 28 subjects with fixed appliances in both arches (16 females and 12 males) and 28 controls without any orthodontic appliance (a same-gender sister or brother)	Saliva	With appliance = 18.5 ± 13.1 ng/ml Without appliance = 11.9 ± 11.4 ng/ml	Tehran
14	Amini, 2011-2012[27]	24 patients with only the maxillary arch stainless steel brackets treatment (12 males and 12 females)	Gingival Crevicular Fluid	Pretreatment (baseline) = 3.894 ± 1.442 mg/g of GCF 1 month after the initiation of treatment = 5.91 ± 2.73mg/g of GCF 6 month after baseline = 19.81 ± 8.45 mg/g of GCF	Department of orthodontics, Dental Branch, Islamic Azad University, Tehran
15	Khane Masjedi, 2014-2015[28]	24 females and 22 males fixed orthodontic patients	Hair	Before treatment = 0.16 ± 0.08µg/g After 6 month = 0.31 ± 0.17 µg/g Difference = 0.15 ± 0.14 µg/g	Orthodontics Department of Ahvaz University, Ahvaz
16	Yassaei, year not reported[29]	32 patients 11 to 24 years old who visited the orthodontic clinic	Saliva	T1: before appliance placement = 5.76 ± 4.4 µg/L T2: 20 days after appliance placement = 6.54 ± 4.73 µg/L T3: 3 months after appliance placement = 5.13 ± 3.09 µg/L T4: 6 months after appliance placement = 5.61 ± 4.18 µg/L	Yazd
17	Amini, 2012[30]	30 patients with fixed orthodontics	Saliva	First time (before orthodontics) = 11.9 ± 5.1 µg/L Second time (3 months later)= 12.4 ± 4.8 Third time (5 min following the induction of stress) = 12.6 ± 4.7 µg/L Fourth time (30 min following the induction of stress) = 14.1 ± 5.3 µg/L	The orthodontics Department of the Azad University, Tehran
18	Tadayon, year not reported [31]	100 women between 30 to 70 years of age from Tehran	Hair	Approximate values based on figure 2 are: Diabetes patients = 2.5 µg/g Healthy women = 2.0 µg/g	Tehran

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Discussion

Environmental exposure to Nickel: In the general population, people get exposed to nickel through air, water, soil, food and tobacco use [6, 7]. The amount of exposure to nickel, depends on the dose, the duration of exposure, the exposure route, personal habits like smoking, consumption of canned food, as well as using hair colors and sprays [32-34].

The results of a study showed that nickel concentration in Tehran residents is more than double the people living in Tekab, located 540 km away from Tehran, which is a small non-industrial city in West Azarbaijan Province with a population of 44,040 in 2011. The authors commented that higher concentrations of nickel in Tehran is related to their life style[19]. Also, it should be considered that in big cities with huge industries, more material containing heavy metals such as nickel are used and released in the environment; therefore residents are at a higher risk of exposure to nickle.

Some studies have showed that patients with type 2 diabetes had a higher hair concentration of Ni [15, 31], which raises the possibility that this environmental contaminant has diabetogenic characteristics.

Studies have shown that stress can lead to a significant increase in nickel release from orthodontic appliances into saliva [23, 30]. Other studies showed that nickel concentrations are higher in urine [22, 25], mucosal cells [20], saliva [16, 21, 26, 29, 35-38], gingival crevicular fluid (GCF) [27] and hair [24, 28] of orthodontic patients; and nickel can cause gingival inflammation [27]. A study from Italy suggested that nickel released from orthodontic appliances can cause DNA damage in oral mucosa cells [39].

Authors think that the large inter individual variations seen in nickel values among orthodontic patients might be attributed to differences in saliva composition, pH and different environmental and personal conditions [21]. Meanwhile, a study from Norway investigating Ni in saliva of patients with fixed orthodontic applainces, thinks there is a high initial release of Ni, and the effect decreases with time [37].

Studies from Iran showed no significant difference between urine nickel values in smokers and non-smokers [17]. A study from Norway showed that there were no significant difference between nickel concentration in urine and blood of smokers and non-smokers, as well [40]. However, a study from Serbia showed that nickel concentrations were significantly higher in smokers than non-smokers [41]. These different results may be explained by differences in the type and number of cigarettes smoked per day by the participants in these studies. The important point that should be considered is that the participants in the Iranian and Norwegian study were industrial workers, but participants in the Serbia study did not have occupational exposure.

Occupational exposure to Nickel: Nickel toxicity and carcinogenicity has been investigated in workers exposed to nickel [11]. Inhalation and dermal contact are important routes for occupational exposure to nickel [5]. Workers may also ingest nickel containing dusts [42]. Occupational groups that can be exposed to nickel include mining, smelting, welding, casting, spray-painting, grinding, electroplating, production, use of nickel catalysts, and polishing of nickel-containing alloys [42].

A study in Tehran showed that the concentration of urinary nickel was significantly higher in plating and finishing workers than controls (quality and normal staffs) and they also showed that there was a significant correlation between breathing zone air and urinary nickel concentrations in plating and finishing workers [17]. Another study from the Chaharmahal and Bakhtiari Province, Iran showed that urinary nickel concentrations in welders and back welders were significantly higher than office staff. This study also showed a direct significant correlation between nickel concentrations in the breathing air zone of welders and their nickel urinary concentrations [18]. Studies from America and Taiwan both showed that urinary nickel concentrations in nickel workers and workers in the steel industry were higher than controls who were healthy unexposed workers [43, 44]. Likewise, a study from New Zealand showed a significant

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relation between respiratory complications and the concentrations of Ni in the breathing air zone of welders [45]. A Norwegian study showed that not only inhalation of nickel and its compounds by workers in industries can cause lung complications, but also accumulated exposure to Ni in water is related to lung cancer [46]. Obviously, nickel concentrations are higher in workers who deal directly with nickel than other people employed in industries.

Conclusion

Considering high nickel contamination in some industrial workers, it seems necessary to do regular surveillance in these occupational groups and avoid unnecessary exposure to nickel as much as possible. Also, safer dental material should be used in orthodontics.

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Conflict of interest

The authors have no competing interests.

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Appendix 1:

	First Author and year of data collection (Ref)	Selection bias	Measurement bias	Attrition bias
1	Soleimani, year not reported [17]	Participant selection was not random and workers who had had surgical therapy during the last 3 months or/and got a vaccine or/and took a radiography were not included. Biological sampling was conducted after working time and at the end of the working week. **(High risk)**	Measurement was done for everyone identically by Atomic absorption spectrometry which is one of the appropriate methods for determining the amount of nickel in urine samples. **(Low risk)**	Apparently all 31 workers participated. **(Can not tell)**
2	Amini, 2013-2014 [16]	"The patients were selected from attendees to the Orthodontics Department of the Azad University during the years 2013-2014. The inclusion criteria comprised the subjects' willingness to participate, the indication for bimaxillary non-ext fixed orthodontic treatment, the age range of 11 to 26 years old, having all the permanent teeth fully erupted (no semi-eruptions, no missing, or extraction) excluding the third molars, the absence of any systemic diseases, any history of allergic reactions, medication intake, alcohol consumption or smoking, the absence of any caries, any metal restorations such as amalgam fillings or fixed prostheses placed before or during the treatment, any hair colors or hairdressings, as well as no history of previous orthodontic treatment of any kind. All the inclusion criteria needed to be met during the study period." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "atomic absorption - spectrophotometry using a calibrated device (high-resolution continuum source AAS Contra (AA700, Analytik Jena, Germany))." **(Low risk)**	Apparently all 24 orthodontic patients participated. **(Can not tell)**
3	Tadayon , year not reported [19]	"The number of hair samples were collected from Tehran and Takab province (northwest of Iran) as control group." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "A Varian model Spectra AA-220 (Mulgrava, Victoria, Australia), atomic absorption spectrometer equipped with a GTA-100 graphite furnace atomizer and deuterium lamp background correction was used with hollow cathode lamps (Varian)." **(Low risk)**	Apparently all 212 people participated. **(Can not tell)**

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4	Saghiri, 2007-2012 [25]	"This retrospective cohort study was conducted on patients with endodontic treatment history as the experimental subjects and the same number of control individuals between fall 2007 and fall 2012. As part of the inclusion criteria for control group, all the patients must have had at least near aged siblings with identical gender and no endodontic treatment history." "The exclusion criteria were applied to patients with systemic diseases, medication intake, smoking or alcohol consumption, and presence of any metallic restoration material such as amalgam or fixed prosthesis which was checked through panoramic X-rays, as well as to those patients having missing or extracted teeth (except for third molars) and individuals who were unwilling to participate. Same-gender and near-aged participants were selected in order to reduce biological differences." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "electro- thermal atomic absorption spectrophotometry (AA280Z GTA120, Varian, Mulgrave, Australia) with 0.01 µg/L accuracy limit." **(Low risk)**	Apparently all 56 people participated. **(Can not tell)**
5	Golbabaei, 2011 [18]	"In this Cross sectional study, the subjects (94 people) were selected from Iranian Gas Transmission Pipelines welders, in regions of Iran, Borujen (Chaharmahal and Bakhtiari Province), in 2011." "In addition, welders work only for one shift (morning shift). The task groups were Foreman, Fitter, Co-Fitter, Full pass, Filling, Filling Cap, Back Weld, and Grinder as well as 25 subjects as control group who were selected from administrative Department." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by " Atomic Absorption Spectrometry (AAS) with a graphite furnace(GBC, Model 932, made of Austria) after microwave digestion." **(Low risk)**	Apparently all 119 people participated. **(Can not tell)**
6	Amini, year not reported (during 3 years) [20]	"Subjects were selected from the pool of patients who registered for a routine checkup at the Department of Orthodontics, Dental school of Azad Medical University within the past 3 years." "A sample of 60 selected subjects was used comprising of a test group of 30 orthodontic patients who had fixed orthodontic appliances in both arches. The control group included 30 subjects without any type of fixed orthodontic appliances or metal restoration in the mouth. The exclusion criteria in both groups were 1) smoking, pre-existing systemic diseases or medications associated with oral mucosa changes and 2) intraoral piercing metal restorations. Informed consent was obtained after the objective of the study was fully explained." Non randomized selection. **(High risk)**	"The concentration of nickel, was quantified using atomic absorption spectrophotometry with a graphite furnace (Varian SpectrAA-220; Mulgrave, Australia).." **(Low risk)**	Apparently all 60 dental patients participated. **(Can not tell)**

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7	Amini, year not reported [21]	"This prospective cohort study was performed on 120 specimens obtained from a cohort of 20 orthodontic patients. The exclusion criteria comprised the presence of any systemic diseases, any history of allergic reactions, medication intake, alcohol consumption or smoking, any caries, metal restorations such as amalgam fillings or fixed prostheses placed before or during the treatment, and having some teeth missing or extracted (excluding the third molars)." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "electrothermal atomic absorption spectrophotometry (at 0.01-µg/L accuracy limit) using a calibrated device (AA280Z GTA120, Varian, Mulgrave, Australia)." **(Low risk)**	Apparently all 20 patents with fixed orthodontics participated. **(Can not tell)**
8	Amini, 2012-2013 [23]	"A quasi-Clinical trial was operated on 10 patients with fixed orthodontics (6 female and 4 male) who were selected among 53 dental patients and refered to the Orthodontics Department of the Azad University during the years 2012-2014." "Inclusion criteria: aged 12 to 25 years with no history of psychological and systemic conditions, alcohol consumption, and smoking, did not take a medications, did not have any metal-based tooth restorations (amalgam restorations, fixed prostheses) or removable orthodontic appliances, and finally willing to participate in the whole part of the study." Non randomized selection. **(High risk)**	Measurement was done for everyone identically. Atomic absorption spectrophotometry (GTA120, Australia) with a graphit oven was used for alalysis of biological samples. **(Low risk)**	Apparently all 10 patients with fixed orthodontics participated. **(Can not tell)**
9	Khadem, year not reported [14]	15 workers were randomly selected from a metal industry. Randomized selection. **(Low risk)**	Measurement was done for everyone identically by electrochemical method (Voltammetry) with polarography device (VA, 757, Computrace, Metrohm) **(Low risk)**	Apparently all 15 workers participated. **(Can not tell)**
10	Amini, year not reported [22]	"This retrospective cohort study was performed on 30 orthodontic patients and on the same number of control subjects." "As part of the inclusion criteria, all the patients must have had at least a same-gender near-age sibling without any orthodontic treatment history. In case either a patient or the matched control participant met any of the following exclusion criteria, both would be disqualified. These comprised the subjects' unwillingness to participate, them having teeth extracted or missing (excluding the third molars), the presence of any systemic diseases, any history of allergic reactions, medication intake, alcohol consumption or smoking, and the presence – of any metal restorations such as amalgam fillings or fixed prostheses, or any soldered/extraoral orthodontic appliances." "In order to lessen the effects of biologic	Measurement was done for everyone identically by "electrothermal atomic absorption spectrophotometry using a calibrated device (AA280Z GTA120, Varian, Mulgrave, Australia) with 0.01-µg/L accuracy limit" **(Low risk)**	Apparently all 60 dental patients participated. **(Can not tell)**

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		differences as well as dietary and hygiene habits on nickel release, the siblings must have been the same gender and near age to the patients; they also must have been living together with them and must not have undergone orthodontic treatment." Non randomized selection. **(High risk)**		
11	Amini, The sampling was performed 16 ± 2 months after the start of treatment with fixed orthodontic appliances [26]	"A total of 56 subjects were included in this study. Twenty eight (16 females and 12 males) were healthy orthodontic patients with fixed appliances in both arches for a period of 12–18 months (study group). The age range of the subjects in this group was from 16 to 19 years (mean 17.5 ± 2.5 years). To limit the effect of food and oral hygiene habits on salivary metal ion concentration, a same-gender sister or brother without any orthodontic appliance formed the control group. All patients were from the clinic of one author (FA). The criteria for the selection were having a same-gender sister or brother; absence of any piercings or metal restorations; good health and medication-free; and absence of any systemic diseases. No palatal or lingual arches or devices soldered or welded to bands or extraoral auxiliary appliances were used." 56 Subject, 28 subjects with fixed appliances in both arches (16 females and 12 males) and 28 controls without any orthodontic appliance (a same-gender sister or brother) Non randomized selection. **(High risk)**	"The samples were analyzed using an atomic absorption spectrophotometer (Varian SpectrAA-220; Varian Australia Pty Ltd, Mulgrave, Australia)." **(Low risk)**	Apparently all 56 subject participated. **(Can not tell)**
12	Amini, 2011-2012 [27]	"This longitudinal study was carried out with 72 samples of GCF, taken at 3 times from 24 patients (12 male, 12 female) with fixed orthodontic appliances. The times were (1) pretreatment (baseline), (2) 1 month after the initiation of treatment, and (3) 6 months after baseline. The subjects were sequentially acquired from a list of about 100 patients attending the Department of Orthodontics (in 2011 and 2012), until 2 groups of 12 female and 12 male patients were enrolled." "The inclusion criteria were patients who were willing to be part of the study and needed fixed orthodontic treatment in the maxillary arch. The exclusion criteria were any diseases, syndromes, allergies, metal restorations, consumption of medication or alcohol, smoking, or previous orthodontic treatment. All inclusion criteria had to be fulfilled during the study period." Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "atomic absorption spectrophotometry with a calibrated device (AA280Z GTA120; Varian, Mulgrave, Australia)" **(Low risk)**	Apparently all 24 dental patients participated. **(Can not tell)**

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13	Khane Masjedi, 2014-2015 [28]	"The patients were selected from attendees to the Orthodontics Department of the University during 2014–15." "The subjects were sequentially acquired. The inclusion criteria comprised the patients' willingness to participate, the indication for fixed orthodontic treatment, no history of previous orthodontic therapy of any kind, having all the permanent teeth fully erupted (no semieruptions, no missing or extraction) excluding the third molars, the absence of any systemic diseases, any history of allergic reactions, medication intake, smoking or alcohol consumption, the absence of any caries , the lack of any metal restorations (e.g., amalgam fillings or fixed prostheses) before or during the treatment, the presence of an adequate length of scalp hair, and the absence of any hair colours or hairdressings. All the inclusion criteria needed to be met during the study period." "The patients were told that if any of the included patients left the study in the middle of the 6-month course (due to any reason such as dying their hair, or receiving dental restorations etc, or simply not wishing anymore to be a part of the study), they would be excluded from the study, and new patients would be screened and included in the study. During this period eight originally included patients were dropped out and replaced with new patients" Non randomized selection. **(High risk)**	Measurement was done for everyone identically by "atomic absorption spectrophotometry using a calibrated device [high-resolution continuum source AAS Contra (AA700, Analytik Jena, Germany)], with detection limits of 1 ppb (0.001 µg/g dry hair mass) for nickel." **(Low risk)**	Apparently all 46 dental patients participated. **(Can not tell)**
14	Amini, 2013-2014 [16]	"This double-blind randomized clinical trial was performed on 60 saliva specimens sampled from 30 orthodontic patients at two time points. The patients were divided into two groups of conventional (control) and MIM (experimental) brackets (n=15 each), as well as two time groups of 30 observations each: baseline (pre-treatment) and 60 days after the treatment initiation." "The patients were selected from attendees to the Orthodontics Department of the Tehran Dental School of Azad University during 2013–2014. The subjects were sequentially enrolled. The inclusion criteria comprised the subjects' willingness to participate, the indication for bimaxillary non-ext fixed orthodontic treatment, subjects being 11–26 years old, having all the permanent teeth fully erupted (no semieruptions, no missing or extraction) excluding the third molars, the absence of any systemic diseases, any history of allergic reactions, medication intake, alcohol consumption or smoking, the absence of any caries, any metal restorations such as amalgam fillings or fixed prostheses placed before or during the treatment, as well as no history of previous orthodontic treatment of any kind."	The biological specimens were shipped to the Central Chemical Analysis Laboratory of Tehran University of Medical Sciences for atomic absorption spectrophotometry using a calibrated device (AA280Z GTA120, Varian, Mulgrave, Australia)." **(Low risk)**	A total of 48 patients were assessed until 30 patients were enrolled. Of the excluded patients, 15 did not meet the inclusion criteria, and three who had been included first, did not attend the second session (so were dropped out of the study and replaced by three new patients assessed from the beginning) **(High Risk)**

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		Non randomized selection. **(High risk)**		
15	Yassaei, year not reported [29]	"This was a cohort study; The sampling was done consecutively on 32 patients referred to the orthodontic ward, aged 11 to 24 years with an average age of 15 years, 3 months." Non randomized selection. **(High Risk)**	"The amounts of metals were determined by graphite furnace atomic absorption spectrometry with an autosampler. Each sample was analyzed three times, and the average was reported." **(Low risk)**	Apparently all 32 dental patients participated. **(Can not tell)**
16	Amini, 2012 [30]	"This quasi-experimental clinical trial was conducted on 30 orthodontic patients. Enrollment was made from a total of 223 patients who were referred to the Department of Orthodontics, Azad School of Dentistry, Tehran, Iran in 2012. Patients who were starting fixed orthodontic therapy and aged between 12 to 25 years old were evaluated for eligibility. Patients were considered eligible for inclusion if they had no history of systemic and psychological conditions, alcohol consumption, and smoking; were not taking medications; did not have any metal-based tooth restorations (e.g., amalgam restorations, fixed prostheses) or removable orthodontic appliances; and were willing to participate in the whole duration of study." Non randomized selection. **(High risk)**	"The metal content of samples was analyzed by an atomic absorption spectrophotometer with a graphite oven (AA 280 Z, GTA 120, Varian, Mulgrave, Australia). Saliva preparation for atomic absorption spectrophotometry was based on the routine protocol of the Analytical Chemistry Laboratory, Bionuclear Research Center, Iran." **(Low risk)**	Apparently all 30 orthodontic patients participated. **(Can not tell)**
17	Tadayon, 2009-2010 [15]	"During 2009-2010 totally 250 women 33-35 years old, living mainly in Tehran (Iran), were investigated. " Non randomized selection. **(High risk)**	"Prior to analysis, samples were washed with 1% (w/v) sodium diethyldithio-carbamate (DDTC), 0.1M HCl, and deionized water. The hair samples were digested afterward in a mixture of HNO3, and H2O2." **(Low risk)**	Apparently all 250 women participated. **(Can not tell)**
18	Tadayon, year not reported [31]	"The study population consisted of 100 women between 35 to 70 years of age from Tehran." Non randomized selection. **(High risk)**	"An atomic absorption spectrometer, Varian model spectra AA-220, was used for flame atomic absorption analysis and for graphite furnace analysis. The apparatus was equipped with a GTA-100graphite furnace atomizer, deuterium lamp as a background corrector, and a Varian programmable sample dispenser" **(Low risk)**	Apparently all 100 women participated. **(Can not tell)**

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