

Report

Allergic contact dermatitis to metal allergens in Iran

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Introduction

Allergic contact dermatitis (ACD) is a classical delayed-type hypersensitivity response to an exogenous allergen. Over 3700 allergens are known to cause ACD in humans. Allergic contact dermatitis may appear acutely as a result of initial sensitization after exposure to the allergen or may be elicited in a previously sensitized individual. Clinical manifestations in ACD include the development of erythematous and scaly plaques. In severe cases, vesiculation and bullae may be seen. The hands, feet, eyelids, and lips are the most common sites of involvement in ACD. In histopathologic examination, epidermal spongiosis with superficial perivascular lymphohistiocytic dermal infiltrate may be seen.¹ Nickel, chromium, and cobalt are important skin sensitizers and can trigger ACD.² Previous research has shown associations between specific human leukocyte antigen alleles and allergy to nickel, chromium, and cobalt.¹

Nickel is the most common allergen worldwide and is used in everyday life extensively. Costume jewelry, such as

Abstract

Background Metallic allergens such as nickel are among the most common causes of allergic contact dermatitis (ACD), but frequencies of contact dermatitis to these allergens may vary in different areas.

Objectives This study aimed to determine the frequencies of ACD caused by three common metallic allergens: nickel sulfate; potassium dichromate; and cobalt chloride.

Methods Data for 1137 patients with clinical diagnoses of contact dermatitis and/or atopic dermatitis evaluated by patch testing in Iran during a 5-year period were retrospectively studied to establish the frequencies of hypersensitivity to these metallic allergens.

Results A total of 313 patients (27.5%) gave positive patch test results for at least one metallic allergen. Allergy to nickel (229 cases, 20.0%) was the most commonly observed, followed by allergy to cobalt (90 cases, 8.0%) and allergy to chromium (70 cases, 6.2%). Nickel allergy was significantly more frequent in females and in subjects aged <40 years, whereas chromium hypersensitivity was more common in males and in subjects aged >40 years. Sensitivity to nickel or chromium was a risk factor for cobalt allergy.

Conclusions Nickel was most commonly identified as a metallic allergen in Iran and tended to affect women aged <40 years. Regulations pertaining to nickel release may decrease the frequency of nickel hypersensitivity in Iran.

earrings and necklaces, wrist watches, and belt buckles, cosmetic products, including metal eyelash curlers, and hand tools, such as wrenches, may contain enough nickel to provoke a sensitivity reaction.³ There is growing evidence of ACD caused by nickel in mobile phones.^{4,5} There is some evidence of a decrease in nickel sensitivity among young females in some regions of the world, such as Denmark, probably as a result of regulations on its use in items with which the body makes close and prolonged contact.^{6,7}

Chromium is used in the leather industry and in the production of paints, anticorrosives, and ceramics, as well as in metal alloys. The most substantial cause of chromium sensitivity has been reported as occupational exposure to cement.^{8,9} Only trivalent Cr³⁺ and hexavalent Cr⁶⁺ oxidation states of chromium act as haptens. The formation of these two types of chromium depends on factors such as pH and temperature. In cement, Cr⁶⁺ is formed when the trivalent compound, Cr₂O₃, is heated to 1400–1500 °C.^{8,9} However, recent studies show that sensitivity to chromium is increasing; this is assumed to reflect the growth in the use of leather products.¹⁰

Cobalt is used to add hardness and strength to metal alloys.³ All cobalt-containing alloys release cobalt at concentrations that can elicit an allergic response in the skin of cobalt-sensitized individuals.¹ Cobalt is often found in combination with other metals, such as nickel and chromium, which may explain frequent instances of co-sensitization to cobalt and nickel or cobalt and chromium.^{3,9} A study from Iran reported a statistically significant association between positive cobalt patch tests and positive reactions to nickel and chromium.¹¹ In the same study, nickel sulfate was detected as the most common cutaneous allergen, with a frequency of 28%.¹¹ The frequencies of sensitization to cobalt chloride and potassium dichromate were 12.8 and 5.2%, respectively, and the areas most frequently involved were the hands (68.4%).¹¹ According to the results of a study conducted in Taiwan, prevalences of sensitization to nickel sulfate, cobalt chloride, and potassium dichromate were 17.7, 7.1, and 4.6%, respectively, which are similar to those reported in other studies from Singapore, Germany, Turkey, and the USA.¹²

The aim of this study was to determine the frequencies of ACD caused by exposure to nickel sulfate, potassium dichromate, and cobalt chloride by patch testing in a large sample in Iran.

Materials and methods

Participants and primary evaluation

Data from patients evaluated by patch testing in Iran were retrospectively studied for allergy to metal allergens including nickel sulfate, potassium dichromate, and cobalt chloride. From January 2004 to December 2008, a total of 1137 patients with clinical diagnoses of contact dermatitis and/or atopic dermatitis (according to the UK Working Party diagnostic criteria¹³) were evaluated by patch testing.¹⁴ The study protocol was reviewed by and received ethical clearance from the Ethics Committee of the Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences. Primary evaluation consisted of obtaining a medical history and a thorough physical examination. A questionnaire, including items on demographic characteristics, location of dermatitis, drug history, probability for occupational dermatitis, personal and familial histories of atopic dermatitis, asthma, allergic rhinitis, and urticaria, was completed for each patient. Subjects who had taken oral corticosteroids at a dosage of >20 mg/d within two weeks prior to the study were excluded.

Patch test methods

Patients were tested with the 28-allergen screening series recommended by the German Contact Dermatitis Research

Group (DKG; <http://www.ivdk.org/dkg/dkgblo.html>) (469 patients) or the European Standard Series¹⁵ (ESS) (668 patients), provided by Hermal GmbH, Reinbek, Germany. Allergens were applied to the upper back using Finn Chambers™ on Scanpor® tape (Epitest Ltd Oy, Tuusula, Finland) for 24–48 hours. Readings were taken at 48 hours and 72 hours according to the guidelines of the International Contact Dermatitis Research Group.¹⁶ Clinical relevance was defined as a history of contact with any material containing metal at the location of the dermatitis as reported by the participant.

Data analysis

Data analysis was performed using SPSS Version 17.0 (SPSS, Inc., Chicago, IL, USA). Interval and ratio variables were described as the mean ± standard deviation (SD), and categorical data were presented as proportions. Independent *t*-test and one-way analyses of variance (ANOVA) and the chi-squared test were used to compare means in quantitative and proportions in categorical variables, respectively. Univariate and multivariate binary logistic regression was used to calculate the odds ratios (ORs) for different levels of indicator variables. A *P*-value of <0.05 was considered to indicate statistical significance.

Results

Of the 1137 individuals included in this study, 313 patients (27.5%) had positive patch test results for at least one metallic allergen. Allergy to nickel sulfate was

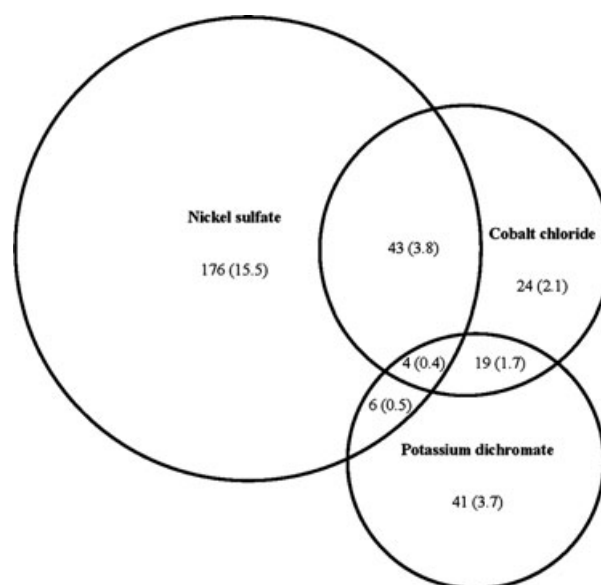


Figure 1 Numbers (%) of patients identified as allergic to one or more metallic allergens

most commonly observed (229 cases, 20.0%), followed by allergy to cobalt chloride (90 cases, 8.0%) and allergy to potassium dichromate (70 cases, 6.2%) (Fig. 1)

MOAHLFA (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Facial dermatitis, Age >40 years) index values for patients with ACD who were not allergic to metallic allergens and those with ACD caused by metallic allergens are shown in Table 1. The only two background factors for which significant differences emerged between the two groups were gender ($P < 0.01$) and age >40 years ($P < 0.05$). MOAHLFA index values for patients identified as allergic to different metallic allergens are demonstrated in Table 2

The mean ages of patients with ACD caused by nickel (26.8 ± 11.6 years) or cobalt (30.0 ± 11.6 years) were significantly lower than that of patients identified as hypersensitive to chromium (34.8 ± 11.4 years) ($P < 0.0001$ and $P = 0.01212$, respectively). The mean ages of subjects sensitive to nickel and cobalt, respectively, showed no statistically significant difference ($P = 0.09685$).

Tables 3 and 4 show ORs calculated using univariate and multivariate binary logistic regression analyses to investigate the relationship between indicator variables and hypersensitivity to nickel and chromium, respectively. According to the results of multivariate analyses, female gender was significantly associated with a 4.17-times higher risk for allergy to nickel, whereas male gender was associated with a 1.82-times higher risk for hypersensitivity

Table 1 MOAHLFA index values for patients with allergic contact dermatitis (ACD)

	All tested patients, n (%)	Patients with ACD not caused by metallic allergens, n (%)	Patients allergic to metallic allergens, n (%)
Male	378/1137 (33.2)	82/208 (39.4)	77/309 (24.9) ^a
Occupational dermatitis	201/939 (21.4)	56/188 (29.8)	60/263 (22.8)
Atopic dermatitis	220/990 (22.2)	31/180 (17.2)	57/306 (18.6)
Hand involvement	788/1095 (72.0)	142/203 (70.0)	221/301 (73.4)
Leg involvement	330/1097 (30.1)	56/204 (27.5)	96/302 (31.8)
Facial involvement	370/1095 (33.8)	65/203 (32.0)	103/301 (34.2)
Age >40 years	254/1091 (23.3)	61/199 (30.7)	64/302 (21.2) ^b

^a $P < 0.01$; ^b $P < 0.05$.

The chi-squared test was used to compare proportions for each MOAHLFA index between patients with ACD caused by non-metallic allergens and those with ACD caused by metallic allergens.

to chromium. Patients with hypersensitivity to cobalt had a 7.72-times higher risk for hypersensitivity to nickel and an 8.05-times higher risk for an allergic reaction to chromium.

Univariate binary logistic regression analysis conducted to assess the role of atopic dermatitis in patients with a positive patch test reaction to cobalt showed no significant

Table 2 MOAHLFA index values for patients identified as allergic to the respective metallic allergens

	Patients allergic to nickel sulfate, n (%)	Patients allergic to cobalt chloride, n (%)	Patients allergic to potassium dichromate, n (%)
Male ^a	28/229 (12.2)	29/90 (32.2)	44/70 (62.9)
Occupational dermatitis ^b	28/198 (14.1)	22/84 (26.2)	28/57 (49.1)
Atopic dermatitis ^c	47/220 (24.1)	25/89 (28.1)	8/66 (12.1)
Hand involvement	162/223 (72.6)	66/89 (74.2)	53/68 (77.9)
Leg involvement ^d	65/224 (29.0)	32/89 (36.0)	31/68 (45.6)
Face involvement ^e	85/223 (38.1)	36/89 (40.4)	12/68 (17.6)
Age >40 years ^f	33/226 (14.6)	19/88 (21.6)	28/66 (42.4)

^a $P < 0.0001$ for all comparisons concerning male gender.

^bFor nickel vs. cobalt, nickel vs. chromium and cobalt vs. chromium: $P = 0.015$, $P < 0.0001$ and $P = 0.005$, respectively.

^cCobalt vs. chromium was the only comparison in which a statistically significant difference with regard to the proportion of patients with atopic dermatitis was detected ($P = 0.016$).

^dNickel vs. chromium was the only comparison in which a statistically significant difference with regard to the proportion of patients with leg involvement was detected ($P = 0.011$).

^eDifferences in the proportions of patients with facial involvement in nickel vs. chromium and cobalt vs. chromium comparisons were statistically significant ($P = 0.002$ for both).

^fNickel vs. chromium and cobalt vs. chromium comparisons detected statistically significant differences with regard to age ($P < 0.0001$ and $P = 0.005$, respectively).

The chi-squared test was used to compare proportions for each MOAHLFA index among patients with allergic contact dermatitis caused by nickel sulfate, cobalt chloride and potassium dichromate.

Table 3 Odds ratios calculated using univariate and multivariate binary logistic regression analyses to investigate the relationship between indicator variables and hypersensitization to nickel

Variable	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Age <40 years	2.00 (1.34–2.99)	1.59 (1.01–2.51)
Female gender	4.50 (2.96–6.83)	4.17 (2.57–6.77)
Hypersensitivity to cobalt	6.35 (4.06–9.93)	7.72 (4.62–12.90)
No suggestive occupation	1.85 (1.19–2.85)	1.38 (0.83–2.25)

OR, odds ratio; 95% CI, 95% confidence interval.

Table 4 Odds ratios calculated using univariate and multivariate binary logistic regression analyses to investigate the relationship between indicator variables and hypersensitization to chromium

Variable	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Age <40 years	2.60 (1.56–4.34)	1.82 (0.97–3.42)
Female gender	3.74 (2.26–6.18)	2.10 (1.12–3.94)
Hypersensitivity to cobalt	7.41 (4.24–12.96)	8.05 (4.19–15.47)
Suggestive occupation	3.99 (2.31–6.88)	2.97 (1.59–5.56)

OR, odds ratio; 95% CI, 95% confidence interval.

difference between patients with and without atopic dermatitis (OR 1.55, 95% confidence interval [CI] 0.96–2.62), but multivariate binary logistic regression analysis for the same factor (OR adjusted for sensitivity to nickel and sensitivity to chromium) gave a significantly different result (OR 1.82, 95% CI 1.05–3.13).

Discussion

In this study, we determined the frequencies of ACD in Iran with respect to three common metallic allergens: nickel sulfate; potassium dichromate; and cobalt chloride. Among 1137 patch-tested patients, 313 (27.5%) individuals gave positive patch test results for at least one metallic allergen. These results are similar to those identified in a study performed in Turkey¹⁷ and lower than those of other studies from Turkey¹⁸ and Lithuania.¹⁹

In the present study, the most frequently encountered metal allergy was nickel hypersensitivity, identified in 20.0% of patients, a rate comparable with those found in Turkey (17.6),¹⁷ Singapore (20.4),⁹ and Taiwan

(17.7%).¹² Cobalt and chromium were the second and third most prevalent metallic allergens, to which hypersensitivity was detected in 8.0 and 6.2%, respectively, of the study population. Similar findings have been reported in some other studies.^{9,11,12,17}

In comparison with the findings of a previous study conducted between 2002 and 2004 in 250 patch-tested patients from Tehran,¹¹ the present study shows an apparently decreasing trend in allergies to nickel (from 28.0 to 20.0%) and cobalt (12.8 to 8.0%). To the best of our knowledge, there are no regulations for limiting the release of nickel in Iran, and we do not imagine that there have been any significant changes in practices such as body piercing in recent years that might explain this apparent decline. Therefore, differences among studies in the frequencies of positive patch test reactions may be partially explained by differences in the study populations.

With regard to the percentage of ACD attributable to nickel, our findings are compatible with the results of the European Surveillance System on Contact Allergies (ESSCA), which was conducted in 10 European countries in 2005/2006 and showed that the mean percentage of ACD to nickel in different regions of Europe ranged from 19.7 to 24.5%.²⁰ In the same study, the results of patch tests for sensitivity to cobalt and chromate differed across the study region.²⁰ The percentage of ACD caused by cobalt ranged from 7.2% in central Europe to 8.8% in northeast Europe.²⁰ The percentage of ACD attributable to chromate was significantly lower in western Europe (i.e. in the UK) than in any of the other three regions.²⁰ The rate of hypersensitivity to chromate reported in the present study is closest to the rate of 5.9% reported from central Europe.²⁰

However, a study conducted by Akasya-Hillenbrand and Özkaya-Bayazit¹⁸ in Turkey identified frequencies of hypersensitivity to chromium and cobalt of 11.8 and 8.5%, respectively; this may be explained by the relatively higher proportion of male participants in this study compared with those cited earlier.^{11,12,17} In the current study, nickel allergy was more frequent (OR 4.17, 95% CI 2.57–6.77) in female than in male participants. Similar gender profiles have emerged in many other studies conducted in different regions of the world.^{9,11,12,17,21} Schram *et al.*²² reported that nickel hypersensitivity was six times more frequent in women. Another study from Turkey reported nickel allergy to be between two and 10 times more frequent in women.¹⁷ The finding in the present study can be explained by the higher tendency towards ear piercing and the use of costume jewelry among girls and young women in Iran. Studies performed by Dotterud and Smith-Sivertsen²¹ and Garner²³ demonstrated a correlation between nickel allergy and number

of body piercings. A number of studies have reported that regulations imposed to limit nickel release to $<0.5 \mu\text{g}/\text{cm}^2$ per week in costume jewelry and hand tools led to a significant decrease in hypersensitivity to nickel.^{6,23,24}

Allergy to chromium was more prevalent in men. This finding is also comparable with those of several other studies conducted elsewhere in the world.^{9,11,12,17-19,21,25} This has been explained by the higher occupational exposure to chromium of men in the construction (through exposure to cement) or leather industries.

The risk for hypersensitivity to nickel and chromium was 7.72 times and 8.05 times, respectively, higher in patients with an allergy to cobalt. This accords with findings in a study conducted by Goon and Goh, who reported that most positive patch test results to cobalt were associated with positive patch tests to nickel and chromium in the same individual, and most positive patch tests to cobalt are considered to reflect a co-sensitization caused by primary nickel or chromate allergies.⁹ In addition, Garner²³ and Hegewald *et al.*²⁵ reported that many patients with cobalt allergy were also sensitive to nickel. This may be explained by the fact that cobalt is usually found with nickel and chromate in both nature and industry.¹⁷

Nickel allergy and hypersensitivity to cobalt were significantly more prevalent in subjects aged <40 years, whereas sensitization to chromium was more frequent in individuals aged >40 years; these findings are comparable with data reported by Hegewald *et al.*²⁵ The lower age of subjects identified as allergic to nickel and cobalt may be explained by the greater exposure to these metals of subjects in younger age groups as a result of the popular trend for ear piercing in preschool and teenage girls in Iran. The higher frequency of chromium allergy in subjects aged >40 years may be explained by the fact that older individuals have been more exposed to this allergen in past decades because of poorer work conditions and fewer protective measures.²⁶

The hand was the most frequent site of involvement for all three metal allergies, reflecting findings of a previous study performed in Iran¹¹ as well as those of a study from Turkey.¹⁸ However, the study from Taiwan¹² reported the upper extremities, face, and hands as the most frequent sites of involvement. The proportions of patients with facial involvement were higher among those with nickel or cobalt hypersensitivity than in the group identified as sensitive to chromium. These differences were statistically significant ($P = 0.002$ for both comparisons; Table 2). Ear piercing and the use of costume jewelry containing nickel and cobalt may explain this finding.

The proportion of patients with atopic dermatitis was smaller among those who were allergic to chromium (12.1%) in comparison with those who were allergic to nickel (24.1% [$P = 0.095$]) or cobalt (28.1% [$P = 0.016$])

(Table 2). This difference may be explained by the nature of atopic dermatitis, which usually manifests at an early age, and the fact that its signs and symptoms may cause affected individuals to avoid exposure to chromium by refraining from jobs such as those in the construction sector.

Conclusions

Nickel was not only the most frequently identified metallic allergen but was also the most frequent cause of ACD (20.0%) in Iran. It was followed by cobalt (8.0%) and chromium (6.2%) as the second and third most common causes of ACD in this study. Prevalences of nickel hypersensitivity were higher in women and in subjects aged <40 years, whereas allergy to chromium was more frequent in men and in individuals aged >40 years. Allergy to either nickel or chromium was a risk factor for cobalt hypersensitivity. Regulations pertaining to nickel release may reduce nickel hypersensitivity in Iran.

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