https://doi.org/10.5272/jimab.2018241.1941

Journal of IMAB - *Annual Proceeding (Scientific Papers)*. 2018 Jan-Mar;24(1)

Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

Original article

CONCURRENT CONTACT SENSITIZATION TO METALS IN DENTAL EXPOSURES

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ABSTRACT

Purpose: Sensitization to metals is a significant problem for both dental patients treated with dental materials and for dental professionals in occupational exposures. The purpose of the present study was to evaluate the incidence of concurrent contact sensitization to relevant for dental practice metals among students of dental medicine, students from dental technician school, dental professionals and patients.

Material and Methods: A total of 128 participants were included in the study. All of them were patch-tested with nickel, cobalt, copper, potassium dichromate, palladium, aluminium, gold and tin. The results were subject to statistical analysis ($p < 0.05$).

Results: For the whole studied population, potassium dichromate exhibited concomitant reactivity most often; copper and tin also often manifested co-reactivity. For the groups, exposed in dental practice, potassium dichromate and tin were outlined as the most often co-reacting metal allergens, but statistical significance concerning the co-sensitization to copper and the other metals was established only for aluminium. An increased incidence and OR for concomitant sensitization to cobalt and nickel was established in the group of dental students; to copper and nickel - in the control group; to palladium and nickel - in the group of dental professionals, the group of students of dental medicine and in the control group; to potassium dichromate and cobalt - in the group of dental students; to copper and palladium - in the control group of dental patients; to potassium dichromate and copper - in the group of dental professionals; to copper and aluminum - in the groups of students from dental technician school and of dental professionals; to copper and gold - in the groups of dental professionals and in the group of dental patients; to potassium dichromate and aluminum - in the group of dental professionals; to potassium dichromate and gold - in the group of dental professionals, and to aluminium and tin - in the groups of dental professionals and in the group of dental patients.

Conclusions: Our data indicate a high risk of concurrent contact sensitization to the studied relevant for dental practice metals. Since the role of occupational exposures can't be excluded, adequate preventive measures and information should be provided. General population also need to be well informed and the European Union regulations to be properly applied.

Keywords: Concurrent contact sensitization, Metals, Students of dental medicine, Dental professionals, Students of Dental technician school

INTRODUCTION

The incidence of contact sensitization to metals in human population is found to be high. Consumer exposures include jewelry, clothing clasps, mobile phones, leather goods, as well as dental restorations. Although this type of exposure is responsible for most cases of metal allergy, the importance of occupational one should be always kept in mind in case of positive patch test results.

Sensitization to metals is a significant problem for both dental patients treated with dental materials and for dental professionals in occupational exposures. It has been established that during a routine dental treatment oral mucosa can be affected by about 10-15 different metals, along with the other dental materials [1]. Often, contact sensitization to one relevant for dental practice metal is accompanied with concomitant/cross sensitization to other metals. Nickel was considered as the most common sensitizer among the metals [2]. Contact sensitization to nickel is often accompanied by such as chromium and cobalt. According to Fowler et al. (2001), contact sensitization to nickel was found in 33.5% of the allergic to gold individuals, and to cobalt – in 18.3% individuals from this group, respectively, compared to 14.2% and 9.0% in the general population. According to the authors, sensitization to gold is significantly associated with female gender and allergic reactions to nickel and cobalt [3]. Duarte et al. (2005) patch tested 1208 patients with contact dermatitis and found positive reactions to two or three of the metals among 18.5% of investigated subjects [4]. Hosoki et al. (2009) patch tested 212 dental patients with suspected allergy to metals. Of these, 69.8% had one or more positive reactions, the most common allergens being nickel (25.0%), palladium (24.4%), chromium (16.7%), cobalt (15.9%) and tin

(12.5% [5]. The incidence of occupational skin diseases of dental personnel was estimated to be 30% - 50% [6] and the incidence of allergies to metals among dental professionals with hand dermatitis is also considered to be high [7].

No data was found in the available literature concerning the manifestation of concomitant/cross sensitization to relevant for dentistry metals among students of dental medicine and from dental technician school. No studies were performed in Bulgaria to evaluate the incidence of concomitant/cross sensitization among dental professionals.

The purpose of the present study was to evaluate the incidence of concomitant/cross contact sensitization to selected, relevant for dental practice metals among students of dental medicine, students from dental technician school, dental professionals and patients in Bulgaria.

MATERIAL AND METHODS

A total of 128 participants, divided into 4 groups, were included in the study: occupationally exposed to metals dental professionals, students of dental medicine, students from dental technician school, and patients without occupational exposure to metals, serving as a control group. Gender characteristics of the studied subjects are presented in Table 1.

Table 1. Gender characteristics of the studied population.

Group	Gender		Total
	female [n / (%)]	male [n / (%)]	[n /(%)]
Occupationally exposed dental professionals	18 (64.3%)	10 (35.7)	28 (21.9%)
Students from dental technician school	29 (76.3%)	9 (23.7)	38 (29.7%)
Students of dental medicine	25 (62.5%)	15 (37.5)	40 (31.3%)
Patients without occupational exposure	17 (77.3%)	5 (22.7)	22 (17.2%)
Total	89 (69.5%)	39 (30.5%)	128 (100.0)

The study was approved by the Medical Ethics Board at Medical University – Sofia. All the participants were informed about the purpose of the study and gave their written informed consent before its commencement.

Skin patch testing

Skin patch testing with nickel(II)sulfate hexahydrate (5.0% pet), cobalt(II)chloride hexahydrate (1.0% pet), copper(II)sulfate pentahydrate (2.0% pet), potassium dichromate (0.5% pet), palladium(II)chloride (2.0% pet), aluminium(III)chloride hexahydrate (2.0% pet), gold(I)sodium thiosulfate dehydrate (2.0% pet) and tin (50.0% pet) – Chemotechnique Diagnostics was performed according to the Jadassohn & Bloch classical methods for diagnosis of contact allergy, by placing the allergens in IQ-Ultra hypoallergenic patches of Chemotechnique Diagnostics (IQ Chambers®,Vellinge, Sweden). Lack of anti-allergic medication constituted a mandatory condition before placing the patches and during the testing. Patches with allergens were applied on the back of the tested individuals; reading of the test was performed on day 2, several hours after removing the patches, with control revision on day 3.

Interpretation of reaction sites was based on the method and the interpretation key recommended by the International Contact Dermatitis Research Group (ICDRG) - Table 2.

Table 2. Interpretation key of skin patch test results based on International Contact Dermatitis Research Group.

Symbol	Meaning
(–)	negative reaction
?	doubtful reaction
+	weak positive reaction (non-vesicular)
++	strong positive reaction (oedematous or vesicular)
+++	extreme positive reaction (ulcerative or bullous)
IR	irritant reaction

Statistical methods

The statistics were calculated with SPSS 19.0. The following statistics available for cross-tabulation were used: Chi2 test, Fisher Exact Test for statistical significance, testing of the ratio of 2 probabilistic odds ratio (OR). Values of $p < 0.05$ were accepted as statistically significant.

RESULTS

The distribution by gender was not uniform, with a predominance of women in all the investigated groups, but without statistical significance ($Chi^2 = 3.8$, $p = 0.187$). The mean age of the studied population was 35 ± 13.22 years. Logically, the mean age in the groups of occupationally exposed dental professionals and the occupationally unexposed patients was significantly higher if compared to the groups of students. Individuals without a history of allergic pathology and skin complaints prevailed in all the studied groups, with no reliable differences in the overall distribution.

The statistical analysis revealed interesting results concerning the manifestation of concomitant/cross sensitization to the metals investigated by us. Data on the significantly increased incidence and OR of concomitant/cross sensitization to the selected metals in the whole population studied by us are summarized in Table 3.

Table 3. Incidence and OR of concomitant/cross sensitization to the selected metals in the whole population.

	$CoCl_2.6H_2O$	$CuSO_4x_5H_2O$	$PdCl_2$	$AlCl_3x_6H_2O$	$AuNa_3(S_2O_3)_2 x_2H_2O$	Sn	$NiO_4S.6H_2O$
$K_2Cr_2O_7$	*p=0.001 OR = 4.142, CI=1.72-9.97	*p=0.031 OR = 2.593, CI=1.08-6.25	*p=0.007 OR = 3.171, CI=1.34-7.50	*p=0.004 OR = 3.896, CI=1.50-10.1	*p=0.007 OR = 3.072, CI=1.33-7.11	* p<0.001 OR=8.087, CI=2.24-29.2	-
$CoCl_2.6H_2O$	-	* p=0.014 OR = 2.823, CI=1.22-6.56	-	-	* p=0.001 OR = 3.484, CI=1.60-7.60	-	*p=0.001 OR = 3.375, CI=1.58-7.21
$CuSO_4x_5H_2O$	-	-	* p=0.026 OR = 2.614, CI=1.10-6.19	* p=0.001 OR = 4.938, CI=1.90-12.9	* p=0.025 OR = 2.560, CI=1.11-5.90	-	* p=0.027 OR = 2.501, CI=1.09-5.72
$PdCl_2$	-	-	-	* p=0.043 OR = 2.596, CI=1.01-6.66	-	* p=0.009 OR = 4.615, CI=1.36-15.7	*p<0.001 OR=8.343, CI=3.45-20.2
$AlCl_3x_6H_2O$	-	-	-	-	- -	* p=0.002 OR = 5.824, CI=1.68-20.2	-
$AuNa_3(S_2O_3)_2 x_2H_2O$	-	-	-	-	-	* p=0.007 OR = 5.030, CI=1.42-17.8	-
Sn							

Evidently, from the results above, potassium dichromate exhibited concomitant reactivity most often - with all metal allergens, except for nickel sulphate. Copper (II) sulfate pentahydrate and tin also manifested co-reactivity often. According to our results, rarest is the co-sensitization to nickel (II) sulfate hexahydrate and the other metals tested by us – statistical significance was demonstrated only for cobalt (II) chloride hexahydrate, copper (II) sulfate pentahydrate and palladium (II) chloride.

Data on the incidence and OR of co-sensitization to the metal allergens in the groups, exposed in dental practice are presented in Table 4.

Table 4. Co-sensitization to metal allergens in the groups, exposed in dental practice.

	$CoCl_2.6H_2O$	$CuSO_4x_5H_2O$	$PdCl_2$	$AlCl_3$ x $_6H_2O$	$AuNa_3(S_2O_3)_2 x_2H_2O$	Sn	$NiO_4S.6H_2O$
$K_2Cr_2O_7$	*p=0.012 OR = 3.125, CI=1.26-7.75	-	*p=0.020 OR = 2.868, CI=1.16-7.11	*p=0.007 OR = 3.667, CI=1.37-9.82	*p=0.016 OR = 2.890, CI=1.20-6.96	*p<0.001 OR=14.286, CI=2.82-72.4	-
$CoCl_2.6H_2O$	-	-	-	-	*p=0.006 OR = 3.154, CI=1.38-7.21	-	*p=0.006 OR = 3.154, CI=1.38-7.21
$CuSO_4x_5H_2O$			-	*p=0.002 OR = 4.600, CI=1.68-12.6	-		-
$PdCl_2$				-		* p=0.019 OR = 4.500, CI=1.17-17.3	* p<0.001 OR=6.000, CI=2.39-15.1
$AlCl_3x_6H_2O$						* p=0.017 OR = 4.647, CI=1.21-17.9	
$AuNa_3(S_2O_3)_2 x_2H_2O$						*p=0.022 OR = 4.667, CI=1.31-19.3	
Sn							

Potassium dichromate and tin can be outlined again as the most often co-reacting metal allergens. Interestingly, in this group statistical significance concerning the co-sensitization to copper(II)sulfate pentahydrate and the other metals was established only for aluminium(III) chloride hexahydrate.

The results on the incidence of concomitant sensitization to nickel(II)sulfate hexahydrate and cobalt(II) chlo-

ride hexahydrate in the studied groups are presented below - Table 5.

Table 5. Distribution of positive skin patch test reactions to cobalt(II)chloride hexahydrate (Co) and nickel(II)sulfate hexahydrate (Ni) among the studied groups

Target group	Negative reaction to Co/ negative reaction to Ni		Positive r reaction to Co/ negative reaction to Ni		Negative reactions to Co/ positive reaction to Ni		Positive reaction to Co/ positive reaction to Ni		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	13	(46.4)	6	(21.4)	4	(14.3)	5	(17.9)	28	(100)
Students from dental technician school	15	(39.5)	10	(26.3)	5	(13.2)	8	(21.0)	38	(100)
Students of dental medicine	13	(32.5)	10	(25.0)	4	(10.0)	**13**	**(32.5)**	40	(100)
Occupationally unexposed patients	13	(59.2)	3	(13.6)	3	(13.6)	3	(13.6)	22	(100)
Total	**54**	**(42.2)**	**29**	**(22.7)**	**16**	**(12.5)**	**29**	**(22.7)**	**128**	**(100)**

The statistical analysis revealed an increased incidence and OR for the occurrence of concomitant sensitization to cobalt and nickel in the group of **dental students** ($\chi 2$=4.354, p=0.037; OR=4.225, CI=1.051-16.984).

The results on the incidence of concomitant sensitization to nickel(II)sulfate hexahydrate and copper(II)sulfate pentahydrate in the defined groups are presented in Table 6.

Table 6. Distribution of positive skin patch test reactions to copper(II)sulfate pentahydrate (Cu) and nickel(II)sulfate hexahydrate (Ni) among the studied groups

Target group	Negative reaction to Cu/ negative reaction to Ni		Positive reaction to Cu/ negative reaction to Ni		Negative reactions to Cu/ positive reaction to Ni		Positive reaction to Cu/ positive reaction to Ni		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	13	(46.4)	6	(21.4)	8	(28.6)	1	(3.6)	28	(100)
Students from dental technician school	19	(50.0)	6	(15.8)	8	(21.1)	5	(13.1)	38	(100)
Students of dental medicine	20	(50.0)	3	(7.5)	12	(30.0)	5	(12.5)	40	(100)
Occupationally unexposed patients	16	(72.7)	-	(0.0)	1	(4.5)	**5**	**(22.7)**	22	(100)
Total	**68**	**(53.1)**	**15**	**(11.7)**	**29**	**(22.7)**	**16**	**(12.5)**	**128**	**(100)**

The statistical analysis revealed an increased incidence and OR for co-sensitization to copper(II)sulfate pentahydrate and nickel(II)sulfate hexahydrate in the control group, where 83.3% of tested individuals had positive reactions to both substances ($\chi 2$=17.255, p<0.001; OR= 6.000, CI= 1.003-35.908).

The results on the incidence of co-sensitization to nickel(II)sulfate hexahydrate and palladium(II)chloride are presented in Table 7.

Table 7. Distribution of positive skin patch test reactions to palladium(II)chloride (Pd) and nickel(II)sulfate hexahydrate (Ni) among the studied groups

Target group	Negative reaction to Pd/ negative reaction to Ni		Positive reaction to Pd/ negative reaction to Ni		Negative reactions to Pd/ positive reaction to Ni		Positive reaction to Pd/ positive reaction to Ni		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	17	(60.8)	2	(7.1)	2	(7.1)	**7**	**(25.0)**	28	(100)
Students from dental technician school	24	(63.2)	1	(2.6)	9	(23.7)	4	(10.5)	38	(100)
Students of dental medicine	16	(40.0)	7	(17.5)	8	(20.0)	**9**	**(22.5)**	40	(100)
Occupationally unexposed patients	16	(72.7)	-	(0.0)	2	(9.1)	**4**	**(18.2)**	22	(100)
Total	**73**	**(57.0)**	**10**	**(7.8)**	**21**	**(16.4)**	**24**	**(18.8)**	**128**	**(100)**

During the statistical analysis was found, with high significance, increased incidence and OR of co-sensitization to palladium and nickel in the group of dental professionals ($\chi2$=12.664, p<0.001; OR= 6.000, CI= 1.003-35.908), where 77.8% exhibited positive reactions to both metal allergens, in the group of students of dental medicine ($\chi2$=5.364, p=0.021; OR=10.667, CI=1.047-108.688) and in the control group, in which all subjects sensitized to palladium exhibited positive reactions and to nickel as well ($\chi2$=13.037, p<0.001).

Data concerning the incidence of co-sensitization to cobalt(II) chloride hexahydrate and potassium dichromate in the investigated groups are summarized in Table 8.

Table 8. Distribution of positive skin patch test reactions to potassium dichromate (Cr) and cobalt(II) chloride hexahydrate (Co) among the studied groups

Target group	Negative reaction to Cr/ negative reaction to Co		Positive reaction to Cr/ negative reaction to Co		Negative reactions to Cr/ positive reaction to Co		Positive reaction to Cr/ positive reaction to Co		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	15	(53.6)	2	(7.1)	8	(28.6)	3	(10.7)	28	(100)
Students from dental technician school	17	(44.7)	3	(7.9)	14	(36.9)	4	(10.5)	38	(100)
Students of dental medicine	13	(32.5)	4	(10.0)	10	(25.0)	**13**	(**32.5**)	40	(100)
Occupationally unexposed patients	16	(72.7)	-	(0.0)	4	(18.2)	2	(9.1)	22	(100)
Total	**61**	**(47.7)**	**9**	**(7.0)**	**36**	**(28.1)**	**22**	**(17.2)**	**128**	**(100)**

The statistical analysis revealed a significantly increased incidence and OR of co-sensitization to potassium dichromate and cobalt (II) chloride hexahydrate in the group of dental students, where 76.5% of individuals sensitized to potassium dichromate exhibited sensitization to cobalt (II) chloride hexahydrate as well ($\chi2$ = 4.354, p = 0.037; OR = 4.225, Cl = 1.051-16.984).

The results on the incidence of co-sensitization to copper(II)sulfate pentahydrate and palladium(II)chloride in the studied groups are presented below - Table 9.

Table 9. Distribution of positive skin patch test reactions to copper(II)sulfate pentahydrate (Cu) and palladium(II)chloride (Pd) among the studied groups

Target group	Negative reaction to Cu/ negative reaction to Pd		Positive reaction to Cu/ negative reaction to Pd		Negative reactions to Cu/ positive reaction to Pd		Positive reaction to Cu/ positive reaction to Pd		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	15	(53.6)	4	(14.3)	6	(21.4)	3	(10.7)	28	(100)
Students from dental technician school	25	(65.8)	8	(21.1)	2	(5.3)	3	(7.8)	38	(100)
Students of dental medicine	20	(50.0)	4	(10.0)	12	(30.0)	4	(10.0)	40	(100)
Occupationally unexposed patients	16	(72.7)	2	(9.1)	1	(4.5)	**3**	**(13.6)**	22	(100)
Total	**76**	**(59.4)**	**18**	**(14.1)**	**21**	**(16.4)**	**13**	**(10.2)**	**128**	**(100)**

A significantly increased incidence and OR for co-sensitization to copper(II)sulfate pentahydrate and palladium(II)chloride in the control group of dental patients was proved by the statistical analysis ($\chi 2$=7.607, p=0.006; OR=24.000, CI=1.615-356.635).

Below – Table 10 presents the results on the incidence of co-sensitization to copper (II) sulphate pentahydrate and potassium dichromate in the studied groups.

Table 10. Distribution of positive skin patch test reactions to potassium dichromate (Cr) and copper (II) sulphate pentahydrate (Cu) among the studied groups

Target group	Negative reaction to Cr/ negative reaction to Cu		Positive reaction to Cr/ negative reaction to Cu		Negative reactions to Cr/ positive reaction to Cu		Positive reaction to Cr/ positive reaction to Cu		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	20	(71.4)	1	(3.6)	3	(10.7)	**4**	**(14.3)**	28	(100)
Students from dental technician school	22	(57.9)	5	(13.2)	9	(23.6)	2	(5.3)	38	(100)
Students of dental medicine	19	(47.5)	13	(32.5)	4	(10.0)	4	(10.0)	40	(100)
Occupationally unexposed patients	17	(77.3)	-	(0.0)	3	(13.6)	2	(9.1)	22	(100)
Total	**78**	**(61.0)**	**19**	**(14.8)**	**19**	**(14.8)**	**12**	**(9.4)**	**128**	**(100)**

A significantly increased incidence and OR for occurrence of co-sensitization to potassium dichromate and copper (II) sulfate pentahydrate in the group of dental professionals was established during the statistical analysis ($\chi 2$ = 9.820, p = 0.002; OR = 26.667, CI = 2.178-326.453), where 80% of the persons sensitized to potassium dichromate manifested sensitization and to copper (II) sulfate pentahydrate as well.

The results on the incidence of concomitant sensitization to copper(II)sulfate pentahydrate and aluminium (III) chloride hexahydrate are presented in Table 11.

Table 11. Distribution of positive skin patch test reactions to copper(II)sulfate pentahydrate (Cu) and aluminium(III)chloride hexahydrate (Al) among the studied groups

Target group	Negative reaction to Cu/ negative reaction to Pd		Positive reaction to Cr/ negative reaction to Pd		Negative reactions to Cu/ positive reaction to Pd		Positive reaction to Cu/ positive reaction to Pd		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	19	(67.9)	4	(14.3)	2	(7.1)	**3**	**(10.7)**	28	(100)
Students from dental technician school	25	(65.8)	6	(15.8)	2	(5.3)	**5**	**(13.1)**	38	(100)
Students of dental medicine	25	(62.5)	5	(12.5)	7	(17.5)	3	(7.5)	40	(100)
Occupationally unexposed patients	17	(77.3)	4	(18.2)	-	(0.0)	1	(4.5)	22	(100)
Total	**86**	**(67.2)**	**19**	**(14.8)**	**11**	**(8.6)**	**12**	**(9.4)**	**128**	**(100)**

The statistical analysis proved, with high significance, increased incidence and OR for co-sensitization to copper(II)sulfate pentahydrate and aluminum(III) chloride hexahydrate in the groups of students from dental technician school ($\chi2$=3.977, p=0.006; OR= 10.417, CI=1.611-47.334), as well as in the group of dental professionals ($\chi2$=7.529, p=0.046).

The results on the incidence of concomitant sensitization to copper(II)sulfate pentahydrate and gold(I) sodium thiosulfate dehydrate in groups are presented below - Table 12.

Table 12. Distribution of positive skin patch test reactions to copper(II)sulfate pentahydrate (Cu) and gold(I)sodium thiosulfate dehydrate (Au) among the studied groups

Target group	Negative reaction to Cu/ negative reaction to Au		Positive reaction to Cu/ negative reaction to Au		Negative reactions to Cu/ positive reaction to Au		Positive reaction to Cu/ positive reaction to Au		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	18	(64.3)	3	(10.7)	3	(10.7)	**4**	**(14.3)**	28	(100)
Students from dental technician school	18	(47.4)	7	(18.4)	9	(23.7)	4	(10.5)	38	(100)
Students of dental medicine	18	(45.0)	3	(7.5)	14	(35.0)	5	(12.5)	40	(100)
Occupationally unexposed patients	17	(77.3)	3	(13.6)	-	(0.0)	**2**	**(9.1)**	22	(100)
Total	**71**	**(55.5)**	**16**	**(12.5)**	**26**	**(20.3)**	**15**	**(11.7)**	**128**	**(100)**

An increased incidence and OR of co-sensitization to sensitization to copper(II)sulfate pentahydrate and gold(I)sodium thiosulfate dehydrate was established in the groups of dental professionals ($\chi2$=5.143, p=0.023; OR= 8.000, CI= 1.158-55.257), as well as in the control group of dental patients, where all individuals, sensitized to Au manifested positive reactions to Cu ($\chi2$=7.480, p=0.006; OR= 0.150, CI= 0.053-0.426).

Data on the incidence of co-sensitization to potassium dichromate and aluminium chloride in the groups defined by us are presented in Table 13.

Table 13. Distribution of positive skin patch test reactions to potassium dichromate (Cr) and aluminum chloride (Al) among the studied groups

Target group	Negative reaction to Cr/ negative reaction to Al		Positive reaction to Cr/ negative reaction to Al		Negative reactions to Cr/ positive reaction to Al		Positive reaction to Cr/ positive reaction to Al		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	21	(75.0)	2	(7.1)	2	(7.1)	**3**	**(10.8)**	28	(100)
Students from dental technician school	25	(65.8)	6	(15.8)	6	(15.8)	1	(2.6)	38	(100)
Students of dental medicine	20	(50.0)	10	(25.0)	3	(7.5)	7	(17.5)	40	(100)
Occupationally unexposed patients	19	(86.4)	2	(9.1)	1	(4.5)	-	(0.0)	22	(100)
Total	**85**	**(66.4)**	**20**	**(15.6)**	**12**	**(9.4)**	**11**	**(8.6)**	**128**	**(100)**

During the statistical analysis, we established, with high significance, increased incidence and OR for the manifestation of co-sensitization to potassium dichromate and aluminum chloride in the group of dental professionals ($\chi 2$=7.370, p=0.007; OR=15.75, CI=1.574-157.602).

Further, we evaluated the incidence of co-sensitization to potassium dichromate and gold in the defined groups. The results are presented in Table 14.

Table 14. Distribution of positive skin patch test reactions to potassium dichromate (Cr) and gold (Au) among the studied groups

Target group	Negative reaction to Cr/ negative reaction to Au		Positive reaction to Cr/ negative reaction to Au		Negative reactions to Cr/ positive reaction to Au		Positive reaction to Cr/ positive reaction to Au		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	20	(71.4)	1	(3.6)	3	(10.7)	**4**	**(14.3)**	28	(100)
Students from dental technician school	20	(52.6)	5	(13.2)	11	(28.9)	2	(5.3)	38	(100)
Students of dental medicine	14	(35.0)	7	(17.5)	9	(22.5)	10	(25.0)	40	(100)
Occupationally unexposed patients	18	(81.8)	2	(9.1)	2	(9.1)	-	(0.0)	22	(100)
Total	**72**	**(56.3)**	**15**	**(11.7)**	**25**	**(19.5)**	**16**	**(12.5)**	**128**	**(100)**

The statistical analysis revealed, with high significance, an increased and OR for co-sensitization to potassium dichromate and gold in the group of dental professionals**,** where 80% of persons sensitized to potassium dichromate exhibited sensitization to gold ($\chi 2$=9.820, p=0.002; OR=26.667, CI=2.178-326.453).

The results from the statistical analysis on the incidence of co-sensitization to aluminium(III)chloride hexahydrate and tin are presented below – Table 15.

Table 15. Distribution of positive skin patch test reactions to aluminium(III)chloride hexahydrate (Al) and tin among the studied groups

Target group	Negative reaction to Al/ negative reaction to tin		Positive reaction to Al/ negative reaction to tin		Negative reactions to Al/ positive reaction to tin		Positive reaction to Al/ positive reaction to tin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dental professionals	22	(78.6)	3	(10.7)	1	(3.6)	**2**	**(7.1)**	28	(100)
Students from dental technician school	30	(79.0)	7	(18.4)	1	(2.6)	-	(0.0)	38	(100)
Students of dental medicine	27	(67.5)	7	(17.5)	3	(7.5)	3	(7.5)	40	(100)
Occupationally unexposed patients	20	(91.0)	-	(0.0)	1	(4.5)	**1**	**(4.5)**	22	(100)
Total	**99**	**(77.3)**	**17**	**(13.3)**	**6**	**(4.7)**	**6**	**(4.7)**	**128**	**(100)**

In the statistical analysis, an increased incidence and OR for co-sensitization to aluminium(III)chloride hexahydrate and tin was found in the group of dental professionals ($\chi 2=5.457$, p=0.019) and in the control group of dental patients ($\chi 2=10.476$, p=0.001).

DISCUSSION

Dental alloys mainly involved in contact allergy are nickel sulphate, chromium, mercury, palladium and gold. The others components of amalgam are silver, tin, copper and trace of other metals like zinc.

Nickel is one of the most important metals involved in contact dermatitis and unfortunately its use is very wide in everyday life [8]. In dentistry, it is a base-metal alloy largely used. Cobalt is a hard, silver-gray metal usually found associated with nickel. It is used in the production of metal alloys and pigments (cobalt blue and cobalt green).Sensitization to cobalt occurs mainly because of its presence in objects that also contain chromium and nickel and is often associated with allergies to other metals [9]. In many cases sensitization is due to the use of costume jewelry.

Back in 1951, Rostenberg and Perkins outlined that the nickel coating of consumer products is the most important cause of allergy to cobalt in patients with dermatitis [10]. It is common that the patients are sensitized to multiple metal ions . In subjects with metal allergic contact dermatitis, e.g. jewellery reactors, reactivity with Ni is most prevalent followed by reactivity with Co, Pd, Au and Cr (e.g. 94·5%, 34%, 17%, 10% and 3%, respectively . Whether this is due to concurrent sensitization, cross-reactivity or, in some cases, both is not fully understood. However, several studies have suggested that sensitization to one metal ion increases the chance of being sensitized to additional metals . Accordingly, concomitant reactivity to cobalt and nickel in patch testing is often observed 11. Probably , this is a reaction of concomitant, more than cross-reactivity, basing on results of animal and in vitro studies [12].

According to Moulon et al., individual Ni-specific T cell clones cross-react with some transition metals (e.g. Cu or Pd), but not with others (e.g. Co, Cr and Pt), presented by identical MHC class II molecules. These results provide an explanation for the multiple metal-reactivities observed in vivo in human patients: they indicate that for Cu and Pd, these co-reactivities in vivo might be due to cross-reactivity at the clonal level, but this is not the case for cobalt allergy, which might result from cosensitization of the patient to cobalt in addition to nickel [12]. It was suggested that sensitization to Co, Cr, Pd and Au results in a cellular immune response of a character similar to the mixed Th1- and Th2-type cytokine profile shown to be induced by Ni [11].

According to the skin patch testing results obtained, for the period 2000 - 2010 the incidence of sensitization to nickel is 39.9%, to cobalt - 27.2%, and to cobalt without concomitant sensitization to nickel - 22.9% [13]. According to the North American Contact Dermatitis group, 40% of cobalt-sensitized patients are negative for nickel in patch testing [14]. According to the results obtained by Edman, 32% of patients with positive reactions to cobalt are not sensitized to nickel [15]. Kranke è Aberer [16] analyzed positive reactions in patch testing to metals among 11 516 patients. The conclusion is that 79% of patients allergic to cobalt were sensitized to nickel, 42% - to palladium and 15% - to chromate.

According to our results, from the whole studied population of 128 subjects, sensitized to Ni but not to Co were 19.5%, to Co but not to Ni - 22.7%, and to both metals – again 22.7%. Notably, the incidence and OR of co-sensitization to cobalt and nickel was significantly increased in the group of dental students - 32.5%. Our data outline Co as a sensitizer of prominent importance in exposure during the practical education in dental medicine.

The sensitization to palladium and nickel in dental practice is an object of intensive studies . Consumers are exposed to palladium primarily from jewelry and dental restorations. In the palladium alloy, this metal is present at 75 %, and it is known that palladium, in ionic form and at sufficiently high concentrations, has toxic and allergic effects on biological systems [8]. Mono-sensitization to palladium is considered to be rare, but very often accompanies allergy to nickel, as palladium and nickel tend to cross react [17,18]. Considering the reported cross-reactivity between Ni and Pd [12], and the fact that *in vitro* responses

to Ni are stronger in general, it is possible that the Pd reactivity is caused predominantly by Ni-induced T cells. In a recently published study, Muris et al. (2015) presented the results from a multicenter study, in which patch testing to palladium and nickel was conducted in 906 patients. Of these, 24.3% exhibited positive reactions to palladium and 25.2% - to nickel. The percentage of monosensitization was 6-7% for both metals. Sensitization to palladium was related to presence of dental crowns in the oral cavity [19].

The results cited above are in concordance with the established in our study. Positive reactions to Ni but not to Pd we observed among 16.4% of the whole tested population (a group of highest risk of sensitization being the youngest ones of students from dental technician school and of dental medicine); to Pd but not to Ni - 7.8% (70% of all positive reactions were in the group of dental students), and to both metals – 18.8%. We could outline as groups at highest risk of cross-sensitization the ones of dental professionals and students of dental medicine. It is difficult to give followed categorical statement concerning the role of occupational exposure in dental practice, since no data in the available literature on this topic was found, and, on the other hand, the lowest incidence of cross-sensitization was found among the group of students from dental technician school. The significantly increased incidence of cross-sensitization in the group of dental patients could be explained with exposures to both nickel-containing jewelry and dental restorations.

The world production of copper is steadily increasing. Although humans are widely exposed to copper-containing items on the skin and mucosa, allergic reactions are infrequently reported [20]. In a few and selected cases, copper can result in clinically relevant allergic reactions –immunologic contact urticaria, allergic contact dermatitis, systemic allergic reactions and contact stomatitis. Reports of immune reactions to copper mainly describe systemic exposure from intrauterine devices and prosthetic materials in dentistry, implicitly excluding induction of the hypersensitivity from contact with the skin as a risk factor [21].

Regarding the incidence of cross-sensitization to Cu and Ni, our results confirm the previously cited statements [21] that it mainly describes systemic exposure (prosthetic materials in dentistry), since as a most vulnerable group was outlined one of dental patients. Further, this was confirmed regarding the incidence of cosensitization to Cu and Pd – it was significantly higher in the control group of dental patients. Among the latter group, a significantly higher incidence of cosensitization to aluminium(III)chloride hexahydrate and tin was established. No categorical statement concerning the role of the type of exposure could be given since a significantly increased incidence of such cosensitization was established among dental professionals as well.

The persistence of metals in the environment and their natural occurrence in rocks, soil and water cause them to be present in the manufacture of pigments and other raw materials used in the cosmetic industry [22]. Heavy metals such as lead, mercury, cadmium, arsenic and nickel, as well as aluminium, copper, iron, chromium and cobalt are detected in various types of cosmetics (colour cosmetics, face and body care products, hair cosmetics, herbal cosmetics, etc.) and may be present in amounts creating a danger to human health [23].

We evaluated the incidence of co sensitization to Cu and Al. It was highest among the students from dental technician school and dental professionals. Since no similar data were found in the available literature, we could suggest the role of the occupational exposure in dental practice for the onset of such co sensitization.

Chromium is the fourth most commonly found substance in the earth's crust. In contrast to other metals, chromium allergy has been reported to be stable or declining [24]. It is mainly used in metallurgy to increase corrosion resistance and give a glossy finish; in alloys such as stainless steel; in plating processes (depositing a protective layer of chrome on objects); in dyes and paints, in leather tanning and wood preservation [25]. Detergents and cosmetics may also contain chromium. Historically, the most important cause of allergy to chromium has been occupational exposure to cement. In children, the most common source is leather, and chromium sensitivity is the largest responsible for shoe contact dermatitis [9, 26]. Trivalent chromium compounds are used for leather tanning, and chromium may be released if leather goods are used. In certain instances, small amounts of hexavalent chromium can be formed and released [27]. Induction of sensitisation only occurs after exposure to hexavalent chromium. The content of hexavalent chromium in leather is regulated in European Union, but the rate of release rather than content is relevant for allergic skin reaction [27, 28]. Lidén et al. (2016) analysed the co-occurrence of allergy to cobalt, chromium, and nickel. Allergy to any metal was shown in 31% of patients, allergy to cobalt in 14%, allergy to chromium in 7%, and allergy to nickel in 20%. Solitary cobalt allergy was as frequent as a concomitant allergy to cobalt and nickel or chromium [29].

According to the results from the present study, potassium dichromate was the most often concomitantly reacting substance - with all metal allergens, except for nickel sulphate. The incidence of co-sensitization to potassium dichromate and cobalt in the whole studied population was 17.2%, with the group of dental students identified as especially vulnerable. Concerning the incidence of co-sensitization to potassium dichromate and copper, in the whole tested population it was much lower – 9.4%, highest being among dental professionals. The latter group was at particular risk of co-reactivity to potassium dichromate and aluminum chloride as well.

Gold is another metal that can cause a contact hypersensitivity. It is widely used in dentistry as well as in piercing. In dentistry, it is mainly used for the restoration of rear dental arches because in that site the strength is more important than the esthetics. The gold alloys are composed of 80 % of this metal. In several studies, it resulted in the most common allergen after the nickel [8, 30]. In a study by Vamnes et al. [31], 25 % of patients showed a positive reaction to gold at the patch test, and there was a statistically significant correlation between positive tests and pres-

ence of dental gold. Also in Ahlgren's study [32], there was a statistically significant correlation between positive patch testing to gold in a rate of 30.4 % among the patients involved in the study and the presence of dental gold in a rate of 74.2 % among the previous rate. Gold, whether yellow or white, may contain nickel in enough quantity to cause sensitization when present in earrings [33].

According to our results, the group of dental professionals was the one at risk of co-sensitization to gold and two other important for dental practice metal allergens – potassium dichromate and copper(II)sulfate pentahydrate. Nevertheless, we can't give a categorical statement about the role of occupational exposure, since statistical significance was also established for the control group of dental patients, where all individuals, sensitized to Au manifested positive reactions to Cu.

CONCLUSIONS

- The group of dental students is at particular risk of co-sensitization to cobalt and nickel. Probably it is due to their extensive exposure to these metals during their activities on removing of old and elaboration of new metal crowns and bridges during their practical education. The students from dental technician school have no exposure in clinical practice to these metals.

- Our data outline Co as a sensitizer of prominent importance in exposure during the practical education in dental medicine.

- We could outline as groups at highest risk of cross-sensitization to Ni and PD the ones of dental professionals and students of dental medicine. The low incidence of cross-sensitization among the group of students from dental technician school could be explained with the shortest duration of exposure during their practical education.

- The group of dental patients was the most vulnerable regarding the cross-sensitization to Cu and Ni, Cu and Pd and Al and tin. Probably these findings mainly describe systemic exposure from numerous consumer sources,

- According to our results, potassium dichromate was the most often concomitantly reacting substance.

- The group of dental professionals was at highest risk of co-sensitization to potassium dichromate and Cu and Al, as well as to Au and potassium dichromate and Cu. Nevertheless, we can't give a categorical statement about the role of occupational exposure, since statistical significance was also established for the control group of dental patients, where all individuals, sensitized to Au manifested positive reactions to Cu.

- Our data indicate a high risk of concurrent contact sensitization to the studied relevant for dental practice metals. Since the role of occupational exposures can't be excluded, adequate preventive measures and information should be provided. General population also need to be well informed and the European Union regulations to be properly applied.

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Please cite this article as: Lyapina M, Dencheva M, Cekova M, Deliverska M, Kisselova-Yaneva A. Concurrent contact sensitization to metals in dental exposures. *J of IMAB*. 2018 Jan-Mar;24(1):1941-1952.
DOI: https://doi.org/10.5272/jimab.2018241.1941

Received: 30/12/2017; Published online: 27/03/2018

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