

Sensitization to palladium and nickel in Europe and the relationship with oral disease and dental alloys

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Summary

Background. The role of palladium and nickel sensitization in oral disease and dermatitis is not fully understood.

Objectives. To investigate whether sensitization to these metals was associated with exposure to dental alloys and oral and skin complaints/symptoms in a European multicentre study.

Methods. In six dermatology clinics, patch tests with palladium (3% Na₂PdCl₄; Pd = 102.0 µmol/g) and nickel (5% NiSO₄·6H₂O; Ni = 190.2 µmol/g) were performed in consecutive patients, and patients' characteristics were collected with a questionnaire and a clinical investigation.

Results. In total, 906 patients were included, of whom 24.3% reacted to palladium and 25.2% to nickel. The rate of monosensitization was 6–7% for both metals. Palladium sensitization (as opposed to no sensitization to both metals) was associated with exposure to dental crowns [odds ratio (OR) 2.0], skin reactivity to metals (OR 2.8), oral lichenoid lesions (OR 4.7), xerostomia (OR 7.3), and metal taste (OR 20.7), but not with eczema, stomatitis, or oral burning sensation. Additionally, xerostomia (OR 8.7) and metal taste (OR 4.6) were associated with sensitization to both metals.

Conclusions. Clinically, it is important for palladium-sensitized patients to undergo an oral examination, with particular attention to the presence of/exposure to dental crowns. In the case of metal contact allergy, exposure to dental crowns could play a role.

Key words: allergic contact dermatitis; cross-reactivity; dental alloys; epidemiology; metals; nickel; oral disease; oral lichenoid lesion (OLL); palladium.

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Sensitization/allergy to palladium is gaining interest, as the prevalence of contact allergy to it has been considerably underestimated. The recent introduction of a more sensitive test allergen, that is, disodium tetrachloropalladate (Na₂PdCl₄), has resulted in the detection of more cases (1–3). Indeed, it has been shown that palladium sensitization is largely underdiagnosed, and approximately half of the palladium-positive patients were missed when only palladium dichloride (PdCl₂) was used for patch testing (4). In that same study, it was found that, unlike nickel sensitization, palladium sensitization

is not sex-related. This shows that, in contrast to nickel sensitization, other sources of exposure are decisive for the development of palladium sensitization.

Human exposure to nickel is very common, because this metal is used in clothing, consumer products, and jewellery. Moreover, high concentrations can be found in food. Nickel is a base metal and susceptible to corrosion. Therefore, allergy to nickel is mainly related to piercings and jewellery (5, 6). Although palladium is used in jewellery, the main sources of palladium exposure are dental alloys (7). In dentistry, palladium is typically used to produce dental crowns and bridge work. It is a noble metal and is therefore resistant to corrosion, which explains why patients sensitized to palladium rarely show skin reactivity to metallic palladium (3, 8, 9). Nevertheless, some case reports have described clinically relevant palladium allergy as a result of exposure to jewellery and piercings (10–20). In contrast to the skin, the oral cavity is a hostile environment, owing to the presence of saliva containing corrosive substances such as hydrogen, chloride ions, sulfide compounds, dissolved oxygen, and free radicals, facilitating corrosion of all metals, including noble ones. It may be assumed that dental alloys in particular play a major role in the aetiology of relevant palladium allergy.

In a recent study, it has been shown that patients with palladium-based dental crowns significantly more often show positive palladium patch test results, palladium-induced lymphoproliferation, and cytokine production [interleukin (IL)-5 and IL-13] (21). To the best of our knowledge, a clear association between exposure to dental crowns and positive palladium patch test results has not yet been shown in a large cross-sectional study.

With regard to the symptoms and/or complaints associated with palladium allergy, little is known. In cross-sectional studies, the most frequently reported oral disorders related to palladium allergy are oral lichenoid lesions (OLLs), stomatitis, gingivitis, cheilitis, burning sensation, metal taste, and dry mouth or xerostomia (21–25). However, none of these is pathognomonic, which is explained by the large number of other allergens that may induce similar symptoms and complaints (26–28). In addition, the immuno-tolerogenic nature of the oral mucosa (29–33) may play a role in the unpredictability of oral disease related to allergy, which has been shown by case reports describing systemic dermatitis resulting from exposure to palladium-containing dental alloys without oral discomfort or lesions (34–38).

In the current study, the main aim was to assess whether sensitization to palladium and/or nickel is associated with clinical variables consisting of exposure to different subsets of dental alloys and oral symptoms/

complaints in six western European dermatology clinics. Because palladium sensitization and nickel sensitization often coexist, we also explored possible differences in associations between monosensitization to both metals. Furthermore, regardless of sensitization to palladium and/or nickel, possible associations between exposure to dental alloys and oral symptoms/complaints were investigated. No attempts were made to determine cause–effect relationships.

Materials and Methods

Patients and participating clinics

Consecutive patients suspected of having allergic contact dermatitis (ACD) with or without eczema were patch tested during 2011 and 2012 at six dermatology clinics. The participating clinics were: VU University Medical Centre, Amsterdam, The Netherlands; Hospital del Mar, Parc de Salut Mar. Universitat Autònoma, Barcelona, Spain; University Dermatological Clinic, Policlinico of Bari, Italy; University Hospital Basel, Switzerland; University Hospital Coimbra University, Portugal; and Hospital K. U. Leuven, Belgium.

Questionnaire

All patients were interviewed by use of a questionnaire containing the questions listed in Table 1. This questionnaire comprised both medical history and clinical data, which were gathered by a dermatologist. History focused on skin reactivity after prolonged contact with metals such as jewellery, piercings, or other metal objects (history of metal ACD), but also oral complaints, such as xerostomia (dry mouth), burning/pain, and metal taste. Although xerostomia is measurable, in this study xerostomia was based on the patient's experience, making it, together with burning/pain and metal taste, a subjective variable.

Clinical data focused on the presence of eczema, which could be subdivided according to its location as facial, extremities, or other. Furthermore, exposure to dental alloys and clinical signs of oral disease, namely OLLs (including redness and ulcers, as these may be difficult to distinguish) and stomatitis, were evaluated. Dental alloys were subdivided into dental amalgam, dental crowns, dental prostheses, and orthodontic retention wires.

Preparation of Na_2PdCl_4

Na_2PdCl_4 3% pet. was prepared at the department of Dental Materials Science of the Academic Centre for Dentistry

Table 1. Questions and responses used in the questionnaire

Q1	Does the patient suffer from eczema? No/Facial/Extremities/Others (to fill in)
Q2	Does the patient suffer from skin reactions resulting from contact with metals, such as jewellery, piercings, or others? Yes/No
Q3	Does the patient suffer from intraoral abnormalities? No/Lichnoid lesions, redness, ulcers/Metal taste/Dry mouth/Others (to fill in)
Q4	The patients has: No dental restorations OR only composite (white) fillings Dental amalgam Dental crowns and/or bridges Metal-containing dental prosthesis Orthodontic retention wires (behind frontal teeth)

Amsterdam (ACTA). Na_2PdCl_4 (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands; CAS no. 13820-53-6) was ground with a porcelain mortar and pestle. Then, 3 g was added to 97 g of pet. (Sigma-Aldrich Chemie BV; CAS no. 8009-03-8). Na_2PdCl_4 with the pet. was then suspended in a glass laboratory bottle by heating (55°C) in a ultrasonic cleaning unit (Branson ultrasonic cleaner; model 3510E-DTH; Branson Ultrasonic Corporation, Danbury, CT, USA) with intermittent stirring for 4 hr until a homogeneous suspension was obtained. Sterile syringes were then filled and labelled. One batch was used to prepare the syringes for all participating clinics.

Patch tests

In addition to the European or national baseline series, including 5% $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ pet. ($\text{Ni} = 190.2 \mu\text{mol g}^{-1}$), all patients were tested with Na_2PdCl_4 3% pet. ($\text{Pd} = 102.0 \mu\text{mol g}^{-1}$). Also, PdCl_2 [1% or 2% pet. (only in Bari and Leuven), that is, $\text{Pd} = 56.4 \mu\text{mol g}^{-1}$ and $\text{Pd} = 112.8 \mu\text{mol g}^{-1}$, respectively] was tested in all patients. However, all analyses were performed with the Na_2PdCl_4 3% pet. results, unless explicitly stated. Other metal allergens, such as gold, chromium, and cobalt, were not investigated in this study. Procedural details per clinic are summarized in Table 2. The observed differences were accepted for the purpose of this study. Patch testing was performed according to ICDRG recommendations. Some clinics preferred to perform readings on D4 instead of D3, which was accepted for the purpose of this study. Except in Basel, Coimbra, and Leuven, all clinics performed standard additional readings after 1 week (D7). Patch tests were regarded as positive if a positive reaction (+, ++ or +++ reaction) to the metal salts was observed at least at one reading. If a positive reaction was observed at more than one reading, the strongest reaction defined

the actual test result. For statistical analyses, all positive reactions (+, ++, or +++) were clustered as positive. Doubtful reactions ($\pm$) and irritant reactions were also recorded, but were regarded as negative.

Exclusion criteria

General exclusion criteria were age under 18 years, pregnancy, systemic corticosteroid or immunosuppressive treatment during the previous 30 days, and topical treatment with corticosteroids or exposure to ultraviolet radiation during the previous 15 days on or around the test area.

Statistics

Statistical analyses were performed with IBM® SPSS® software version 21 (IBM, New York, USA). To identify clinical differences between sensitization to one or both metals, patients were divided into four groups: (i) patients monosensitized to palladium (only a positive patch test reaction to palladium); (ii) patients with concomitant positive reactions to palladium and nickel; (iii) patients monosensitized to nickel (only a positive patch test reaction to nickel); and (iv) patients with negative patch test results for both metals. Pearson's chi-square tests were used to compare these groups with respect to the clinical variables [exposure to (different subsets of) dental alloys and the presence of symptoms and/or complaints]. Adjusted residuals were calculated to help to interpret the differences between groups in the presence of the characteristic, with values higher than 2 or lower than -2 indicating a large deviation. When the chi-square test result was statistically significant ($p < 0.05$), odds ratios (ORs) with 95% confidence intervals (CIs) were calculated on the basis of 2×2 cross-tables, in which the three groups with sensitized patients (i, ii, and iii) were compared with patients with negative patch test results for both metals (group iv). In addition, ORs were calculated for palladium-positive patients (groups i and ii) and nickel-positive patients (groups ii and iii) relative to double-negative patients (group iv). The variation in the distribution of the investigated variables between clinics was expressed as adjusted residuals.

Possible relationships between patients with specific dental alloys (amalgam, crowns, etc.) on the one hand and clinical features, such as skin reactivity to metals (history of metal ACD) and various oral symptoms and/or complaints, on the other were also investigated with Pearson's chi-square tests, adjusted residuals, and subsequent ORs. Finally, the Z-test for proportions of independent groups (Z_{indep}) was used where appropriate.

Table 2. Summary of the patch test details per institute

	NiSO ₄ ·6H ₂ O	General	General
Amsterdam	Supplier: Trolab Dilution: 5% Vehicle: Pet.	Tape used: Fixomull Chambers used: Van der Bend Reading days: D2, D3, D6/D7	Informed consent: Not required Ethical approval: Not required Baseline series: European
Barcelona	Supplier: Trolab Dilution: 5% Vehicle: Pet.	Tape used: Fixomull Chambers used: Finn Reading days: D2, D5/D7	Informed consent: Yes Ethical approval: Not required Baseline series: European
Bari	Supplier: Euromedical Dilution: 5% Vehicle: Pet.	Tape used: Micropore™/Mefix Chambers used: Van der Bend Reading days: D2, D3/D4, D7	Informed consent: Yes Ethical approval: Not required Baseline series: Italian (national)
Basel	Supplier: Trolab Dilution: 5% Vehicle: Pet.	Tape used: IQ Ultra Chambers used: IQ Ultra Reading days: D2/D3, D4	Informed consent: Yes Ethical approval: Not required Baseline series: European
Coimbra	Supplier: Chemotechnique Dilution: 5% Vehicle: Pet.	Tape used: Fixomull Chambers used: Finn Reading days: D2, D3/D4	Informed consent: Not required Ethical approval: Not required Baseline series: European
Leuven	Supplier: Trolab Dilution: 5% Vehicle: Pet.	Tape used: Mefix Chambers used: IQ Ultra Reading days: D2, D4 (D7)	Informed consent: Not required Ethical approval: Not required Baseline series: European

Trolab: Trolab, Almirall Hermal GmbH, Reinbek, Germany. Bial: Bial – Portela & C^o., S.A., S. Mamede do Coronado, Portugal. Chemotechnique: Chemotechnique Diagnostics, Vellinge, Sweden. Fixomull[®] BSN Medical, Almere, The Netherlands. Mefix: Mefix[®] Mölnlycke Health Care. Micropore: 3M™ Micropore™ Medical Tape. IQ Ultra: IQ Ultra™, Chemotechnique Diagnostics, Vellinge, Sweden. Van der Bend: Van der Bend BV, Brielle, The Netherlands. Finn: Finn Chambers[®] Allerderm, SmartPractice[®], Phoenix, AZ, USA.

Patch test reactions to palladium and nickel (n = 906)

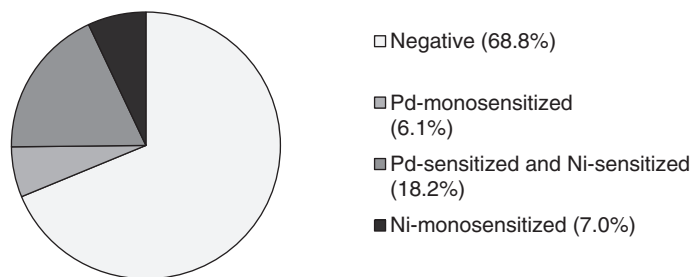


Fig. 1. Negative and positive (+, ++, or +++) patch test results for nickel (Ni) (5% NiSO₄·6H₂O; Ni = 190 μmol g⁻¹) and palladium (Pd) (3% Na₂PdCl₄; Pd = 102 μmol g⁻¹) in the 906 consecutive patients visiting one of the six dermatology clinics in Amsterdam (n = 66), Barcelona (n = 117), Bari (n = 90), Basel (n = 175), Coimbra (n = 189), or Leuven (n = 252).

Results

In total, 906 consecutive patients with completed questionnaires were tested at the six clinics: Amsterdam (n = 66), Barcelona (n = 118), Bari (n = 90), Basel (n = 175), Coimbra (n = 190), and Leuven (n = 267). Of these patients, 30% were male and 70% were female. Of all patients, 24.3% (n = 220/906) showed positive patch test reactions to palladium and 25.2% (n = 228/906) to nickel. As reported earlier, in this same sample nickel monosensitization was clearly associated with female sex [female/male ratio of 57:6 (*p* < 0.001)], whereas palladium monosensitization was not sex-related [female/male ratio of 35:20 (*p* > 0.05)] (4). The proportions of palladium and nickel monosensitization were not significantly different (*Z*_{indep}; *p* > 0.05), at 6.1% and 7.0%, respectively (Fig. 1).

Dermatological variables

In Table 3, the results of the comparison of the four groups of patients are summarized. As expected, a history of metal ACD (skin reactivity to metals) was clearly associated with sensitization to both nickel and palladium; however, for palladium monosensitization, no association was found by use of the Pearson's chi-square test (Table 3). Nevertheless, the OR for skin reactivity to metals was 1.9 and was statistically significant for palladium monosensitization as compared with patients without reactivity to palladium and nickel (Table 3). This discrepancy results from the use of different groups for the analyses. For the Pearson's chi-square test, four groups were used [palladium-positive (group i), both palladium-positive and nickel-positive (group ii), nickel-positive (group iii), and double-negative (group iv)], whereas for the OR the palladium positives were compared with the double negatives.

Table 3. Distribution of proportions of palladium (Pd) and nickel (Ni) sensitization (in terms of positive patch test results) within patients with a given characteristic (presence of eczema, dental crowns, etc.). The difference between the expected proportions (within the whole population) are expressed in adjusted residuals

		Pd Monosensitized	Pd Sensitized	Pd and Ni Positive	Ni Sensitized	Ni Monosensitized	Pd and Ni Negative
Whole population (%) n = 906		6.1 n = 55	–	18.2 n = 165	–	7.0 n = 63	68.8 n = 623
Skin reactivity to metals*	% within skin reactivity	5.7	–	40.5	–	13.8	39.9
36.8% (n = 333)	Adjusted residual	–0.4	–	+13.3	–	+6.2	–14.3
	Odds ratio (95% CI)	1.9 (1.1–3.5) ^a	8.6 (6.1–12.2) ^b	16.6 (10.7–25.7) ^c	14.2 (9.8–20.6) ^d	10.0 (5.5–18.0) ^e	a,b,c,d,e
Eczema in general*	% within eczema	4.4	–	18.5	–	8.4	68.7
75.8% (n = 687)	Adjusted residual	–3.8	–	+0.4	–	+3.1	–0.1
	Odds ratio (95% CI)	0.4 (0.2–0.7) ^a	–	–	–	3.7 (1.5–9.4) ^e	a,e
Facial eczema	% within eczema	3.8	–	22.2	–	8.4	65.7
26.5% (n = 239)	Adjusted residual	–1.8	–	+1.9	–	+1.1	–1.2
	Odds ratio (95% CI)	–	–	–	1.4 (1.0–2.0) ^d	–	d
Eczema on extremities	% within eczema	4.6	–	19.7	–	8.0	67.7
75.8% (n = 687)	Adjusted residual	–1.8	–	+1.1	–	+1.2	–0.6
	Odds ratio (95% CI)	–	–	–	–	–	–
Eczema at other locations	% within eczema	5.2	–	16.8	–	8.1	69.9
75.8% (n = 687)	Adjusted residual	–0.5	–	–0.5	–	+0.7	+0.4
	Odds ratio (95% CI)	–	–	–	–	–	–
Dental alloys	% within dental alloys	5.7	–	20.2	–	7.2	66.9
57.6% (n = 526)	Adjusted residual	–0.5	–	+1.8	–	+0.4	–1.4
	Odds ratio (95% CI)	–	–	–	–	–	–
Dental crowns*	% within crowns	9.3	–	25.0	–	6.4	59.3
15.5% (n = 140)	Adjusted residual	+1.7	–	+2.3	–	–0.3	–2.6
	Odds ratio (95% CI)	2.0 (1.0–3.9) ^a	1.8 (1.2–2.7) ^b	1.8 (1.1–2.7) ^c	1.6 (1.0–2.3) ^d	–	a,b,c,d
Dental amalgam	% within amalgam	6.5	–	21.4	–	8.5	63.7
39.2% (n = 355)	Adjusted residual	+0.4	–	+2.0	–	+1.4	–2.7
	Odds ratio (95% CI)	–	1.4 (1.1–2.0) ^b	1.5 (1.1–2.1) ^c	1.5 (1.1–2.1) ^d	–	b,c,d
Dental prosthesis	% within prosthesis	7.1	–	22.4	–	3.1	67.3
10.8% (n = 98)	Adjusted residual	+0.5	–	+1.2	–	–1.6	–0.3
	Odds ratio (95% CI)	–	–	–	–	–	–
Orthodontic retention wire(s)	% within wires	6.5	–	21.4	–	8.5	63.7
1.7% (n = 15)	Adjusted residual	+0.4	–	+2.0	–	+1.4	–2.7
	Odds ratio (95% CI)	–	–	–	–	–	–
Oral symptoms/complaints*	% within symptoms	6.6	–	29.7	–	7.7	56.0
10.2% (n = 91)	Adjusted residual	+0.2	–	+2.9	–	+0.3	–2.7
	Odds ratio (95% CI)	–	2.0 (1.2–3.1) ^b	2.2 (1.3–3.6) ^c	1.9 (1.2–3.1) ^d	–	b,c,d
OLLs	% within OLL	8.3	–	30.6	–	2.8	58.3
4.1% (n = 36)	Adjusted residual	+0.6	–	+1.9	–	–1.0	–1.4
	Odds ratio (95% CI)	–	–	–	–	–	–
Stomatitis	% within stomatitis	0.0	–	20.0	–	13.3	66.7
1.7% (n = 15)	Adjusted residual	–1.0	–	+0.2	–	+1.0	–0.2
	Odds ratio (95% CI)	–	–	–	–	–	–
Xerostomia*	% within xerostomia	10.0	–	55.0	–	10.0	25.0
2.2% (n = 20)	Adjusted residual	+0.7	–	+4.3	–	+0.5	–4.2
	Odds ratio (95% CI)	–	7.7 (2.7–21.9) ^b	8.7 (3.0–25.5) ^c	7.4 (2.6–21.0) ^d	–	b,c,d
Metal taste*	% within metal taste	0.0	–	46.2	–	15.4	38.5
1.4% (n = 13)	Adjusted residual	–0.9	–	+2.6	–	+1.2	–2.4
	Odds ratio (95% CI)	–	3.4 (1.0–11.4) ^b	4.6 (1.4–15.3) ^c	4.5 (1.4–13.8) ^d	–	b,c,d
Burning/pain	% within burning/pain	5.0	–	20.0	–	5.0	70.0
2.2% (n = 20)	Adjusted residual	–0.2	–	+0.2	–	–0.4	+0.1
	Odds ratio (95% CI)	–	–	–	–	–	–

CI, confidence interval; OLL, oral lichenoid lesions, including redness and ulcers.

A Pearson's chi-square test (2×4) was performed for every variable and for the four separate groups (Pd-positive, both Pd-positive and Ni-positive, Ni-positive, and both Pd-negative and Ni-negative); adjusted residuals are also given. Odds ratios (95% CIs) are given for the comparison of the separate groups with the group without positive test results. Each superscript alphabet denotes the odds ratio for a subset of groups (2×2).

*Pearson's chi-square test: $p < 0.05$.

The presence of eczema was positively associated with nickel monosensitization (positive adjusted residual) but negatively related to palladium monosensitization (negative adjusted residual) (Table 3). Within the subgroups of eczema (facial, extremities, and other), the relationship with nickel sensitization was strongest for facial eczema [OR 1.4 (95% CI 1.0–2.0)], whereas eczema on other parts of the body was not statistically significant.

Dental alloys

Dental alloys were subdivided into amalgam fillings, dental crowns, prostheses, and orthodontic retention wires. In general, patients with dental alloys did not show statistically significant elevated levels of sensitization to palladium and/or nickel (Table 3). Regarding the subgroups, a relationship with both palladium and nickel was found only for patients with amalgam fillings ($n = 355$) and dental crowns ($n = 140$). Interestingly, only for dental crowns could a relationship with palladium monosensitization be discerned (Table 3).

Oral symptoms and complaints

Of all patients 10.2% ($n = 91/906$) had oral symptoms and/or complaints, and these patients showed significantly more often sensitization to both palladium and nickel (Table 3). Within the subgroups of symptoms and/or complaints, only xerostomia (dry mouth) and metal taste were strongly associated with palladium and nickel sensitization (Table 3). Oral burning/pain, stomatitis and OLLs were not associated with sensitization to these metals. Patients with dental alloys are aware of this, and could experience the investigated complaints more intensively, because they may attribute them to their dental alloys. In order to eliminate this possible bias, additional analyses were performed only within the group of patients with dental alloys. These additional analyses gave similar results, and are therefore not shown and/or further discussed.

Dermatology clinics

Table 4 summarizes the distribution (number and percentage) of the investigated characteristics among the different clinics, and the adjusted residuals are given when values were higher than 2 or lower than -2 . Reactivity to both metals per clinic was previously reported (4), but has been added for completeness. As relatively small numbers of patients with oral symptoms or complaints were found per clinic, further analyses on clinic level would be inconclusive. It was clear that patients with various metal-containing dental restorations (amalgam, crowns,

and prostheses) were not evenly distributed, with percentages ranging from 7.4% to 39.4% for crowns, 11.0% to 53.3% for amalgam, and 6.1% to 18.9% for prostheses. Also, considerable variation was found for skin reactivity to metals, eczema, and oral symptoms and/or complaints (Table 4).

Dental alloys and (oral) symptoms and complaints

The occurrence of clinical symptoms and/or oral complaints in patients with specific dental alloys was compared with that in patients without any dental alloys. The results are summarized in Table 5. Eczema was not associated with the presence of any dental alloys; in fact, patients with dental alloys tended to present eczema less frequently than those without (Table 5). However, skin reactivity to metals was strongly associated with dental alloys, in particular amalgam, dental crowns, and orthodontic retainer wires. As expected, patients with dental alloys also showed increased risks for oral complaints and/or symptoms. Those with dental crowns showed the most pronounced associations and ORs for skin reactivity to metals (history of metal ACD), OLLs, xerostomia, and metal taste (Table 5). Stomatitis and burning/pain were not associated with exposure to dental alloys, or with any of the subgroups (data not shown).

Discussion

This multicentre, cross-sectional study is unique, as patch test results and various dermatological, dental and oral disease variables were included, providing more insights into the differences between palladium and nickel sensitization and their association with dental alloys, as well as their role in oral and skin disease and complaints.

Nickel versus palladium sensitization

A large overlap between palladium and nickel sensitization was found, and their prevalence of $\sim 25\%$ was similar in this sample ($n = 906$) (Fig. 1), although, between clinics, considerable variation was found (Table 4). Clinically, this may result in difficulties in determining the relevance of a positive test reaction to these metals, especially in the case of palladium sensitization, as discussed above. Interestingly, the rates of monosensitization to both metals were also equal, confirming that cross-reactivity is not absolute, and $\sim 25\%$ of the sensitized patients showed monosensitization to one of these metals. This high rate of palladium monosensitization is explained by the improved palladium patch test sensitivity provided

Table 4. Distribution of the patch test reactivity to both palladium and nickel and clinical variables (percentage and number) among the participating dermatology clinics

	Whole population n = 906 100%	Amsterdam n = 66 7.4%	Barcelona n = 117 13.2%	Bari n = 90 10.0%	Basel n = 175 19.7%	Coimbra n = 189 21.3%	Leuven n = 252 28.4%
Ni-negative and Pd-negative PT	68.8% n = 623	66.7% n = 44	69.5% n = 82	63.3% n = 57	60.0% (−2.6) n = 105	67.4% n = 128	77.5% (+3.6) n = 207
Pd-positive PT	24.3% n = 220	31.8% n = 21	19.5% n = 23	26.7% n = 24	36.0% (+4.0) n = 63	23.3% n = 44	16.9% (−3.4) n = 45
Pd monosensitization	6.1% n = 55	1.5% n = 1	10.2% (+2.0) n = 12	2.2% n = 2	17.1% (+6.8) n = 30	3.2% n = 6	1.5% (−3.7) n = 4
Ni-positive PT	25.2% n = 228	31.8% n = 21	20.3% n = 24	34.4% (+2.1) n = 31	22.9% n = 40	29.5% n = 56	21.0% n = 56
Ni monosensitization	7.0% n = 63	1.5% n = 1	11.0% n = 13	10.0% n = 9	4.0% n = 7	9.5% n = 18	5.6% n = 15
Pd-positive and Ni-positive PT	18.2% n = 165	30.3%+ n = 20	9.3%− n = 11	24.4% n = 22	18.9% n = 33	20.0% n = 38	15.4% n = 41
Eczema	75.8% n = 687	66.7% n = 44	87.3% (+3.1) n = 103	92.2% (+3.8) n = 83	51.4% (−8.4) n = 90	83.7% (+2.8) n = 159	77.9% n = 208
Facial eczema	26.5% n = 239	45.5% (+3.6) n = 30	23.7% n = 28	31.5% n = 28	16.6% (−3.3) n = 29	35.8% (+3.3) n = 68	21.3% (−2.3) n = 56
Extremity eczema	48.2% n = 437	54.5% n = 36	50.8% n = 60	53.3% n = 48	26.3% (−6.5) n = 46	51.5% n = 97	56.2% (+3.1) n = 150
Other eczema	19.1% n = 173	7.6% (−2.5) n = 5	50.0% (+9.2) n = 59	12.2% n = 11	14.9% n = 26	17.9% n = 34	14.2% (−2.5) n = 38
Skin reactivity to metals	36.8% n = 333	37.9% n = 25	22.0% (−3.6) n = 26	45.6% n = 41	34.9% n = 61	40.0% n = 76	39.0% n = 104
Dental crowns	15.5% n = 140	39.4% (+5.6) n = 26	13.6% n = 16	33.3% (+4.9) n = 30	18.3% n = 32	7.4% (−3.1) n = 14	8.2% (−3.9) n = 22
Amalgam	39.2% n = 355	30.3% n = 20	36.4% n = 43	53.3% (+2.9) n = 48	11.0% (−5.1) n = 39	41.1% n = 78	47.6% (+3.3) n = 127
Prostheses	10.8% n = 98	6.1% n = 40	12.7% n = 15	18.9% (+2.6) n = 17	8.6% n = 15	11.1% n = 21	9.7% n = 26
Orthodontic retention wires	1.7% n = 15	1.5% n = 1	0.0% n = 0	0.0% n = 0	2.9% n = 5	1.1% n = 2	2.6% n = 7
OLLs	4.1% n = 36	9.1% (+2.2) n = 6	3.4% n = 4	2.2% n = 2	5.1% n = 9	1.1% (−2.4) n = 2	5.2% n = 13
Stomatitis	1.7% n = 15	0.0% n = 0	0.0% n = 0	10.1% (+6.5) n = 9	0.0% n = 0	1.6% n = 3	1.2% n = 3
Xerostomia	2.3% n = 20	19.7% (+9.9) n = 13	0.0% n = 0	1.1% n = 1	0.6% n = 1	0.0% (−2.4) n = 0	2.0% n = 5
Metal taste	1.5% n = 13	9.1% (+5.4) n = 6	3.4% n = 4	1.1% n = 1	0.6% n = 1	0.5% n = 1	0.0% (−2.3) n = 0
Burning/pain	2.3% n = 20	0.0% n = 0	3.4% n = 4	0.0% n = 0	2.3% n = 4	1.6% n = 3	3.6% n = 9

OLL, oral lichenoid lesions, including redness and ulcers; PT, patch test.

When the proportion of a given variable largely deviated from the expected proportion [within the whole population (leftmost column)], the adjusted residuals are given in parentheses (values higher than 2 or lower than −2).

by using Na_2PdCl_4 instead of PdCl_2 as a test allergen. In particular, these monosensitized patients can provide information about the differences between sensitization to both metals and their clinical relevance. It must be said that the data from this study did not provide information on the cause–effect relationship between the investigated variables.

PdCl_2 versus Na_2PdCl_4

In total, 10.7% (97/906) of the patients reacted positively to PdCl_2 , whereas 24.3% (220/906) of the patients reacted positively to Na_2PdCl_4 . One patient showed reactivity only to PdCl_2 , whereas all other patients reacting to PdCl_2 also showed positive patch test reactions to Na_2PdCl_4 . As compared with reactivity to nickel, the rate

Table 5. Distribution of proportions of skin reactivity to metals [history of metal allergic contact dermatitis (ACD)], oral symptoms as a group, oral lichenoid lesions (OLLs), xerostomia and metal taste in patients with various metal-containing dental restorations relative to those without any dental alloys (n = 410) (first row)

Patients with:	Eczema	Metal ACD	Oral symptoms and/or complaints	OLLs	Xerostomia	Metal taste
No dental alloys (%) n = 410	78.5	28.0	5.1	1.8	1.3	0.3
Dental alloys (%) n = 496	73.6	44.0***	14.4***	5.9**	3.0	2.4**
Adjusted residuals	-1.7	+4.9	+4.5	+3.1	+1.8	+2.7
OR (95% CI)	NS	2.0 (1.5–2.7)	3.1 (1.9–5.3)	3.4 (1.5–7.9)	NS	9.8 (1.3–76.9)
Amalgam (%) n = 355	74.4	43.7***	14.4***	6.2**	3.1	2.0
Adjusted residuals	-1.4	+4.5	+4.4	+3.1	+1.7	+2.3
OR (95% CI)	NS	2.0 (1.5–2.7)	3.2 (1.8–5.4)	3.7 (1.5–8.7)	NS	NS
Crowns (%) n = 140	72.9	52.1***	19.3***	7.9**	8.6***	5.0***
Adjusted residuals	-1.4	+5.2	+5.1	+3.4	+4.2	+4.0
OR (95% CI)	NS	2.8 (1.9–4.2)	4.5 (2.4–8.3)	4.7 (1.8–12.4)	7.3 (2.5–21.1)	20.7 (2.5–169.7)
Prosthesis (%) n = 98	70.4	37.8	21.4***	7.1**	4.1	6.1***
Adjusted residuals	-1.7	+1.9	+5.2	+2.9	+1.9	+4.4
OR (95% CI)	NS	NS	5.1 (2.6–9.9)	4.3 (1.5–12.4)	NS	25.6 (3.0–215.5)
Orthodontic retention wires (%) n = 15	86.7	73.3***	0.0	0.0	0.0	0.0
Adjusted residuals	+0.8	+3.8	-0.9	-0.5	-0.4	-0.2
OR (95% CI)	NS	7.1 (2.2–22.6)	NS	NS	NS	NS

CI, confidence interval; NS, not significant; OR, odds ratio.

Pearson's chi-square tests (2×2), including adjusted residuals, and, in the case of statistical significance, ORs with 95% CIs are given.Pearson's chi-square test: * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$.

of palladium monosensitization was 1.4% (n = 13) and 6.1% (n = 55) for PdCl₂ and Na₂PdCl₄, respectively. For patch test reactivity to PdCl₂, the same analyses were performed as for Na₂PdCl₄, although these will be discussed only briefly in this section. Associations between reactivity to PdCl₂ and patient characteristics were similar to those for nickel (data not shown). This is explained by the large overlap of reactivity between these two test allergens. In fact, 87% of the patients reacting to PdCl₂ also reacted to nickel. On comparison of the analyses for monosensitization to both palladium test allergens, it was found that the associations were generally stronger for PdCl₂ than for Na₂PdCl₄ (data not shown). This confirms the associations found for Na₂PdCl₄. Indeed, PdCl₂ is a more specific test allergen than Na₂PdCl₄, although it is approximately two times less sensitive than Na₂PdCl₄ (2–4), and therefore misses approximately half of the palladium-sensitized patients.

Dermatological variables

Skin reactivity to metals was strongly related to both palladium and nickel sensitization. However, the association with palladium is primarily based on concomitant and/or cross-reactivity to nickel. In fact, a negative association was found for palladium monosensitization, whereas a strong positive association was found for nickel monosensitization (Table 3). However, a positive OR of 1.9 could be calculated for patients with skin reactivity

to metals and palladium monosensitization (palladium monosensitization against no sensitization to either nickel or palladium) (Table 3), suggesting that there is a relationship. This discrepancy can be explained by the elimination of patients with positive patch test reactions to nickel. Furthermore, some bias could have occurred, because palladium monosensitization was related to the presence of dental crowns, which, in turn, was related to skin reactivity to metals. Nevertheless, the OR for nickel monosensitization was approximately five times higher than that for palladium monosensitization, confirming that skin reactivity to metals is mainly an issue of nickel sensitization.

The presence of eczema was associated with nickel sensitization, and monosensitization in particular, but not with palladium monosensitization, which showed a negative association. Moreover, the use of dental alloys was not related to eczema and tended to show a negative association (Table 5). Together with the results concerning skin reactivity to metals, these findings support the idea that palladium is hardly of clinical relevance for ACD. Indeed, patients with eczema or skin reactivity to metals showed statistically less frequent palladium monosensitization than nickel monosensitization ($Z_{\text{indep}}: p < 0.05$) (data not shown).

Faurschou et al. recently reviewed the issue of palladium allergy. They concluded that there was no difference in the prevalence of palladium sensitization among patients with intraoral and skin symptoms: 7.4% (range 1.3–13.9%) and 7.8% (range <1.0–19.0%), respectively

(8). In this study, a similar distinction between these subsets of patients could be made. Table 3 shows that 22.9% (4.4% + 18.2%) of the eczema patients and 36.3% (6.6% + 29.7%) of the oral disease patients were sensitized to palladium, which is a significant difference (Z_{indep} ; $p < 0.01$) (data not shown). Nevertheless, palladium sensitization was more frequent in patients with skin reactivity to metals than in patients with oral symptoms, that is, 46.2% versus 36.3%, respectively (not significant). This is most likely explained by the high levels of cross-reactivity between palladium and nickel, because, for palladium monosensitization, the opposite was true (5.7% versus 6.6%; not significant). There are two explanations for this discrepancy between our findings and the conclusions of Faurschou et al. First, earlier studies were conducted with PdCl_2 as a test allergen, which has clearly led to an underestimation of palladium sensitization, and hence incomplete results. Second, only two studies considered in that review compared both patient groups, whereas the vast majority of the included studies were based on either dermatitis patients or dental patients, which may have resulted in a considerable bias, owing to differences in inclusion criteria, test concentration (1% versus 2% PdCl_2), inter-regional differences, etc. Table 4 shows that, in this study, the prevalence of eczema and skin reactivity to metals (a history of metal ACD) varied considerably among clinics, suggesting that different indication protocols for patch testing per clinic are used or that the prevalence of specific clinical symptoms/complaints varies per region.

Dental alloys

The results did not show a statistically significant association between exposures to dental alloys as a group and palladium and/or nickel sensitization. However, there were associations for the subgroups. Patients with dental crowns were more frequently sensitized to palladium, which was confirmed by a positive relationship for palladium monosensitization and a negative relationship for nickel monosensitization (Table 3).

Fifty-two per cent of the patients with dental crowns reported skin reactivity to metals (Table 5). Dental crowns may contain a broad variety of metals, including, nickel, palladium, gold, silver, cobalt, and chromium. Corrosion of dental alloys is a continuous process resulting in constant ion release, which could lower the patient's threshold for elicitation via the skin. Moreover, in the case of true cross-reactivity between palladium and nickel at the T cell receptor level, as demonstrated by different groups (39–41), oral exposure to palladium could also influence the threshold level for nickel elicitation, resulting in metal

ACD. This might explain the high levels of skin reactivity to metals observed in patients with dental crowns. It is of interest that only 38.7% of the eczema patients reported skin reactivity to metals (Z_{indep} ; $p < 0.01$) (data not shown). Unfortunately, no data were available on the composition of the dental crowns.

In general, amalgam does not contain nickel or palladium, although a few amalgams may contain 1–2% by weight of palladium. Therefore, the association between dental amalgam and sensitization to both metals is unexpected (Table 3). As the presence of amalgam was frequently observed (39.8% within the whole population), several confounding factors could play a role.

Oral symptoms

The presence of oral symptoms/complaints in general was clearly associated with both palladium and nickel sensitization (Table 3). Therefore, in patients with oral disease attributable to allergy, these metals should be considered as possible causative factors, although other allergens may be involved (26–28). It must be stressed that the results from the current study provide no information on the cause–effect relationships of the investigated variables. OLLs are mostly associated with dental gold-based alloys and amalgam (42–46), and this was confirmed in the current study, as OLLs were found more frequently in patients with dental amalgam and crowns (Table 5). Currently, it is not clear what role metal sensitization/allergy plays in the aetiology of OLLs, as the value of patch testing to identify the aetiology of OLLs is debated (47–50). Recently, it was shown that gold-based alloys were associated with OLLs, but this was not reflected by gold-specific immune reactivity either *in vivo* (patch testing) or *in vitro* (cytokine production and lymphocyte proliferation assays) (21). In that same study, no association was found between OLLs and palladium-based dental alloys. Also, in a Swedish study, no relationship was found between OLLs and palladium sensitization in 83 OLL patients (51).

Interestingly, metal taste was found to be associated with nickel sensitization (Table 3) and the presence of dental crowns (Table 5), which may contain considerable amounts of nickel. Although metal taste is not necessarily indicative of sensitization or allergy, it is a strong indication of exposure, and is hence potentially pathological. Nickel, in particular, is sensitive to pH fluctuations, leading to increased ion release in acidic environments (52), possibly explaining the observed associations.

Xerostomia was strongly associated with both palladium and nickel sensitization (Table 3) and the presence of dental crowns (Table 5). Lack of saliva has important negative impact on oral barrier function. Although saliva facilitates corrosion, it has an important washing action;

it contains mucins that bind covalently to the epithelium surface, which may concentrate secretory immunoglobulins A (IgA) and antiviral lysozyme, and thereby limit the attachment of microorganisms. Therefore, a reduction in the amount of saliva compromises barrier function and may facilitate antigen penetration. Furthermore, it is well known that, independently of its aetiology, as in Sjögren's syndrome or as a side-effect of many pharmaceutical drugs, reduced saliva production decreases the saliva's pH and its buffering capacity (53). Hence, xerostomia can contribute to increased (nickel) ion release from dental alloys. From this perspective, xerostomia could be considered to be a cause rather than a consequence of sensitization to intraoral metals; however, the current data are insufficient to determine whether this is actually the case.

Strengths and weaknesses of the study

The most important strengths of this multicentre, cross-sectional study are: (i) the large number of patients included ($n = 906$); (ii) the uniformity of the data gathering; (iii) the comparison of oral disease and skin disease patients within one study; and (iv) the inclusion of dental and oral symptomatic variables.

The most important weakness of this study is the absence of a dental professional during the clinical examination. Oral disorders are diverse, and may be difficult to recognize under suboptimal inspection circumstances. Even general practice dentists may overlook intraoral lesions, as many more lesions were observed by specialized dentists, such as those working in adverse reaction units (54). In this context, it is noteworthy that metal-based

dental restorations are mostly veneered with porcelain, and are thus often difficult to distinguish from natural teeth by non-dentists. Other weaknesses are the absence of patch test results for other metal allergens, and gold in particular, and the lack of the dental alloys' compositions. Despite these weaknesses, the findings are relevant for daily dental and dermatology practice.

Conclusions

It can be concluded that the prevalence of palladium sensitization (3% Na_2PdCl_4) is comparable to that of nickel, and was significantly elevated in patients with dental crowns. Sensitization to both palladium and nickel was more frequent in patients with oral complaints such as xerostomia and metal taste. Furthermore, exposure to dental alloys and dental crowns, in particular, was strongly associated with a history of metal ACD, OLLs, xerostomia, and metal taste. Therefore, clinically, it is important for palladium-sensitized patients to also undergo an oral examination, with particular attention to the presence of dental crowns. Also, in the case of metal ACD, exposure to dental crowns could play a role. Therefore, in particular cases, review by the patient's dentist may be helpful.

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