

The relationship between dental metal allergy, periodontitis, and palmoplantar pustulosis: An observational study

Yurina Takaoka ^a, Yosuke Akiba ^{a,*}, Masako Nagasawa ^a, Akiko Ito ^{b,c}, Yukiko Masui ^{b,c}, Nami Akiba ^a, Kaori Eguchi ^a, Haruna Miyazawa ^{d,e}, Koichi Tabeta ^d, Katsumi Uoshima ^a

^a Division of Bio-Prosthodontics, Faculty of Dentistry & Graduate School of Medical and Dental sciences, Niigata University, Niigata, Japan.

^b Department of Dermatology, Nagata Clinic, Niigata, Japan.

^c Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

^d Division of Periodontology, Faculty of Dentistry & Graduate School of Medical and Dental sciences, Niigata University, Niigata, Japan.

^e Clinical and Translational Research Center, Niigata University Medical and Dental Hospital, Niigata, Japan

Abstract

Purpose: This study aimed to investigate the relationship between dental metal allergy, periodontitis, and palmoplantar pustulosis among patients from a dental metal allergy clinic over a period of 8 years.

Methods: This study included 436 patients who visited our dental metal allergy clinic between April 1, 2009 and March 31, 2016. Diagnoses of skin diseases, periodontal records, dental metal series patch test results, and electron probe microanalysis (EPMA) data were obtained from medical records. Relative risk (RR) values were estimated from these data.

Results: Of the 359 patients who underwent the patch test, 241 showed a positive reaction. Of the 187 patients who underwent EPMA, 113 had allergenic metals in their dental prostheses. These patients were suspected to have a dental metal allergy. Furthermore, 150 of the 436 patients were diagnosed with palmoplantar pustulosis (PPP). The RR of metal allergy between patients with PPP and healthy subjects was 3.88. The RR of periodontal disease between patients with PPP and PPP-negative patients in the national average was 2.54.

Conclusions: In this study, both dental metal allergy and periodontitis showed a high RR for PPP.

Keywords: dental metal allergy, palmoplantar pustulosis, skin diseases

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1. Introduction

Metal alloys have long been used in the dental profession. Although a range of acrylic materials have been introduced recently, metal alloys are still widely used in dental prostheses.

Dental metal allergy refers to the symptoms of contact dermatitis, which is suspected to be associated with the use of metal alloys in dental treatment; however, it does not necessarily reflect a causal relationship. Since being reported in 1928, several clinical, *in vitro*, and animal studies have investigated its prevalence and etiology[1]. Nevertheless, the cause of dental metal allergy remains poorly understood, despite a recent increase in the number of affected patients in Japan. Although the pathophysiological mechanisms remain unclear, several skin diseases have been suggested to be associated with dental metal alloys, including palmoplantar pustulosis (PPP), dyshidrotic eczema, contact dermatitis, and oral lichen planus[2–6]. Specific types of dermatitis have also been reported to be associated

with periodontal disease and apical periodontitis[2,4,7–11]. Studies suggest that the treatment of chronic inflammation, and the replacement of dental metals present in the prostheses may result in the improvement of the skin diseases.

This study aimed to determine the relationship between dental metal allergy, PPP, and periodontitis among a group of patients from a dental metal allergy clinic.

2. Materials and Methods

2.1. Patients

This study included 436 patients who visited our dental metal allergy clinic between April 1, 2009, and March 31, 2016. All patients provided signed informed consent to participate in the clinical study and to undergo dental treatment, patch testing, and electron probe microanalysis (EPMA). Patients who did not consent to the examination or inclusion in the clinical study, or received a diagnosis that did not require further examination, were excluded. The study protocol was approved by the Research Ethics Committee of our university (2009-5044) and was performed in accordance with the Declaration of Helsinki.

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*Corresponding author: Yosuke Akiba, Division of Bio-Prosthodontics, Faculty of Dentistry & Graduate School of Medical and Dental sciences, Niigata University 2-5274, Gakkocho-dori, Chuo-ku, Niigata 951-8514, Japan

E-mail address: yoakiba@dent.niigata-u.ac.jp

Table 1. Reagents of the dental metal series used in the patch test

No	Metal	%	Base
1	CoCl ₂	0.5	Aq
2	NiSO ₄	2.5	Aq
3	K ₂ Cr ₂ O ₇	0.5	Aq
4	HgCl ₂	1	Aq
5	AuS ₄ O ₆	0.5	Aq
6	ZnCl ₂	0.5	Pet
7	MnCl ₂	0.5	Pet
8	AgBr	2	Pet
9	PdCl ₂	1	Aq
10	H ₂ PtCl ₆	0.5	Aq
11	SnCl ₂	1	Aq
12	CuSO ₄	1	Aq
13	FeCl ₃	2	Aq
14	AlCl ₃	2	Aq
15	InCl ₃	1	Aq
16	IrCl ₄	1	Aq
17	TiO ₂	0.5	Pet
18	SbCl ₃	1	Pet
19	MoCl ₅	1	Aq
20	CdSO ₄	1	Aq

Aq: Purified water, Pet: Petrolatum

2.2. Assessed variables

The variables included were sex, age, dental caries, periodontal disease, dental metal series patch test results, EPMA of metals within the dental prostheses, and skin disease diagnoses. The presence of periodontal disease was determined using radiographs, probing, and periodontal pocket depth measurements conducted by the periodontist. In this study, patients with a periodontal pocket depth of ≥4 mm were diagnosed with periodontitis. The prevalence of periodontal disease was calculated by dividing the number of patients with a periodontal pocket depth of ≥4 mm by those who underwent the periodontal pocket depth measurement. For comparison, the periodontal pocket depth data reported in the “Survey of Dental Diseases,” conducted by the Ministry of Health, Labor and Welfare, Japan in 2016[12] were used as the “national average.” When caries or periodontal disease was diagnosed, the treatment was performed either at our hospital, or at a local private dental clinic.

The patch testing and diagnosis of skin diseases were performed by a dermatologist at the same dermatology clinic. The patch test included the dental metal series by Torii Pharmaceutical Corporation, Tokyo, Japan (Table 1). The reagent was placed on a Patch Tester (TORII®; Torii Pharmaceutical Corporation, Tokyo, Japan) or Finn Chambers® on a Scanpor® tape (Smart Practice, Phoenix, AZ)[13], and affixed to the back of the patients for 48 hours. The reactions were noted 2, 3, and 7 days after patch placement and were assessed on the basis of the International Contact Dermatitis Research Group (IC-DRG) criteria[14,15]. Patients showing a positive reaction (weak positive [+]) or strong positive [++, +++]) on days 3 and 7 were diagnosed with a metal allergy. To confirm any delayed reactions, the tested area was reinvestigated 1 month later in some patients.

Metals present in the dental prostheses were sampled by sandpaper scraping without damaging the prostheses, and qualitatively

Table 2. Contingency table for the estimation of the relative risk for suspected allergenic metal

Suspected allergenic metal	Patch test result to suspected allergenic metal	
	Positive (P)	Negative (N)
Exposed (E)	EP (E and P)	EN (E and N)
Unexposed (U)	UP (U and P)	UN (U and N)

analyzed using EPMA (EPMA-1610, Shimadzu, Japan). In cases involving a single prosthesis, such as the crown, inlay, or amalgam filling, a single metal sample was collected. In cases involving removable or fixed partial dentures, metal samples were collected from each component, such as the clasp, bar, rest, soldering, and crown. In cases requiring the replacement of the metal prosthesis with a cast post and core, the samples were collected from the cast post and core.

2.3. Statistical tests and parameters

The relative risk (RR) of metal allergy is the ratio of the probability of a metal allergy diagnosis for a suspected allergenic metal in an exposed group to the probability of a metal allergy diagnosis for the suspected allergenic metal in the unexposed group. The RR was estimated for each metal detected in the EPMA. The RR of the suspected allergenic metal was estimated using a 2 × 2 contingency table (Table 2). The point estimate of the RR of the suspected allergenic metal was calculated using the following formula:

$$RR=\{EP/(EP+EN)\}/\{UP/(UP+UN)\}=EP(UP+UN)/UP(EP+EN)$$

- E: Exposed to the suspected allergenic metal
- U: Not exposed to the suspected allergenic metal
- P: Patients who tested positive on the patch test for suspected allergenic metals
- N: Patients who tested negative on the patch test for suspected allergenic metals

The odds ratio (OR) is a statistic used to quantify the strength of association between two variables, such as the incidence of metal allergies and PPP and the incidence of periodontitis and PPP. An OR of 1 indicates two independent variables, whereas an OR >1 indicates an association between two variables, with the occurrence of one event increasing the odds of the other. Conversely, an OR <1 suggests that the two variables are negatively correlated, with the occurrence of one event reducing the odds of the other[16].

The RR and OR for the prevalence of metal allergy and PPP and the prevalence of periodontitis and PPP were estimated from a 2 × 2 contingency table (Table 3). To compare the results of the metal allergy test, we used the patch test data reported from healthy subjects in 1993[17]. To compare the incidence of periodontal disease, we used the “national average” as reported in the “Survey of Dental Diseases,” by the Ministry of Health, Labor and Welfare, Japan in 2016[12]. The point estimates of the RR of the prevalence of metal allergy and PPP and of periodontitis and PPP were calculated using the following formula:

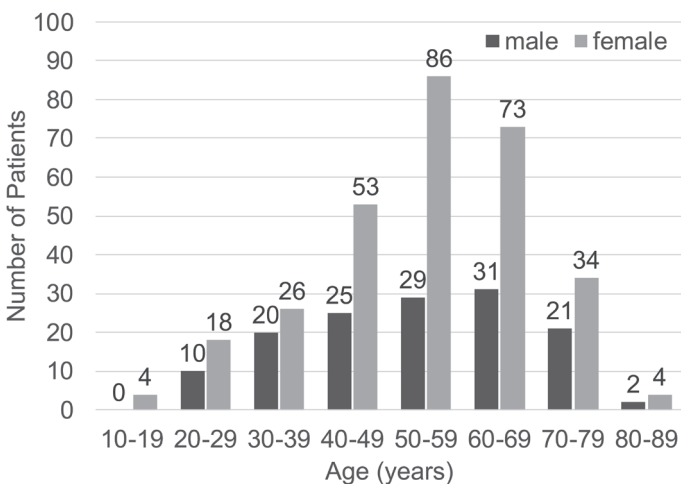
$$RR=\{Pp/(Pp+Np)\}/\{Pn/(Pn+Nn)\}=Pp(Pn+Nn)/Pn(Pp+Np)$$

Table 3. Contingency table for estimating the relative risk and odds ratio between PPP and metal allergy or periodontitis.

Diagnosis of metal allergy	Diagnosis of PPP	
	Positive (P) (92+42=134)	Negative (N) (330+705=1035)
Positive (p) (92+330=422)	Pp (P and p) (92)	Np (N and p) (330)
Negative (n) (42+705=747)	Pn (P and n) (42)	Nn (N and n) (705)

Diagnosis of periodontitis	Diagnosis of PPP	
	Positive (P) (100+39=139)	Negative (N) (169+1711=3380)
Positive (p) (100+1669=1769)	Pp (P and p) (100)	Np (N and p) (1669)
Negative (n) (39+1711=1750)	Pn (P and n) (39)	Nn (N and n) (1711)

PPP, palmoplantar pustulosis

**Fig. 1.** Age distribution of patients who visited our clinic.

The effects of metal allergy and periodontal disease on PPP were confirmed using the OR, which was calculated using the following formula:

$$OR = \frac{Pp}{Pn} \times \frac{Np}{Nn} = \frac{Pp \cdot Nn}{Pn \cdot Np}$$

P: Patients with a PPP-positive diagnosis

N: Patients with a PPP-negative diagnosis

p: Patients with a metal allergy-positive or periodontitis-positive diagnosis

n: Patients with a metal allergy-negative or periodontitis-negative diagnosis

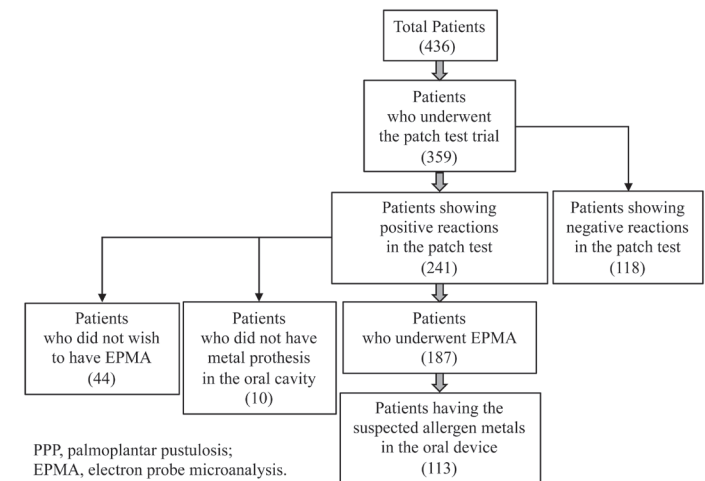
3. Results

3.1. Age distribution

A total of 436 patients (138 males and 298 females) visited our dental metal allergy clinic between 2009 and 2016 (**Figure 1**). Most male patients were in their 60s (31/138, 22.5%), followed by those in their 50s (29/138, 21.0%) and 40s (25/138, 18.1%). The majority of the fe-

Table 4. Skin disease distribution among all patients assessed

Skin disease	Number
Palmoplantar pustulosis	150
Dyshidrotic eczema	80
Contact dermatitis	45
Oral lichen planus	43
Others: psoriasis, asteatotic eczema, dyshidrotic eczema, eczema, keratosis, atopic dermatitis, and prurigo	117

**Fig. 2.** Flowchart of classification for patients with dental metal allergy.

male patients were in their 50s (86/298, 28.9%), followed by those in their 60s (73/298, 24.5%), 40s (53/298, 17.8%), and 70s (34/298, 11.4%).

3.2. Disease distribution

The most commonly diagnosed dermatitis was PPP (150/436, 35.8%), followed by dyshidrotic eczema (80/436, 18.3%), contact dermatitis (45/436, 10.3%), and oral lichen planus (43/436, 9.9%) (**Table 4**). Some patients were also diagnosed with psoriasis, eczema (asteatotic and dyshidrotic type), keratosis, atopic dermatitis, and prurigo.

3.3. Patch testing with metal allergens

Of the 436 patients, 359 underwent a patch test. Altogether, 241 (241/359, 67.1%) patients showed a positive reaction to at least one of the metal allergens (**Figure 2**).

The most common metal that elicited a positive reaction was nickel (Ni) (83/241, 34.4%), followed by cobalt (Co) (67/241, 27.8%), palladium (Pd) (64/241, 26.6%), and gold (Au) (49/241, 20.3%) (**Figure 3**).

3.4. EPMA for metals within dental prostheses

Of the 241 patients who tested positive on the patch test, 187 were analyzed for metals within the dental prostheses (e.g., inlays, crowns, bridges, and denture components). The number of patients who did not wish to undergo EPMA were 44, and the number of patients who did not have a metal prosthesis in the oral cavity were 10 (**Figure 2**).

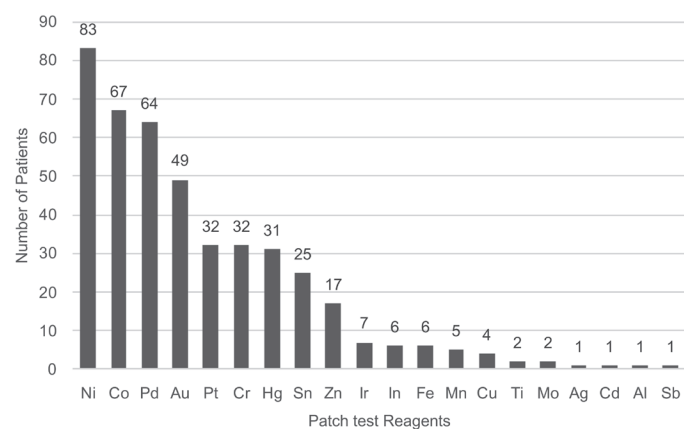


Fig. 3. Results of the patch tests. The graph shows the number of positive tests for each metal reagent tested.

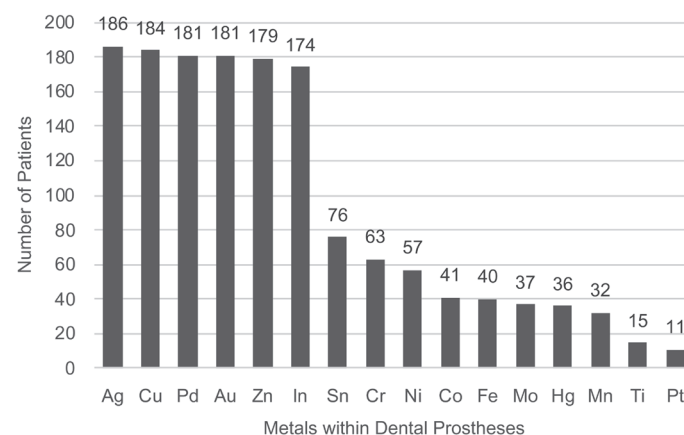


Fig. 4. Results of the electron probe microanalysis (EPMA) for metals contained in dental prostheses.

The EPMA positivity rates of the metals, which indicate the percentage of patients having these metals in their prosthesis, were as follows: 99.5% for silver (Ag) (186/187), 98.4% for copper (Cu) (184/187), 96.8% for palladium (Pd) (181/187), 96.8% for gold (Au) (181/187), 98.4% for zinc (Zn) (179/187), and 93.0% for indium (In) (174/187) (**Figure 4**).

3.5. Prevalence of suspected allergenic metals in the dental prostheses and the RR of dental metal allergy

The prevalence of the suspected allergenic metals in the dental prostheses and the RR of metal allergies were determined by matching the results of the patch test and EPMA. Among the 187 patients in whom EPMA was performed, 60.4% (113/187) had a dental prosthesis containing the suspected allergenic metals (**Figure 2**). Pd, Au, and Ni were the most prevalent allergenic metals in the prostheses (**Figure 5**). The RR of dental metal allergy was relatively higher for Ni (1.47), Co (1.25), and mercury (Hg) (1.25) than for other metals (**Table 5**).

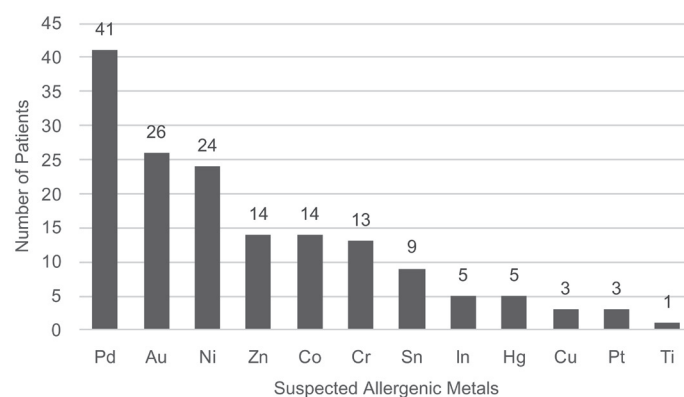


Fig. 5. Prevalence of suspected allergenic metals in the dental prostheses.

3.6. Age distribution of PPP patients

In our clinic, 150 patients were diagnosed with PPP. Most patients were in the 55-64-year age group (53/150, 35.3%), followed by those in the 45-54-year age group (41/150, 27.3%). Therefore, the percentage of PPP patients in the 45-64-year age group was 62.7% (94/150) (**Figure 6**).

3.7. Prevalence of suspected allergenic metals in the dental prostheses of patients with PPP

The patch test was performed in 134 of the 150 patients with PPP, and 68.7% (92/134) had a positive reaction. Among these 92 patients, 74 underwent EPMA. There were 11 patients who did not wish to undergo EPMA, and the number of patients who did not have a metal prosthesis in the oral cavity was 7. A majority (49/74, 66.2%) of these patients had a dental prosthesis that contained the suspected allergenic metal and were considered to have a “dental metal allergy” (**Figure 7**).

3.8. Prevalence of periodontitis among patients with PPP

Among the 49 patients with PPP who were patch test-positive and had dental prostheses containing the suspected allergenic metal, 46 underwent a periodontal examination and 76.1% (35/46) were diagnosed with periodontitis. On the other hand, 73.7% (28/38) of the patch test-negative patients with PPP were also diagnosed with periodontal disease (**Figure 7**). The prevalence of periodontitis in patients with PPP was higher as compared with the PPP-negative patients in the national average (1669/3380, 49.4%), which was calculated using the data reported in the “Survey of Dental Diseases,” by the Ministry of Health, Labor and Welfare, Japan in 2016[12] (**Figure 8**). The PPP patients in the 45-64-year age group, who were patch test-negative (19/25, 76.0%) or positive for the suspected metals in the dental prostheses (23/30, 76.7%) also had a higher prevalence of periodontitis compared with the national average in the same age group (534/1028, 51.9%) (**Figure 9**).

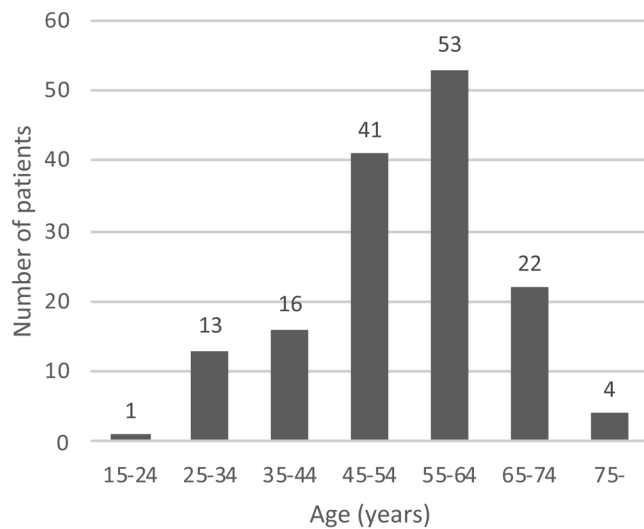
3.9. RR and OR for the prevalence of a diagnosis of metal allergy and PPP or of periodontitis and PPP

The RR and OR were calculated from the number of patients (**Table 3**). The RR of metal allergy in patients with PPP compared with healthy individuals was 3.88. The RR of periodontal disease in patients with

Table 5. Relative risk and odds ratio of dental metal allergy

Metal	Number of Patients								RR	OR
	P	N	E	U	EP	EN	UP	UN		
Pd	43	144	181	6	41	140	2	4	0.68	0.59
Au	29	158	180	7	26	154	3	4	0.34	0.23
Ni	63	124	55	132	24	31	39	93	1.48	1.85
Zn	15	172	179	8	14	165	1	7	0.63	0.59
Co	55	132	40	147	14	26	41	106	1.25	1.39
Cr	42	139	63	118	13	50	29	89	0.84	0.80
Sn	21	166	76	111	9	67	12	99	1.10	1.11
In	5	182	174	13	5	169	0	13		
Hg	23	169	35	157	5	30	18	139	1.25	1.29

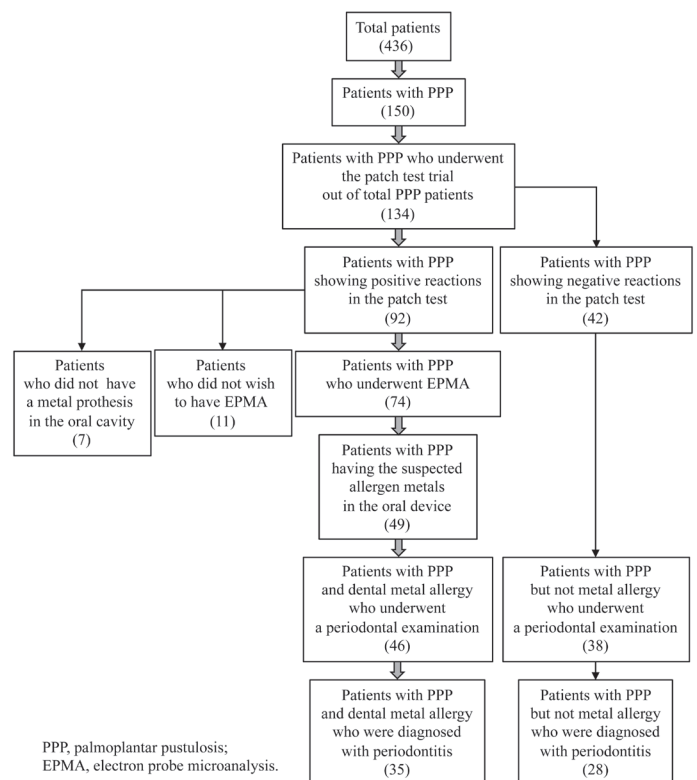
P: Patients that tested positive to the patch test for the suspected allergenic metal.
 N: Patients that tested negative to the patch test for the suspected allergenic metal.
 E: Exposed to the suspected allergenic metal.
 U: Not exposed to the suspected allergenic metal.
 EP: E and P,
 EN: E and N
 UP: U and P
 UN: U and N

**Fig. 6.** Age distribution of patients with palmoplantar pustulosis.

PPP compared with PPP-negative patients in the 2016 survey was 2.54. The OR for metal allergy between patients with PPP and healthy subjects was 4.68. The OR for periodontal disease between patients with PPP and the PPP-negative patients in the national average was 2.63.

4. Discussion

This is the first report to estimate the RR and OR between metal allergy, periodontitis, and PPP in patients who visited a dental metal allergy clinic. The OR for metal allergy between patients with PPP and healthy subjects was 4.68. The OR for periodontal disease between patients with PPP and the PPP-negative patients in the national average was 2.63. These results suggest that PPP may be associated with metal allergies and periodontal disease.

**Fig. 7.** Flowchart of classification for PPP patients with dental metal allergy and periodontitis.

Ni is one of the most common allergenic metals. In the present study, Ni had the highest positivity rate on the patch test, which is consistent with the results of the previous studies[2,11]. The RR and OR of metal allergies were relatively higher in the dental metals. This may be attributed to the widespread use of Ni in a variety of products, ranging from cosmetics to jewelry[18]. Ni triggers an inflammatory response by directly activating the human toll-like receptor 4[19], which could explain its high positivity rate on the patch test. How-

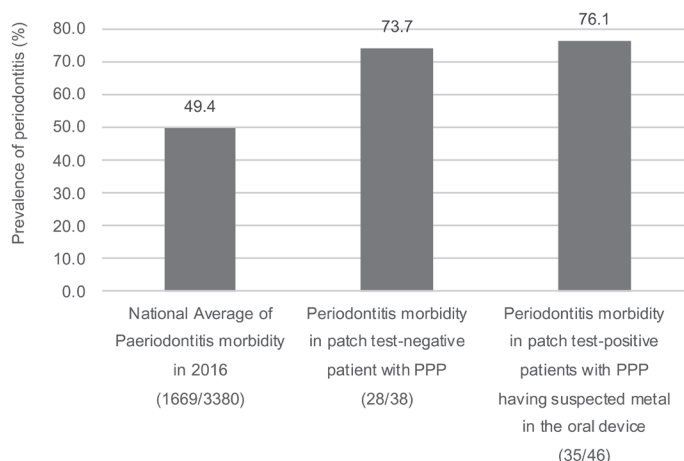


Fig. 8. Prevalence of periodontitis among patients with palmoplantar pustulosis.

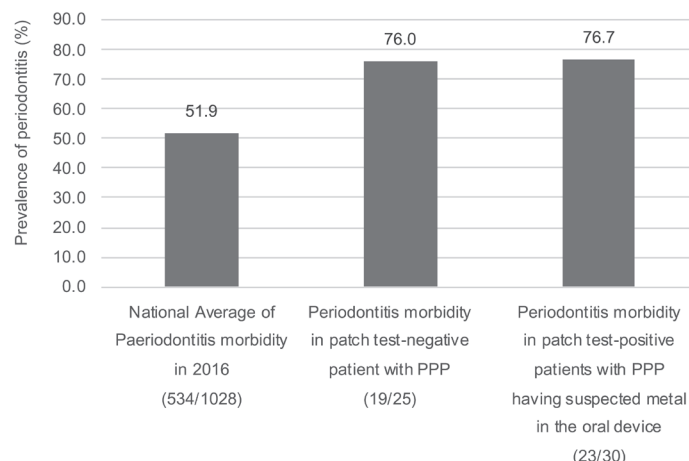


Fig. 9. Prevalence of periodontitis among patients aged 45–54 years with palmoplantar pustulosis.

ever, the percentage of Ni was low in patients who underwent EPMA for the dental prostheses.

Co also showed a high positive score on patch testing and a high RR and OR. Co is often used in pigments, alloys, metallic or non-metallic products and materials, such as jewelry, cosmetics, tools, and leather, and as a siccative in paints[20,21]. Therefore, exposure to Co can occur frequently. Co is also considered as one of the essential elements; for example, vitamin B12, also known as cobalamin, contains Co[21]. A previous study suggested that Ni, which showed the highest positivity rate on patch testing, acts as an adjuvant in Co sensitization[22]. These factors may have contributed to Co showing a higher positive score on patch testing, as compared with other metals.

On the other hand, Ag, Cu, Pd, Au, Zn, and In were higher in patients who underwent EPMA, but showed a lower RR and OR for metal allergy. All six metals are constituents of an alloy that is commonly used in dental prostheses and is covered under the health insurance system of Japan. There is a possibility that the number of positive patients was small as compared with the frequency of use.

In this study, we did not analyze the specific types of metal prostheses, such as full cast crowns, porcelain fused to metal crowns, metal inlays, clasps, or bars. Regardless of the metal prostheses, the metals detected by EPMA potentially contributed to the onset of metal allergies. In our clinical study, the metal element, and not the type of metal prostheses, was important for diagnosing dental metal allergy. The EPMA could not detect metals in the cast post and core without crown removal. Therefore, it was performed during the replacement of the metal prostheses. When suspected allergen metals were detected in the cast post and core, the latter were replaced with fiber post and resin core.

The disease distribution results showed that approximately one-third (150/436, 35.8%; **Figure 7**) of the patients were diagnosed with PPP, which is known to be associated with metal allergy[23]. Some clinical reports suggest that the replacement of the dental prostheses containing suspected allergenic metals may contribute to the improvement of PPP[5,6]. In our study, 68.7% (92/134; **Figure 7**) of the PPP patients showed a positive reaction to the patch test, and 66.2% (49/74; **Figure 7**) of the PPP patients had a dental prosthesis

that contained the suspected allergenic metal. The RR is the ratio of probabilities that compares the incidence or risk of an event among groups with a specific exposure to that of groups with no exposure. The OR describes the likelihood of an event occurring in a treatment group relative to the odds of an event occurring in a control group. Based on the RR, there was a 3.88 times higher risk of a metal allergy in the PPP patients than in healthy individuals, while the OR of metal allergy between patients with PPP and healthy subjects was 4.68.

For calculating the RR and OR, we used the pocket depth data reported in the “Survey of Dental Diseases,” by the Ministry of Health, Labor and Welfare, Japan in 2016[12], and the patch test data from healthy subjects reported in 1993[17], as mentioned earlier. In this context, “healthy” means without metal allergy or PPP.

Meanwhile, dermatologists have reported that metal allergy is not the main cause of PPP[3,4,7,8,13,23]. Among patients with PPP, the prevalence of periodontitis in both the patch test-positive patients with dental prostheses containing the suspected allergenic metal (35/46, 76.1%; **Figure 7**) and the patch test-negative (28/38, 73.7%; **Figure 7**) patients was higher than the national average (1669/3380, 49.4%; **Table 3** and **Figure 8**)[12].

The periodontal disease risk was 2.54 times higher in patients with PPP than in PPP-negative patients. The OR for periodontal disease between patients with PPP and the PPP-negative patients in the national average was 2.63. In the “Survey of Dental Diseases,” by the Ministry of Health, Labor and Welfare, Japan in 2016[12], which contained data from 3380 patients aged 15–19 years to over 85 years, the periodontal pocket depth was measured by a periodontist. In the present study, patients with a periodontal pocket depth of >4 mm were diagnosed with periodontitis. The prevalence of periodontitis increases with age and mostly affects individuals in the age group of 65–75 years. In contrast, 62.6% (94/150) of the PPP patients were in the 45–64-year age group in our study. Therefore, we compared the prevalence of periodontitis in 45–64-year old patients between those diagnosed with periodontal disease in the national average and the PPP patients in our clinic. From our results, the PPP patients in the 45–64-year age group, who were patch test-negative (19/25, 76.0%; **Figure 9**) or positive for suspected metals in the dental prostheses (23/30, 76.7%; **Figure 9**), showed a higher prevalence of peri-

odontitis as compared with the national average (534/1028, 52.0%; **Figure 9**) [12].

Previous reports from dermatologists have recommended that practitioners should initially investigate and treat the focal infections, such as apical lesions and periodontitis, rather than immediately removing the dental prostheses containing the suspected allergenic metals [9,10,13].

One of the reasons for delaying the prosthetic replacement was to avoid financial burden to the patients, as the non-metallic prostheses were not covered by our country's health insurance system at that time. Recently, several non-metallic prostheses have been included under the health insurance system, thereby reducing the patients' economic burden. Furthermore, previous reports by dermatologists have shown that 79.1% of the patients who removed the allergenic metal from their prostheses reported conditions that were diagnosed as being "improved" or "remarkably improved" [13]. Considering the results of the present study and the basic principles of dental treatment, we concur with these recommendations and suggest treating periodontitis before the replacement of the suspected allergenic metal-containing dental prostheses. A patch test and EPMA should be performed, if possible, before removing the dental prostheses to identify the suspected allergenic metals.

Despite a comprehensive evaluation, we were unable to suggest a definitive treatment plan. Therefore, further studies are needed to elucidate the causative role of dental metal allergy in dermatitis, and the effect of replacing the dental prostheses containing suspected allergenic metals in such cases.

5. Conclusions

In this study, dental metal allergy and periodontitis showed a high RR and OR for PPP.

Conflicts of interest

There are no conflicts of interest to declare.

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