

Metal allergen of the 21st century – a review on exposure, epidemiology and clinical manifestations of palladium allergy

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Summary

Consumers are mainly exposed to palladium from jewellery and dental restorations. Palladium contact allergy is nearly always seen together with nickel allergy, as palladium and nickel tend to cross-react. We aimed to analyse the available palladium patch test data and case reports to determine whether the prevalence of palladium mono-sensitization has increased. Based on available patch test data from the period 1986–2008, a total of 10 778 patients were patch tested with palladium chloride. The median prevalence of palladium allergy was 7.8% (range <1.0–19.0%) in dermatitis patients and 7.4% (range 1.3–13.9%) in dental patients. The median prevalence of palladium mono-sensitization (defined as the presence of palladium allergy and the absence of nickel allergy) was 0.2% (range 0–1.6%) in dermatitis patients and 0.5% (range 0–7.2%) in dental patients. A slight increase in the prevalence of palladium mono-sensitization was observed over the study period. We conclude that clinically relevant palladium allergy should mainly be suspected in patients who present with allergic contact granulomas at sites of piercing, but also in patients who have clinical disease and palladium patch test reactivity without concomitant nickel reactivity. Palladium salts should be included in dental screening patch test series. Palladium use in jewellery should be limited until we know more about the risk of sensitization.

Key words: dental; epidemiology; jewellery; palladium allergy; prevalence; relevance.

Palladium is a precious, silvery-white metal that belongs to the platinum group of metals (palladium, platinum, rhodium, ruthenium, iridium, and osmium). Palladium was discovered by the British chemist William Hyde Wollaston in 1803. Consumers (and patients with dermatitis) are mainly exposed to palladium from jewellery and dental restorations, but palladium is also found in electronics (where it is used in electrodes in multi-layer ceramic capacitors), aircraft spark plugs, surgical instruments, and catalytic converters in the automobile industry (1). In the 1950s, Sheard suggested the existence

of allergic contact dermatitis (ACD) caused by palladium in a platinum-allergic patient who reacted to a palladium ring (2). Palladium contact allergy is nearly always seen together with nickel allergy. This observation has mainly been explained by cross-reactivity between palladium and nickel, although this is not fully understood (3–5). The high prevalence of palladium allergy among dermatitis patients is therefore often neglected, as it is considered to be clinical marker of nickel allergy, and because it is often difficult to determine palladium exposure and clinical relevance in patients who are mono-sensitized to palladium. Hence, palladium is not usually included in routine patch test series in Europe and North America. Nevertheless, palladium allergy has been a subject of debate for decades. First, palladium is increasingly used in dentistry and jewellery, and it has been debated whether the use of nickel in jewellery has or will be replaced by the

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use of palladium following the EU Nickel Directive (6, 7). Second, the prevalence of palladium allergy has allegedly increased in recent years (4). Third, palladium exposure may result not only in ACD but also in clinically severe sarcoidal-type allergic contact granulomas (8).

On the basis of the available literature, this review aimed to analyse available palladium patch test data and case reports, to determine whether the prevalence of palladium mono-sensitization has increased. Furthermore, it reviewed palladium exposures as well as clinical manifestations and relevance.

Materials and Methods

The studies included in this review were identified from literature searches in PubMed-Medline, EMBASE, Web of Science, and dermatology textbooks. The following search terms were used: palladium, nickel, metal, contact allergy, dermatitis, allergic contact dermatitis, sensitivity, hypersensitivity, sensitization, granuloma, general population, patch test, epidemiology, and jewellery. Additionally, the databases were searched by the use of the 'related articles' function and by searching the publications by specific authors in the scientific area. Finally, references were localized by the use of reference lists in selected articles. Only English language articles were included.

Throughout this review, palladium mono-sensitization was defined as patch test reactivity to palladium but not to nickel. Prevalence estimates were ranked, and the median was selected as an average estimate of the prevalence of palladium allergy. The temporal development of palladium mono-sensitization was investigated. When patch test results straddled more than 1 year, the median year was considered to be representative (for example, when 1990–1996 was indicated, 1993 was designated as the representative year). Data analysis was performed with Microsoft Excel 2002 (Redmond, Seattle, Washington State, USA).

Results

Between 1986 and 2008, a total of 10 778 patients were patch tested with palladium chloride. Patients were stratified into two groups: dermatitis patients ($n = 6808$; including one group of healthy adults and one group of workers from a catalyst manufacturer) (Table 1); and patients who were patch tested with a dental screening series (typically, dental patients with oral disease, but also dental professionals) ($n = 3970$) (Table 2). Tables 1 and 2 show the prevalence of palladium and nickel allergy together with a characterization of the study populations

and the patch test concentrations used. The median prevalence of palladium allergy was 7.8% (range <1.0–19.0%) in dermatitis patients and 7.4% (range 1.3–13.9%) in dental patients. The median prevalence of palladium mono-sensitization (defined as the presence of palladium allergy and the absence of nickel allergy) was 0.2% (range 0–1.6%) in dermatitis patients and 0.5% (range 0–7.2%) in dental patients. A slight increase in the prevalence of palladium mono-sensitization was observed over the study period (Fig. 1). Only two studies have investigated the development of palladium allergy over time. Cristaudo et al. showed that the prevalence of mono-sensitization to palladium increased from 0.1% in 1996–1997 to 1.8% in 2007–2008 among 5350 patients (6). Larese Filon et al. found a steep increase in palladium allergy in 4446 consecutive patients tested over a decade (4). Thus, the prevalence increased significantly from 0.8% in 1992 to 9.7% in 2000. The temporal development of nickel allergy did not fully mirror this development, although an increase was observed from about 16% in 1992 to 27% in 2000. No data on the development of palladium mono-sensitization were given.

Discussion

This study showed that palladium allergy is very frequent in dermatitis and dental patients (Tables 1 and 2). Thus, the median prevalence of palladium allergy was 7.8% (range <1.0–19.0%) in dermatitis patients and 7.4% (range 1.3–13.9%) in dental patients. As expected, the prevalence of palladium allergy was markedly higher in female than in male patients (Tables 1 and 2), a finding that may have several explanations. First, nickel allergy and palladium allergy are often observed together (and, because nickel allergy is much more prevalent in women, a higher prevalence of palladium allergy is expected). Second, the more frequent use of jewellery by women will probably result in higher frequencies of palladium allergy. However, exposure to palladium from dental restorations is expected to be similar in men and women. Based on the findings from this review, the prevalence of palladium mono-sensitization appeared to be stable over a 20-year period, although a slight increase is suggested on visualization of the data (Fig. 1). A possible increase was suggested by the only two studies that investigated the development of palladium allergy over time (4, 6). However, one should interpret the results from these studies with caution, because random error may have occurred.

Palladium exposure

Palladium is found in ores combined with platinum, gold, and copper (15). Palladium is typically used in alloys

Table 1. Studies that have investigated the prevalence of palladium allergy in dermatitis patients; the list may not be exhaustive

Author (reference)	Year	Country	Palladium patch test concentration (%)	n _{total}	n _{women}	n _{men}	Age (years)	Palladium allergy prevalence (%)			Nickel allergy prevalence (%)		
								Women	Men	Total	Total	Men	Women
de Fine (9)	1989–1990	Denmark	1	1307	815	492	—	—	—	2.4	0.2	—	—
Augthun (10)	1990	Germany	1	486	—	—	—	—	—	7.4	0.4	17.9	—
Rebanel (11)	1990	Poland	1	100	—	—	Mean: 36.1 (range 21–58)	—	—	10	0	—	—
Camarasa (12)	1991	Spain	1	1521	—	—	—	—	—	2.7	0.2	—	—
Aberer (13)	1990–1991	Austria	1	1382	—	—	—	—	—	8.3	0.6	23.4	—
Vincenzi (14)	1991–1992	Italy	1	2300	—	—	—	—	—	7.4	0.08	22.0	—
Todd (15)	1992	UK	1	536	357	179	—	3.1	1.1	2.4	0	—	—
Goncalo (16) (referred to in Kanerva)	1992	—	—	—	—	—	—	—	—	7.8	0	—	—
Marcusson (17) ^e	1994	Sweden	1	112	77	35	Mean: 39 (range 12–73)	—	—	<1	—	17.0 ^b	—
Brasch (18)	1990–1995	Germany	—	49	—	—	6–15	—	—	2.0	0	18.3	—
Santucci (19)	1995–1996	Italy	1	1000	—	—	—	—	—	9.1	0.1	55.0	—
Krånke (20)	1996	Austria	1	11 516	—	—	Mean (women): 39 Mean (men): 40	—	—	8.0	—	23.0	—
Laresse Filon (4)	1991–2000	Italy	1	4446	3077	1369	Mean: 40.1	6.7	2.3	5.3	0.4	24.0	31.3
Santucci (21)	1999	Italy	1	749	574	175	Mean: 37.6 (range 14–76)	—	—	19.0	—	48.0	—
Finch (7)	1999	UK	1	342	210	132	—	—	—	9.4	0.9	21.3	—
Durosaro (22)	1997–2006	USA	2	910	—	—	—	14.9	3.2	12.1	1.0	—	—
Akasya-Hillenbrand (23)	1996–1999	Turkey	1	542	303	239	Mean: 33.5 (range 3–82)	14.8	2.5	9.4	—	19.1	5.4
Erich (24)	2001	USA	1	118 ^c	0	118	Median: 25 (range 18–43)	—	0.9	0.9	0.9	—	—
Orion (25)	2003	Israel	1	216	138	78	—	—	—	13.0	0.5	23.0	—
Bordel-Gómez (26)	2000–2005	Spain	1	1092	673	418	Mean: 41.1	17.1	3.1	11.7	0.2	—	—
Cristaudo (27)	2005	Italy	1	153 ^d	16	137	Mean: 34 (range 21–60)	—	—	0.7	—	—	—
Cristaudo (6)	2006	Italy	1	3093	—	—	—	—	—	13.0	1.6	—	—

—, Not given.

^aNo concomitant nickel allergy.^bNickel patch test result was based on 559 patients.^cMale students.^dWorkers from a catalyst manufacturer.^eMean age 39 years for women and 46 years for men.

Table 2. Studies that have investigated the prevalence of palladium allergy in dental patients and/or dental workers (typically, results from dental screening test series); the list may not be exhaustive

Author	Year	Country	Palladium patch test concentration (%)	Palladium patch test			Age (years)	Palladium allergy prevalence (%)				Nickel allergy prevalence (%)		
				n _{total}	n _{women}	n _{men}		Women	Men	Total	Mono-sensitization ^a	Total	Men	Women
Stenman (28) Van Loon (29) Koch (30) Marcusson (17)	1981–1987	Sweden	1	151	119	32	Mean: 48.6	1.7	0	1.3	0	14.6	3.1	17.6
	1986	Holland	2.5	63	—	—	—	—	—	11.1	—	25.4	—	—
	1991–1996	Germany	1	194	—	—	—	—	—	13.9	7.2	—	—	—
	1992–1993	Sweden	1	397	326	71	Mean age: 48–52 ^b (range 13–89)	—	—	8.0	0.5	22.0	—	—
Vilaplana (31)	1994	Spain	1.5	66	44	22	Mean (women): 48 Mean (men): 57	9.1	0	6.1	—	31.8	4.5	47.7
Kanerva (16)	1996	Finland	2	700 ^c	417	283	Mean: (range 14–18)	11.0	1.0	7.0	0.4	19.0	3.0	30.0
Kanerva (32) Lee (33)	1994–1998	Finland	—	2540 ^d	—	—	—	—	—	4.2	—	14.6 ^e	—	—
	2001	Korea	—	49 ^f	3	46	Mean: 37.4 (range 21–61)	—	—	10.2	—	18.4	—	—
Khamaysi (34)	2000–2004	Israel	—	121 ^g	91	32	—	—	—	7.4	0.8	13.2	—	—
Dittrichova (35)	2005–2006	Czech Republic	2	183	—	—	—	—	—	12.0	—	12.9	—	—
Raap (36)	2003–2008	Germany	1	206	—	—	—	—	—	4.9	1.0	4.9	—	—

—, Not given.

^aNo concomitant nickel allergy.^bForty-eight years in men and 52 years in women.^cSchoolchildren who had received orthodontic treatment with metallic appliances.^dCase mix of dental patients and dental professionals.^eNickel allergy prevalence based on 1693 patients only.^fForty-nine patients recruited from a total of 1038 dental technicians.^gEight were dental professionals.

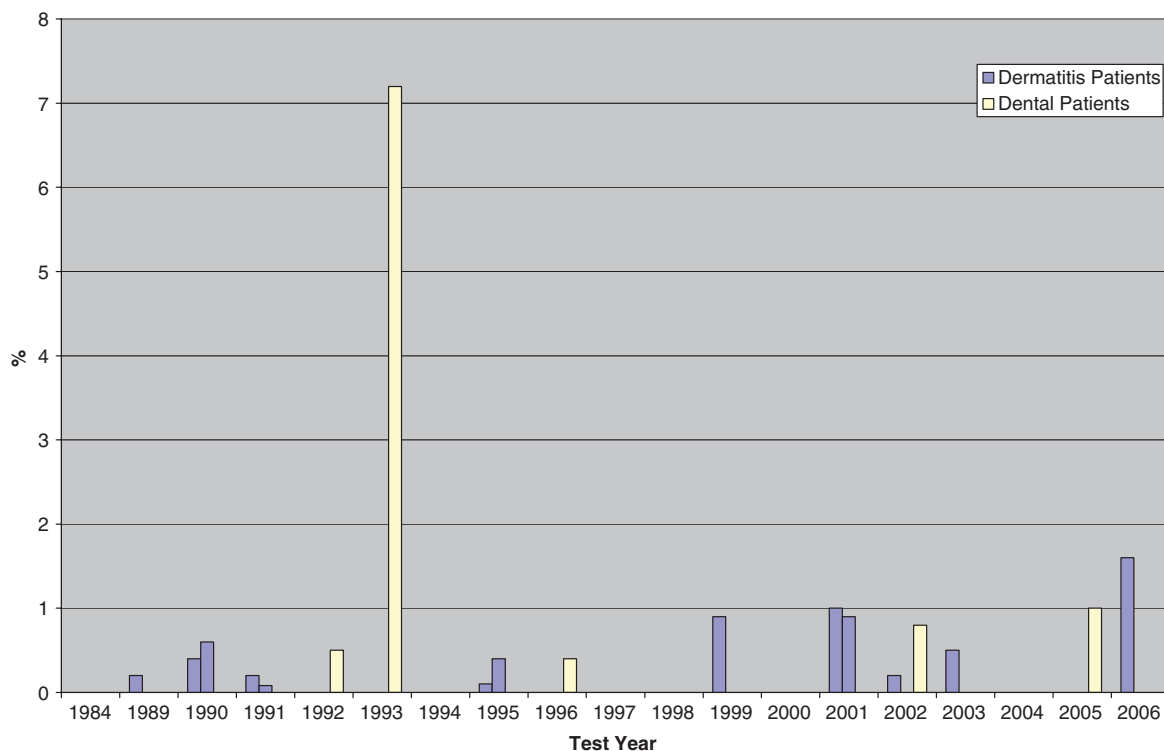


Fig. 1. Temporal development of palladium allergy without concomitant nickel allergy among patch-tested dermatitis patients (blue bars) and dental patients (yellow bars).

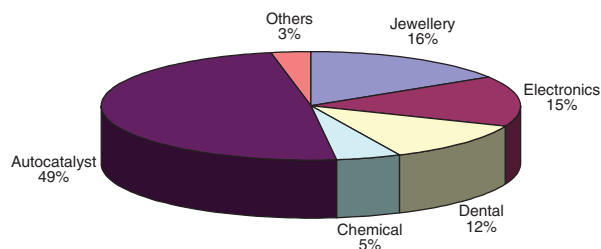


Fig. 2. Palladium demand by application in 2006 according to the United Nations Conference on Trade and Development (UNCTD) (<http://www.unctad.org/infocomm/anglais/palladium/uses.htm>).

together with nickel, silver, copper, or zinc (31). Palladium exposure may occur following skin contact with consumer items (jewellery and dental materials inserted in the oral cavity) and occupational items (catalytic converters, electronics, spark plugs, and dental materials) (Fig. 2). Occupational ACD caused by palladium exposure is infrequent but does exist (37). Consumer exposure will be discussed here.

Dentistry. In dentistry, the use of palladium has, to a substantial degree, replaced the use of amalgam and gold, mainly because of concerns about mercury toxicity and

the increasing price of gold (13, 31). Palladium–silver alloys and other palladium-containing alloys were introduced into dentistry in 1973, and rapidly gained popularity (13, 31, 38). Palladium is usually mixed with gold or silver, as well as copper and zinc, in varying ratios to produce alloys suitable for dental inlays, crowns, and bridges. Small amounts of ruthenium or iridium are sometimes added (39). The most common application of palladium is in crowns, where the alloy forms the core onto which porcelain is bonded to build up an artificial tooth. The aim of using platinum group metals (such as palladium and platinum) in dental alloys is to provide strength, stiffness, and durability; the other alloyed metals provide malleability. Generally, palladium-based alloys have a white appearance and a good range of solubility with other metals, as well as good mechanical properties. Palladium displays excellent corrosion resistance and biocompatibility in the oral environment (39). The overall content of palladium alloys seems not to correspond to the degree of palladium release into different cell culture media (40). Apparently, copper–palladium–tin fusions display the highest palladium solubility (6–22.5 μg palladium/ cm^2 /day) (39). One study showed that tooth brushing and toothpaste may increase palladium release (41). One clinical study

found elevated palladium concentrations in saliva from patients with metallic dental applications when compared to controls (referred to in (39)). In Japan, the government operates a specific mandate stating that all government-subsidized dental alloys have to include a palladium content of at least 20%. This alloy is used in approximately 90% of all Japanese dental treatments, making Japan the largest palladium-consuming region for dental applications, followed by North America and then Europe (<http://www.stillwaterpalladium.com/dental.html>).

Jewellery. Palladium is referred to as the metal of the 21st century (<http://www.stillwaterpalladium.com/index.html>). Its steel-white appearance makes it an attractive jewellery alternative to white gold and platinum (<http://ezinearticles.com/?Palladium-Jewelry:-The-Affordable-Treasure&id=288163>). In a recent article from the *Wall Street Journal* titled 'Palladium, platinum's cheaper sister, makes a bid for love', Elizabeth Holmes describes the increasing popularity of palladium in jewellery (http://www.danforthdiamond.com/media/image/WSJ_Article_Palladium.pdf). Palladium was first used in jewellery in the 1940s, as governments reserved platinum for military purposes. Today, palladium is once again being frequently used in jewellery, owing to advances in the casting of palladium. According to John Stark, chair of Palladium Alliance International (a group formed in 2006 to promote palladium for use in jewellery), about 80% of sales of palladium jewellery are in China. At present, palladium is mainly found in jewellery sold in boutiques and middle-market stores; however, palladium is slowly entering higher-end stores such as Cartier, Chopard, Hermes, and Gucci. According to the *Wall Street Journal* article, Palladium Alliance International has launched an intensive campaign in Asian markets, aimed at people in their twenties and college students, and is preparing a similar campaign in the United States. A benefit of palladium is that it is over 40% lighter than platinum. Weight is a consideration that is especially important in earrings, as heavier metals and bigger designs can stretch the ear lobe and be too heavy to wear. As palladium costs much less than platinum, it is expected to take a large share of the market (<http://ezinearticles.com/?Palladium-Jewelry:-The-Affordable-Treasure&id=288163>). Despite the use of palladium in jewellery produced in Asia, a recent analysis of 29 inexpensive earrings purchased in Thailand and China showed no content of palladium (42).

Cross-reactivity

Several studies have addressed cross-reactivity between palladium and nickel, and also cross-reactivity with other metals.

In vitro. In a panel of human nickel reactive T-lymphocyte clones, Pistor et al. found that 6 of 20 displayed cross-reactivity with palladium (43). Similarly, Moulon et al. investigated the proliferative response of nickel-specific T-lymphocyte clones from 4 nickel-allergic patients in the presence of different metals, including palladium (44). On the basis of their findings, the authors suggested that cross-reactivity is restricted to metals that may adopt identical coordination geometry in their protein-bound state. Thus, nickel and palladium both prefer square planar arrangements, as opposed to, for example, cobalt, which forms tetrahedral complexes, and chromium, which forms octahedral complexes (44). Bordignon et al. investigated blood samples from 40 patients who were patch tested (10 were nickel-allergic, 10 were allergic to palladium, 10 were allergic to both nickel and palladium, and 10 had no allergy to nickel or palladium) (45). Interferon (IFN)- γ responses from peripheral blood mononuclear cells (PBMCs) isolated from patients allergic to nickel and palladium were observed when PBMCs were exposed to nickel as well as to palladium, indicating cross-reactivity.

In vivo. Wahlberg et al. performed two studies with guinea pigs. In the first study, nickel-sensitized animals reacted to nickel but not to palladium chloride, whereas palladium-sensitized animals reacted to palladium as well as to nickel sulphate (3). However, in the second study, using the repeated open application test (ROAT), they could not reconfirm this finding, and discussed whether the ROAT more adequately mimics exposure conditions than the patch test (46). Kränke et al. showed that 8% of 11 516 patch-tested dermatitis patients had palladium allergy and that 94.6% had concomitant nickel allergy (20). Lisi et al. patch tested 60 cobalt-allergic patients, and showed that 83% were nickel-allergic and 40% were allergic to nickel and palladium (47). Bordel-Gomez et al. presented patch test data from 1092 patients tested between 2000 and 2005 (26); 11.7% had palladium allergy, and 97% of these had concomitant nickel allergy. Hindsén et al. showed that patients with nickel and palladium allergy had flaring of patch test sites previously tested with palladium following oral nickel exposure, suggesting cross-reactivity (5).

Taking these findings together, there are substantial *in vitro* and *in vivo* data to support palladium and nickel cross-reaction. The strong association with nickel undoubtedly explains the high prevalence of palladium allergy seen in dermatitis patients. Furthermore, it should be considered that several studies have shown that patch test reactivity to palladium is often seen together with positive patch test reactivity to cobalt, gold, chromium,

copper, platinum, and other metals (19, 20, 22, 34, 48, 49). Concomitant exposure and sensitization explain some of the high concordance rates. So far, few data have been published on cross-reactivity with gold. In a large patch test study, Durosaro and el-Azhary showed that about half of palladium-allergic patients also reacted to gold (22). They speculated that this was explained by concomitant exposure to gold and palladium from dental alloys. Khamaysi et al. showed that, in a mixed patch test population of dental professionals and patients with oral disease, the prevalence of gold allergy was 14%, whereas nickel and palladium accounted for, respectively, 13.2% and 7.4%. Marcusson also showed that the prevalence of gold and palladium allergy was higher in dental patients (23% and 8%, respectively) than in dermatitis patients (6% and <1%, respectively) (17). The association between palladium and gold (a prevalent cause of contact allergy (50)) may also contribute significantly to the high prevalence of palladium allergy. Future studies on the prevalence of palladium allergy should also include patch test data on gold.

Clinical presentation

Palladium hypersensitivity may be expressed clinically in several ways. There are, as yet, no convincing data to support which of the following manifestations is the most frequent. Thus, the current impression is mainly based on case reports.

Allergic contact dermatitis. Palladium allergy may result in ACD. Two independent case reports of ACD caused by palladium plating in titanium spectacle frames have been published (51, 52). Katoh et al. reported facial ACD caused by palladium-containing dental crowns in a patient sensitized to palladium but not to nickel (53). Munro-Ashman et al. reported ACD on the hands and face of a chemist exposed to palladium and other metals (37). Guerra et al. reported ACD following contact with firearms and a bar used for weightlifting (54). Also, airborne ACD caused by aerosolized palladium in a chemist has been reported (55).

Allergic contact granuloma. Several case reports have described allergic contact granuloma related to palladium exposure. Jappe et al. described a 15-year-old girl with yellow-brownish nodules on both ear helices (56). Patch testing showed 3+ reactivity to palladium chloride (and also to nickel and cobalt) that persisted for more than 25 days. Histology of the patch test reaction showed dermal granulomas like those found in the nodule on the helix. A Spanish case report described a 26-year-old man

who developed painful nodules on the helices 10 days after ear-piercing (57). Patch testing showed mono-sensitization to palladium chloride, and furthermore, 20 days after skin testing, an infiltrated erythematous plaque persisted at the site of testing with similar histology to that of the nodules on the helices (i.e. sarcoidal granulomatous reactions). Intralesional corticosteroid injections cleared the eruption. Goossens et al. described 2 patients with allergic contact granuloma (8). A 27-year-old woman who was ear-pierced 5 years earlier began to wear earrings 1 year before the development of allergic contact granuloma. The patient was mono-sensitized to palladium, and was treated with corticosteroid injections on four occasions, with limited success. Chemical analysis of the earring showed palladium at the surface of the pin. The second case was a 56-year-old woman with palladium and nickel allergy who developed itching nodules on the helices of both ears. Palladium was not found in earrings from this patient. The authors underscored that the use of palladium is not a safe alternative to nickel in jewellery. Thijs et al. reported a 21-year-old woman with papulo-nodular lesions on the right earlobe after ear-piercing (58). Repeated intralesional corticosteroid injections gave only temporary regression. Patch testing showed strong reactivity to palladium, but also reactivity to nickel. Blum et al. described a 19-year-old woman with allergic contact granuloma in the earlobe caused by her earring (59). Patch testing showed positive reactions to nickel and palladium, but also to pure metallic palladium. Treatment with corticosteroid injections proved partly successful, but had to be repeated once, with a 4-month interval. Finally, Casper et al. also showed sarcoidal-type allergic contact granuloma in tissue from two female patients aged 21 and 29 years (60). Apparently, they wore 'medical' earrings made of palladium and platinum, owing to antecedent allergic nickel dermatitis.

Oral symptoms. Numerous reports have described oral symptoms in palladium-allergic individuals exposed to dental materials containing palladium (17, 32, 35). In most case reports, removal of metallic implants has resulted in the disappearance of symptoms. One patient with concomitant palladium and gold allergy developed gingival hyperplasia involving the hard palate, owing to a palladium-containing denture (61). Contact stomatitis was shown in a patient with a maxillary gold-palladium alloy-fixed partial denture shortly after placement (62). It is of particular interest that metal patch testing showed 3+ patch test reactivity to palladium chloride 1% in petrolatum only. One report showed linear lichen planus from the right cheek to the jaw in a palladium-allergic patient with metal compounds made

of palladium–silver–gold (63). Concomitant platinum patch test reactivity was considered to be a result of cross-reactivity, as no platinum had been inserted into the oral cavity. A case of intraoral lichen planus caused by palladium exposure has also been published (64). Burning mouth was described in a patient who was mono-sensitized to palladium (confirmed on two occasions), owing to a palladium-containing dental framework supporting ceramic dental crowns (65).

Other manifestations. One report showed occupational asthma caused by palladium exposure in a worker exposed to fumes of an electroplating bath (66). A similar finding was made by Yoshida et al. (67). One report described chronic urticaria and localized angio-oedema following exposure to a palladium-containing dental bridge (68).

Clinical relevance of palladium allergy

The clinical relevance of palladium allergy has been much debated. Critics claim that palladium allergy is never, or very rarely, of clinical relevance, whereas others suggest that palladium allergy may be of relevance, as indicated by case reports. Below, the main findings from the literature are presented.

Oral versus cutaneous disease. One study showed that 55% of 106 patients with palladium allergy had oral disease and that 29% had dermatitis, suggesting that palladium allergy could be mainly of relevance in oral disease (22). Of 9 patients with patch test reactivity to palladium only, 4 were asymptomatic and had patch testing performed prior to implant surgery, 4 had oral disease, and 1 had dermatitis. Marcusson found evidence to support the idea that the prevalence of palladium allergy is higher in dental than in dermatitis patients, as he showed that the prevalence of gold and palladium allergy was significantly higher in the first group (17). Van Loon et al. could not replicate this finding in a small study in which 63 patients were stratified into groups of contact stomatitis and dermatitis (29). However, it should be noted that the distribution of nickel allergy was different between the two groups. The accumulation of data included in this review suggested that the overall prevalence of palladium allergy is comparable in dermatitis and dental patients. A Japanese case report underscored the clinical relevance of palladium allergy in a patient with palladium allergy (but no nickel allergy) who reacted with ACD to a dental crown (53). The crown was removed, resulting in clearing of the dermatitis, but, strangely, the patient strangely requested that the crown be reinserted,

which resulted in ACD reappearance after only 1 day. Cristaudo et al. found that all patients who were mono-sensitized to palladium, in their case series of 5350 patients, had intraoral symptoms and wore palladium-containing dental prostheses (6). They also found higher levels of palladium in saliva in these patients than in controls. Gawkrödger et al. stratified patch-tested patients into two groups on the basis of self-reported reactivity to jewellery (49). No patients were found to be allergic to palladium without also being allergic to nickel. The authors concluded that the addition of an extended metal patch test series did not produce a greater number whose jewellery reactivity was explained by allergy to metals other than nickel. Uter et al. showed that highly sensitive nickel-allergic patients reacted to palladium chloride upon patch testing four times more often than nickel-allergic patients with low sensitivity (69). The above findings suggest that palladium allergy is mainly of clinical relevance in patients with oral disease, and is only rarely of relevance in patients patch tested for cutaneous disease (except for allergic contact granuloma).

Reactivity to metallic palladium. The clinical relevance of palladium allergy has also been investigated by testing palladium-allergic patients with pure metallic palladium foil. Todd and Burrows patch tested 12 palladium-allergic patients with pure palladium metal foil, but found no positive test reactions (15). Similarly, de Finé Olivarius and Menné patch tested 19 palladium-allergic patients with metallic palladium discs, but found no positive test reactions (9). A 1-week corrosion test of the palladium discs revealed palladium release at 5 ng. Thus, the palladium on copper discs showed very good corrosion resistance. Santucci et al. patch tested 87 patients who were sensitized to both nickel and palladium with metallic palladium foil, but found no positive reactions (70). Uter et al. patch tested 103 nickel-allergic patients with pure palladium (and nickel) metal plates, and found only one positive test reaction to the palladium plate (69). However, this reaction was observed in a patient who had not reacted to palladium chloride. It is of note that 74% reacted to the metallic nickel plates. Augthun et al. patch tested 18 palladium-allergic patients with pure palladium metal foil, and found only one positive reaction (10). Koch and Baum published a case report describing a patient with contact stomatitis who was patch test-positive to both platinum and palladium chloride in pet. as well as metallic palladium and a metal plate of a gold–palladium dental alloy (71). Blum et al. found positive patch test reactivity to pure metallic palladium in a patient with allergic contact granuloma caused by a piercing earring and positive patch test reactivity to nickel and palladium

chloride (59). It is clear that palladium-allergic patients very rarely react to metallic palladium. This is probably explained by the fact that palladium does not react with sweat or chloride solutions unless strong oxidants or complexing agents are present (72).

Strength of patch test reactivity. One large epidemiological study offered information on patch test reactivity (22). Durosaro and el-Azhary showed that in 110 patients with contact allergy to 2% palladium chloride, 31% had 1+, 46% had 2+ and 23% had 3+ reactivity. Furthermore, Orion et al. patch tested 236 patients and showed that 13% had palladium allergy and that 14% of these had stronger patch test reactivity to palladium than to nickel (25). Thus, palladium patch test reactivity covers all strengths of reactions. On the basis of the accumulation of case reports, palladium allergy in combination with nickel allergy is usually only of relevance when patch test reactivity to palladium is strongest.

Immunological studies. Bordignon et al. performed an *in vitro* study, and showed that subjects with positive patch test reactivity to nickel and palladium gave an *in vitro* response characterized by the release of IFN- γ after nickel stimulation and of interleukin-10 after palladium stimulation (45). This finding suggests that palladium exposure in dual-sensitized individuals may not necessarily result in ACD. However, in palladium-mono-sensitized individuals, palladium exposure resulted in IFN- γ release, indicating clinical relevance of palladium mono-sensitization. Minang et al. showed that different metals, including nickel, cobalt, chromium, and palladium, all gave a similar mixed Th1–Th2 response in patients with positive patch test reactions to these metals, whereas non-sensitized controls did not have such response (73).

General remarks

This review confirms that palladium allergy is common and nearly always observed together with nickel allergy. Two studies have suggested an increasing trend of palladium allergy in recent years (4, 6), but the accumulation of data included in this review could not confirm a dramatic increase in palladium mono-sensitization over time. Future studies are clearly warranted to monitor palladium allergy, as palladium is being increasingly used in jewellery and dentistry. New alloys may be developed, resulting in increased corrosion and palladium release. Patch test studies should include data on palladium mono-sensitization and, if possible, also on gold (and nickel) allergy. Overall, palladium allergy seems to be rarely of clinical relevance, albeit this more often the case in patients with oral disease than in patients with cutaneous disease. Thus, general screening for palladium allergy should mainly be restricted to dental patients. It is possible that, in the future, there will be a higher number of clinically relevant cases of palladium allergy and that the indication for patch testing will be changed. At present, clinically relevant palladium allergy should mainly be suspected in patients who present with allergic contact granulomas at sites of piercing, but it should also be suspected in patients who have clinical disease and palladium patch test reactivity (strong) without concomitant nickel reactivity (if nickel allergy is present, it should preferably be weaker than palladium reactivity). The development of a palladium spot test for the detection of palladium release could greatly improve our understanding of the connection between palladium exposure and palladium allergy. Furthermore, studies in which palladium-allergic subjects are exposed to palladium-containing jewellery would be interesting. Finally, analysis of palladium release from palladium-containing jewellery after 1 week in the sweat test would increase our understanding of this issue. Taking these findings together, it remains to be verified whether palladium is truly the metal of the 21st century, or whether it is also the metal allergen of the century.

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