Palladium in dental applications: ideal immunological choice

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Abstract

The oral mucosa is constantly exposed to various irritants and allergens, including noble metals such as palladium (Pd), a metal with suitable biocompatibility and anticorrosive properties. Based on recent literature, this work focuses on Pd allergy in dental practice, covering clinical symptomatology, epidemiological data, and immune mechanisms. Predominant manifestations of Pd allergy include oral lichenoid contact injury, systemic or oral allergic contact dermatitis/mucositis (ACD), cheilitis, and burning mouth syndrome. Studies on allergy diagnosis have revealed that Pd is the principal dental metallic allergen in extended patch test batteries. Being less allergenic than nickel, chrome, or cobalt, Pd allergy affects over 6% of ACD-suspected patients, but up to 51% of oral allergy subjects exposed to the culprit allergen who also presented antecedent metal hypersensitivity reactions, often as cross-reactivity to nickel. Recent evidence indicates that a solely Pd-related allergy can cause oral symptoms in patients without skin lesions in metal-exposed regions. Pd allergy frequently affects females and dentistry practitioners and technicians, despite the recent restriction on nickel use. As a cellular allergy type, Pd hypersensitivity represents a mixture of T-cell interactions, in which variable region complementarity-determining region 3 of specific CD8+ T-cell receptors recognize the complex primary histocompatibility class I/peptide on the antigen-presenting cell surface, activating also further immune cells like NK T and a mixture of T helper (Th) ones. A combination of stimulated Th1, Th2, and Th17 cells, as well as eosinophil infiltrations in Pd allergy, corresponds to cytotoxic (and potentially compensatory antitoxic) effects during high-concentration allergen exposures that may also extend mucosal inflammatory processes, as in the case of BIDEAR (Barrier Integrity Damage-Elicited Allergic Response). This work concludes that Pd allergy occurs more frequently than previously suspected, and that suitable materials can successfully replace dental Pd-containing structures following metal analysis.
Keywords: palladium, cellular allergy, dental practice, immune response, oral allergy, T helper cells, T-cell receptors.

Keywords: **Palladium allergy, Dental alloys, Allergic contact dermatitis/mucositis (ACD), T-cell–mediated hypersensitivity**

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Introduction

Palladium (Pd) is a chemical element with atomic number 46, belonging to the Nickel (Ni) group. Today's widespread use of Pd is primarily in catalytic converters, followed by jewelry, watchmaking, aircraft spark plugs, electrical contacts, and medical applications, including blood sugar test strips, surgical instruments, and orthopedic and dental restorative structures (1-4). The dentistry industry accounts for less than 1% of Pd's global usage, as seen in some amalgam alloys with anti-corrosive properties and a lustrous appearance during final restoration and occlusal reconstruction (5,6). Often used in metal-ceramic restoration substructures since the 1980s, Pd-based dental alloys have been associated with several complications, including porosity at metal-ceramic interfaces, frequent solder-joint failures, and later Pd allergies (7).

Oral allergy (OA) reactions occur during exposure to various irritants and allergens, including dental materials (8,9). Metal allergy is an environmental disorder that manifests as local or systemic allergic contact dermatitis (ACD) and mucositis weeks or months following initial exposure (5,10-13). Ni, chromium (Cr), and cobalt (Co) are the most common metal allergens. However, a few precious metals, such as gold (Au) and titanium (Ti), also show a particular interest in the dental practice. Regarding noble metals, Pd is in the same group and often causes cross-reactions with Ni (10,14,15). The rapid expansion of Pd-containing products has increased percutaneous and per-mucosal exposure for the population (16). Besides its widespread use in several dental alloys, the rising popularity of dental implant surgery is another reason for this close attention (16-18).

This work focuses on recent knowledge of Pd allergies in stomatological practice. It included all relevant publications identified using the search terms "palladium," "allergy," and "stomatology" in the PubMed database. Then, the selection expanded with more recent decade-relevant works, removing the last term during the additional search.

Epidemiologic Data: OA Manifestations, Allergy Frequencies, and Cross-Reactions

Clinical presentations: Although metallic biomaterials have improved quality of life, metal allergies, especially to Pd, have recently increased among predisposed patients (19). Metal hypersensitivity reactions (MHR), including Pd allergy in the oral mucosa, manifest oral lichen planus / lichenoid lesions, cheilitis, burning mouth syndrome, stomatitis/mucositis, palmoplantar pustulosis/dyshidrotic eczema, and systemic dermatitis (1,8,9,16,17,20-22). Oral symptoms during "amalgam disease" include tender or aching teeth, metallic taste, and sore and dry mouth (22). As one of the most positively tested metals observed in subjects with oral lichenoid contact injuries, Pd causes white-type lesions in the buccal mucosa (23). According to several studies, Pd sensitized nearly 16% of patients with oral lichen planus, whereas Kim et al. reported a lower value (1,8,20,23). In summary, these data confirm that technological advances in dentistry are associated with increased oral exposure and diverse manifestations of Pd-induced ACD.

Diagnostic tests and Pd sensitization rates among OA patients: ACD toward metals can be reliably detected by laboratory tests, such as *in vivo* by patch testing (PT), and *in vitro* by lymphocyte transformation test (LTT) and MELISA (Memory Lymphocyte Immunostimulation Assay), including tests that evaluate the cytokine release by primary cultures of peripheral blood mononuclear cells (24,25). Observations for 96 hours, 7 days (or even later PT readings) are uncommon. However, the most frequent positive haptens are metals such as Au, Co, and Pd (26). PT sodium tetrachloropalladate (Na_2PdCl_4) and palladium dichloride ($PdCl_2$) enable the detection of Pd allergy (27).

Using metal allergens for PT, at least half of patients with OA responded positively to any metal (8,16,18,20,22). Hosoki et al. reported the highest rates, with over three-quarters of subjects manifesting a positive PT to one or more allergens (16). Dental alloys contained the positively tested metal element(s) in most patients with a positive reaction to any metal element in the PT (18). At least one-third to one-half of patients who underwent treatment to remove the metal experienced symptom improvement (18,20,23). Replacing restoration with a suitable material, such as a ceramic implant, can resolve these cases (9).

Based on diverse surveys, the PT positivity among OA subjects for most allergenic metals has rated as follows: Ni (22.5-51.6%), Cr (22.7-40.9%), Co (15.9-33.3%), Pd (14.8-50.5%), while other metals like Zinc (Zn), Mercury (Hg), Copper (Cu), Au, Ti, etc. have shown lower positivity rates (Table 1) (1,8,9,14,16,18,22,28-34). Similar findings about clinical aspects, increased metal allergy prevalence (including Pd sensitization), etc., are exhibited by dentistry patients who reported pathological symptoms after metal exposure, dental technicians, or patients with certain additional gastrointestinal disorders (29-32).

Table 1. Positivity rate of metal PT reagents in stomatology patients (1, 8, 9, 14, 16, 18, 22, 28-34)

Metal allergen	Concentration and vehicle	Positivity rate (%)
$PdCl_2/Na_2PdCl_4$	1/2% aq./pet.	6.8-50.5%
$NiSO_4$	2% aq.	22.5-51.6%
$K_2Cr_2O_7$	0.5% aq.	22.7-40.9%
$CoCl_2$	2% aq.	15.9-33.3%
$SnCl_4$	1% aq.	16.2-22.6%
$ZnCl_2$	2% pet.	10.8-13.8%
H_2PtCl_6	0.5% aq.	13.4-18.3%
$IrCl_4$	1% aq.	11.1-20.4%
$HAuCl_4$	0.2% aq.	8.1-17.2%
$HgCl_2$	0.05% aq.	4.5-17.2%
$FeCl_3$	2% aq.	3.4-4.3%

To be continued

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$TiCl_4$	0.1% aq.	2.7-6.8%
$CuSO_4$	2% aq.	3.1-5.1%
$InCl_3$	1% aq.	2.9-4.3%
Al_2O_3	2% aq.	0.6-2.2%
$MnCl_2$	2% pet.	0.4-1.1%
AgBr	2% pet.	0.0-0.1%

Legend: aq. - aqueous, pet. - petrolatum, PT - patch testing, AgBr - silver bromide, Al_2O_3 - aluminum oxide, $CoCl_2$ - cobalt chloride, $CuSO_4$ - copper sulfate, $FeCl_3$ - iron chloride, $HAuCl_4$ - chloroauric acid, H_2PtCl_6 - hydrogen hexachloroplatinic acid, $HgCl_2$ - mercury chloride, $InCl_3$ - indium chloride, $IrCl_4$ - iridium chloride, $K_2Cr_2O_7$ - potassium chromate, $MnCl_2$ - manganese chloride, $NiSO_4$ - nickel sulfate, $PdCl_2$ - palladium chloride, Na_2PdCl_4 - sodium tetrachloropalladate, $SnCl_4$ - tin chloride, $TiCl_4$ - titanium chloride, $ZnCl_2$ - zinc chloride.

In dental practice, MHRs to Ni and Pd are often observed in females following exposure to jewelry and piercings (14,18,28,33). This contingent exhibits higher PT positivity rates to many metals in subjects with an earlier MHR after exposure to pierced metals (33). More specifically, the inflamed piercing-exposed areas exhibit higher Ni alone or Ni-Pd co-positivity and relatively lower Pd-only one (6.5%). In contrast, OA subjects without inflammation at the piercing-exposed areas show a 2-fold higher rate of solely Pd positivity (12.8%) (Table 2). As long as analysis of pierced jewelry composition has revealed high Ni and low Pd levels, Pd sensitization may arise from cross-reactivity rather than direct exposure to piercings and earrings (33).

Meanwhile, the absence of an inflammatory response to this jewelry among several patients who were positive for Pd only can explain the reaction to Pd alloys, commonly used in fixed prosthetic structures. A previous ACD is also a risk factor for increased PT positivity among OA patients (16). Regarding the principal metal (Co, Cr, Ni, or Pd) salts, this index ranged from 33% (Co) to over 50% (Ni, Pd), thus higher than in patients without previous MHR. The presence of Au, Cu, Ag, and Hg in amalgam alloys explains the lower prevalence of positivity rates for the respective metals (33).

The LTT for commonly used metals in dentistry among OA patients who showed irritable bowel syndrome also revealed frequent sensitization to at least one metal, mostly Ni or Zn, followed by other metals, including Pd (31). Similar to PT positivity rates, the protein and gene expression levels of the human leukocyte antigen HLA-DR were significantly higher in Ni-Cr prosthesis subjects than in the other groups, followed by Cr-Co, Au, and Ti alloys (28). Cr, Ni, and to a lesser extent, Pd also exhibited a higher prevalence of allergy-positive reactions than other metals after intensive dental interventions (16). In contrast to Pd, Ti has shown lower ACD rates than Ni co-sensitizations only (16,18).

The cross-reactivity is conditioned by the structural molecular similarity between different compounds that can bind the same IgE antibodies or T lymphocytes sensitized to one of the culprit allergens (34). Consequently, the patient may develop allergic responses to other elements of the same group without prior sensitization. As mentioned, cross-reactivity between Pd and Ni is common among dental allergy patients (14,33). However, many patients are sensitized only to Pd, usually after the implantation of orthopedic devices (33). Liu et al. reported that up to 83.3% of Pd allergy subjects were allergic to Ni, while up to 47.6% of Ni-sensitized subjects were allergic to Pd (Table 2) (14). These results revealed that the proportion positive for both Pd and Ni salts was higher than that for any salt alone, and oral Pd exposure is more tolerable than Ni.

Pd sensitization rates among non-oral allergy patients in dentistry: The pre-implant PT is not routinely

Table 2. Estimations of the positivity rates for Pd reagents (1,8,9,14,16,18,22,28,33,35-42)

Contingent Type	Clinical Condition	Positivity rate (%)
General population	-	1.0-2.0%
Dentistry patients	OA	14.8-50.5%
Dentistry patients	No OA	14.8-24.9%
Dentistry patients	OA and previous MHR	34.0-50.5%
ACD patients	Any MHR	6.8-21.9%
Oral prosthesis patients	Pd positivity	83.3% (Ni)
Oral prosthesis patients	Ni positivity	47.6%
ACD patients	No Ni sensitization	8.2% (solely)
ACD patients	No other metal sensitization	1.4% (solely)
ACD (OA) patients	Piercing inflammation	6.5% (solely)
ACD (OA) patients	Piercing (no inflammation)	12.8% (solely)

Legend: ACD - allergic contact dermatitis, OA - oral allergy, MHR - metal hypersensitivity reaction, Ni - nickel, Pd - palladium, (solely) - positive response to Pd only.

recommended in patients with no MHR history, as a positive PT does not consistently predict in vivo metal-induced complications (13). Like oral symptoms, dermatological lesions following dental restoration and positive MHR history, however, need PT application, pre-implant examination, and combined metal element analysis of intra-oral restorations to identify the culprit allergen (16,18,43). As mentioned, installing dental restorations with other materials after removing the previous ones can fix the problem (9,43). Thus, minimal selective removal of intra-oral metal restorations by non-destructive, intra-oral metal element analysis can ameliorate allergic (cutaneous) symptoms (43).

As a significant clinical and public health problem, ACD to metals in the general population is less prevalent than in dental patients (35,36). As mentioned, the most common indications for evaluation referral have been those showing symptoms after implantation of a metal device and those with a history and concern of metal allergy before a metal device implantation (37). At least 40% of dentistry contingents with only skin allergy symptoms exhibited one or more positive PT reactions to a metal allergen, often to Ni, Co, Cr, etc. (33,35,37,38). Thus, according to How et al., PT revealed that three-quarters of patients (76.6%) with suspected ACD developed at least one positive reaction. Among ACD patients, the most frequently detected metal salt allergens were nickel sulfate (35.3%), potassium dichromate (16.5%), and cobalt chloride (10.2%) (38). As expected, several surveys reported similar epidemiological rates (33,35,37-39). Among them, Silva Belluco et al. observed a female dominance (83%), common hand affection (43%), and frequent occupational history (19%) (39). Regarding Pd, several studies have confirmed higher sensitization rates among healthcare workers and technicians compared to the general population, often associated with Ni (30,35,37,38,40). Their professional contact with Pd-containing objects is considered a possible occupational factor (40).

Apart from the mentioned metal salts, $PdCl_2$ or Na_2PdCl_4 exhibited relatively high metal sensitization rates in the extended diagnostic series. Thus, $PdCl_2$ (1% and 2%, respectively) tested positive among 7.6% and 10.8% of ACD-suspected patients (35,36,38,40). Among them, women aged 26-55 years showed higher values. However, few authors reported a more frequent Pd sensitization (up to 21.9%), predominantly among dentistry patients without OA symptoms that were tested for suspected ACD (37-39). Skin monosensitization occurred in 1-2% of the patients tested, and only 8.2% of patients sensitized to Pd were not co-sensitized to Ni (Table 2) (36,37,40). Regarding Pd polysensitization in the general population, Ni was the most relevant co-allergenic metal, mostly in females (35,37,39). According to González-Ruiz, the prevalence of sensitization to $PdCl_2$ (8.6%) among dermatology patients was higher than the prevalence of sensitization to potassium dichromate (6.5%), lower than the prevalence of sensitization to nickel sulphate (19.1%), and similar to the prevalence of sensitization to cobalt chloride (9.6%) (36). These data indicate that general Pd sensitization is more common than previously accepted, despite lower positivity rates than OA patients, especially those with an antecedent MHR (16,33,37).

Like other studied contingents, the salts of many metals (like Ti, Rhodium (Rh), Vanadium (V), Zn, Aluminum (Al), Indium (In), Iridium (Ir), Au, Tin (Sn), Cu, Molybdenum (Mb), Zirconium (Zr), Hg, Manganese (Mn), etc.) exhibit less frequently a PT positivity, predominantly as co-sensitization to Ni and a lesser extent Pd (16,18,32,33,37,42,44-46). There is evidence that invasive procedures, such as dental implants, arthroplasties, venous embolisms, and orthopedic surgery, have, in rare cases, led to sensitization to these haptens (13,16,18,32,42,46,47). According to Hosoki et al., patients with oral implants exhibited a higher $TiCl_4$ PT-positivity (25%) compared to those without implants (4.7%) (16). In contrast, pure metals, such as Ti, In, or Ir, did not cause such responses (16,45). A previous ACD history is a further risk factor for PT positivity to these metals in patients with metal implants, like orthopedic or plastic surgery (16). A study conducted by Haddad et al., enrolling 60 orthopedic surgery patients with and 40 without previous ACD, showed different positivity frequencies: for Ni (19/60 vs. 4/40) and Pd (10/60 vs. 4/40). Other metals, including Co, Au, Hg, Sn, Mb, Ti, or Cu, did not exhibit such discrepancies (42). Localized and generalized skin reactions have been associated with implant failure and loosening. These cases may require a custom-made solution, as no standard metal implant is free from certain elements, such as V in tibial prostheses (32,46).

According to EU medical legislation, manufacturers should comply with higher quality and safety standards for medical devices to meet appropriate safety concerns (4,33). Regarding metal products, the use of Pd has expanded after the Ni restriction in objects showing prolonged contact with the skin, to prevent contact allergy to Ni (40,41). In the general population, the prevalence of Ni allergy has nearly halved among younger subjects for both genders from the late 1990s to early 2010s: females from 33.4% to 19.1%; males from 5.9% to 2.1% (41). The Ni-Pd and Ni-Co concomitant reactions among young females also decreased significantly. In contrast, isolated Pd and Co allergy remained stable (1.4% and 2.3%, respectively) for both genders (41).

These data suggest that allergy to metals, including those not included in the standard series, like Pd, may be more prevalent than previously suspected, especially among high-risk subpopulations (37). Given the high prevalence of hypersensitivity to $PdCl_2$ (or Na_2PdCl_4), the baseline series should include a Pd salt, despite the frequency of Ni co-sensitization (36).

The literature emphasizes that many metals can damage human health. However, the Pd usually fulfills the stomatological biocompatibility demands (4). Understanding the alloy corrosion and allergy rates from dentists helps reduce the risk of allergic reactions. Therefore, the PT is recommended for hypersensitive patients, and caution is required when planning oral alloys and implants to help select dental metals for future prosthetic and orthodontic treatments (28,29). The PT confirmed Pd as a principal ACD-related

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allergen, detecting it more frequently among patients with oral diseases than on the skin, and as a cross-allergy with Ni (1,16,33). Meanwhile, some authors agree that adequate knowledge of MHR and ACD will be helpful for patients showing incurable eruptions, itching, or pain in the oral mucosa (16).

Immuno-Pathological Characteristics of Pd-Related Allergy

Immune response: Metal use in dentistry is associated with adverse reactions, including diverse MHR forms. Elicited after direct contact with skin or mucosa, these inflammatory conditions can be irritant or allergic. Clinical allergy symptoms include local skin rash, itching, redness, swelling, and lesions (24). Metal-related ACD is a delayed-type hypersensitivity reaction, characterized by lymphocyte recruitment in the sites of allergic inflammation (5,6,48).

Experimental PT applications in pig skin have shown that Pd ion concentrations in the viable skin were lower than those of Ni and Co (49). This indicates that Ni and Co ions penetrated the skin more efficiently than Pd, and thus may sensitize and elicit ACD more easily. The relatively inefficient ionic Pd skin penetration corresponds to the activation of a broader T-cell fraction *in vitro* than further allergenic metal ions (49). Thus, during ACD, lymphocyte recruitment expresses the effects of cytokines and allergen-specific CD4+ and CD8+ T cells on the affected tissue (5,6,24,48). A MELISA-related study revealed that Pd also induces strong lymphocytic proliferative responses in patients with oral or systemic symptoms, but not in similarly exposed unaffected subjects (25).

Meanwhile, studies on mice have shown that Pd-specific T cells responsible for ACD pathogenesis interfere with the antigen-presenting cells (APCs) developed during the sensitization phase, and fexofenadine hydrochloride significantly suppresses the quantity of these lymphocytes (50). Animal intraoral metal contact allergy models demonstrate that infiltrating T cells in Ni-sensitized, Pd-, or Cr-challenged mice express CD8, cytotoxic granules, and inflammation-related cytokines (11). This Pd-related model evidenced significant swelling and histologically pathological features five days after the challenge (17). The allergized oral mucosa (or other allergized tissues) revealed accumulation of CD3+ CD4+ T cells that produce high levels of T helper (Th)2 cytokines (17). Together with slightly increased Th2 cytokines, this model has later shown the induced expression of the CD25, interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, suggesting that CD4+ Th1 cells have locally expanded in response to Pd (48). Interestingly, histamine stimulation increased IFN-γ production by T

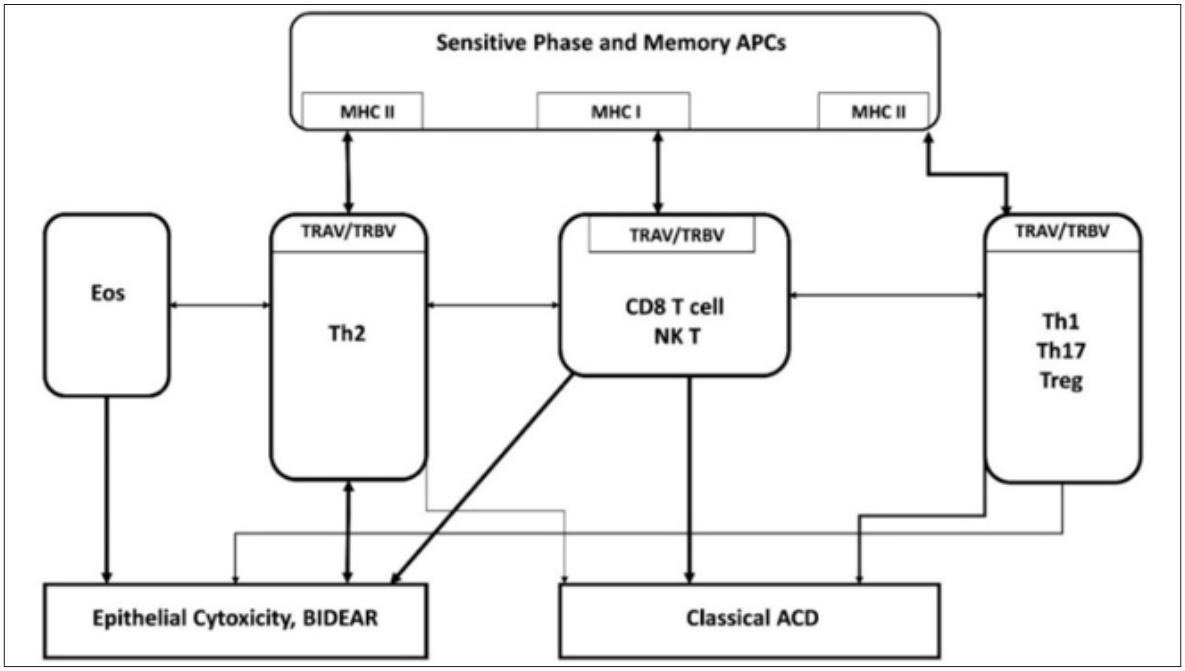


Figure 1. The immunopathology of metal hypersensitivity (2,4,5,6,11,12,15,17,19,24,31,32,48-51,55-62)
The MHRs to Pd involve different clonal and T cell fractions, in which their variable TCR regions TRAV and TRBV, in the CDR3, interact with the MHCs (CD8+ T and NK T cells with MHC class I and CD4+ ones with MHC class II) of APCs. The borderline epithelial allergen concentration usually leads to a classical ACD, in which CD8+ cytotoxic cells predominantly involve mononuclears, such as Th1, Th17, and Treg. A toxic allergen exposure (increased concentration, epithelial injury, etc.) can lead to or be promoted by a predominant Th2 response, additional eosinophil infiltration, and necrotic cytotoxicity (epithelial apoptosis, BIDEAR). Legend: APC - antigen-presenting cell, Th - T helper cell, Treg - T-regulatory cell, CD8 T cell - cytotoxic T lymphocyte, NK T - natural killer T cell, Eos - eosinophil, CD - claustrum of differentiation, BIDEAR - barrier integrity damage-elicited allergic response, MHC - major histocompatibility complex, TRAV and TRBV - α and β chains of variable CDR3 (complementarity-determining region 3) in the TCR (T-cell receptor). The arrow thickness corresponds to the influence levels.

lymphocytes, enhancing a specific synthesis in CD8+ T cells. The antihistamine olopatadine suppressed the CD8+ T-cell effect, inhibiting the tissue swelling in mice with Pd allergy (6). Additionally, an experimental nanoparticle treatment expressing superoxide dismutase and catalase activities significantly suppressed the expression of IFN-γ, IL-1β, and TNF-α genes in these animals (3). These models show that a Pd-specific T-cell population with mixed Th1/Th2-type response tendencies may be involved in the Pd-induced intraoral metal contact allergy (17,48). In this complex, the metallic allergen may interact with Toll-like receptor-4 on immune and non-immune cells, triggering a cascade of pro-inflammatory cytokines (51). Apart from Th1/Th2 cytokines, Th17 cells are involved in this process. Different therapeutic strategies that decrease IL-17 levels have been implicated to mitigate inflammatory-allergic reactions (51). Additionally, the simultaneous increase of IL-10 levels may restore the immune equilibrium between T regulatory and Th17 cells, acting as an anti-inflammatory cytokine (51-54).

At the center of the MHR lies the ability of a metal allergen to form T-cell epitopes recognized by specific T-cell receptors (TCR) (15). In this process, certain TCR chains play a dominant and critical role in the antigen specificity of Pd-induced Th1 cells (48). The TCR-characterization repertoire in Pd-allergic mice suggests that Pd-specific T-cell populations are limited in TCR V and J genes, with diversity at the clonal level (17). Technological advances, such as activation-induced marker assays and TCR high-throughput sequencing, recently provided new insights into the interaction of metallic allergens with the αβ TCR-peptide-major histocompatibility complex interface (15). More concretely, metal allergens, such as Pd and Ni, functionally bind and activate the TCR-specific TRAV (TCRα variable) and TRBV (TCRβ variable) gene sequences or histidine in the complementarity-determining region 3 (CDR3), the principal antigen-binding area (Figure 1) (15,19,48,55). Additionally, the infiltrated oligoclonal T cells in the allergized footpads and T-cell clones identified from Pd-injected mouse tissues frequently shared identical CDR3 sequences containing TRAV18-1 and TRBV8-2, compared with T cells in the lymph nodes (48). These findings reinforce the principal role of TCR in CD8+ T-cell interactions.

A mouse model of Ni and Cr-sensitized and Pd-challenged cross-reactive metal allergy developed spongiotic edema and intra- and peri-epithelial infiltration of CD4+ T cells in the inflamed skin, mimicking the natural ACD (55). The TCR analysis of allergic mice revealed that many T cells bear specific TRAV regions concerning mucosal invariant T and invariant natural killer (NK) T cells. These results indicate that the mentioned T cell subpopulations induce the development of Pd cross-reactive allergy, and that the related invariant mucosal-associated cells were also involved in the cross-reactivity between different metals (55).

The activated CD8+ T cells also stimulate the APC function, expressing specific TCR sequences as memory APCs in the recipient mice, thus developing Pd allergy through involvement of the major histocompatibility complex class I (MHC I) (19). As TCR of CD8+ T cells recognizes the MHC I/peptide complex, the antigen specificity to this complex seems to be generated during Pd allergy. In this process, the induction of Pd-responsive TCR-expressing T-cell line activation leads to a temporal MHC I internalization, suggesting that this process is critical for antigenicity generation through a mechanism that includes differential peptide loading on MHC I (5). These findings confirm that Pd allergy involves diverse T-cell fractions and mixed cytokine responses, including CD8+ and Th1 subtypes. Thus, the TCR variable parts of CDR3 regions in CD8+ T cells recognize the MHC I/peptide complex at the APC surface, activating the sensitization phase and memory APCs, or further inflammatory T cells (NK T, etc.).

The mucosal environment and immunology of toxic responses: The ability to avoid hypersensitivity or corrosive reactions in the oral cavity affects the longevity of dental alloys and implants (56). The mucosal damage includes delayed immune responses, epithelial corrosion, and toxic effects on local tissues. Thus, the comparative analysis of Ti, Pd-silver (Ag), and Ni-Cr cytotoxic effects on human gingival fibroblasts in saliva and Dulbecco's Modified Eagle medium (DMEM) after gingivectomy procedures revealed that only the pure Ti displayed no pathologic effect on fibroblast viability, which contrasted with Ni-Cr being the most cytotoxic (56). Meanwhile, Ag-Pd alloys exhibit acceptable corrosion resistance, which is inferior to that of Ti. The viability of fibroblasts in saliva was inferior to DMEM for all alloys, indicating that artificial saliva increased the cytotoxic effect of the tested alloys more than DMEM (56). During daily ionic exposure through vapor or corrosion, dental restorative metals, including Pd, release small amounts of material into the saliva, which develops an acidic environment. This can lead to frequent MHR, connective tissue diseases, or toxicity (57-59). Different metal ions, including Pd and the more biocompatible Ti ones, can react with halogens (such as dentifrice fluoride), generating acidic environments and increased corrosion too (16).

Inducing an intraoral cross-reaction, the parenteral stimulation in mice mimics the allergen exposure that follows epithelial denudation in humans, which is caused by local trauma or a corrosive environment (11,16,33,50). In such circumstances, direct contact between the metal and immune cells may also cause a cytotoxic response. Thus, animal intraoral metal contact allergy models that show postauricular intracutaneous cross-sensitization and oral mucosa challenge to Ni, Cr, and Pd disclosed that infiltrating CD8+ T cells express cytotoxic granules and inflammatory cytokines (11). A study among orthodontic patients detected Ni or Pd sensitization through the LTT, revealing that threshold levels of saliva ion concentration can induce the ACD-related response. In borderline sensitization cases, saliva ion concentrations were up to 20 times higher than the reference (60). The intense exposure of the immune cells to Pd on the connective tissue is observed in a woman with red-violaceous papulonodular lesions on the pierced ears. PT revealed a strong positive reaction to Pd and Ni, supporting the diagnosis of granulomatous contact dermatitis (63). Similar to this

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condition, pierced jewelry may pose a greater risk for Ni and Pd-related sensitization than other sorts because moisture, such as bodily fluids and sweat, can more easily release metal ions, especially if the skin around the pierced hole shows injured epithelium (33).

Despite the lack of an IL-18 increase by different metal salts (like Pd, Ti, or Ni ones) to detect the sensitization potential in an *in vitro* reconstructed human epidermis (RhE), a stratum corneum skin penetration was obtained after topical RhE exposure since EC50 values suggested a decrease in metabolic activity (4). PT-relevant Ni, Pd, and Ti salt concentrations elicited localized cytotoxicity, manifested as an epidermis separation at the basement membrane zone, formation of vacuoles, apoptotic nuclei, decreased metabolic activity, and (pro)inflammatory cytokine release (61). Nickel(II) sulfate hexahydrate, nickel(II) chloride hexahydrate, titanium(IV) bis(ammonium lactato) dihydroxide, and calcium titanate manifested significant cytotoxicity, whereas palladium(II) chloride, sodium tetrachloropalladate(II), titanium(IV) isopropoxide, and titanium(IV) dioxide showed mild one. **These data suggest that t**he PT can damage the patient's skin through toxic mechanisms, while the higher allergen concentrations may cause necrotic epidermolysis.

The oral ACD, especially to Ni and Pd, and aberrant inflammatory responses mediated by specific subsets of T cells have been observed through LTT in several ulcerative lesions of the gastrointestinal tract, like colitis and irritable bowel syndrome, suggesting an involvement of dental metal hypersensitivity in their pathogenesis (12,31). Also, a subject exhibiting oral ACD with lichenoid mucosal lesions adjacent to a bridge and crowns implanted several weeks previously, developed probably a painful contact-allergic gastritis (32). PT showed positive reactions to gold sodium thiosulfate, manganese(II) chloride, nickel(II) sulfate, palladium chloride, vanadium(III) chloride, or zirconium(IV) chloride. Meanwhile, the gastroscopy and histological analysis of stomach biopsies revealed ulcerative eosinophilic gastritis. Eosinophils can cause relative tissue lesions, which are also considered barrier destroyers (64,65).

Pd exposure can induce allergic reactions in different ways (2). Apart from reports concerning an increased eosinophil concentration in airways following nanoparticle exposure in vivo in rodent models of allergies and inflammation, an intracellular relocation of actin cytoskeleton is associated with an increase in eosinophil adhesion onto human endothelial EA.hy926 cells without eosinophil necrosis or apoptosis. These results show that Pd nanoparticles can target the cytoskeleton and induce the adhesion of human eosinophils by an actin-dependent mechanism (2). Exposing the 3D models to Pd nanoparticles induced increased secretion of IL-8; yet, the chronic bronchitis-like model released significantly more IL-8 than the traditional model. The levels of IL-8 in the basal medium and apical lavage medium were in the same range. However, the apical medium secreted significantly more matrix metalloproteinase (MMP-9) than the basal medium (66).

The development of spongiotic edema with intra- and peri-epithelial infiltration of helper CD4+ and cytotoxic CD8+ T cells in the inflamed skin, like in the human ACD, the development of Th2-response, like in immediate and respiratory allergies, the increased allergic inflammation around pierced jewelry, the oral ACD development at metal concentrations under the threshold levels, and the effect of antihistamines on CD8+ T-cell-induced effects, correlate with antitoxic IgE responses toward concentrated allergens in the connective tissue and the initiation of an allergic carrier by previously non-predisposed subjects (6,17,33,48-50,54,55,60,62,67,68). The development of allergies, following the increased allergen concentration in the subepithelial layer of altered epithelium, also supports the presence of the so-called BIDEAR (barrier integrity damage-elicited allergic response), which is observed in immediate and delayed allergy cases (54,67,68).

The recent findings confirm a complex interaction between different lymphocytic fractions, in which metal allergens, including Pd, bind and activate variable TCR gene regions that belong to CDR3 (5,6,15,17,19,24,48,55). Concerning metal-related OA, the TCR/MHC I complex interface between CD8+ T cytotoxic and APCs leads to sensitization and memory APC activation, including the involvement of NK T cells (11,55,69,70, 73, 74, 75). Apart from CD8+ T cells, the development of metal allergy involves diverse CD4+ cells, including Th1, Th2, Th17, and T regulatory ones, which interact with each other and APCs due to specific cytokines and MHC II (Figure 1) (6,17,48,51,55). The partially similar response to the immediate allergies (Th2 immune response, eosinophil infiltration), the experimental effectiveness of antihistamines, the increased exposure of immune cells in the subepithelial layers to concentrated allergens after epithelial damage or subcutaneous experimental allergen inoculation, the mucosal eosinophil-related inflammation of gastrointestinal mucosa, etc., support the idea that eosinophils act as barrier destroyers and that the cytotoxic and Th2-related response to a concentrated allergen could be considered a reaction to toxic exposure levels (64,65,67,68, 71,72, 76).

Conclusions and Future Directions

Playing a decisive role in restorative dentistry, Pd alloys cause MHRs more often than previously suspected. Pd allergy is more frequently detected among OA patients than other ACD subjects, especially females, because of exposure to piercing jewelry.

The ACD to Pd usually exhibits lichen planus, cheilitis, burning mouth syndrome, stomatitis or mucositis, and systemic dermatitis.

The Ni restriction did not reduce the incidence of Pd allergy, even among dentistry practitioners and technicians.

Diagnostic tests, including PT, should include Pd salts to detect a Pd allergy in patients with antecedent ACD, or when the (oral) allergic symptoms occur after restorative dentistry procedures. Longer-term observations are recommended in cases of susceptible MHR.

Most Pd sensitizations demonstrate cross-reactivity to

Ni. However, Pd-only cases usually show OA injuries but not ACD lesions in the skin exposed to metal jewelry.

The removal of culprit structures and replacement with suitable materials ameliorates the symptomatology and represents an appropriate solution.

Pd allergy is a delayed cellular allergic reaction that involves different T-cell fractions. The variable CDR3 region of TCR on the surface of CD8+ cytotoxic T cells recognizes the MHC I/peptide complex of APCs, affecting T-regulatory and a mixture of Th cells that recognize the MHC II.

The intensive metal exposure of immune cells during underlying epithelial damage or subepithelial antigen inoculation in animal experiments also leads to a Th2-like response, eosinophilic infiltration, and inflammation of the gastrointestinal mucosa.

Dentistry practitioners should be attentive when planning oral alloys and implants to select potential allergic metals for imperative prosthetic and orthodontic treatments.

The literature has documented several public health implications, emphasizing the principal role of prevention and management in Pd-related allergies. This includes the need for public education on the risks associated with dental prosthetic structures and pierced jewelry. Besides metals such as Ni, Cr, and Co, public awareness campaigns could inform individuals about potential allergic reactions to Pd salts. Moreover, directive adoption that restricts its release could significantly reduce the global incidence of Pd allergy. Such preventive measures could reduce clinical requirements and improve the welfare of at-risk individuals.

Author contributions

DM and AB validated the data and methodology, and helped as co-writers with relevant discussions. EÇM conceptualized the study, prepared the original draft, and supervised the revision. All authors accepted the text content.

Conflict of interest

Nothing to declare.

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