ORIGINAL ARTICLE

STANDARDIZED PATCH TESTING IN ORAL CONTACT ALLERGY: A NECESSARY FRAMEWORK FOR RELIABLE RESEARCH

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Abstract: (1) *Background*: Contact allergic sensitization to dental materials is an underdiagnosed cause of oral mucosal disease. A lack of a standardized patch testing protocol leads to significant heterogeneity across studies, making it impossible to determine the true prevalence of these sensitizations. (2) *Methods*: We propose a standardized methodological framework for prospective multicenter research, updating our previously proposed short patch test series in line with current international guidelines. (3) *Results*: A practical, concise series of contact haptens is presented, along with a uniform testing protocol, chamber specifications, a reading schedule, and detailed criteria for interpreting reactions. (4) *Conclusions*: The adoption of a standardized methodology is necessary for generating reliable, comparable, and aggregable epidemiological data on contact allergy to dental materials in the Romanian population.

Keywords: dental materials, allergy, patch testing

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1. Introduction

There is a growing number of patients experiencing suspected delayed-type hypersensitivity reactions in the oral cavity, which coincides with the increasing complexity of dental materials and oral hygiene products. The most common manifestations include: oral lichenoid lesions, burning mouth syndrome, gingivitis, allergic contact stomatitis, recurrent aphthous stomatitis, cheilitis, perioral dermatitis, and orofacial granulomatosis. Clinical manifestations of such oral contact hypersensitivity are polymorphic and frequently mimic idiopathic or systemic mucosal diseases. Differential diagnosis is challenging and requires detailed history, patch testing, and elimination of suspected materials [1-4].

While patch testing is considered the gold standard for diagnosis, the lack of standardized methods leads to inconsistent data that cannot be effectively compared or combined across medical centers [5-7].

This article proposes a unified methodological framework for patch testing in patients suspected of having oral contact allergies. The primary goal is to facilitate reliable multicenter research and to accurately determine the prevalence of contact sensitization to dental materials and oral products in the Romanian population.

2. Materials and method

Based on a comprehensive review of the biomedical literature spanning several decades, our previously published study proposed a shortened series of screening patch tests specifically designed for patients suspected of having oral contact allergies to dental rehabilitation materials. The goal was to promote clinical sustainability and reduce the costs associated with extensive or occupational patch testing by focusing on the most prevalent and clinically relevant hapten categories. This optimized diagnostic panel was organized into major groups: metals, acrylates, epoxy resins, and odorant constituents. We aimed to improve diagnostic efficiency by eliminating rare, highly cross-reactive, or potentially toxic haptens, and by excluding unnecessary controls such as white petrolatum and the skin irritant sodium lauryl sulfate. This proposed series was designed to ensure a high pick-up rate for common dental allergen hypersensitivities [1].

According to current European guidelines, patch testing should preferably be performed on the upper back, with the outer surface of the upper arms being an acceptable alternative. Occlusion time is 48 hours, and readings are mandatory at D2 (48 h) and D3/D4 (72 h/96 h), with an optional late reading after 1 week (D8–D10) for some metals such as gold and acrylates.

The most commonly recommended chambers in modern European and international guidelines for patch testing in dental research are manually loaded square/rectangular inert plastic chambers with an inner test area of 0.64 cm^2 and round plastic or aluminum chambers with an inner test area of 0.5 cm^2, placed on hypoallergenic adhesive backing tapes. Using preloadable, patented, inert, quadrate unit chambers made of soft polyethylene foam, with integrated filter papers, mounted on premium-quality, biocompatible, aluminum-free, hypoallergenic, low-irritation carrier tape that allows moisture vapor transmission and

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provides adhesion and removal with minimal skin trauma and little to no adhesive residue, is comfortable and reliable for closed-patch testing that clearly defines the test area facilitating differentiation between allergic and irritant reactions, and helps prevent leakage. The recommended petrolatum dose for such a chamber is about 25 mg (40 mg/cm²) obtained from a thin 5 mm cylinder from the 5 mL pre-filled syringe [6-9].

All reactions should be interpreted according to the recently updated morphological criteria from the International Contact Dermatitis Research Group (ICDRG). The ICDRG introduced its first patch test classification in the 1970s, which was revised a decade later after many weak reactions were misclassified as allergic. However, allergists and dermatologists still struggle to consistently distinguish between weak allergic reactions and doubtful reactions. To address these inconsistencies and reduce discrepancies in expert readings, a new ICDRG classification has been developed very recently. This updated system provides clearer definitions to account for the unavoidable differences in how individuals interpret patch tests [10].

3. Results

An updated, proposed short series of the most relevant 14 topical haptens for dental practice is presented in Table 1 to support a standardized, multicenter research approach to oral contact allergy, a form of delayed-type hypersensitivity resulting from a specific T-cell-mediated immune response to low-molecular-weight compounds. In contrast to complete allergens (such as pollen or animal proteins) that can independently elicit an immune response in other forms of allergy, haptens are not immunogenic on their own. These small, chemically reactive molecules must penetrate the stratum corneum and bind to epidermal and dermal proteins, thereby forming hapten–carrier protein complexes that acquire antigenic properties and can induce contact hypersensitivity and allergy [1,8].

The most common haptens implicated in dental contact allergy originate primarily from two major categories of dental materials. The first category comprises metals released from casting alloys used in inlays, crowns, bridges, dentures, and dental amalgam. The second category includes organic compounds, notably methacrylate monomers present in composite resins, dentin bonding agents, and provisional restorations, as well as epoxy resins incorporated in root canal sealers. Additional clinically relevant haptens are fragrance-related ones derived from various other dental materials, including provisional restorative materials, periodontal dressings, and impression materials, as well as flavoring haptens found in oral hygiene products such as toothpastes, mouthwashes, and dental gels. These substances are the predominant sources of exposure that cause contact sensitization in patients undergoing oral rehabilitation [1,4,8].

Despite being the gold standard for diagnosing contact allergy, interpretation of patch test reactions remains subjective, relying heavily on visual assessment and palpation. The interpretation must be performed in accordance with the updated ICDRG classification and current European best-practice recommendations [6,7,10-12].

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Table 1. Updated proposal for a short patch test series in dental research on oral contact hypersensitivities.

Hapten group	Contact hapten for patch testing	Concentration*
Metals in casting alloys for inlays, crowns, bridges, dentures, and dental amalgam	Nickel (II) sulfate hexahydrate	5% pet
	Cobalt (II) chloride hexahydrate	1% pet
	Potassium dichromate	0.5% pet
	Gold (I) sodium thiosulfate dihydrate	2% pet
	Sodium tetrachloropalladate (II) hydrate	3% pet
	Mercury (II) amidochloride	1% pet
Methacrylates in dental composite resins, dentin bonding agents, prosthetic materials, and epoxy resin in root canal sealants	2-Hydroxyethyl methacrylate (HEMA)	2% pet
	Bisphenol A glycerolate dimethacrylate (Bis-GMA)	2% pet
	Epoxy resin of bisphenol A	1% pet
Fragrance-related haptens in provisional restorative materials, root canal sealers, and periodontal dressings	Eugenol	2% pet
	Myroxylon pereirae resin (Balsam of Peru)	25% pet
	Colophonium (Colophony)	20% pet
Flavoring haptens in oral hygiene products such as toothpastes, mouthwashes, dental gels	Carvone (R-carvone)	5% pet
	Propolis	10% pet

* Vehicle: pet = petrolatum

Table 2. Updated interpretation of patch test reactions [6, 10].

Skin reaction	Definition
Negative (–)	No visible reaction in the test chamber area (no visible morphology) or a reaction hardly discernible from the surrounding skin morphology as background noise
Irritant (IR)	Typical rapid decrescendo pattern (marked improvement or resolution after unit removal); Various morphological features, depending on the chemical nature of the irritant, its concentration, duration of exposure, and individual skin susceptibility, including: mild to moderate: dry or shiny skin, scaling, cigarette-paper wrinkling or silky texture, soap effect, discrete patchy or follicular macular erythema; localized: demarcated "edge effect" with no infiltration or "ring effect"; inflammatory/vascular/poral: petechiae, follicular pustules, punctate deposits; severe toxic*: bullae/large blisters, erosions, crusts, or, rarely, necrosis
Doubtful (+?)	Presence of erythema and/or infiltration and/or papules and/or vesicles exceeding (2 times more intense) the surrounding skin morphology as background noise, but without fulfilling the minimum criteria to be classified as an allergic reaction
Weak allergic (+)	Erythema and infiltration covering the whole test area, possibly leaving a rim due to chamber pressure, possibly a few papules
Moderate allergic (++)	Erythema and infiltration with many papules (always more than a few) covering the whole test area, possibly a few vesicles
Strong allergic (+++)	Erythema and infiltration with many vesicles (always more than a few) (sometimes coalescing, sometimes bullae) covering the whole test area (sometimes extending outside the test area, but gradually fading), possibly a few papules**
Presently unclassifiable reaction (PUR)	Extremely strong reaction covering more than one test area, making it impossible to establish/rule out contact allergy to a specific contact sensitizer; Can be considered a localized "angry back" ("excited skin syndrome").

*When patch testing insufficiently known chemicals, a strong irritant reaction can mask an underlying co-existing contact allergy.
**Pustules and erosions may occasionally be part of strong allergic reactions and as a stage of evolution of bullous reaction.

Skin reactions in patch testing are classified according to a standardized morphological system. The main categories include: negative reaction (–), irritant reaction (IR), doubtful reaction (?+), weak allergic reaction (+), moderate allergic reaction (++),

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strong allergic reaction (+++), and presently unclassifiable reaction (PUR). This classification, based on the updated ICDRG criteria, enables consistent and reproducible interpretation of patch test results by evaluating the presence, intensity, and extent of erythema, infiltration, papules, vesicles, and bullae, as well as specific irritative features such as the demarcated edge effect or decrescendo pattern.

The detailed morphological criteria for negative, irritant, doubtful, and allergic reactions of varying intensity are presented in Table 2.

A printed reading plate designated for the inert quadrate patch units may facilitate visual interpretation of the skin reactions [8], but does not substitute for specialist expertise. Noninvasive imaging technologies, including dermatoscopy (dermoscopy), ultrasonography, thermography, optical coherence tomography, reflectance confocal microscopy, and 3D imaging systems, offer promising alternatives to traditional visual grading by enabling objective assessment of patch test reactions, but are not internationally clinically validated [12, 13].

4. Discussion

Epicutaneous patch testing is the gold standard in vivo method for diagnosing delayed-type hypersensitivity to contact haptens, including those present in dental materials and oral hygiene products. Its high diagnostic value lies in the direct visualization of the immune response in the skin under controlled conditions, making it the most reliable and widely validated technique currently available. There is a need for ongoing allergen surveillance, periodic review, and updates to patch test series to enhance diagnostic accuracy and patient care [1, 6, 7, 14].

Metals in the proposed short screening series for patch testing are selected from the dental materials for patient series, with nickel, cobalt, and chromium as essential components. The main dental sources include nickel in alloys used for crowns, bridges, partial dentures, orthodontic wires, and some clasps; cobalt in non-precious dental alloys and certain porcelain-fused-to-metal restorations; and chromium in dental casting alloys, some cements, and impression materials. These metals are among the most frequent sensitizers in patients with dental restorations and are still widely present in a broad range of non-precious and semi-precious dental alloys used in daily practice [1, 4, 15, 16].

Although the use of dental amalgam has been prohibited in the European Union as of 1 January 2025 [Regulation EU 2024/1849], many patients still have old amalgam restorations. Therefore, patch testing for mercury remains relevant in the diagnostic screening of patients with suspected oral contact allergy, at least in the coming years [1, 4, 17, 18]. Even though a few dental alloys continue to contain gold and palladium, patch testing with gold as sodium thiosulfate and palladium as sodium tetrachloropalladate remains necessary for screening patients with suspected oral contact allergy, given the high frequency of positive reactions and the demonstrated clinical relevance in the literature [1, 4, 19, 20].

Titanium and zirconium compounds were deliberately excluded from the proposed short screening series. Although titanium dental implants and zirconia restorations are widely

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used, true contact sensitization to these materials is considered extremely rare. Moreover, patch testing with currently available preparations demonstrates low sensitivity and often questionable clinical relevance. Therefore, patch testing with zirconium (IV) chloride 1% pet, titanium (III) nitride, and titanium (IV) oxalate hydrate 5% pet should be reserved for carefully selected patients with unexplained implant failure or a strong clinical suspicion of hypersensitivity [21-25].

2-Hydroxyethyl methacrylate (HEMA), Bis-GMA (bisphenol A glycerolate dimethacrylate), and epoxy resin based on bisphenol A, also known as diglycidyl ether of bisphenol A (DGEBA), are significant methacrylate and epoxy haptens commonly found positive when patch testing with the dental materials for patient series. HEMA is one of the most prevalent sensitizers among dental acrylates. Owing to its high water solubility and hydrophilic nature, HEMA is frequently incorporated into dentin bonding agents as a key component in almost all modern dentin adhesives (both etch-and-rinse and self-etch systems). It is also deliberately added to many composite resins as a diluent monomer in flowable, universal, and some conventional composites because it reduces viscosity and improves wettability. It is also frequently found in provisional composites, crown-and-bridge resins, and some temporary cements due to its good handling properties and polymerization characteristics. When used as a standalone aliphatic monomethacrylate monomer screening marker, HEMA detects more than 90% of patients with acrylate allergies. Bis-GMA is the primary aromatic dimethacrylate monomer in most dental composite resins and is a common hapten in patients who react to tooth-colored fillings, bonding agents, and sealants. When Bis-GMA is added to HEMA, the diagnostic rate for dental acrylate allergy reaches 100%. DGEBA is present in root canal sealers, some bonding agents, and various epoxy-based dental materials. It is considered a classic contact hapten, even though direct exposure is generally lower than that of acrylates. Although there is significant cross-reactivity and frequent concurrent sensitization between Bis-GMA and DGEBA, including both haptens in a short screening series is justified to increase diagnostic sensitivity [1, 26-28].

Eugenol, Myroxylon pereirae resin (commonly known as Balsam of Peru), and colophonium are among the most significant fragrance-related and natural resin haptens found in dental materials. Eugenol is the primary phenylpropanoid found in clove oil and serves as a key component in zinc oxide-eugenol cements. It is utilized in temporary fillings, cavity bases/liners, and temporary cements due to its sealing, analgesic, anti-inflammatory, and antibacterial properties. Balsam of Peru, a natural aromatic resin derived from the bark of the Myroxylon pereirae tree, has historically been included in some dental cements, cavity varnishes, impression materials, and periodontal dressings. It is sometimes used in medicated dental products for its healing properties and mild antiseptic effects. Colophonium, also referred to as colophony or rosin, is a natural resin extracted from the sap of coniferous trees, primarily pine. It is added to fluoride varnishes to enhance adhesion to enamel and is used in periodontal dressings, surgical

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packs, and various dental materials, including cements, cavity varnishes, impression materials, and root canal sealers. Colophonium is valued for its excellent adhesive and sealing capabilities, as well as its ability to form a protective film. Eugenol, Balsam of Peru, and colophonium constitute important contact sensitizers in patients with oral mucosal reactions and are established components of dental materials for patient series, thereby substantially enhancing the diagnostic yield of the proposed short series [1, 29-31].

Carvone and propolis were also included as the relevant flavoring haptens from oral hygiene products. These substances are frequently responsible for allergic contact reactions to toothpastes, mouthwashes, and dental gels. R-carvone, a key component of spearmint flavorings, is one of the most common sensitizers in this group with strong clinical relevance, while propolis, a natural bee product used in some dental formulations, frequently elicits positive patch test reactions, also with clear relevance [1, 32, 33].

The proposed standardized patch testing framework described above addresses current limitations in dental research on contact allergy to dental materials in Romania and provides a practical, cost-effective tool for generating comparable national data.

Patch testing is currently the best method for assessing suspected hypersensitivity reactions to dental materials and oral products in vivo. The lymphocyte transformation test (LTT) is rarely used as an in vitro alternative in selected cases. LTT involves isolation of peripheral blood mononuclear cells (PBMCs), culture in the presence of the suspected allergen/antigen (at non-toxic concentrations and an optimal lymphocyte-to-antigen ratio), and measurement of lymphocyte proliferation by tritiated thymidine incorporation after day 5. Test specificity is increased by the prior addition of 5% autologous serum and recombinant interferon alpha-2b. Results are expressed as stimulation index (SI). A SI value greater than 3 indicates definite sensitization, SI 2–3 is borderline positive, and SI < 2 is negative. Negative and positive controls (mitogenic and antigenic) are essential for validity. LTT combination profile dental check includes metals: gold, nickel, palladium, chromium, cobalt, platinum, mercury, copper, silver, tin, and acrylates: methyl methacrylate (MMA), HEMA, triethylene glycol dimethacrylate (TEGDMA), and Bis-GMA. LTT root canal filling materials includes: raw gutta-percha, Balsam of Peru, eugenol, polydimethylsiloxane (PDMS), silicone oil, bismuth oxide, and turpentine oil, colophony, triethanolamine, peanut oil, paraformaldehyde, bisphenol A, epichlorohydrin, while LTT endoprosthetics: chromium, cobalt, molybdenum, nickel, titanium, vanadium, niobium, aluminum, zirconium (IV) oxide, methyl methacrylate, N,N'-dimethyl-p-toluidine, benzoyl peroxide, hydroquinone, gentamicin. However, LTT is significantly more expensive, technically demanding, and involves the use of radioactive tritiated thymidine, which limits its routine application in large-scale epidemiological studies [34-36].

5. Conclusions

The implementation of a standardized patch testing methodology represents an important advancement in the research on contact sensitization to dental materials in Romania.

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We kindly propose the nationwide approach of such a protocol, along with an updated mini-series of haptens, as a foundational step for future multicenter studies. This will facilitate a better understanding of the true prevalence of sensitization in our population and improve patient care.

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