

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.intl.elsevierhealth.com/journals/dema

Five hundred patients reporting on adverse effects from dental materials: Frequencies, complaints, symptoms, allergies

Pauline Mittermüller^a, Karl-Anton Hiller^{a,*}, Gottfried Schmalz^{a,b},
Wolfgang Buchalla^a

^a University of Regensburg Medical Center, Department of Conservative Dentistry and Periodontology, 93042 Regensburg, Germany

^b University of Bern, Department of Preventive, Restorative and Pediatric Dentistry, Bern, Switzerland

ARTICLE INFO

Article history:

Received 23 April 2018

Received in revised form

21 September 2018

Accepted 22 September 2018

Available online xxx

Keywords:

Adverse effects

Dental materials

Complaints

Symptoms

Allergy

Patch test

Stomatognathic diseases

Burning mouth

Lichenoid eruptions

Gingivitis

ABSTRACT

Objective. Information on patients with real or claimed adverse reactions towards dental materials in large patient cohorts is rare. Therefore, the aim of the present study was to investigate patients reporting on complaints and symptoms to dental materials over a 16-year period.

Methods. Five hundred patients were characterized by one single dental team regarding age and sex distribution, subjective complaints and objective intraoral symptoms, and allergy status relevant to dental materials.

Results. Elder patients and females predominated. Subjective complaints were reported by 490 patients, ranging from 1 to 12 complaints per patient. Most often, burning mouth (44%), tooth-/jawache (22%) and dry mouth (20%) were reported. In 54% no objective intraoral symptom was diagnosed. The main objective intraoral symptoms were tongue anomalies (lingua plicata or geographica; 14%), gingivitis adjacent to restorations (12%), redness of the palate or the edentulous ridge (7%), oral lichen planus (6%), grayish discolorations, lichenoid contact lesions, and leukoplakia (<5%). Patch testing of 416 (83%) patients revealed that allergy was diagnosed as contributing to the complaints or symptoms in 70 (14%) patients with metals being the most frequent allergens. Gingivitis adjacent to restorations (3.2%), redness of the palate or edentulous ridge (1.4%) and whitish lichen-like lesions (1.8%) were associated to allergy from dental materials.

Significance. The high number of subjective complaints per patient and their wide variety suggests that most patients seriously suffered. Furthermore, the fact that only 46% of the patients had objective intraoral symptoms demands for an interdisciplinary collaboration to elucidate other than dental causes.

© 2018 The Academy of Dental Materials. Published by Elsevier Inc. All rights reserved.

1. Introduction

A wide variety of dental materials is being used in dentistry in order to treat dental diseases and to meet the demands of the patients. Most of these materials are intended for long-term

* Corresponding author.

E-mail address: karl-anton.hiller@ukr.de (K.-A. Hiller).

<https://doi.org/10.1016/j.dental.2018.09.012>

0109-5641/© 2018 The Academy of Dental Materials. Published by Elsevier Inc. All rights reserved.

intraoral use. Inevitably, in some cases adverse reactions have been claimed to be caused by these materials.

A commonly named reason for material related complaints are allergies. Many studies or reviews on allergies to dental materials and their frequency are available in the literature. Metals are the most often diagnosed allergens. Among the allergies to acrylates, 2-hydroxyethyl methacrylate was found most frequently. It was concluded that allergy is a recognized, but rare cause for adverse effects [4,11,27–29,36,41,48,58]. These data are mainly derived from single case reports, from dermatological studies, or from studies with small number of patients [4,28,29,48,58].

There are plenty of other studies available directed to a broader and more descriptive approach. Studies with larger patient numbers report mostly on amalgam related adverse effects [32,34,59]. Data of adverse effects from dental materials are available for up to 206 [48], 253 [34], or 331 [58] patients. Information on material related adverse effects not focussing on amalgam in larger cohorts from clinical studies is lacking [53]. A larger number of participants are reported for questionnaire studies, in which, however, the patients themselves were not clinically investigated. The UK national survey of adverse reactions evaluated 1075 questionnaires [55]. Most patient related adverse reactions were reported to be due to metals, mainly amalgam associated oral lichenoid reactions.

Literature data on the prevalence of adverse clinical reactions to dental materials suggest that the frequency is low [16,24,53]. According to Kallus and Mjör [24] 46 cases with suspected adverse effects out of 13,325 (0.35%) patients were reported. Hensten-Pettersen and Jacobsen [16] estimated the frequency of adverse effects to be 1:300 in prosthodontic patients. Jacobsen and Hensten-Pettersen reported on 1% adverse patient reactions in orthodontics [21] and on one case every other year per periodontist [22]. Furthermore, it is often difficult to prove that the patient's complaints or symptoms are caused by the suspected dental material [36]. Therefore, it can be assumed that one reason for the low patient numbers of clinical studies in this field may be the fact that these reactions apparently occur rather seldom. A further reason may be the wide variety of different dental materials available due to the demands of modern dentistry. Finally, the lack of knowledge of the composition of the dental materials used is an additional problem; e.g. for the necessary individual adaptation of an allergy test the suspected allergens need to be known.

A classical way to compensate for low numbers of participants in clinical studies is the combination of data from different studies, e.g. in the format of a meta-analysis. However, this is problematic with the available reports, because different clinical studies have been conducted by different clinicians with possibly different approaches to diagnosis or the allocation of further examinations like allergy tests. For example, it is not generally accepted, when patch testing for verifying an allergy is indicated. Thus a single centre study with a larger number of participants but using the same standardized methods for anamnesis and clinical examination was deemed necessary.

In our Department we performed from 1995 to 1997 a government-funded study (Federal Ministry for Health, Germany) with patients complaining about adverse effects from dental alloys, except for amalgams. All dentists in the

region of Eastern Bavaria with about 1 million inhabitants had been informed and asked to refer patients with such complaints to the Department of Conservative Dentistry and Periodontology of the University of Regensburg Medical Center, Regensburg [11]. In this group of 86 patients wearing metal restorations except amalgams, in less than 10% of the patients a metal allergy was the reason for observed adverse effects. Patients also often reported or claimed on materials related complaints, which may be induced by other factors like medication or illness. As a consequence, the treatment of patients with complaints allegedly attributed to dental materials was regarded as a challenge in dental practice.

Based on these experiences, a specialized doctor's consultation hour expanding to patients with suspected adverse effects from all dental materials was installed for referred patients and those coming on their own initiative. The dentist primarily in charge of these patients (PM, formerly P Garhammer) and her dental assistant did not change over the whole period of time, which we consider to be an important aspect of this study. This examiner thus has a more than 20 years of clinical experience in such examinations and diagnoses.

Therefore, the aim of this study was to analyse a large cohort of 500 patients (examined and diagnosed from 1998 to 2015 by the same team) regarding age and sex distribution, type of subjective complaints or objective intraoral symptoms, and allergy status relevant to dental materials. Regarding the large patient number, it was further expected to be able to more reliably relate different complaints or symptoms to the presence of an allergy.

2. Materials and methods

All patients visiting our specialized consultation hour for suspected adverse effects from dental materials between end of 1998 and beginning of 2015 were included into this study. These 500 patients came on their own initiative, or they were referred to by dentists or physicians from the region of Eastern Bavaria with about one million inhabitants. No further in- or exclusion criteria were applied.

2.1. Clinical examination

Standardized anamnesis questionnaires and clinical examination procedures, based on the study from 1995 to 1998, were used [11]. First, general (general health) and specific (oral health) anamneses were taken, including information on type, location, time of appearance and duration of the subjective complaints. Second, thorough extraoral and intraoral examinations, including dental status, periodontal status, and descriptive status of the oral mucosa were performed. Photo documentations, X-ray-examinations, mainly orthopantomograms and dental films, were performed according to the individual medical indication. The general oral hygiene was determined using the Papilla Bleeding Index (PBI) according to Saxer and Mühlemann [52] with scores 0 (no bleeding), 1 (a single discrete bleeding point), 2 (several isolated bleeding points or a single line of blood appears), 3 (the interdental triangle fills with blood shortly after probing), and 4 (profuse bleeding occurs after probing, blood flows immediately

into the marginal sulcus). From these scores the proportion of affected sites was calculated and expressed as percentage. To reduce the effects of bacteria as causes of gingivitis adjacent to crowns or double crowns, a professional plaque removal and rinsing with chlorhexidine was performed in the practice of the referring dentist or in our Department at least one week prior to the examinations. All clinical examinations and assessments were performed by one clinically experienced dentist (PM) and her dental assistant.

2.2. Allergy test

Allergy testing was carried out by means of patch testing, if delayed (type IV) allergy reactions were clinically suspected [8]. If the patient agreed, allergy testing was performed at the Department of Dermatology, University of Regensburg Medical Center. The European standard series and series being relevant to dentistry, e.g. metal compounds and acrylates, were fixed with the Hayes Test Chamber N (HAL Allergie, Düsseldorf, Germany; Hermal, Hamburg, Germany; Almirall Hermal, Reinbek, Germany) at the upper back of the patient. Additionally, in some cases allergy testing with small discs or honed chips of suspected specific dental materials in petrolatum was performed individually; e.g. if the patient provided us with such specimen taken by the referring dentist and testing of these specimens was requested. Depending on their size, these samples were fixed at the upper back using the above mentioned test chamber or individually shaped plaster. Sharp edges were rounded off to avoid skin injuries. Only patch test reactions relevant to dental materials were considered for evaluation.

Forty-eight hours after application, the different materials and test compounds were removed, and the skin reactions were read and classified according to the recommendations of the "German Dermatologic Society (Deutsche Dermatologische Gesellschaft, DDG) and the German Society for Allergy and Clinical Immunology (Deutsche Gesellschaft für Allergie und klinische Immunologie, DGAKI)" [8]. On the third day after the beginning of the patch test, the skin was evaluated again. Additionally, few late readings after seven days were performed according to the recommendations of the DDG and DGAKI (e.g. if no decision could be made whether it was an allergic or an irritant reaction at earlier readings) [8].

If patients were not able to visit the Department of Dermatology of the University of Regensburg Medical Center for allergy testing (e.g. due to long travel distances to Regensburg), an equivalent allergy testing using the same procedures was arranged by an allergist nearby the hometown of the patient. The allergist was provided by us with detailed information concerning the materials to be tested. Allergy testing was not performed, if the patient submitted a complete test record of recent allergy testing.

The clinical relevance of an allergen being a component of the dental restoration of a patient was rated as "no", "presumable" and "yes". An allergen was defined to be clinically relevant, if the allergen was a component of the suspected dental restoration, and if there was a clear coincidence of the localization or the time of insertion of the restoration and the manifestation of the symptoms [11,46]. A presumable relevance was defined as high clinical evidence, but an individual

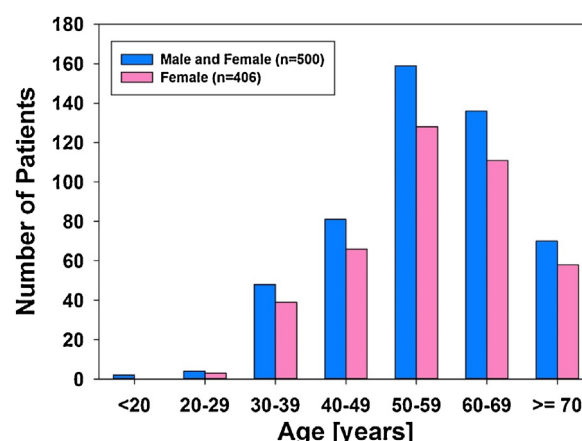


Fig. 1 – Age and sex distribution of the 500 patients.

proof was lacking, e.g. standard denture acrylates contain benzoyl peroxide, but the exact brand and components were not known.

2.3. Statistical analysis

Information on the anamnesis, subjective complaints, objective intraoral symptoms, and patch tests are descriptively presented as frequency tables. Data on the PBI are given as medians with respective 25th and 75th percentiles. Data of this study were retrospectively retrieved and processed completely anonymized. Allocation of data to patients' identity was not possible. Therefore, approval of the institutional review board was not required.

3. Results

3.1. Number of patients, age and sex distribution, general oral hygiene

Out of the 500 patients, 406 were female and 94 male. Patients in the age group from 50 to 59 years predominated. In each age group were more female than male patients, except for patients younger than 20 years (Fig. 1). The PBI could be determined in 470 out of 500 patients. In 30 patients the PBI could not be measured because the patients were edentulous, or they refused the measurement, or diseases (e.g. valvular transplant) argued against the measurement without antibiotic medication. The median PBI was 41.7% (quartiles 31.0–53.0%; Fig. 2).

3.2. Subjective complaints

No subjective complaint was reported by 2% (n=10) of the 500 patients, e.g. because the complaints had abated after the appointment had been made. The results on the frequency of 40 subjective complaints reported by 10 (2%) or more patients are presented in Table 1. Multiple entries per patient were possible. A wide variety of subjective complaints was reported, including local symptoms in the oral cavity like gingivitis, as well as more general symptoms like weak-

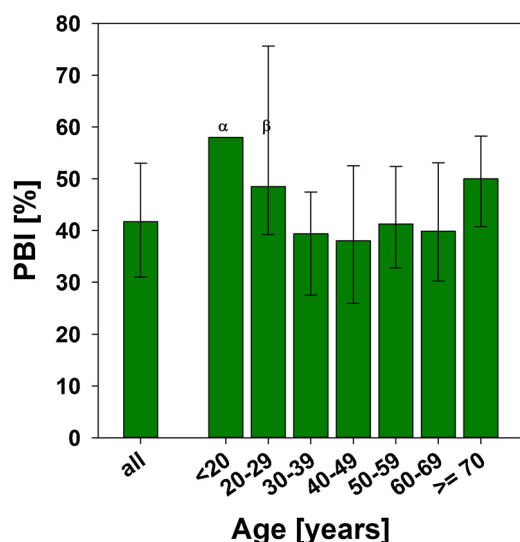


Fig. 2 – PBI [%] of all patients, and categorized by 10 year age groups. $\alpha \sim n = 1$, $\beta \sim n = 4$.

ness. In detail, burning mouth (43.6%), tooth-/jawache (21.8%) and dry mouth (20.0%) were mentioned most often. No routinely laboratory tests were performed for diagnosis of burning mouth in the present study. In this sense, our definition of burning mouth includes the burning mouth syndrome, but is broader. More than 10% of the patients complained of gingivitis, metal taste and paraesthesia like tingling/numbness. The list of subjective complaints reported by less than 2% of the patients comprises 102 entries, e.g. dizziness, hair loss, loss of appetite, aphtous stomatitis, forgetfulness, and poor wound healing.

Most of the patients reported several subjective complaints. The frequency distribution of the number of subjective complaints reported per patient (Fig. 3) shows that most patients had two (24.4%), three (19.2%) or four (18.0%) subjective complaints. Overall, 12% of the patients had one and 86% had two or more subjective complaints.

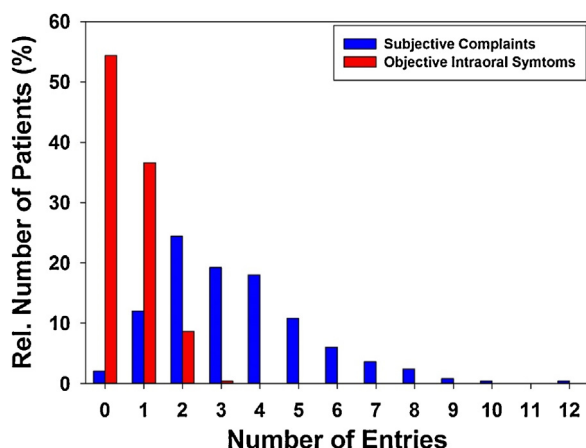


Fig. 3 – Frequency distribution (100% = 500 patients) of the number of subjective complaints and objective intraoral symptoms.

Table 1 – Subjective complaints reported by the 500 patients.

Subjective complaint ^a	Frequency (%) ^b
No subjective complaint	2.0
Burning mouth	43.6
Tooth-/jawache	21.8
Dry mouth	20.0
Gingivitis	18.4
Metal taste	17.6
Paraesthesia	11.6
Weakness	9.4
Gingival bleeding	8.0
Headache/migraine	7.2
Sour taste	6.4
Swelling	6.4
Intestinal problems	6.0
Electrical sensations	5.6
Sensation of pressure	5.6
Bitter taste	5.4
Painful swallowing/sore throat	5.4
Reduced sense of taste	5.0
Gingival pain	4.8
Red palate	4.8
Articular pain	4.6
Poor denture retention/incorrect bite	4.0
Red/inflamed tongue	3.8
Salty taste	3.6
Blisters	3.4
Dry lips	3.4
Facial pain	3.4
Itching	3.2
Speech impairment	3.0
Foreign body sensations with denture	2.8
Painful tongue	2.6
Problems with the eyes	2.6
Dyspnoea/asthmatic attack	2.4
Increased mucus	2.4
Reduced ability for chewing	2.4
Rough/sharp-edged denture	2.4
Acne/problems with the skin	2.2
Drooling	2.0
Muscular pain	2.0
Neck pain	2.0
Problems with the temporomandibular joint	2.0

^a Subjective complaints reported by 10 (2%) or more patients are listed.

^b 100% = 500 patients, multiple entries per patient were possible.

3.3. Objective intraoral symptoms

The frequencies of the objective intraoral symptoms diagnosed from 5 (1%) or more patients are summarized in Table 2. Again, multiple entries per patient were possible. In detail, 54.4% of the patients showed no objective intraoral symptom at all. Most patients with objective intraoral symptoms showed anomalies of the tongue (14.4%, lingua plicata or lingua geographica, Fig. 4). Twelve percent of the patients had gingivitis adjacent to crowns or double crowns, which persisted after the professional plaque removal (Fig. 5). A red palate/edentulous ridge (Fig. 6) was diagnosed in 6.6% of the patients followed by oral lichen planus (5.6%), grayish discoloration (4.8%), lichenoid contact lesion (3.2%; Fig. 7), leukoplakia (1.8%), generalized (i.e. including extraoral cutaneous reaction) lichen planus (1.2%), and hyperplasia of the

Table 2 – Objective intraoral symptoms diagnosed from the 500 patients and their frequencies.

Objective intraoral symptom ^a	Frequency (%) ^b
No symptom	54.4
Anomalies of the tongue	14.4
Gingivitis	12.0
Red palate/red edentulous ridge	6.6
Oral lichen planus	5.6
Grayish discoloration	4.8
Lichenoid contact lesion	3.2
Leukoplakia	1.8
Generalized lichen planus	1.2
Hyperplasia of the palatal mucosa	1.0

^a Objective intraoral symptoms diagnosed from 5 (1%) or more patients are listed.

^b 100% = 500 patients, multiple entries per patient were possible.

**Fig. 4 – 44-year-old male patient with lingua plicata and lingua geographica.****Fig. 5 – 30-year-old female patient with gingivitis adjacent to a silver based alloy.**

palatal mucosa (1.0%). The list of objective intraoral symptoms diagnosed in less than 1% of the patients comprises 15 entries, e.g. periimplantitis, apthous stomatitis, and blisters.

The frequency distribution of the number of objective intraoral symptoms diagnosed per patient (Fig. 3) shows that

**Fig. 6 – 49-year-old female patient with redness of the palate adjacent to a cobalt chromium alloy.**

more than half (54.4%) of the patients had no objective symptoms. 36.6% of the patients had one, 8.6% had two, and 0.4% had three objective symptoms.

3.4. Allergy testing

Out of the 500 patients, 315 (63%) had a patch test done before the clinical examination for this study (Table 3). After our clinical examination 160 (32%) patients underwent a patch test, 59 out of them additionally to the test they had done before, because their test records were incomplete. Altogether 416 (83%) patients had a full set of patch test results.

3.4.1. Patch test results to dental materials

Positive patch test results to dental materials are presented in Table 4. From the standard and dental series nickel and palladium were the most frequent allergens in dental materials (19.2% and 12.6%, respectively), followed by

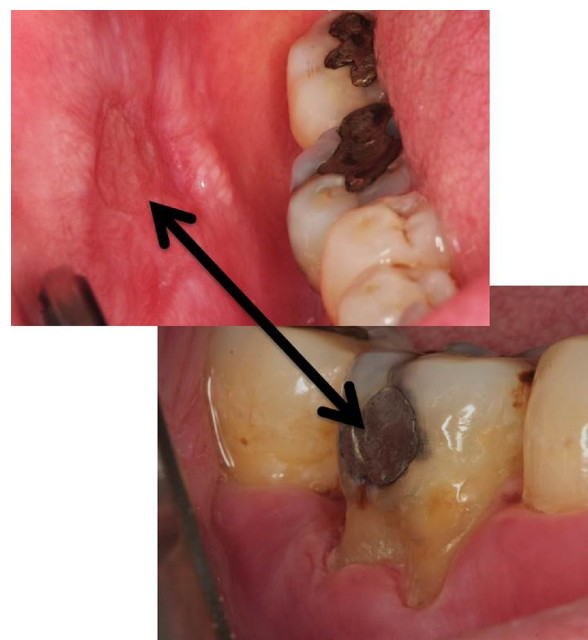
**Fig. 7 – 45-year-old female patient with lichenoid lesion adjacent to an amalgam filling.**

Table 3 – Frequency distribution of patch tests.

Patch test performed before our examination	Patch test arranged during our examination		All
	No	Yes	
No	16,8% (84)	20,2% (101)	37,0% (185)
Yes	51,2% (256)	11,8% (59)	63,0% (315)
All	68,0% (340)	32,0% (160)	100% (500)

balsam of Peru (9.6%), cobalt chloride (9.4%), benzoyl peroxide (9.2%), sodium thiosulfatoaurate (7.6%), and amalgam (6.2%). In at least 2% of the patients, patch test reactions

to ammoniated mercury, colophony, potassium dichromate, ethyleneglycol dimethacrylate, amalgam alloying metals, methyl methacrylate, hydroxyethyl methacrylate, and triethyleneglycol dimethacrylate were found (Table 4, column A).

The list of diagnosed allergens to dental materials identified in less than 5 (1%) patients comprises 13 entries, e.g. bisphenol A, ammonium heptamolybdate, and cobalt sulphate, whereby only the latter was presumable clinically relevant in one patient.

For the group of detected allergens with a frequency higher than 2%, in about two thirds or more of the cases the allergen was not a component of the suspected intraoral restoration. This was the case for e.g. nickel 87.5%, palladium 66.7%, balsam of peru 100% (base: frequency of the allergen),

Table 4 – Allergens relevant to dental materials diagnosed by patch testing from 500 patients, their frequency and clinical relevance. Frequency of the allergen was depicted as well as the frequency of patients with the allergen being no component of the intraoral restoration in question. The clinical relevance of an allergen being a component of the intraoral restoration in question was further qualified into the categories no, presumable, and yes.

Allergen ^a	Relative number (%) of patients ^b				
	Frequency of the allergen	Allergen was not in the dental restoration	Allergen was in the dental restoration and its clinical relevance was		
			No	Presumable	Yes
Standard and dental series:					
	A ^d	B	C	D	E
Nickel sulphate 6-H ₂ O 5%	19.2 ^c	16.8	0.0	0.4	0.0
Palladium chloride 1%	12.6	8.4	0.6	1.6	0.4
Balsam of peru 25%	9.6	9.6	0.0	0.0	0.0
Cobalt chloride 6-H ₂ O 1%	9.4	7.4	0.0	0.8	0.2
Benzoyl peroxide 1%	9.2	5.4	0.2	1.0	0.6
Sodium thiosulfatoaurate 0.25%	7.6	2.0	0.8	2.6	0.8
Amalgam 5%	6.2	5.0	0.2	0.0	0.2
Ammoniated mercury 1%	4.2	3.6	0.0	0.0	0.4
Colophony 20%	3.4	3.4	0.0	0.0	0.0
Potassium dichromate 0.5%	3.2	2.6	0.0	0.2	0.4
Ethyleneglycol dimethacrylate 2%	2.6	1.2	0.2	0.4	0.0
Amalgam alloying metals 20%	2.2	2.2	0.0	0.0	0.0
Methyl methacrylate 2%	2.2	1.4	0.0	0.4	0.0
(2-Hydroxyethyl) methacrylate 1%	2.2	1.4	0.2	0.0	0.0
Triethyleneglycol dimethacrylate 2%	2.0	0.8	0.2	0.4	0.0
BIS-GMA 2%	1.8	0.6	0.6	0.2	0.0
Copper sulphate 1% or 2%	1.8	1.2	0.0	0.0	0.0
Tin (II)-chloride 0.5%	1.6	0.8	0.0	0.4	0.2
Epoxy resin 1%	1.6	1.6	0.0	0.0	0.0
Potassium dicyanoaurate (in water) 0.002%	1.4	0.6	0.0	0.4	0.0
Diurethane dimethacrylate 2%	1.4	0.6	0.0	0.0	0.0
Titanium (IV) oxide 0.1%	1.4	1.0	0.0	0.0	0.0
Eugenol 1%	1.2	1.0	0.0	0.2	0.0
Ammonium tetrachloroplatinate 0.2%	1.2	0.8	0.0	0.0	0.0
Hydroquinone 1%	1.2	0.2	0.0	0.2	0.2
Small disks or honed chips of dental materials:					
Dental alloys	1.8	1.2	0.0	0.4	0.2
Denture acrylates	1.0	0.6	0.0	0.2	0.2
Resin based composites	1.0	0.6	0.0	0.2	0.0

^a Allergens relevant to dental materials diagnosed from 5 (1%) or more patients are listed.

^b 100% = 500 patients.

^c For a specific allergen, the four columns depicting the allergen being in the intraoral restoration or not (B–E), do not necessarily sum up to the frequency of the allergen (A), because in some cases it was unclear if the allergen was or was not in the dental restoration. Furthermore, if the allergen was in the restoration, the clinical relevance ('no', 'presumable', 'yes') could not be resolved in each case.

^d Letters A–E identify columns.

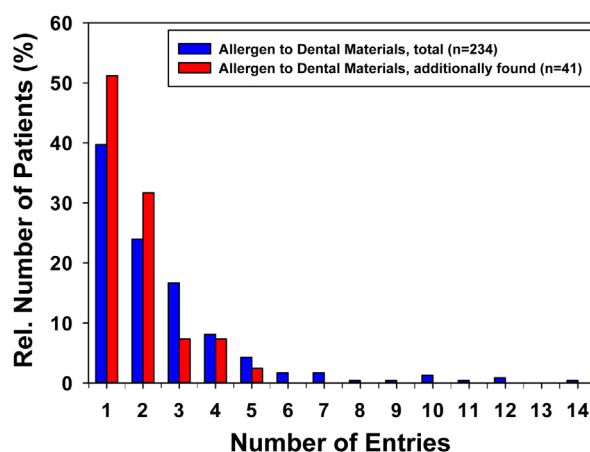


Fig. 8 – Frequency distribution of the number of allergens to dental materials per patient (100% = 234 patients with diagnosed allergens to dental materials, blue bars) and the number of allergens to dental materials additionally diagnosed during the examination in the University of Regensburg Medical Center, (100% = 41 patients with additionally diagnosed allergens to dental materials, red bars). (For interpretation of the references to colour in the text and figure legend, the reader is referred to the web version of this article.)

except for sodium thiosulfatoaurat (26%) and ethyleneglycol dimethacrylate (46%). If the allergen was not a component of the intraoral restoration, the allergen was rated clinically not relevant in these patients (Table 4, column B).

The gold salt sodium thiosulfatoaurate was the allergen with the highest clinical and presumable relevance (0.8% and 2.6%, respectively), followed by benzoyl peroxide (0.6 and 1.0%, respectively), and palladium chloride (0.4 and 1.6%, respectively) (Table 4, columns D and E).

Positive skin reactions to small disks or honed chips of dental alloys, denture acrylates or resin based composites were observed in less than 2% of the patients. From these positively tested materials a clinical relevance was diagnosed in one (0.2%) patient for both, dental alloys and denture acrylates. Allergens to resin based composites were not found clinically to be relevant (Table 4, column E).

3.4.2. Patients with positive patch tests

Out of the 500 patients, 234 (47%) had positive patch test reactions to at least one of the tested possible allergens. The frequency distribution of the number of positive patch tests to dental materials (100% = 234 patients) shows that 39.7% of the patients had one allergen (Fig. 8, blue bars); 23.9% and 16.7% of the patients had two or three allergens, respectively. More than three allergens were diagnosed in 19.7% of the patients. The maximum of 14 allergens was found in one (0.4%) patient. Cross-reactivity to Ni and Pd were found in 39 (7.8%) of the patients, whereas Ni or Pd alone were positive in 57 (11.4%) or 24 (4.8%) patients, respectively.

A clinical relevance of the positively tested allergens was diagnosed in 4% (n = 20) of the patients, and a presumable clinical relevance in 10.0% (n = 50) altogether in 70 patients (14%

Table 5 – In 70 (14% of the 500) patients an allergen, diagnosed by a patch test was component of the restoration and diagnosed clinical relevant or presumable clinical relevant: frequency distribution of the number of these allergens per patient.

Number of clinical relevant (yes or presumable) allergens per patient	Number of patients
1	39
2	11
4	1
5	1

of the 500 patients, or 29.9% of the tested 234 patients). Sixty one of them showed one or two relevant (yes or presumable) allergens, and the maximum number of these allergens per patient was five in one patient (Table 5).

In 41 (8.2%) of the 500 patients a dental material allergen was found during the examination in the University of Regensburg Medical Center, in addition to the already known allergens (Fig. 8, red bars). In 21 (51.2%) of these 41 patients one additional dental material allergen was diagnosed, and up to five additional allergens were found.

4. Discussion

4.1. Study design

The design of the present study was mainly based on our previous study [11]. Both were conducted as diagnostic studies of an open type where patients and dentists potentially knew which product each patient had received. This is not an epidemiological study. However, patients came from a well-defined region (Eastern Bavaria) with about one million inhabitants, but probably not all dentists referred patients to our clinic or patients might have refused to visit our department. Most notably, in the former [9–11] and present studies the dentist and her dental assistant did not change.

4.2. Number of patients and frequency of adverse clinical reactions

Five hundred patients with real or claimed dental material related adverse health effects visited our special consultation hour during 16 years, which means roughly 31 new cases per year with only very small variations over the years. Similar patient numbers per year were reported in the literature in comparable studies with 29 [11], 36 [34], 34 [48]. However, the reference time period in those studies was far less than 16 years as in the present study. Reports of an observation period of a comparatively long time period in combination with one single dental team as in the present study were not available in the literature. Such frequencies can now be related either to the number of treated patients or to the population. In the recently published report of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on adverse effects of dental restorative materials it was estimated that less than 0.3% of the patients show a local adverse reaction including allergic reactions [51]. This is in line with data from different patient groups mentioned above [16,21,22,24].

However, these data are not population based. Although the present study design does not represent a classical epidemiologic approach, a population based frequency of 0.003% for newly reported real or claimed adverse effects for the region of Eastern Bavaria (1 million) per year can be calculated. The fact that this value has been rather constant over the recent 16 years adds to the validity of this figure. Therefore, our data confirm the statement that the frequency of adverse reactions towards dental materials is low. Combining patients with adverse reactions to dental materials to a disease entity, the frequency is in the order of magnitude of the group of seldom diseases being less than 1 on 2000 [23].

4.3. Age and sex distribution, general oral hygiene

Generally, patients between 50 and 59 years of age predominated, followed by patients between 60– and 69 years, which is in accordance with our previous study [11]. Similar data were reported in the literature: in a clinical study monitoring adverse reactions to dental materials Lygre et al. [34] found that the most prevalent age group was 40–59 years. In a multidisciplinary examination of patients with illness attributed to dental fillings the median patient age was 45 years [32]. In patients with burning mouth syndrome the mean age was 59.5 years [35].

A reason for this age distribution may be the fact that patients in this age group are exposed to a large number of dental materials. According to the Fourth German Oral Health Study [40] the number of restorations and lost teeth increases with age, leading to an age dependent increase of restorations and fixed and removable dentures, with a peak in the age group between 45 and 60 years. In any case, our study confirms the specific age distribution which had been reported in earlier studies. The predominance of females found in the present study was also reported in other clinical studies [32,34,59], and in the Adverse Reactions Reporting Project of Scott et al. [55]. In patients with burning mouth syndrome 86% of the patients were females [35].

It can be assumed that the high portion of females in middle and elder age groups might be caused by endocrine changes. However, literature reviews show that the role of hormones affecting oral health (e.g. burning mouth) and hormone replacement therapy is not yet confirmed [39,57]. Furthermore, we found that also in younger patients females predominate, which is somewhat contradictory to the role of hormones. It has also been speculated that females are more likely to report on adverse reactions than males or females are more likely to experience an adverse reaction [50,55]. In any case, this study confirms the specific sex distribution as was reported in earlier studies.

Oral hygiene using the PBI was assessed in order to investigate, if the patients of the present study are characterized by an insufficient oral hygiene behaviour. The median PBI of all patients was 41.7%, and categorized by age groups PBI was 50% or less (Fig. 2). Oral hygiene data from the literature for patients claiming dental materials adverse effects were not available. In the Fourth German Oral Health Study [40] the PBI was 55% for the corresponding age groups. Therefore, it can be concluded that in general, oral hygiene may not be a relevant cause for the reported adverse effects.

4.4. Allergy

Patch testing is the recognized instrument suitable for routine diagnostics to prove sensitization (delayed type IV reactions) to a substance causing an allergic contact reaction of the skin or the adjacent mucous membranes [54]. Its reproducibility, if applied twice at the same time (synchronous reproducibility) at the upper back, ranges within 60–90% [54]. In the general population the one-year prevalence of contact dermatitis is 5% (males) to 11% (females) [8]. However, there is discussion about the substances to be included in the standard series, e.g. Muris et al. suggest testing sodium tetrachloropalladate instead of palladium chloride for diagnosing palladium sensitization [43].

In contrast to Holmstrup [17], who recommended patch testing only if visible mucosa lesions are located beneath dental restorations, we additionally performed patch testing in patients with both subjective complaints (burning mouth [35] or itching) or objective oral symptoms to dental materials. Our approach is in line with other patch test reports in patients with oral diseases like gingivitis or lichenoid reactions, and in patients with burning mouth [11,48,58]. Altogether, we had patch test data available from 416 (83.2%) out of the 500 patients. In studies with the main emphasis on dentistry, complete information on the allergy status of such a large cohort was not reported.

The available results from patch tests were further evaluated according to the relevance related to the clinical situation (see above). According to Torgerson et al. [58] the determination of the clinical relevance of the patch test results is a most challenging part of patch test interpretation. In their opinion, relevance is theoretically a “pure” concept, but in practice, such purity can never be achieved (for definition of “relevance” see materials and methods). We conclude that a highly specialized dental team in cooperation with dermatologists is necessary to reliably assess patch test results.

4.4.1. Allergens in general (column A in Table 4)

The allergens with the highest frequencies in the present study were nickel (19.2%), followed by palladium, balsam of Peru, cobalt, benzoyl peroxide, gold, and amalgam, which is in line with data from the literature [11,20,29,49,59]. In our previous study nickel and palladium were the most frequently observed allergens [11]. Vamnes et al. [59] found as allergen most commonly nickel, gold, cobalt, palladium, and mercury in patients of an adverse reaction unit for dental biomaterials. In another study on the top of the allergen list in patients with oral diseases like oral lichen planus or burning mouth syndrome were nickel, gold, chrome, cobalt, palladium, and mercury [29]. In a comprehensive German study of the IVDK (Informationsverbund dermatologischer Kliniken (Information Network of Departments of Dermatology)) that included 756 patients with records of mucosal alterations or problems related to dental materials the allergens nickel, palladium, gold, benzoyl peroxide, and amalgam showed highest frequencies [49]. According to Hostynek [20] the high frequency of nickel allergy in the population is a result of nickel’s ubiquitous occurrence in tools and articles of everyday use, leading to frequent and long term exposure.

The frequency of positive patch test reactions to nickel and palladium alone or their cross-reactivity was similar to results reported by Muris et al. [42], when palladium chloride (PdCl_2) was tested as in our study. However, Muris et al. [42] showed that the introduction of the more sensitive test allergen disodium tetrachloropalladate (Na_2PdCl_4) resulted in about two fold higher cross-reactivity.

In the present investigation the frequency of positive patch test reactions to metals was much higher as compared to acrylates, where ethylenglycol dimethacrylate (2.6%), methyl methacrylate (2.2%) and 2-hydroxyethyl methacrylate (2.2%) had highest frequencies. In a multicenter study including more than 4000 patients. Kanerva et al. [27] also reported that the most common positive patch test reactions were to metals and most frequent allergy to acrylates was to 2-hydroxyethyl methacrylate (2.8%). Other authors also stated that metals used in dental practice are the most commonly reported causes of intraoral contact allergies, though hypersensitivity to resins is increasingly mentioned in the literature, as a consequence of their increasingly reported widespread use [36]. In the study of Kim et al. [29] methyl methacrylate was the most frequently occurring acrylate with 2.3% positive reactions in 44 patients with oral diseases. Torgerson et al. [58] also found low positive reaction rates with acrylates in 331 patients with oral diseases, whereby 2-hydroxyethyl methacrylate provoked the most positive reactions with 5.2%. We confirm that positive patch test reactions to metals remain an important issue despite an increasing use of acrylate containing restorative materials.

The low frequency of positive patch test reactions to small disks or honed chips of dental materials in the present study (<2%) may be due to the fact that the substances of the dental series release more ions, molecules or particles than solid disks or chips [26]. In order for a material to induce allergic manifestations, it must first undergo corrosion and particle release [36]. Accordingly, in our previous study with alloy disks, none of the 86 patients showed positive reactions [11]. To the best of our knowledge, other studies including patch testing of small disks or honed chips of the patients' dental materials, except for palladium [3], are not available. We conclude that patch testing of individual materials remains less relevant compared to testing of standardized series.

4.4.2. Patients with allergens and relevance of those allergens (columns C–E in Table 4)

The number of patients with a positive patch test in general was 234 (46.8% of 500 patients or 56.2% of the 416 tested patients). This is in line with reported 44.7% positive tested patients with oral diseases [58]. Studies only focusing on metals report on 13.6% [47] and 20.2% [11] positive patch test results. The allergen with the highest frequency of the clinical relevance in the present study was the gold salt sodium thiosulfatoaurate with a relevance of 0.8% and a presumable relevance of 2.6%, followed by benzoyl peroxide, palladium chloride, potassium dichromate, ammoniated mercury, cobalt chloride, and tin chloride.

Regarding the number of patients with an allergen rated clinically relevant, in only 4% of the patients a clinical relevance, and in 10% a presumable clinical relevant positive patch test reaction was diagnosed. In these 70 out of 234 positive

tested cases a dental material could be identified as contributing to the oral findings or the complaints of the patient. This discrepancy is in line with data from another study, where contact allergy to dental metals was investigated: out of 206 patients in only 14 cases (6.8%) a clinically relevant reaction could be found [48]. A similarly low portion of relevant patch test reactions (<10%) was observed in our previous study [11]. Compared to these reported low portions of clinically relevant patch test results, Torgerson et al. [58] reported on a prevalence of 65%. However, their 100% value was the number of positive patch test reactions in their study population, in contrast to the number of all recruited 500 patients in our study. Notably, the authors themselves raise concerns over comparing their findings with other studies because of differences in patient selection criteria, allergens, test protocols, and data analysis. Therefore, it can be concluded that positive patch test reactions regarding dental materials are not necessarily clinically relevant.

4.4.3. Additional patch testing

During our examination 160 (32%) patch tests were arranged. From 59 (11.8%) of these patients their previously performed patch tests were completed by an additional patch test arranged during our examination. Compared to the already known patch test results before the patient visited our Department, in 41 of these 59 patients up to five positive reactions to dental materials were found additionally during our examination. This additional information is a benefit for the patients, because the risk of adverse reactions from dental materials can be minimized for future restorative procedures, if the patient knows and is able to communicate which allergens have to be avoided.

4.5. Subjective Complaints

In the present study the patients reported on a wide variety of subjective oral and general complaints. The subjective oral complaints (e.g. burning mouth, tooth-/jawache, dry mouth, and metal taste) are similar to the complaints reported in the literature with dental patient groups relating their various subjective problems to dental materials [11,32,34,59]. Here the main clinical problem is that such complaints may have several and also non dental material related reasons like drugs or non-oral diseases. As an example, patients with diabetes mellitus or rheumatoid arthritis often suffer from dry mouth [44]. Scully and Bagan [56] describe that dry mouth has a variety of possible causes like tobacco smoking, alcohol use or drugs (e.g. antidepressants, antihypertensive agents). Concerning burning mouth syndrome, many other etiologies have been reported, ranging from nutritional factors to "intolerances" from dental materials, but none have been found to account for a substantial portion of patients [15].

The question is, if an allergy may be a contributing factor for these subjective oral complaints. In the present study 218 (43.6% of 500) patients reported on burning mouth. In 28 (5.6% of 500; 12.9% of 218) patients a clinically relevant or presumable relevant allergen was found (e.g. gold, benzoyl peroxide, cobalt, palladium, tin). In contrast, Raap et al. [48] found no clinical relevant allergens in patients with burning mouth. Among patients with burning mouth syndrome and positive

patch test reactions, Lynde et al. [35] reported on 74% possible and 16% questionable relevance. This wide variety might be due to individually different strategies for the diagnosis of clinically relevant allergens. Moreover, allocation of an allergen to burning sensations in the whole mouth with presumably different dental materials inserted is more difficult than to localized symptoms like gingivitis adjacent to a metal restoration. Our findings indicate that allergy might be contributing to patients' burning mouth sensations. Patch testing might be a useful diagnostic tool in patients with burning mouth.

Apparently, the situation becomes even more complicated in patients with non-oral related complaints like weakness, headache, or intestinal problems. Symptoms reported in this study are similar to those described in the literature [11,32,34,59]. Many other diseases may be a cause for these complaints allegedly attributed to dental materials. For example, Langworth et al. [32] found a high prevalence of general symptoms like diffuse pain in muscles or joints, and a high number of medical disorders (e.g. anaemia, cardiac disease, thyroid malfunction, asthma). In many cases this explained the symptoms of the patients. Gottwald et al. [14] found in patients with complaints related to amalgam higher levels of psychic distress, a higher incidence of depression and somatization disorders as well as different styles of coping with anxiety compared to controls.

Considering both, subjective oral and non-oral complaints, other causes for subjective complaints have to be identified in an interdisciplinary collaboration to avoid unnecessary and potentially unsuccessful dental treatment.

4.6. Objective intraoral symptoms

4.6.1. Anomalies of the tongue

Anomalies of the tongue (lingua plicata, lingua geographica) were recorded in 14.4% of the patients in our specialized consultation hour, being the most frequently observed objective intraoral symptom, and their prevalence was 16% in our previous study [11]. Our findings in the present study are in line with 11.5% patients with anomalies of the tongue reported by Ching et al. [6].

Out of the 238 patients with burning mouth, 44 (18.5%) were diagnosed with anomalies of the tongue in the present study, whereas Ching et al. [6] reported on 26.7% patient with tongue anomalies in their burning mouth syndrome group and on 11.5% in their control group. From these findings one might derive that about 19% of patients, irrespective of any study group, would have tongue anomalies and burning mouth, being in line with the 18.5% in our study.

Nine out of the 72 (14.4%) patients with tongue anomalies had relevant or presumable relevant allergens. However, these allergens were associated with other intraoral complaints or symptoms like lichenoid lesions, gingivitis, or denture stomatitis. Honarmand et al. [19] found a significant relationship between geographic tongue and a history of allergic diseases. In their study, however, allergic diseases were considered as a whole and were not separately evaluated for type I (atopic) and type IV (delayed) allergies. Goregen et al. [13] observed a 22.5% rate of positive patch test response against nickel in 40 patients with geographic tongue. However, as a limiting factor in their study, the oral cavity was not examined for evidence of

the allergens. Furthermore, the authors recommended larger sample sizes for future research. A review [36] concluded, that current scientific knowledge makes it possible to discard an allergic basis for geographic tongue, which is in line with our findings. Therefore it can be concluded that the association between allergens and tongue anomalies is not completely understood and dental materials are unlikely to be causative.

4.6.2. Gingivitis

Gingivitis adjacent to metal restorations after plaque reduction measures was found in our study in 12.0% of the patients, in our previous study, focusing on dental alloys excluding amalgams, 23% were found [11]. Torgerson et al. reported on a lower frequency of 7.6%, but no plaque reduction measure were reported [58].

Again, allergy has been discussed as a reason for these – apparently not plaque related – reactions. In the present study out of the 60 (12% of 500) patients with gingivitis after plaque reduction measures, 16 (3.2% of 500, 26.7% of 60) patients were found with at least one positive relevant or presumable relevant patch test reaction. The most frequent allergens found were gold (7) and palladium (6). Two non-metallic allergens (eugenol and benzoyl peroxide) were recorded.

Fillings and crowns containing acrylates have been rarely reported to cause gingivitis [25]. In the study of Torgerson et al. [58] from the 25 patients with gingivitis, 16 patients had at least one positive patch test reaction, and 12 of 25 had at least one relevant reaction. All five most common allergens were metals. Besides the fact that no plaque reductions measures were reported, generally fragrances and preservatives were included in the patch tests of this study [58]. This might explain the higher number of relevant patch test reactions compared to our previous and present data, where only fragrances used in dentistry were evaluated. In our previous study on dental alloys in only two out of 20 cases (10%) an allergy to a metal was assumed to be the possible cause of the gingivitis [11]. Again, due to inhomogeneous study protocols, the results may not be directly compared [58]. We conclude that gingivitis adjacent to metal restorations after plaque reduction measures may be associated to allergic reactions from dental materials and patch testing is recommended in this instance.

4.6.3. Redness of the palate or the edentulous ridge

Redness of the palate or the edentulous ridge adjacent to a denture was found in the present study in 6.6% (33) of the patients. Out of these patients, five patients also had a hyperplasia of the palatal mucosa. In our previous study [11] in seven (8%) of the 86 patients a denture stomatitis was diagnosed. A comparison to the literature is hardly possible, since usually the term “stomatitis” without further explanation is used [48,58].

In the present study out of the 33 patients (6.6% of 500) with denture stomatitis seven patients (21.2% of 33) had at least one positive relevant or presumable relevant patch test reaction (e.g. chromium, palladium, gold, hydroquinone, benzoyl peroxide). In our previous study limited to dental alloys [11] in seven (8%) of the 86 patients a denture stomatitis was diagnosed. No relevant metal allergy was found in these seven patients [11]. Metals like palladium, gold or manganese may

cause a denture stomatitis [12]. In a case report of Pardo et al. [45] manganese in a removable partial denture was found as allergen contributing to the itching and burning sensations, to a diffuse oedema/erythema, and to an aphthous lesion in the region of the prosthesis. Koutis and Freeman [31] found positive patch testing to samples of a resin denture material and to 2-hydroxyethyl methacrylate in an edentulous patient with painful redness adjacent to a new denture. Studies on the redness of the palate or edentulous ridge are scarce and are mainly based on case studies. Therefore, it can be concluded that based on our findings, redness of the palate or the edentulous ridge may be associated to allergic reactions from dental materials and patch testing is recommended.

4.6.4. Whitish lichen-like lesions

Whitish lichen-like lesions were observed in 3.2% (16) of the 500 patients of the present study as oral lichenoid contact lesion, in 5.6% (28) as oral lichen planus, and in 1.2% (6) of the patients as generalized (including cutaneous) lichen planus. Rapp et al. reported on 4.4% (9 of 206) patients with oral lichen planus, other lichen-like lesions were not mentioned [48]. Torgerson et al. found 17.8% (59 of 331) patients with lichenoid tissue reactions [58].

Out of the 16 (3.2% of 500) patients with oral lichenoid contact lesions in the present study we found four patients (25% of 16) with at least one relevant or presumable relevant positive patch test reaction (e.g. amalgam, cobalt, gold). Out of the 28 (5.6%) patients with oral lichen planus five patients (17.9% of 28) with at least one relevant or presumable relevant positive patch test reaction were observed (e.g. gold, amalgam, palladium, tin). In the six (1.2%) patients with generalized lichen planus no relevant allergens were found. Oral lichenoid contact lesions have been described in response to hypersensitivity to amalgam or other metals (e.g. gold, palladium) [1,7,28,30,38,58], and to acrylic or resin based composite [7,33,34]. Rapp et al. found in seven of nine (77.8%) patients with oral lichen planus a clinical relevance of the patch test results [48]. Torgerson et al. reported on 33.9% (20 of 59) patients with lichenoid tissue reactions caused by an allergen [58]. Therefore, it can be concluded that allergens may be causative for whitish lichen-like lesions but not for patients with generalized lichen planus. Patch testing is recommended for lichenoid lesions and lichen planus, but not for generalized lichen planus.

4.6.5. Grayish discolorations

Grayish discolorations of the gingiva were found in 4.8% of the patients in the present study and were associated with a history of amalgam fillings. The patients did not report on subjective complaints and no association with allergies was observed in this study. Amalgam particles may have been transplanted into the tissues during tooth preparation. This submucosal collection of embedded amalgam persists unchanged for many years and is present in less than 1% of adults [5]. No treatment is necessary, except perhaps further observation. However, if the lesion changes (enlargement, ulceration, erythema), further examinations, including referral and biopsies, are necessary [37].

4.6.6. Leukoplakia

Leukoplakia was observed in 1.8% of the patients in the present study. Oral leukoplakia is the most common oral lesion with a precancerous nature [18]. Alanko et al. [2] found out of 24 patients with both oral mucosal diseases and positive patch test reactions two (8.3%) patients with solitary leukoplakia and mercury allergy (diagnosis verified histologically in one patient). In other studies about patients with oral diseases leukoplakia was not mentioned in association with contact allergy [48,58]. In a review about contact allergy to dental materials was stated that there is no allergic basis for leukoplakia [36], which is in line with our data. None of the nine patients with leukoplakia in the present study had a relevant allergy. Therefore, one might assume that allergies do not play a major role in association with leukoplakia.

5. General experiences from the study

According to our long lasting experiences, but not supported by reported data, counseling, examination, diagnosis and treatment of patients reporting on adverse effects from dental materials is time-consuming and difficult to manage on a daily basis in a dental practice. Therefore, special consultation hours preferably with a continuous dental team are eligible. The dermatologist should be informed about the inserted dental materials and their components. The interpretation of patch testing results requires knowledge about the brand name or composition of the suspected materials. A highly specialized dental team in cooperation with dermatologists is preferable to reliably assess patch test results. The high number of subjective complaints per patient and their wide variety suggests that the patients seriously suffered in most cases. Furthermore, the fact that only 46% of the patients had objective intraoral symptoms demands for an interdisciplinary collaboration with other medical disciplines to identify other than oral causes for the complaints and symptoms.

6. Conclusions

Although this study was not a classical epidemiological investigation, the number of patients with suspected adverse effects from dental materials is low. Middle- or old aged females are predominating. The discrepancy between the high number of subjective complaints and the low number of objective intraoral symptoms demands an interdisciplinary collaboration to identify other than dental causes for the impairment of the patient in order to avoid unnecessary, expensive and stressful dental treatment. Allergy is a recognized but rare cause for adverse effects. Patch testing of standardized series revealed that metals are most often diagnosed allergens. Gingivitis adjacent to dental restorations, redness of the palate or the edentulous ridge and whitish lichen-like lesions are the objective intraoral symptoms which may be associated to allergy from dental materials.

Acknowledgements

We thank the Department of Dermatology, University of Regensburg Medical Center, Regensburg, for the close and

excellent cooperation regarding the performance of allergy tests. We thank Petra Fancso, dental assistant, having an empathic contact to the patients. The confidence of the referring dentists is gratefully acknowledged.

REFERENCES

- [1] Ahlgren C, Bruze M, Moller H, Gruvberger B, Axell T, Liedholm R, et al. Contact allergy to gold in patients with oral lichen lesions. *Acta Derm Venereol* 2012;92(March (2)):138–43.
- [2] Alanko K, Kanerva L, Jolanki R, Kannas L, Estlander T. Oral mucosal diseases investigated by patch testing with a dental screening series. *Contact Dermat* 1996;34(April (4)):263–7.
- [3] Augthun M, Lichtenstein M, Kammerer G. Studies on the allergenic potential of palladium alloys. *Dtsch Zahnarztl Z* 1990;45(August (8)):480–2.
- [4] Bakula A, Lugovic-Mihic L, Situm M, Turcin J, Sinkovic A. Contact allergy in the mouth: diversity of clinical presentations and diagnosis of common allergens relevant to dental practice. *Acta Clin Croat* 2011;50(December (4)):553–61.
- [5] Buchner A. Amalgam tattoo (amalgam pigmentation) of the oral mucosa: clinical manifestations, diagnosis and treatment. *Refuat Hapeh Vehashinayim* (1993) 2004;21(July (3)):25–8, 92.
- [6] Ching V, Grushka M, Darling M, Su N. Increased prevalence of geographic tongue in burning mouth complaints: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;114(October (4)):444–8.
- [7] Ditrichova D, Kapralova S, Tichy M, Ticha V, Dobesova J, Justova E, et al. Oral lichenoid lesions and allergy to dental materials. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2007;151(December (2)):333–9.
- [8] Schnuch A, Aberer W, Agathos M, Becker D, Brasch J, Elsner P, Frosch PJ, Fuchs T, Geier J, Hillen U, Löffler H, Mahler V, Richter G, Szliska C. Patch testing with contact allergens. *JDDG* 2008;770–5, <http://dx.doi.org/10.1111/j.1610-0387.2009.06787.x>.
- [9] Garhammer P, Hiller KA, Reitinger T, Schmalz G. Metal content of saliva of patients with and without metal restorations. *Clin Oral Investig* 2004;8(December (4)):238–42.
- [10] Garhammer P, Schmalz G, Hiller KA, Reitinger T. Metal content of biopsies adjacent to dental cast alloys. *Clin Oral Investig* 2003;7(June (2)):92–7.
- [11] Garhammer P, Schmalz G, Hiller KA, Reitinger T, Stolz W. Patients with local adverse effects from dental alloys: frequency, complaints, symptoms, allergy. *Clin Oral Investig* 2001;5(December (4)):240–9.
- [12] Gawkrödger DJ. Investigation of reactions to dental materials. *Br J Dermatol* 2005;153(September (3)):479–85.
- [13] Goregen M, Melikoglu M, Miloglu O, Erdem T. Predisposition of allergy in patients with benign migratory glossitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110(4):470–4.
- [14] Gottwald B, Kupfer J, Traenckner I, Ganss C, Gieler U. Psychological, allergic, and toxicological aspects of patients with amalgam-related complaints. *Psychother Psychosom* 2002;71(July (4)):223–32.
- [15] Grushka M, Ching V, Epstein J. Burning mouth syndrome. *Adv Otorhinolaryngol* 2006;63:278–87.
- [16] Hensten-Pettersen A, Jacobsen N. Perceived side effects of biomaterials in prosthetic dentistry. *J Prosthet Dent* 1991;65(January (1)):138–44.
- [17] Holmstrup P. Reactions of the oral mucosa related to silver amalgam: a review. *J Oral Pathol Med* 1991;20(January (1)):1–7.
- [18] Holmstrup P, Dabelsteen E. Oral leukoplakia-to treat or not to treat. *Oral Dis* 2016;22(September (6)):494–7.
- [19] Honarmand M, Farhad ML, Shirzaei M, Sehhatpour M. Geographic Tongue and associated risk factors among Iranian dental patients. *Iran J Public Health* 2013;42(2):215–9.
- [20] Hostynek JJ. Sensitization to nickel: etiology, epidemiology, immune reactions, prevention, and therapy. *Rev Environ Health* 2006;21(October (4)):253–80.
- [21] Jacobsen N, Hensten-Pettersen A. Occupational health problems and adverse patient reactions in orthodontics. *Eur J Orthod* 1989;11(August (3)):254–64.
- [22] Jacobsen N, Hensten-Pettersen A. Occupational health problems and adverse patient reactions in periodontics. *J Clin Periodontol* 1989;16(August (7)):428–33.
- [23] Julkowska D, Austin CP, Cuttillo CM, Gancberg D, Hager C, Halftermeyer J, et al. The importance of international collaboration for rare diseases research: a European perspective. *Gene Ther* 2017;24(September (9)):562–71.
- [24] Kallus T, Mjor IA. Incidence of adverse effects of dental materials. *Scand J Dent Res* 1991;99(June (3)):236–40.
- [25] Kanerva L, Alanko K, Estlander T. Allergic contact gingivostomatitis from a temporary crown made of methacrylates and epoxy diacrylates. *Allergy* 1999;54(December (12)):1316–21.
- [26] Kanerva L, Kerosuo H, Kullaa A, Kerosuo E. Allergic patch test reactions to palladium chloride in schoolchildren. *Contact Dermat* 1996;34(January (1)):39–42.
- [27] Kanerva L, Rantanen T, Aalto-Korte K, Estlander T, Hannuksela M, Harvima RJ, et al. A multicenter study of patch test reactions with dental screening series. *Am J Contact Dermat* 2001;12(June (2)):83–7.
- [28] Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to the clinical presentations. *Contact Dermat* 2006;55(October (4)):216–8.
- [29] Kim TW, Kim WI, Mun JH, Song M, Kim HS, Kim BS, et al. Patch testing with dental screening series in oral disease. *Ann Dermatol* 2015;27(August (4)):389–93.
- [30] Koch P, Bahmer FA. Oral lichenoid lesions, mercury hypersensitivity and combined hypersensitivity to mercury and other metals: histologically-proven reproduction of the reaction by patch testing with metal salts. *Contact Dermat* 1995;33(November (5)):323–8.
- [31] Koutis D, Freeman S. Allergic contact stomatitis caused by acrylic monomer in a denture. *Australas J Dermatol* 2001;42(August (3)):203–6.
- [32] Langworth S, Bjorkman L, Elinder CG, Jarup L, Savlin P. Multidisciplinary examination of patients with illness attributed to dental fillings. *J Oral Rehabil* 2002;29(August (8)):705–13.
- [33] Lind PO. Oral lichenoid reactions related to composite restorations. Preliminary report. *Acta Odontol Scand* 1988;46(February (1)):63–5.
- [34] Lygre GB, Gjerdet NR, Gronningsaeter AG, Bjorkman L. Reporting on adverse reactions to dental materials? intraoral observations at a clinical follow-up. *Community Dent Oral Epidemiol* 2003;31(June (3)):200–6.
- [35] Lynde CB, Grushka M, Walsh SR. Burning mouth syndrome: patch test results from a large case series. *J Cutan Med Surg* 2014;18(May (3)):174–9.
- [36] Mallo PL, Diaz DC. Intraoral contact allergy to materials used in dental practice. A critical review. *Med Oral* 2003;8(November (5)):334–47.
- [37] McCullough MJ, Tyas MJ. Local adverse effects of amalgam restorations. *Int Dent J* 2008;58(February (1)):3–9.

- [38] McParland H, Warnakulasuriya S. Oral lichenoid contact lesions to mercury and dental amalgam—a review. *J Biomed Biotechnol* 2012;2012, 589569.
- [39] Meurman JH, Tarkkila L, Tiitinen A. The menopause and oral health. *Maturitas* 2009;63(May (1)):56–62.
- [40] Micheelis W, Schiffner U. Fourth German oral health study (DMS IV). Deutscher Zahnärzte Verlag; 2006.
- [41] Minciullo PL, Paolino G, Vacca M, Gangemi S, Nettis E. Unmet diagnostic needs in contact oral mucosal allergies. *Clin Mol Allergy* 2016;14(1):10.
- [42] Muris J, Goossens A, Goncalo M, Bircher AJ, Gimenez-Arnau A, Foti C, et al. Sensitization to palladium in Europe. *Contact Dermat* 2015;72(January (1)):11–9.
- [43] Muris J, Kleverlaan CJ, Rustemeyer T, von Blomberg ME, van Hoogstraten IM, Feilzer AJ, et al. Sodium tetrachloropalladate for diagnosing palladium sensitization. *Contact Dermat* 2012;67(August (2)):94–100.
- [44] Napenas JJ, Brennan MT, Fox PC. Diagnosis and treatment of xerostomia (dry mouth). *Odontology* 2009;97(July (2)):76–83.
- [45] Pardo J, Rodriguez-Serna M, De La Cuadra J, Fortea JM. Allergic contact stomatitis due to manganese in a dental prosthesis. *Contact Dermat* 2004;50(January (1)):41.
- [46] Purello-D'Ambrosio F, Gangemi S, Minciullo P, Ricciardi L, Merendino RA. Burning mouth syndrome due to cadmium in a denture wearer. *J Investig Allergol Clin Immunol* 2000;10(March (2)):105–6.
- [47] Raap U, Stiesch M, Kapp A. Contact allergy to dental materials. *J Dtsch Dermatol Ges* 2012;10(June (6)):391–6.
- [48] Raap U, Stiesch M, Reh H, Kapp A, Werfel T. Investigation of contact allergy to dental metals in 206 patients. *Contact Dermat* 2009;60(June (6)):339–43.
- [49] Richter G, Geier J. Dental materials—problem substances in allergologic diagnosis? I: analysis of test results in patients with mouth mucosa/dental material problems. *Hautarzt* 1996;47(November (11)):839–43.
- [50] RKI. Gesundheitliche Lage der Männer in Deutschland. Robert Koch Institut; 2014.
- [51] Rodriguez-Farre E, Testai E, Bruzell E, De JW, Schmalz G, Thomsen M, et al. The safety of dental amalgam and alternative dental restoration materials for patients and users. *Regul Toxicol Pharmacol* 2016;79:108–9.
- [52] Saxer UP, Muhlemann HR. Motivation and education. *Schweiz Monatsschr Zahnheilkd* 1975;85(September (9)):905–19.
- [53] Schedle A, Ortengren U, Eidler N, Gabauer M, Hensten A. Do adverse effects of dental materials exist? What are the consequences, and how can they be diagnosed and treated? *Clin Oral Implants Res* 2007;18(June (Suppl. 3)):232–56.
- [54] Schnuch A, Aberer W, Agathos M, Becker D, Brasch J, Elsner P, et al. Performing patch testing with contact allergens. *J Dtsch Dermatol Ges* 2008;6(September (9)):770–5, <http://dx.doi.org/10.1111/j.1610-0387.2008.06787.x>.
- [55] Scott A, Egner W, Gawkrödger DJ, Hatton PV, Sherriff M, van Noort R, et al. The national survey of adverse reactions to dental materials in the UK: a preliminary study by the UK adverse reactions reporting project. *Br Dent J* 2004;196(April (8)):471–7.
- [56] Scully C, Bagan JV. Adverse drug reactions in the orofacial region. *Crit Rev Oral Biol Med* 2004;15(4):221–39.
- [57] Suri V, Suri V. Menopause and oral health. *J Midlife Health* 2014;5(July (3)):115–20.
- [58] Torgerson RR, Davis MD, Bruce AJ, Farmer SA, Rogers III RS. Contact allergy in oral disease. *J Am Acad Dermatol* 2007;57(August (2)):315–21.
- [59] Vamnes JS, Lygre GB, Gronningsaeter AG, Gjerdet NR. Four years of clinical experience with an adverse reaction unit for dental biomaterials. *Community Dent Oral Epidemiol* 2004;32(April (2)):150–7.