Healing of oral lichenoid lesions after replacing amalgam restorations: A systematic review

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Objective. We sought to systematically review the literature related to oral lichenoid lesions (OLLs) and amalgam restorations.
Study design. Cohort and case-controlled studies (no randomized controlled trials or controlled clinical trials available) were reviewed with respect to inclusion criteria and data on patients with OLLs, treatment interventions, and the measurement of outcomes.
Results. Fourteen cohort and 5 case-controlled trials met the criteria. The study population consisted of 1158 patients (27% male and 73% female; age range, 23-79 years). From 16% to 91% of patients had positive patch test results for at least 1 mercury compound. Of 1158 patients, 636 had to have their restorations replaced. The follow-up period ranged from 2 months to 9½ years. Complete healing ranged from 37.5% to 100%. The greatest improvements were seen in lesions in close contact with amalgam.
Conclusions. Protocols must be standardized to obtain valid results. The replacement of amalgam restorations can result in the resolution or improvement of OLLs. Patch testing seems to be of limited value. The topographic relationship between an OLL and an amalgam restoration is a useful—but not conclusive—marker.
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The biocompatibility of dental amalgam—or, more specifically, the toxic and allergenic potential of mercury, its main constituent—has received a tremendous amount of attention in recent years. The biodegradation of dental materials is of fundamental importance to their biocompatibility because the release of elements is nearly always necessary for an adverse reaction to occur.[1] Electrochemical reactions constitute 1 of the major forms of interaction between dental amalgam and the oral fluids that result in degradation of the structure.[2-4] The most severe corrosion of amalgam restorations takes place in localized corrosion cells, such as pits and crevices. The other major cause of degradation in the oral cavity is through mechanical forces to which restorations are subjected.[5] There are significant synergisms among electrochemical and mechanical forces.

A release of mercury has been reported to occur with the use of different types of amalgam alloys.[6] In addition to mercury, other elements may be released from amalgam restorations.[7] Oral tissues such as the mucous membranes, gingivae, dentin, and dental pulp have been reported to be pathways of mercury uptake.[8-11] Increased mercury content has been observed in gingival biopsy specimens taken from areas in close contact with amalgam.[11] Bolewska et al[9] reported that in 20 of 21 (95%) patients with mucosal lesions confined to a contact zone with amalgam only, substantial accumulations of mercury were visible in both fibroblasts and macrophages. However, few patients with oral lichen planus (OLP) lesions either partially in contact with amalgam fillings or completely without contact and few in the control groups (ie, those with normal mucosa not in contact with amalgam fillings and those with normal mucosa in contact with amalgam) exhibited accumulations of mercury. The term *oral lichenoid lesion* (OLL) is commonly used to describe OLP lesions that develop in contact with dental restorations,[12] lesions associated with medications, those of graft-versus-host disease, and lesions associated with systemic diseases.[13]

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The clinical appearances and histopathologic changes associated with OLLs and OLP are similar, and currently there is no reliable method to distinguish between them.[13] However, if an OLL is related to a causative factor, then the removal of this factor may result in the resolution of the clinical lesion. This contrasts with patients having OLP, who may require palliative care and monitoring over many years; the premalignant nature of OLP is also a major concern.[14] In either situation, the etiology and pathogenesis still remain to be fully elucidated. Is OLP a multivariate group of diseases with common features or is it a disease characterized by its submucosal infiltrate as an immunologic response? In the case of OLLs caused by dental materials, either the material or its corrosion product is thought to act locally to alter the antigenicity of basal keratinocytes that then become the target for cell-mediated autoimmune damage.[15,16] Many lesions on the oral mucosa that have lichenoid characteristics appear to have arisen from contact with restorations, particularly dental amalgam.[12,16-18] The results of clinical studies have shown that the replacement of dental amalgam restorations with restorations of other materials has resulted in the resolution, or at least the improvement, of these OLLs.[9,19-22] However, the diagnosis of OLLs and the value of the replacement of dental amalgam restorations with respect to patient management are still matters of controversy. At present, a diagnosis of OLLs caused by dental materials depends on the following: (1) their clinical presentation, (2) confirmatory histologic results suggestive of OLP/OLL, (3) the results of a patch test to mercury (whose benefit in the case of an OLL remains unclear), and (4) an understanding of the anatomic relationship between the lesions and the amalgam restoration.[12,19,20,23,24] There is thus a considerable need for further research both to clarify the etiology of OLLs and OLP and to provide tests to distinguish between these clinically and histologically similar lesions. This would then lead to better-defined treatment approaches and outcomes.

Decisions about the organization and delivery of health care should be informed by the knowledge base of the effectiveness of the interventions or policies. A systematic review is the process of systematically locating, appraising, and synthesizing evidence from previous scientific studies to obtain a current, and hopefully more reliable, overview. It reduces large quantities of information into manageable portions; enables one to formulate policy and develop guidelines for the efficient use of resources; limits bias; and improves accuracy.[25]

The aim of this study was to systematically review the research literature on the association between dental amalgam restorations and OLLs.

OBJECTIVES

We sought to determine the effectiveness of replacing amalgam restorations with respect to the healing of OLLs; to clarify the topographic relationships between OLLs and amalgam restorations; and to review the use of patch tests as predictors of the outcome of the replacement of amalgam with an alternative material in patients with OLLs.

REVIEW METHODS

Search strategy

Electronic databases are searched. Data from MEDLINE (1966-2000), EMBASE (1980 to 2000), and the Cochrane Library (Issue 2, 2000) were reviewed. A search strategy was devised for MEDLINE (OVID) with the help of a trained librarian. This strategy was adapted for use with the other databases. Search terms used included both MeSH and free-text terms, as follows.

MeSH
- Lichen planus, oral
- Lichen planus (pre-1993)
- Lichenoid lesion, oral
- Lichenoid reaction, oral
- Contact lesions, oral
- Mercury
- Dental amalgam
- Dental restoration, permanent.

Free-text
- Lichen planus
- Lichenoid and (reaction$ or lesion$)*
- Hypersensitivity
- Allerg$
- Amalgam
- Mercury
- Dental restoration$
- Filling$.

*The $ symbol represents truncation symbol.

Review lists are screened. In addition to electronic searches, reference lists of existing reviews in the area of lichenoid reactions reported to be caused by dental amalgam restorations (ie, regarding lichenoid reaction lesions, LP, hypersensitivity, or allergy to dental materials [including amalgam]) were screened. Experts in the field were contacted to help identify other articles. Because of limits in resources, non−English-language articles were not included in the review.

Inclusion criteria

Types of participants. Patients with lichenoid reactions of any clinical forms (reticular, striated, atrophic, erosive, and ulcerative) who fulfilled the following criteria were included:

1. Amalgam restorations suspected as a causal factor.
2. Lichenoid reactions diagnosed clinically with or without histopathologic confirmation or patch testing.

Types of intervention. The amalgam restoration was totally or partially replaced. Replacement dental materials could be ceramic, metal ceramic, gold, composite, glass ionomer, or resin-modified glass ionomer restorations.

Types of outcome measures. When possible, a follow-up assessment of 3, 6, and 12 months of treatment was recorded. The clinical results were graded as one of the following:

- Complete healing (ie, the absence of all clinical symptoms and signs)
- Marked healing (ie, reduction in size or severity, or both, of the lesion)
- No improvement or worse.

Patient satisfaction was also recorded if discussed in the primary study.

Study design

Ideally, we sought to examine the effectiveness of replacing amalgam restorations with respect to the healing of lichenoid reactions; only randomized controlled trials (RCTs) or controlled clinical trials (CCTs) meeting the aforementioned inclusion criteria for participant and intervention type and outcome measures were included in the review. In the absence of any RCTs or CCTs, cohort studies and case-control studies were included.

Assessment of relevance

Two reviewers (Y.I., P.B.) independently assessed all available titles and abstracts of potentially relevant studies. To confirm eligibility, assess quality, and extract data using a piloted data-extraction form, these reviewers also evaluated the full-text articles of selected studies independently.

Assessment of validity

We acknowledge that the reliability of a study's results is dependent on the study design. Thus, all included studies were assessed by using modified quality assessment checklists. Two reviewers carried out this process independently and in duplicate. Discrepancies were resolved by discussion and consensus and—if necessary—by referral to a third reviewer (A.J.D. or A.M.G.).

Issues regarding the quality of the studies on the replacement of dental amalgam restorations for the treatment of lichenoid reactions will be discussed later in this article.

Data extraction

A data extraction form was devised and piloted on a selection of relevant articles by two reviewers (Y.I. and P.B.). Discrepancies were again taken to a third party (A.J.D.). The data extracted were related to study design, patient characteristics, position and type of OLL, details of the histologic confirmation, details of patch test results, number of patients receiving replacement restoration(s), the duration of follow-up, and healing.

Data analyses

Details of the data extraction were tabulated, and the study characteristics were discussed. Because of the heterogeneity in the studies in terms of study design, patient characteristics, the use of replacement materials, and outcome measures, no formal statistical pooling of data was undertaken.

RESULTS

Studies

A preliminary search of the literature suggested that there were no RCTs or CCTs in the area of study. The review therefore included any cohort and case-controlled studies that met the inclusion criteria for participants (patients), treatment interventions (replacement of amalgam restorations with an alternative material), and measurement of outcomes as previously defined.

Nineteen studies of variable quality were found that met the inclusion criteria: 14 were cohort studies[12,17,20,22,24,26-34] and 5 were case-controlled.[19,21,35-37] The studies included a total of 1158 patients, and the majority of these studies were carried out in Scandinavian countries 12/19 (63.2%).

In general, cases were selected from patients who were referred for investigation of their lesions and the possible relationship of these to restorations. Sample sizes of the included studies were variable (Table I). Four studies included a small number of treated patients—between 4 and 8 patients.[12,26,27,32] Other studies included a large number of patients, such as those of Henriksson et al[24] (131 patients) and Bratel et al[37] (129 patients). In many studies, the conclusions were dependent on the authors' experience more than their results may suggest.

Of the 14 single-cohort studies, it was felt that only 1 study included a nonrepresentative patient population.[17] In this study, the authors included only those patients with the erosive form of OLP. The majority of the cohorts provided clear inclusion criteria (12/14, 85.7%) and included patients at a similar point in their disease progression (11/14, 78.6%). Patients were followed up

Table I. Location of studies, number of included patients and their age and gender

Study	*Country*	*Patients investigated (no)*	*Age (y)*	*Male/Female*
Finne et al (1982)[26]	Sweden	29	23-73	12/17
Lind et al (1986)[17]	Norway	52	51 (24-68)	13/39
James (1987)[12]	UK	29	55 (32-70)	7/22
Bolewska et al (1990)[21]	Denmark	25 close contact	49 (29-74)	4/21
		24 exceeding contact	52 (32-74)	12/12
Skoglund and Egelrud (1991)[27]	Sweden	24	49 (35-69)	9/15
Laine et al (1992)[28]	Finland	91	M: 51 (23-76)	26/65
			F: 43 (25-62)	
Skoglund (1994)[22]	Sweden	48 (from 55)	50.4 (31-78)	12/36
Pang and Freeman (1995)[29]	Australia	19 (from 41)*	52.6 (28-72)	2/17
Smart et al (1995)[31]	UK	13	44.8	1/12
Henriksson et al (1995)[24]	Sweden	159	M 52.5, F 53.1	46/113
Koch and Bahmer (1995)[30]	Germany	11	44.8	4/7
Ostman et al (1996)[36]	Sweden	30 close contact	52	10/39
		19 no contact		
Bratel et al (1996)[37]	Sweden	142 close contact	58 ± 10	28/114
		19 exceeding contact	54 ± 10	5/14
Alanko et al (1996)[32]	Finland	13	NR	3/10
Ibbotson et al (1996)[33]	UK	109 OLLs	50	32/77
		22 OLLs + 10 skin LP	51	10/22
		66 other lesions	40	25/41
Laine et al (1997)[19]	Finland	12 positive PT	46.7	1/11
		11 negative PT	52.3	1/10
Laine et al (1997)[20]	Finland	118	M: 50.4	16/102
			F: 49.6	
Koch and Bahmer (1999)[35]	Germany	19 close contact	M: 40; F: 44	5/14
		25 no contact	M: 52; F: 51	7/18
Laine et al (1999)[34]	Finland	19	56.9 (36-79)	5/14

OLL, Oral lichenoid lesion; *LP*, lichenplanus; *PT*, patch test results.
*19 had positive patch results.

for longer than 3 months in 12 of the studies (85.7%), and outcomes were assessed by using objective criteria in 10 of the studies (71.4%).

All of the included case-control studies had the disease state of the cases reliably assessed. Only 1 study showed some risk of bias in the selection of patients for inclusion in the study.[37] All 5 studies used suitable, comparable control groups. In all but 1 study,[36] the intervention was assessed in the same way for both cases and control subjects. However, the response rates differed between groups in 2 studies.[21,35] None of the studies appeared to have overmatched the cases and control subjects (ie, matching the patients and controls on factors related to exposure).

Patients

A total of 1158 patients whose oral lesions were suspected as related to their amalgam restorations were investigated. The age of patients ranged between 23 and 79 years. The mean age ranged from a minimum of 40 years[35] to a maximum of 58 years.[37] The gender of patients ranged between 9%[19] and 41%[26] for male subjects and between 91%[26] and 59%[19] for female subjects (Table I). A total of 293 of 1158 patients (25%) were male and 865 of 1158 (75%) were female. In all 636 of the 1158 patients had their amalgam restorations replaced with alternative materials.

Lesions

Oral mucosal lesions may manifest in variable forms with striae and plaques and in erythematous, erosive, atrophic, or ulcerative forms. Subjective discomfort or soreness from the oral mucosa is usually associated with the atrophic or the erosive form. The type of lesion was not recorded in some studies.[19,20,24,28,32-34,37] However, available data revealed that the erosive form of OLLs was reported more frequently (9 studies) than reticular or striae forms,[12,17,22,36] with only 2 studies reporting ulcerative cases[22,36] (Table II). Skoglund and Egelrud[27] classified lesions on a scale from 1 to 5 depending on the histologic findings. The position of the lesions was not clearly recorded in many studies.[12,19-22,26,28,30-34,36,37] However, the majority of OLLs were found on the buccal mucosa and on the lateral border of the tongue.[20,24,34] Some lesions were found on the gingiva;[20,24] a few lesions were on the lips, palate, and the floor of the mouth[20,29,34] (Table II).

Table II. Characteristics of oral lichenoid lesions

	Position of lesions			Type of lesions			Topographic relationships between lesions and amalgam restorations		
Study	*Buccal mucosa*	*Tongue*	*Others*	*Reticular/ plaque*	*Erosive/ atrophic*	*Ulcerative*	*Close contact*	*Exceeding contact*	*No contact*
Finne et al (1982)[26]	NR			15/29	14/29	0/29	29 cases of lesions adjacent to amalgam restorations		
Lind et al (1986)[17]	45	NS	NS	0/52	52/52	0/52	All 52 close or exceeding contact		
James (1987)[12]	NS			3/29	26/29	0/29	All 29 close or exceeding contact		
Bolewska et al (1990)[21]	NR			NC			Group 1: 25/25	24/24	
Skoglund and Egelrud (1991)[27]	24	6		Graded (1-5)			NR		
Laine et al (1992)[28]	NR			NR			18	NC	NC
Skoglund (1994)[22]	NR			6/48	34/48	8/48	33/48	14/48	1/48
Pang and Freeman (1995)[29]	19	12	Palate, 3	14	7		19 (from 41)/19		
Smart et al (1995)[31]	NR			0/13	13/13	0/13	13/13		
Henriksson et al (1995)[24]	257 lesions in 155 pts	98 lesions in 52 pts	Gingiva, 23	NR			108/159	23/159	28/159
Koch and Balmer (1995)[30]	NR			7/11	4/11	0/11	10/11		1/11
Ostman et al (1996)[36]	NR			8/49	35/49	6/49	Group 1: 30/30	19/19 or no contact	
Bratel et al (1996)[37]	NR			NR			Group 1: 142/142	19/19	
Alanko et al (1996)[32]	NR			NR			NR		
Ibbotson et al (1996)[33]	NR			NR			NR		
Laine et al (1997)[19]	NR			NR			Group 1: 6/10	4/10	
							Group 2: 5/8	3/8	
Laine et al (1997)[20]	116	94	Gingiva, 42; palate, 5; lips, 7; floor of mouth, 1	NR			74/118	44/118	
Koch and Bahmer (1999)[35]	NR			Group 1: 11/19	8/19		Group 1: 19/19		
				Group 2: 18/25	7/25				25/25
Laine et al (1999)[34]	19	12	Lip, 1	NR			11/19		

NR, Not recorded; *NS,* not specific; *NC,* not clear; *pts,* patients.

In general, the majority of lesions were in close contact or in partial contact with amalgam restorations. The clinical diagnosis of OLLs was dependent in part on the contact of lichenoid lesions (LLs) with amalgam. Nineteen studies—for example, that of Henriksson et al[24]—used these topographic relationships as the main indicator, whereas other studies did not report these relationships clearly[12,17,26-28,32,33,36] (Table II).

Patch test

Different mercury compounds were used to investigate the possible role of sensitivity to mercury in the

Table III. Positive patch testing results for mercury compounds

Study	One mercury compound	Mercury chloride		Metallic mercury		Ammoniated mercury				Mercury ammonium chloride	Phenyl mercuric nitrate	Phenyl mercuric acetate	Thiomersal
		0.1%	0.5%	1.0%	5.0%	0.1%	1.0%	2.0%	5.0%	1.0%	0.05%		0.1%
Finne et al (1982)[26]	18/29				18/29								
Lind et al (1986)[17]	18/52												
James (1987)[12]	10/29				9/29			10/29			1/29		1/29
Bolewska et al (1990)[21]	11/21		11/21										
	1/20		1/20										
Skoglund and Egelrud (1991)[27]	8/24									8/24			
Laine et al (1992)[28]	18/33		12/33		6/33								5/33
Skoglund (1994)[22]	19/48									19/48			
Pang and Freeman (1995)[29]	19/41	6/8		19/41			15/41				1/6		0/41
Smart et al (1995)[21]	13/13									13/13			
Henriksson et al (1995)[24]	3/17												
Koch and Bahmer (1995)[30]	10/11	6/11								8/11			
Ostman et al (1996)[36]	15/30												
	2/19												
Bratel et al (1996)[37]													
Alanko et al (1996)[32]	7/13												
Ibbotson et al (1996)[33]	21/109					21/10							
	0/22					9							
	2/66					0/22							
						2/66							
Laine et al (1997)[19]	12/12	10/12			10/12					7/12		7/12	
	0/11	0/11			0/11					0/11		0/11	
Laine et al (1997)[20]	80/118	67/118			50/118					36/118		35/118	34/118
Koch and Bahmer (1999)[35]	15/19								11/19	11/19			
	3/25												
Laine et al (1999)[34]	10/19		9/19		3/19							5/19	8/19

etiology of OLLs (Table III). The applied mercury compound(s), their concentrations, and reading times varied among studies and sometimes in the same study.[29] In general, patches were applied to the back or the forearm of the patients for 24 to 48 hours, and the results were read after 24 hours; however, further readings of results were made after a few days (2-17 days) in three studies.[26,29,30] Positive patch test results for at least 1 mercury compound were recorded in 91% of the subjects tested (10/11)[30]; however, the delayed reading increased the rate of positive reactions in this study. The second-highest positive patch test rate was 68% (80/118).[20] The lowest rate of positive patch testing was 16% (21/131).[33] In the study by Henriksson et al,[24] only 17/159 patients were patch-tested, 3 of whom had positive reactions. Only patients with positive patch test results were evaluated by Smart et al.[31] Of 614 patients who had their amalgam restorations replaced, 348 (57%) were patch-tested (Tables III and IV). Of those, 239 (69%) had positive patch test results for at least 1 mercury

Table IV. Positive patch testing results for amalgam containing alloy

Study	Silver nitrate 1%	Copper sulphate 2%	Cupric nitrate 5%	Zinc sulphate 5%	Zinc chloride 1%	Zinc 2.5%	Tin	Amalgam powder (5%, 10%, or 20%)	Amalgam disk
Finne et al (1982)[26]									
Lind et al (1986)[17]	3/52								
James (1987)[12]			8/29	1/29					
Bolewska et al (1990)[21]									
Skoglund and Egelrud (1991)[27]	0/24	0/24							
Laine et al (1992)[28]	1/33					0/33	0/33	6/33	
Skoglund (1994)[22]									
Pang and Freeman (1995)[29]									1/2
Smart et al (1995)[31]									
Henriksson et al (1995)[24]									
Koch and Bahmer (1995)[30]	0/11	0/11			1/11			7/11	
Ostman et al (1996)[36]									
Bratel et al (1996)[37]									
Alanko et al (1996)[32]									
Ibbotson et al (1996)[33]									
Laine et al (1997)[19]	1/12							3/12	
	1/11							0/11	
Laine et al (1997)[20]								5/118	
Koch and Bahmer (1999)[35]	0/19	0/19						1/19	
Laine et al (1999)[34]								1/19	

compound. The rates of positive reactions to different mercury compounds varied among studies. However, mercury chloride (0.1%) was accompanied by the highest rate of positive reactions. The rates of positive reactions to 0.1% mercury chloride ranged between 43% (10/23)[19] and 75% (6/8)[29]; to 0.5% mercury chloride, between 29% (12/41)[21] and 47% (9/19)[34]; and to 1% mercury ammonium chloride, between 30% (7/23)[19] and 73% (8/11).[30] The lowest recorded number of cases of a positive reaction was to thiomersol, ranging from 0% (0/41)[29] to 42% (8/19).[34] In a control series, 303 patients free of OLL were also patch-tested, 4.6% of them reacted positively to mercury.[29] A few patients showed a positive reaction to other elements in dental amalgam (Table IV), particularly to amalgam powder; rates ranged between 4% (5/118)[20] and 64% (7/11).[30] Lichenoid changes were recorded in the biopsy specimens from test sites in some patients with a positive patch test result.[30] However, the lymphocyte proliferation test applied to confirm the patch test results in the diagnosis of allergy has been reported to be invalid.[19]

Treatment

Different criteria were used to select patients who needed their amalgam restorations replaced. Patient populations ranged from 4 patients[26] to 131 patients.[24] A total of 636 of 1158 (55%) patients had their amalgam restorations replaced by alternative materials (Table V). In general, the replacement of amalgam restorations in patients with OLLs implied a dependence on the clinical diagnosis (ie, the lesions' manifestations and their location in relation to the amalgam restorations). The replacement of amalgam restorations was carried out for some patients even where there was no contact with amalgam. Positive patch testing was required in 8 studies before such replacements were undertaken.[16,26-32] In 9 studies, patients with positive or negative patch test results had their amalgam restorations replaced.[17,19-22,33-36] In 2 remaining studies (Table V), patch tests were not used or were used just for a few patients[24,37]; the topographic relationships among the amalgams and lesions were used as the main parameter. Histologic investigations were carried out in most studies, mainly to exclude other lesions. The replacement of amalgam restorations was either for those in contact with lesions or for all amalgam restorations (Table VII). The replacement materials were not reported in 5 of the studies.[12,20,28,33,35] The remaining studies using a variety of materials including gold, resin composite, porcelain, glass ionomer, and acrylic (Table V).

Outcomes

The follow-up period ranged from 2 to 114 months (Table VI). The follow-up period was 3 months or more in 16 studies; 2 studies included cases with follow-up periods of less than 3 months.[31,34] In the study by Henriksson et al,[24] the follow-up period was not clear. The clinical results in most studies were graded as follows: *complete healing* (ie, the absence of all clinical symptoms and signs), *marked healing* (ie, changes in the

Table V. Healing in patients who received replacements for their amalgam restorations

	Healing									
	Complete			*Marked*			*No improvement*			
Study	*Positive patch result*	*Negative patch result*	*Total (%)*	*Positive patch result*	*Negative patch result*	*Total (%)*	*Positive patch result*	*Negative patch result*	*Total (%)*	*Patient satisfaction*
Finne et al (1982)[26] No. = 4	3	0	**3 (75%)**	1	0	**1 (25%)**	0	0	**0**	NR
Lind et al (1986)[17] No. = 18	16	10	**16 (88.9%)**	1	0	**1 (5.6%)**	0	1	**1 (5.6%)**	NR
James (1987)[12] No. = 6	5	0	**5 (83.3%)**	1	0	**1 (16.7%)**	0	0	**0**	Yes
Skoglund and Egelrud (1991)[27] No = 8	3	0	**3 (38%)**	4	0	**4 (50%)**	1	0	**1 (12%)**	NR
Laine et al (1992)[28] No. 15	7	0	**7 (47%)**	6	0	**6 (40%)**	2	0	**2 (13%)**	NR
Skoglund (1994)[22] No. 48	9	13	**22 (46%)**	9	12	**21 (44%)**	1	4	**5 (10%)**	Yes
Pang and Freeman (1995)[29]* No. = 15	13	0	**13 (86%)**	1	0	**1 (7%)**	1	0	**1 (7%)**	Yes
Smart et al (1995)[31] No. = 13	11	0	**11 (84%)**	1	0	**1 (8%)**	1	0	**1 (8%)**	Yes
Henriksson et al (1995)[24] No. = 131	NR		**84 (64%)**	NR		**27 (21%)**	NR		**20 (15%)**	NR
Koch and Bahmer (1995)[30] No. = 10	7	0	**7 (70%)**	3	0	**3 (30%)**	0	0	**0**	NR
Ostman et al (1996) [36†]	14	13	**27 (93%)**	0			1	1	**2 (7%)**	NR
Group 1 = 29	0	6	**6 (32%)**	0			2	11	**13 (68%)**	
Group 2 = 19										
Bratel et al (1996)[37]	NR	NR	**50 (45%)**	NR	NR	**55 (50%)**	NR	NR	**5 (5%)**	NR
Group 1 = 110	NR	NR	**2 (10%)**	NR	NR	**10 (53%)**	NR	NR	**7 (37%)**	
Group 2 = 19										
Alanko et al (1996)[32] No. = 7	7	0	**7 (100%)**	0	0	**0**	0	0	**0**	NR
Ibbotson et al (1996)[33‡] No. = 22	16	3	**19 (86%)**	1	2	**3 (14%)**	0	0	**0**	NR
Laine et al (1997)[19]	5	0	**5 (50%)**	1	0	**1 (10%)**	4	0	**4 (40%)**	NR
Group 1 = 10	0	2	**2 (25%)**	0	4	**4 (50%)**	0	2	**2 (25%)**	
Group 2 = 8										
Laine et al (1997)[20] No. = 77	28	3	**31 (40%)**	27	9	**36 (47%)**	7	3	**10 (13%)**	NR
Koch and Bahmer (1999)[35]	9	0	**9 (50%)**	4	0	**4 (22%)**	2	3	**5 (23%)**	NR
Group 1 = 18			**2 (33%)**			**0**			**4 (67%)**	
Group 2 = 6										
Laine et al (1999)[34] No. = 19	7	0	**7 (37%)**	2	2	**4 (21%)**	1	7	**8 (42%)**	NR

The study of Bolewska et al (1990)[21] was excluded from this table because the number of patients was not clear before and after the treatment.
NR, No record.
*One patient lost during follow-up.
†One patient died.
‡These authors mixed the groups of patients with complete and marked healing.

size and/or in the severity of the clinical form of the lesion), and *no improvement or worse*. However, Ibbotson et al[33] mixed together the number of patients with complete and marked healing. The percentage of patients achieving complete healing ranged from 37.5% (3/8)[27] to 100% (7/7)[32] (Table V). Four studies showed that all patients had lesions that healed or improved.[12,26,30,32] High rates of no-improvement were recorded in other studies e.g. 42 % (8/19)[34] and 33% (6/18).[19] Taking together the available data, 85% of patients (518/612) had their lesions heal or improve after the replacement of their dental amalgam restorations.

Table VI. Number of patients who had their amalgam restorations replaced, the alternative materials and the follow up period

Study	No. of patients with amalgams replaced	Alternative materials used	Follow-up (mo)
Finne et al (1982)[26]	4	Gold, composite, or glass ionomer	12
Lind et al (1986)[17]	18	Gold, composite, or porcelain	4-36
James (1987)[12]	6	NR	3-24
Bolewska et al (1990)[21]	22	Group 1: gold fused to porcelain 4, composite 17 both 1 Group 2: composite 9	6
Skoglund and Egelrud (1991)[27]	8	NR	12-24
Laine et al (1992)[28]	15	Gold, 3; composite, 6; glass ionomer, 3; gold and composite, 3	38 (20-72)
Skoglund (1994)[22]	48	Gold, composite, porcelain, or glass ionomer	3-36
Pang and Freeman (1995)[29]	16	Gold, composite, porcelain, or glass ionomer	41 (2-114)
Smart et al (1995)[31]	13	Composite	NS
Henriksson et al (1995)[24]	131	Gold, composite, porcelain, or glass ionomer	36
Koch and Bahmer (1995)[30]	10	Gold, 6; composite, 4	5-41
Ostman et al (1996)[36]	Group 1: 30 Group 2: 19	Gold, 16; full porcelain, 12; composite, 5; porcelain fused to metal, 15; and acrylic, 17	45-72
Bratel et al (1996)[37]	Group 1: 110 Group 2: 19	Gold, 29%; porcelain fused to metal, 51%; composite, 10%; and other restorative materials, 10%	6-12
Alanko et al (1996)[32]	7	NR	NS
Ibbotson et al (1996)[33]	22	Composite	12-24
Laine et al (1997)[19]	Group 1: 10 Group 2: 8	NR	12
Laine et al (1997)[20]	77	NR	6-12
Koch and Bahmer (1999)[35]	Gp1 18 Gp2 6	Gold, composite, or porcelain	6-33
Laine et al (1999)[34]	19	NR	2-6
Total	636		

NS, not specific; *NR*, not record.

After the replacement of the amalgam fillings, the lesions healed or improved markedly and the symptoms resolved dramatically from 1 week to 3 weeks, with spontaneous remission also being recorded.[17] OLLs on the trunk and/or genital area were reported in 3 patients. The replacement of dental amalgam restorations resulted in complete resolution in 1 patient.[28] Two patients experienced recurrence.[31] One patient developed a squamous cell carcinoma at the lateral border of the tongue adjacent to—but not in the same area as—the previous lesion.[36]

All lesions on the lateral surface of the tongue healed when all amalgam fillings were removed, whereas gingival lichenoid reactions did not respond to the removal of amalgam fillings.[24] No statistically significant difference in the healing of the lesions in the buccal mucosa between partial or total removal of amalgam could be found.[24,36] Bratel et al[37] used randomly selected subgroups, finding that metal-ceramic crowns did not facilitate the healing of OLL to the same extent as did gold crowns. Similar results were reported by Ostman et al[36] and Skoglund.[22] The replacement of 22 amalgams with non γ-2 amalgam yielded no response.[21]

Studies showed variable rates of healing of OLLs irrespective of the patch test results. Similar rates of healing were found for patients with positive or negative patch test results in some studies,[17,19,36] whereas others revealed significant differences among them.[34] However, when the available data (Table V) are taken together, 214/239 (90%) with positive patch tests and 74/109 (68%) with negative results had complete/marked healing of the OLLs.

Five studies presented details about the response of lesions with regard to their topographic relationships with amalgam restorations (Table VIII).[19,22,24,35,37] Their results showed a significant difference in healing related to the topographic relationship of the amalgam and the OLL. The greatest improvements were noted when there was close contact between the OLL and the restoration and the least when there was no contact.

Table VII. Healing of OLLs after total or partial replacement of amalgam restorations

	Complete healing		*Marked healing*		*No improvement*	
Study	*Complete replacement*	*Partial replacement*	*Complete replacement*	*Partial replacement*	*Complete replacement*	*Partial replacement*
Finne et al (1982)[26]	3/4		1/4			
James (1987)[12]	5/6		1/6			
Laine et al (1992)[28]	7/10	0/5	1/10	5/5	2/10	0/5
Skoglund and Egelrud (1991)[27]	15/31	7/17	13/31	8/17	3/31	2/17
Pang and Freeman (1995)[29]	13/15		1/15		1/15	
Henriksson et al (1995)[24]	49/69	35/62	13/69	14/62	7/69	13/62
Laine et al (1999)[34]	6/11	1/18	2/11	2/8	3/11	5/8
Total	98/146 (67%)	43/92 (47%)	32/146 (22%)	29/92 (32%)	16/146 (11%)	20/92 (22%)

Complete healing was found when lesions were in close contact with amalgam in 45% to 77% of patients.[24,37] Taken together, the results of these 5 studies showed that when lesions were in close contact with amalgam restorations, 93% (246/266) of lesions healed or improved after the replacement of the amalgam restorations. However, when the lesions exceeded the area of contact with the amalgam restorations, 70% (42/60) of patients showed improvement compared with 46% (11/24) when there was no contact.

DISCUSSION

This study aimed to systematically review the literature from 1966 to 2000 related to the healing of OLLs after the replacement of amalgam restorations. Nineteen studies of variable quality were found that met the inclusion criteria; 14 were cohort and 5 case-controlled studies. Studies covered the treatment of 1158 patients, and the majority of these studies were performed in Scandinavian countries. The term *oral lichenoid lesions* (*OLLs*) was used in this review to describe lesions of the oral mucosa accompanied by the presence of amalgam restorations. Different terms were used in the literature; LLs have sometimes been considered part of OLP[12,17,26,32] or described as *contact allergies*,[21] *OLLs*,[19,20,27,29,30,34,35] *contact lesions*,[22,37] or *oral lichenoid reactions*.[24,36]

Oral mucosal lesions may manifest in variable forms (with striae and plaques) as erythematous, erosive, atrophic, or ulcerative lesions. The buccal mucosa and lateral border of the tongue are most often affected, but in some cases, the gingivae, lips, and the floor of the mouth are affected. Lesions may be in close or partial contact with amalgam restorations or even without contact with amalgam. Subjective discomfort or soreness from the oral mucosa was usually associated with the atrophic or erosive forms. Patient symptoms ranged from mild to severe symptoms, with the majority being graded as moderate.[24] However, it is difficult to link an allergic response with some local oral complaints such as a metallic taste or dryness.[38-40] The prevalence of OLLs among women is approximately 3 times that of men, with the highest rates in those 50 years of age and older. The clinical manifestations of OLLs are similar to those of OLP. Henriksson et al[24] suggested that the classical picture of OLP—that of widespread reticular bilateral lesions with pronounced striae affecting the entire buccal mucosa and sometimes the lateral surfaces of the tongue—is not related to amalgam restorations.

The LLs induced by dental materials may represent the oral manifestation of a chronic irritation in some patients, be the clinical result of a delayed hypersensitivity reaction in others[24] or represent a local immunologic effect.[15,16] Regardless of the cause of the lichenoid reaction, a long period of exposure seems to be required before the LL manifests itself on the oral mucosa.[24] Hypersensitivity reactions of the oral mucosa are less common than those on the skin. There may be other contributing factors in eliciting clinical reactions, such as impaired mucosal integrity.[41] The barrier function of the contacting oral tissues is important and may be impaired by trauma, endocrine status, salivary flow, and probably saliva composition. Age, genetic background, race, sex, site, and history of dermatitis may all be important factors.[42]

Regardless of the etiology of the lichenoid contact lesion, replacing amalgam restorations has been suggested to resolve these lesions. However, a variety of criteria have been used to select patients who need their amalgam restorations replaced, including the following: clinical diagnosis, form of the lesions, topographic relationships among the lesions and amalgam restoration, and the results of patch testing. Substitute materials have included gold, composite, porcelain, glass ionomer, and acrylic. Partial removal of amalgam restorations including only the amalgam fillings in contact with the LL is sufficient to obtain adequate healing.[24,36] However, total removal has been suggested as a therapy for patients with long-standing atrophic or erosive lesions without contact with amalgam.[24] For 90% of the patients reviewed in this study, the lesions improved markedly or healed completely and their symptoms resolved after

Table VIII. Healing of OLLs regarding their topographical relationships with amalgam restorations

	Complete healing			*Marked improvement*			*No improvement*		
Study	*Close contact*	*Exceeding contact*	*No contact*	*Close contact*	*Exceeding contact*	*No contact*	*Close contact*	*Exceeding contact*	*No contact*
Henriksson et al (1995)[24]	73/94 (78%)	7/20 (35%)	4/17 (24%)	14/94 (15%)	9/20 (45%)	4/17 (24%)	7/94 (7%)	4/20 (20%)	9/17 (52%)
Skoglund and Egelrud (1991)[21]	15/33 (45%)	6/14 (43%)	1/1 (100%)	16/33 (49%)	6/14 (43%)	0/1	2/33 (6%)	2/14 (14%)	0/1
Bratel et al (1996)[37]	50/110 (45%)	2/19 (11%)	–	55/110 (50%)	10/19 (53%)	–	5/110 (5%)	7/19 (37%)	–
Laine et al (1997)[19]	7/11 (64%)	0/7	–	3/11 (27%)	2/7 (2%)	–	1/11 (9%)	5/7 (71%)	–
Koch and Bahmer (1999)[35]	9/18 (50%)	–	2/6 (33%)	4/18 (22%)	–	0/6	5/18 (23)	–	4/6 (67%)
Total	154/266 (58%)	15/60 (25%)	7/24 (29%)	92/266 (35%)	27/60 (45%)	4/24 (17%)	20/266 (7%)	18/60 (30%)	13/24 (54%)

replacing their amalgam restorations. This improvement was found after a short time (from 1 week to 3 months) of replacing their amalgam restorations. The percentage of patients for whom complete healing was achieved ranged from 37.5 %[27] to 100%.[32] Spontaneous remission also occurred.[17]

A significant difference in healing was found related to the topographic relationship of the amalgam and the OLL.[19,22,24,35,37] The greatest improvements were noted when there was close contact between the OLLs and the restoration and the least improvement when there was no contact. In the present review, complete healing was found when lesions were in close contact with amalgam from 45% to 77% of the time.[24,37] Even when lesions were not in contact with amalgam, patients experienced improvement. Nevertheless, parafunctional habits may cause close contact between lesions and amalgam fillings and occasionally lead to errors in classification.[24]

Patch testing is now widely used to detect sensitivity to specific substances in patients with suspected contact allergy. Patch tests results may vary substantially, depending on the compounds, the concentration of material, the vehicles that were used for testing, and on the criteria for the evaluation of a patch test. Sensitization is not necessarily followed by symptoms of allergy, and a positive patch test does not indicate that the substance is a sole or contributing cause of allergy.[43] Patch testing to mercury compounds is notoriously problematic, with questions raised of irrelevant and irritant reactions.[44] For example, mercury chloride has been suggested to be highly irritant.[45] Burrows[46] discovered that allergy to 1 mercury compound does not imply allergy to all mercury compounds or the metal itself. Several studies have mentioned the possibilities for the occurrence of false-positive and false-negative reactions.[47-48] A positive patch test reaction may have relevance to the present or past or may be unexplained.[49] Cases of sensitization to metallic mercury have been described after the use of thermometers,[50] after experimental exposure,[51] and in dentists.[52] White and Brandt[53] showed that positive patch test results for mercuric chloride increased in dental students—that is, from 2% in freshmen to 10.8% in seniors. Mercury hypersensitivity has been found in 3.2% of the general population, 3.4% in individuals with amalgam fillings, in 1.6% without amalgam fillings, and in 62% of patients with OLL tested with metallic mercury only.[26] A rising incidence of allergy to ammoniated mercury has been reported, with 2.5% positive reactions in 2634 patch tests (in 1962 and 1963) increasing to 4.9% of 1273 patients patch-tested in 1967.[54] Contact with metallic mercury can result in sensitization. However, Nebenfuhrer et al[55] found that in 148 positive patch test results for mercuric compounds, a clinical relevance could be found in only 15% of them.

There is only partial correspondence between a positive patch test result and healing of OLLs after the replacement of amalgam; 90% of patients improved after removing amalgam restorations when the results of the patch test were positive and 68% improved when it was negative. Despite the higher rate of healing in patients with positive patch test results, a significant percentage of patients with negative patch test results also improved as well, which supports the view that a patch test has limitations as an indicator for replacing amalgam restorations.

Epimucosal tests have been described with the purpose of transferring the conditions of the epicutaneous test to the oral mucosa. The epimucosal test uses a maxillary appliance that carries the test substances in wells on the mucosal side.[56-58] Yontchev[40] suggested that there is no need to perform an epimucosal test to detect contact allergy in the oral mucosa, because the epicutaneous test gives the appropriate information. Holmstrup[59] concluded that skin testing is preferable because of its higher sensitivity and specificity and the fact that the procedure is simpler. A negative skin test

result is a more valuable result than a negative mucosal test result. The lymphocyte proliferation assay (LyPro) has been applied to confirm the diagnosis of allergic reactions to metals.[19,60] Laine et al[19] indicated that this assay seems not to be a specific test for identifying the patients who would benefit from amalgam replacement. In contrast, Stejskal et al[60] found it a useful tool to study metal allergy. However, they used a modified LyPro test called the memory lymphocyte immunostimulation assay.

A further study on amalgam-contact hypersensitivity lesions and LP published in 2003 essentially supports the findings of this review but differs in placing value on patch testing.[16] In contrast, a clinical study reported by some of the authors in 2002, on the effect of amalgam replacement on adjacent LLs, fully supports the findings of this review.[61]

CONCLUSIONS

- There are a lack of CCTs and RCTs with respect to OLL and only a limited number of trials from outside the Scandinavian countries.
- There is a need to standardize protocols when assessing adverse reactions to dental amalgam. Amalgam components other than mercury (eg, tin, silver, zinc) and frictional elements should be considered in the etiology of OLLs related to amalgam restorations.
- OLL may be elicited by amalgam restorations with a mercury compound possibly being a major etiologic factor.
- The replacement of amalgam restorations can result in the resolution or improvement of OLL in most instances. The topographic relationship between the OLL and the amalgam restoration is a useful prognostic marker but is not a conclusive indicator of outcome.
- Evidence from observational studies suggests that patch testing seems to be of limited value as an indicator for replacing amalgam restorations in OLL and predicting outcome.

REFERENCES

1. Wataha JC, Malcolm CT, Hanks CT. Correlation between cytotoxicity and the elements released by dental casting alloys. Int J Prosthodont 1995;8:9-14.
2. Marek M. Interactions between dental amalgams and the oral environment. Adv Dent Res 1992;6:100-9.
3. Marek M. Dissolution of mercury from dental amalgam at different pH values. J Dent Res 1997;76:1308-15.
4. Moberg LE, Johansson C. Release of corrosion products from amalgam in phosphate containing solutions. Scand J Dent Res 1991;99:431-9.
5. Gil FJ, Espias A, Sanchez LA, Planell JA. Comparison of the abrasive wear resistance between amalgams, hybrid composite material and different dental cements. Int Dent J 1999;49:337-42.
6. Berglund A. An in vitro and in vivo study of the release of mercury vapor from different types of amalgam alloys. J Den Res 1993;72:939-46.
7. Ilikli BG, Aydin A, Isimer A, Alpaslan G. In vitro corrosion behaviour and microhardness of high-copper amalgams with platinum and indium. J Oral Rehabil 1999;26:170-6.
8. Hahn LJ, Kloiber R, Vimy MJ, Takahashi Y, Lorscheider FL. Dental "silver" tooth fillings: a source of mercury exposure revealed by whole-body image scan and tissue analysis. FASEB J 1989;3:2641-6.
9. Bolewska J, Holmstrup P, Moller-Madsen B, Kenrad B, Danscher G. Amalgam associated mercury accumulations in normal oral mucosa, oral mucosal lesions of lichen planus and contact lesions associated with amalgam. J Oral Pathol Med 1990;19:39-42.
10. Larsson A, Warfvinge G. The histopathology of oral mucosal lesions associated with amalgam or porcelain-fused-to-metal restorations. Oral Dis 1995;1:152-8.
11. Freden H, Hellden L, Milleding P. Mercury content in gingival tissues adjacent to amalgam fillings. Odontol Revy 1974;25: 207-10.
12. James J, Ferguson MM, Forsyth A, Tulloch N, Lamey PJ. Oral lichenoid reactions related to mercury sensitivity. Br J Oral Maxillofac Surg 1987;25:474-80.
13. van der Waal I. Noninfectious diseases of the oral mucosa. Section 1, part 4: lichen planus. In: Millard HD, Mason DK, editors. Perspectives on 1998 World Workshop in Oral Medicine. Ann Arbor (MI): University of Michigan; 2000. p. 57-61.
14. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. J Am Acad Dermatol 2002;46:207-14.
15. Sugerman PB, Savage NW, Walsh LJ, Zhao ZZ, Zhou XJ, Khan A. The pathogenesis of lichen planus. Crit Rev Oral Biol Med 2002;13:350-65.
16. Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam-contact hypersensitivity lesions and oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:291-9.
17. Lind PO, Hurlen B, Lyberg T, Aas E. Amalgam-related oral lichenoid reaction. Scand J Dent Res 1986;94:448-51.
18. Mobacken H, Hersle K, Sloberg K, Thilander H. Oral lichen planus: hypersensitivity to dental restoration material. Contact Dermatitis 1984;10:11-5.
19. Laine J, Kalimo K, Happonen RP. Contact allergy to dental restorative materials in patients with oral lichenoid lesions. Contact Dermatitis 1997;36:141-6.
20. Laine J, Happonen RP, Vainio O, Kalimo K. In vitro lymphocyte proliferation test in the diagnosis of oral mucosal hypersensitivity reactions to dental amalgam. J Oral Pathol Med 1997;26:362-6.
21. Bolewska J, Hansen HJ, Holmstrup P, Pindborg JJ, Stangerup M. Oral mucosal lesions related to silver amalgam restorations. Oral Surg Oral Med Oral Pathol 1990;70:55-8.
22. Skoglund A. Value of epicutaneous patch testing in patients with oral, mucosal lesions of lichenoid character. Scand J Dent Res 1994;102:216-22.
23. Jameson MW, Kardos TB, Kirk EE, Ferguson MM. Mucosal reactions to amalgam restorations. J Oral Rehabil 1990;17:293-301.
24. Henriksson E, Mattsson U, Hakansson J. Healing of lichenoid reactions following removal of amalgam. A clinical follow-up. J Clin Periodontol 1995;22:287-94.
25. Mulrow CD. Rationale for systematic reviews. BMJ 1994;309: 597-9.
26. Finne K, Goransson K, Winckler L. Oral lichen planus and contact allergy to mercury. Int J Oral Surg 1982;11:236-9.
27. Skoglund A, Egelrud T. Hypersensitivity reactions to dental materials in patients with lichenoid oral mucosal lesions and in patients with burning mouth syndrome. Scand J Dent Res 1991; 99:320-8.
28. Laine J, Kalimo K, Forssell H, Happonen RP. Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. Br J Dermatol 1992;126: 10-5.

29. Pang BK, Freeman S. Oral lichenoid lesions caused by allergy to mercury in amalgam fillings. Contact Dermatitis 1995;33:423-7.
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 Dermatitis 1995;33:323-8.
31. Smart ER, Macleod RI, Lawrence CM. Resolution of lichen planus following removal of amalgam restorations in patients with proven allergy to mercury salts: a pilot study. Br Dent J 1995;178:108-12.
32. Alanko K, Kanerva L, Jolanki R, Kannas L, Estlander T. Oral mucosal diseases investigated by patch testing with a dental screening series. Contact Dermatitis 1996;34:263-7.
33. Ibbotson SH, Speight EL, Macleod RI, Smart ER, Lawrence CM. The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions. Br J Dermatol 1996;134:420-3.
34. Laine J, Konttinen YT, Beliaev N, Happonen RP. Immunocompetent cells in amalgam-associated oral lichenoid contact lesions. J Oral Pathol Med 1999;28:117-21.
35. Koch P, Bahmer FA. Oral lesions and symptoms related to metals used in dental restorations: a clinical, allergological, and histologic study. J Am Acad Dermatol 1999;41:422-30.
36. Ostman PO, Anneroth G, Skoglund A. Amalgam-associated oral lichenoid reactions. Clinical and histologic changes after removal of amalgam fillings. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:459-65.
37. Bratel J, Hakeberg M, Jontell M. Effect of replacement of dental amalgam on oral lichenoid reactions. J Dent 1996;24:41-5.
38. Holmstrup P. Oral mucosa and skin reactions related to amalgam. Adv Dent Res 1992;6:120-4.
39. Yontchev E, Hedegard B, Carlsson GE. Reported symptoms, diseases, and medication of patients with orofacial discomfort complaints. Int J Oral Maxillofac Surg 1986;15:687-95.
40. Yontchev EA. Studies of individuals with orofacial discomfort complaints. An investigation of a group of patients who related their sufferings to effects of dental materials and constructions. Swed Dent J Suppl 1986;38:1-45.
41. Hensten-Pettersen A, Jacobsen N. Toxic effects of dental materials. Int Dent J 1991;41:265-73.
42. Berardesca E, Distante F. The modulation of skin irritation. Contact Dermatitis 1994;31:281-7.
43. Burr ML. Epidemiology of clinical allergy. [monographs]. Karger Publishing; New York. 1993.
44. Camisa C, Taylor JS, Bernat JR Jr, Helm TN. Contact hypersensitivity to mercury in amalgam restorations may mimic oral lichen planus. Cutis 1999;63:189-92.
45. Lundstrom IM. Allergy and corrosion of dental materials in patients with oral lichen planus. Int J Oral Surg 1984;13: 16-24.
46. Burrows D. Hypersensitivity to mercury, nickel and chromium in relation to dental materials. Int Dent J 1986;36:30-4.
47. Fisher AA. The misuse of the patch test to determine "hypersensitivity" to mercury amalgam dental fillings. Cutis 1985;35:110, 112, 117.
48. Kalveram KJ, Rapp-Frick C, Sorck G. Misleading patch test results with aluminum Finn chambers and mercury salts. Contact Dermatitis 1980;6:507-8.
49. Fisher AA. Contact dermatitis. 3rd ed. Lee & Febiger; Philadelphia. 1986.
50. Nakayama H, Niki F, Shono M, Hada S. Mercury exanthem. Contact Dermatitis 1983;9:411-7.
51. Swinyer LJ. Allergic contact dermatitis from metallic mercury. Contact Dermatitis 1980;6:226-7.
52. Ancona A, Ramos M, Suarez R, Macotela E. Mercury sensitivity in a dentist. Contact Dermatitis 1982;8:218.
53. White RR, Brandt RL. Development of mercury hypersensitivity among dental students. J Am Dent Assoc 1976;92:1204-7.
54. Fregert S, Hjorth N. Increasing incidence of mercury sensitivity: a possible effect of organic mercury compounds. Contact Dermatitis 1969;5:88.
55. Nebenfuhrer L, Korossy S, Vincze E, Gozony M. Mercury allergy in Budapest. Contact Dermatitis 1984;10:121-2.
56. Moffa JP, Beck WD, Hoke AW. Allergic response to nickel containing dental alloys. J Den Res 1977;56(Spec. Iss. B):78.
57. van Loon LA, van Elsas PW, van Joost T, Davidson CL. Contact stomatitis and dermatitis to nickel and palladium. Contact Dermatitis 1984;11:294-7.
58. Axell T, Spiechowicz E, Glantz PO, Andersson G, Larsson A. A new method for intraoral patch testing. Contact Dermatitis 1986;15:58-62.
59. Holmstrup P. Reactions of the oral mucosa related to silver amalgam: a review. J Oral Pathol Med 1991;20:1-7.
60. Stejskal VD, Forsbeck M, Cederbrandt KE, Asteman O. Mercury-specific lymphocytes: an indication of mercury allergy in man. J Clin Immunol 1996;16:31-40.
61. Yaser I. In vivo and in vitro studies of biocompatibility in some restorative materials [thesis]. Manchester (England): University of Manchester; 2002.

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