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Adverse reactions to dental biomaterials: Experiences from a specialty clinic☆

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ABSTRACT

Objectives: The Dental Biomaterials Adverse Reaction Unit was initiated by the Norwegian health authorities in 1992 as a response to the public concern regarding the safety of dental amalgam and other dental materials. In this paper, experiences from the Unit are briefly summarized.
Methods: The Norwegian health authorities' strategy included four main topics: (i) development of a manufacturer-independent system for monitoring adverse reactions related to dental materials, (ii) funding of a specialty unit for clinical examinations of referred patients, (iii) development of official guidelines for examination and treatment of patients with health complaints attributed to dental materials, and (iv) funding of an experimental treatment project for patients with health complaints attributed to dental amalgam.
Results: From the start, more than 2700 adverse reaction reports were received. In the initial years, amalgam was the most frequent material mentioned in the reports. Reports about polymer-based composite materials have not increased after the prohibition of amalgam in Norway. Clinical examination of referred patients is complex and time consuming, and it is important to consider differential diagnoses. There are methodological challenges associated with the design of experimental treatments used on patients with adverse reactions attributed to dental materials. However, the results from the treatment project indicate lower symptom load after replacement of amalgam with other dental restorative materials.
Significance: Producer independent adverse reaction reporting can provide valuable information about the safety of these materials and could serve as a complement to the mandatory reporting system described in the European medical device regulations (MDR).

1. Introduction

1.1. Background

A large number of substances are used in modern dental biomaterials. Several kinds of monomers are used in resin-based restorative materials, and different metals are used in alloys for crowns, bridges and implants, while metal oxides are included in ceramic materials [1]. Most of the dental materials placed in patients are intended for long-term permanent use, and patients can be exposed to these materials for several decades. Since the oral cavity is a tough environment, materials will be exposed to degradation, and substances will be released. Some of the substances are allergenic or toxic, and subsequently there is a risk for adverse reactions in the exposed patients. In addition, the detailed compositions of the materials are sometimes trade secrets, and thus, no or only little information regarding the ingredients is available.

Most commonly, adverse reactions related to dental materials are caused by hypersensitivity reactions to substances released from the materials ("critical substance"; Table 1).

1.2. Patient safety

In recent decades, patient safety has become increasingly important [18], and many patient organizations have been established [19]. Adverse events, side effects, and adverse reactions are key components in the field of patient safety (Fig. 1). Observed adverse events, side effects, and adverse reactions should be reported and registered systematically. For unwanted reactions to dental biomaterials the term "adverse reactions" is used.

Over the last three decades there have been intense discussions in

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Table 1
Examples of potential adverse reactions to dental materials.

Material	Critical substance*	Exposure	Mechanisms	Example of clinical manifestation	References
Polymer based materials (including bonding material and fissure sealants, cements)	Methacrylates (monomers)	Local (intraoral) Inhalation	Hypersensitivity/ allergy	Intraoral contact lesion Airway reactions Urticaria	Moore, [3] Hallström, [4]
Temporary cements with eugenol	Eugenol	Local (intraoral)	Hypersensitivity/ allergy	Intraoral contact lesion	Barkin, [5] Sarrami, [6]
Temporary cements with colophony	Colophony	Local (intraoral) Systemic	Hypersensitivity/ allergy	Intraoral contact lesion Allergic contact dermatitis	Bruze, [7]
Impression materials (polyether)	"Base paste component"	Local (intraoral)	Hypersensitivity/ allergy	Intraoral contact lesion	Mittermuller, [8]
Cobalt-chromium alloys	Cobalt	Local (intraoral)	Hypersensitivity/ allergy	Palmoplantar pustulos (PPP)	Song, [9]
Gold and palladium alloys	Gold Palladium	Local (intraoral) Systemic (gastro-intestinal absorption)	Hypersensitivity/ allergy	Oral lichenoid lesion Allergic contact mucositis Allergic contact dermatitis	Tvinnereim, [10] Garau, [11] Vamnes, [12]
Amalgam	Mercury	Local (intraoral) Systemic (inhalation, gastro-intestinal absorption)	Hypersensitivity/ allergy Toxicity	Oral lichenoid lesion Allergic contact dermatitis Airway reaction "Micromercurialism"	Issa, [13] McGivern, [14] Kal, [15] Weidenhammer, [16] Langworth, [17]

* Released substance that can be assumed to constitute the primary risk of adverse reactions.
Adapted from [2].

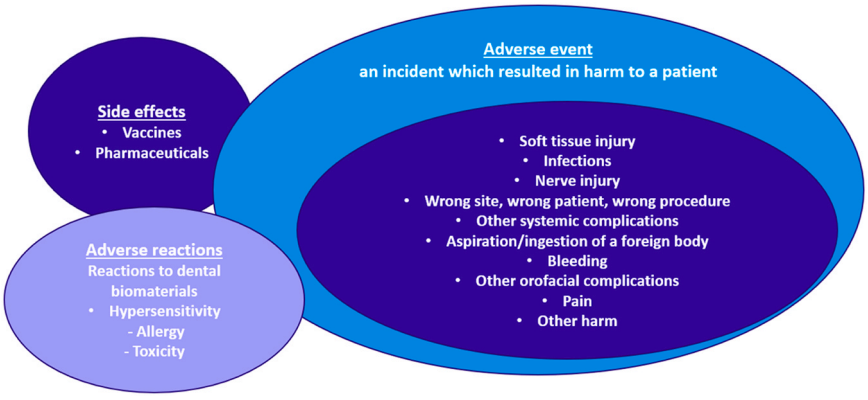

Fig. 1. Patient safety components related to the dental patient: adverse events, side effects, and adverse reactions. (adapted from [20] and [21]).

both Scandinavia and many other parts of the world about the safety of dental amalgam [22]. The reason is the content of mercury and the potential risk for adverse reactions from exposure to elemental mercury (Hg^0) [1]. In addition, there has also been a focus on the safety of polymer-based restorative materials [23]. Specifically, the potential risk associated with the release of bisphenol A from polymer-based restorative materials has caught interest [24,25].

1.3. Risk management strategy of the Norwegian Health Authorities

In the light of the discussions in the 1990 s about the safety of dental amalgam and other dental biomaterials, the Norwegian health authorities developed a risk management strategy comprising the following items:

a. Monitoring system for adverse reactions related to dental materials.
b. Funding of a clinical specialty unit with medical and dental experts.
c. Development of official guidelines for examination and treatment of patients with health complaints attributed to dental materials.
d. Funding of an experimental treatment project for patients with health complaints attributed to dental amalgam.

As a part of the strategy, the Norwegian Dental Biomaterials Reaction Unit was funded by the Ministry of Health and Care Services in 1992, and located at the University of Bergen, Norway. An expert report regarding adverse reactions related to dental biomaterials was commissioned by the Ministry of Health and Care Services in 1998 and published by the Norwegian Board of Health Supervision [26]. The report had a multidisciplinary focus on adverse reactions to dental biomaterials with contributions from material experts, toxicologists, dermatologists, immunologists, philosophers, and psychiatrists. Other aspects of patient safety like accidents that may happen to a patient during dental treatment (like soft tissue injury, infections, nerve injury, bleeding, aspiration of a foreign body, etc.) or side effects from pharmaceuticals were not topics of this action.

Another important part of the strategy was the development of official guidelines for the examination and treatment of patients with suspected adverse reactions to dental materials. The first version was published in 2008 by the Norwegian Directorate of Health [27].

In 2006, a White Paper (*Stortingsmelding*) on the future of dental service in Norway [28] described the need for an experimental treatment project for patients with adverse reactions attributed to dental restorative materials (dental amalgam). The primary aim of this project was to gain knowledge about potential changes of general health and

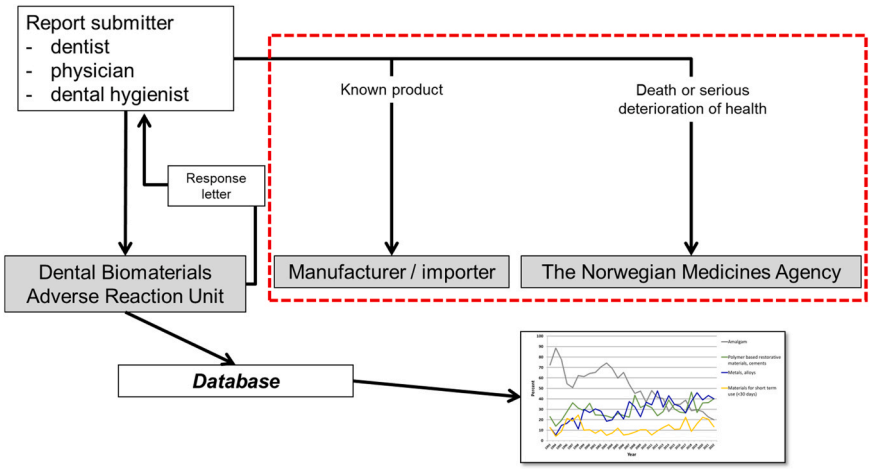

Fig. 2. Diagram illustrating the reporting of adverse reactions to dental biomaterials in Norway. The mandatory reporting, in accordance with the EU Medical Devices Regulation 2017/745 (MDR), is indicated (dashed line).

quality of life after treatment, which included removal of amalgam restorations and replacement with other dental restorative materials. Thus, the aim of the project was not to explore the mechanisms behind the ill health of the patients but to provide and evaluate the experimental treatment.

In the current paper, experiences from the Norwegian Dental Biomaterials Adverse Reaction Unit are described, including (i) the reporting of adverse reactions, (ii) clinical examination of referred patients, and (iii) experimental treatment of patients with health problems attributed to amalgam restorations.

2. Reporting of adverse reactions

One of the cornerstones of the strategy was to develop and implement a monitoring system for adverse reactions related to dental biomaterials. The developed monitoring system allows dentists, dental hygienists and physicians in Norway to report observed adverse reactions related to dental biomaterials to the Dental Biomaterials Adverse Reaction Unit. The reporting form can be downloaded from the internet (www.bivirkningsgruppen.no). Moreover, it is printed regularly in the Norwegian Dental Journal and included in the most used electronic patient record system in Norway. An English version of the form is available at https://bivirkningsgruppen.norceresearch.no/en/forms.

Each received report is assessed at the Dental Biomaterials Adverse Reaction Unit. If the report includes a specified material and the manufacturer of the material is known, the reporter is asked to send a report to the manufacturer or importer of the material as well (Fig. 2). This procedure ensures that the mandatory reporting procedure described in the EU Medical Devices Regulation 2017/745 (MDR) is followed. If the report involves a severe reaction, which could cause death or a serious deterioration in health, the reaction should in addition be reported to the Norwegian Medicines Agency (Fig. 2). However, severe adverse reactions are seldom observed in relation to dental biomaterials.

The reporting form includes essential information about the report submitter, data about the patient, symptoms and findings, type of treatment associated with the reaction, and types of materials suspected to be cause of the reaction(s). The reporter's and the patient's assessments of the relationship between the material used and the reaction should also be indicated [29]. The report is anonymous (only the age and sex of the patient is included in the form), and the Norwegian Data Protection Authority has approved the form being sent by e-mail to the Dental Biomaterials Adverse Reaction Unit.

The reporting to the Dental Biomaterials Adverse Reaction Unit is voluntary, but the Norwegian Health Economics Administration (HELFO; https://www.helfo.no/english) reimburses dentists who submit adverse reaction reports. In 2023, the reimbursement was 630 NOK (about 59 USD). When restorations or dentures are replaced, at the expense of the Norwegian Health Economics Administration, with other dental materials because of allergic reactions (contact lesions) to these materials, reporting this occurrence to Dental Biomaterials Adverse Reaction Unit is required.

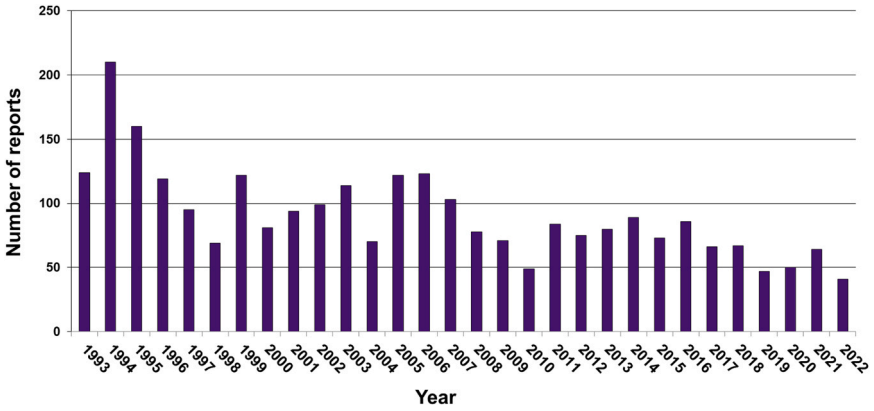

Fig. 3. Number of reports per year.

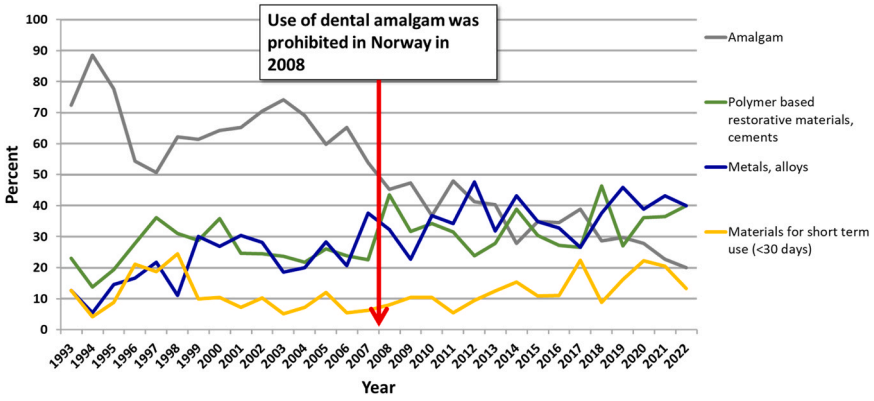

Fig. 4. Types of materials involved in reports (% by year). The percentage of reports associated with the four main material groups are given. More than one material can be mentioned in a single report ('multiple response') and thus, the sum for each year exceeds 100%. Data from [30].

2.1. Results from the reporting of adverse reactions

From 1993 to 2022, a total of 2725 reports concerning suspected adverse reactions were received (Fig. 3). As of 01.01.2023, the population in Norway is 5.5 million, and thus, yearly population-adjusted reporting is about one report per 100,000 inhabitants. Most of the reports were submitted by dentists in private practice [30].

For each year, the proportion of reports regarding four main categories of materials was calculated using a multiple response procedure. Since one report can involve more than one material category, the sum for each year can exceed 100%. The following categories were used:

- Amalgam
- Polymer based restorative materials and cements
- Metals and alloys (other than amalgam)
- Materials for short term use (<30 days)

In the beginning of the registration period, the main part of the reports was about reactions attributed to dental amalgam (Fig. 4).

For environmental reasons, the general use of dental amalgam in Norway was prohibited in 2008 [31], and it is mainly polymer-based restorative materials (resin-based composites) that have replaced amalgam as the restorative material for larger cavities in premolars and molars [32]. Since polymer-based restorative materials have a significant potential to cause allergic reactions due to the content of allergenic monomers (Table 1), it is important to note that data from the adverse reporting registry show no increase in adverse reaction reports related to polymer-based restorative materials after the ban of amalgam in Norway (Fig. 4).

The proportion of reports regarding metals and alloys (other than amalgam) has increased over time from about 10% in 1993 to about 40% in 2022. The awareness of possible allergic reactions to gold alloys [33] and the inclusion of gold (as gold(I)sodium thiosulfate dihydrate) in skin allergy tests for dental materials [34], could possibly partly explain the increase. It should, however, be made clear that data presented in Fig. 4 are summaries of suspected reactions and, in most cases, do not show verified (certain) reactions.

2.2. Examples of reported severe reactions

Most reactions are relatively mild and could, for example, be related to a local contact allergy (i.e., oral lichenoid contact reactions related to amalgam) or subjective symptoms attributed to amalgam. Severe reactions are seldom reported. In 2017, a reaction after treatment with an endodontic material was reported [35]. The patient was treated with a temporary endodontic material containing polyethylene glycol (PEG) and experienced an anaphylactic reaction shortly after leaving the dental office. The patient was sent to the hospital for emergency care and was discharged after one day. The reaction was reported according to the mandatory procedure to the manufacturer and to the Norwegian Medicines Agency, and in addition to the Dental Biomaterials Adverse Reaction Unit. Since the instructions for use did not include any information about the risk for anaphylactic reactions to the substances in the material, repeated examinations by specialists were necessary to detect the culprit substance. An oral provocation test with Movicol (Macrogol 3350) resulted in an urticarial rash, which confirmed the diagnosis [35]. A recent review article on hypersensitivity reactions to PEG mentioned the low awareness of PEG's allergenic potential and the lack of suspicion towards this kind of excipient [36]. Even though the reaction was reported to the manufacturer and the Norwegian Medicines Agency, no information was given to the users to increase patient safety regarding the use of PEG in endodontic materials. However, the reaction was published in the Norwegian Dental Journal as a case report [35].

A couple of years later, another serious reaction was reported after treatment with the same temporary endodontic material. The endodontic procedure was uncomplicated, and the patient was in good general condition after the treatment. Within minutes of leaving the dental office, the patient experienced a skin rash and subsequently developed an anaphylactic reaction and became unconscious. The patient later died at the hospital [37]. The reaction was reported to the Dental Biomaterials Adverse Reaction Unit, and according to the mandatory procedures to the manufacturer and the Norwegian Medicines Agency. However, no information was given from the manufacturer to the users, but a case report was published in the Norwegian Dental Journal [37].

According to the database at the European Chemicals Agency (ECHA), there are no risks associated with the use of polyethylene glycol (*"According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified"*) [38]. The risk assessment provided from the database at the ECHA does not consider parenteral administration (e.g., intravenous, intramuscular, or subcutaneous injection). A literature search in PubMed (16.08.2023; using the expression "Polyethylene glycol (PEG) AND hypersensitivity") showed 333 references, and one of these was the review article by Wenande and Garvey [36] mentioned above.

To improve patient safety, it could be argued that it should be clearly specified in the instructions for use that PEG can cause anaphylactic reactions. In addition, it could also be recommended that patients treated with endodontic materials that contain PEG should stay at the dental office for 30 min after treatment, similar to the clinical routines in conjunction with vaccinations, in case there is a reaction [39].

2.3. Lack of information about ingredients

It is well known that the information about ingredients in dental materials is sometimes inadequate. In some cases, the safety data sheets

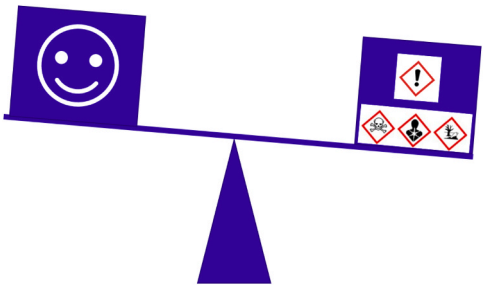

Fig. 5. Illustration of the risk - benefit assessment associated with the decision regarding choice of dental biomaterials in the clinical situation. Some materials could have large technical advantages, but also biological disadvantages. The patient should be informed about the pros and cons of the materials and give informed consent, which should be documented in the dental record.

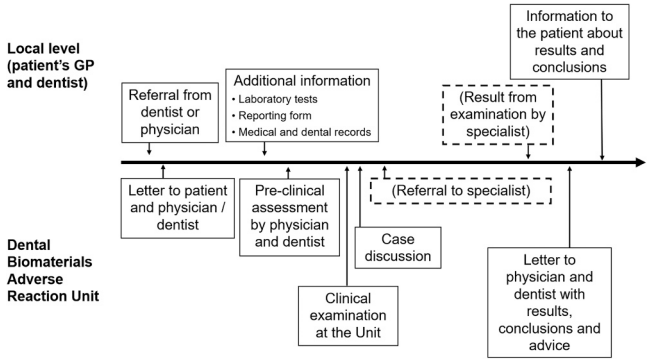

Fig. 6. Timeline for the examination of referred patients. In some cases patients are referred for specialist examination (e.g., dermatologist for allergy test).

(SDS) and the Instructions for Use (IFU) are less useful when additional information on the ingredients is needed [40,41]. Even though the manufacturer is responsible for the risk assessment and that the risk for adverse reactions shall be acceptable, the patient and the dentist should have access to adequate information in order to make a risk assessment in the individual case if indicated (Fig. 5).

In summary, voluntary manufacturer-independent reporting of adverse reactions related to dental biomaterials is useful, cost effective, and could be implemented with limited resources as a complement to the mandatory reporting. Data collected could provide information about time trends and changes over time and provide signals indicating new types of reactions. In addition, infrequent reactions could be detected, and reactions to chemicals with an unknown risk for adverse reactions could potentially be observed. For a detailed assessment of the reported reactions, a clinical examination is usually needed [42].

3. Clinical examination

The over-all objectives of the clinical examination of patients that are referred to the Dental Biomaterials Adverse Reaction Unit are as follows:

- Provide medical and dental examinations.
- Diagnose possible diseases and conditions and give medical and odontological advice.
- Detect possible adverse reactions and provide relevant advice.

Dentists and physicians can refer patients for examination at the Dental Biomaterials Adverse Reaction Unit. The clinical examination is based on the Norwegian guidelines from the Norwegian Directorate of Health [27] and includes collaboration between the local dentist and physician (family physician/GP), and the Dental Biomaterials Adverse Reaction Unit (Fig. 6).

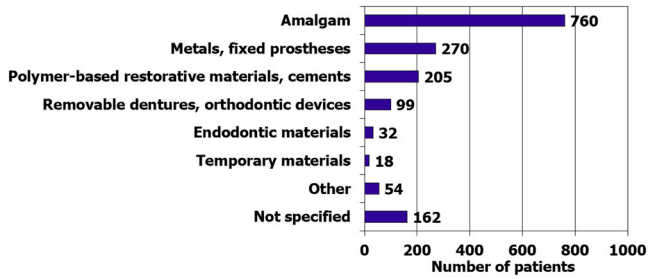

Fig. 7. Cumulative number of patients showing reasons for referrals 1993 to 2022.

Table 2
Indications of a skin allergy test in cases of suspected contact allergies concerning dental materials (from [44] and [27]).

– Objective reactions in the oral mucosa, clinically consistent with a contact reaction or lichenoid reaction, and topographically related to dental restorative materials
– Outbreak of skin eruptions / eczema in connection with dental treatment, and when other etiology is not obvious
– Clinical suspicion of a contact allergy (allergic contact eczema) concerning a substance that is planning to be used in dental treatment

3.1. Clinical staff

The Dental Biomaterials Adverse Reaction Unit currently has four clinical positions: Three dentists (special advisers), two full time and one part time, and a part-time (one day a week) physician (general practice). The head of the Unit (professor) has a full time position [30].

3.2. Reasons for referrals

The most common reason for referral is reactions related to amalgam (Fig. 7). Metals and fixed prostheses and polymer-based restorative materials and cements were also common causes for referrals. Temporary materials, endodontic materials, removable dentures, and orthodontic devices were less commonly mentioned as a cause for referral [30]. In recent years the number of referrals concerning amalgam has decreased, while referrals concerning metals, fixed prostheses, polymer-based restorative materials, and cements are relatively constant [30].

3.3. Clinical examination

All patients who received a clinical examination were seen by both a physician and at least two dentists. About 60 min were usually allocated for the medical examination, and an additional 60 min or more were allocated for the dental examination. A central part of the examination is to obtain anamnestic information about the start of the symptoms in relation to dental treatment. Blood samples were collected and analyzed in advance at the local family physician's office. Blood tests usually included erythrocyte sedimentation rate, serum ferritin, B-12 / folic acid, electrolytes, S-creatinine, liver tests, glucose, and thyroid function [43]. Copies of the dental records, medical records, and other relevant information (e.g., clinical photos, x-rays, written correspondence) were collected and reviewed before the clinical examination at the Unit (Fig. 6). In some cases, when the collected documentation was sufficient, and it was assessed that clinical examination at the Unit would most likely not contribute with significant information, the response letter (Fig. 6) was sent based on the collected documents and clinical photos. When indicated, patients were referred to a dermatologist for a skin allergy test regarding dental materials (Table 2).

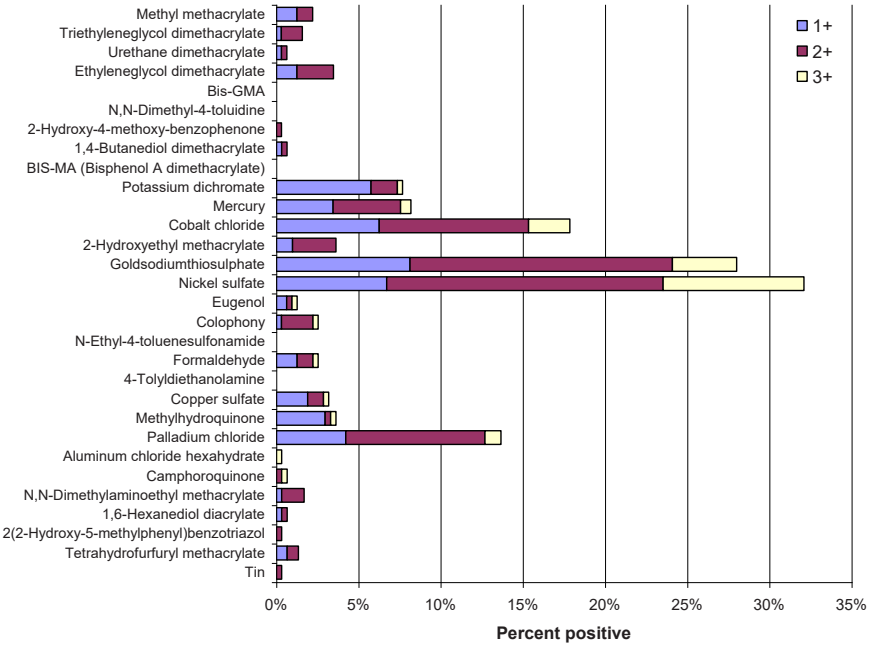

Fig. 8. Results from the allergy testing of 398 patients. (adapted from [43]).

3.4. Clinical examination – findings

Generally, patients referred for reactions attributed to dental amalgam had concentrations of mercury in blood and urine within the reference range [43,45]. No patient was diagnosed as mercury poisoned. Contact allergies were diagnosed after skin allergy test (usually the Dental Screening series DS-1000 from Chemotechnique Diagnostics [34]). Nickel, gold, cobalt, palladium, mercury, chromium, and different methacrylates were the most common substances with a positive test reaction (Fig. 8). In the case of a positive test, the clinical relevance should always be assessed, preferably by both a dermatologist and a dentist. Patients with contact allergic lesions and a positive test result for the suspected substance were recommended to remove the offending material. Patients with a positive test result for a substance who did not show signs of contact allergic lesions to that substance were recommended to avoid future treatment with materials containing the substance. Serious diseases were detected in some patients in conjunction with the examinations, and possible differential diagnoses should be considered [27]. In many cases, additional medical or odontological examinations were recommended.

3.5. Clinical questions in conjunction with the examination of adverse reactions

The following check list was developed to support the diagnostic procedure.

1. What materials were used?
   a. What substances do they contain?
2. What risks could be related to these substances?
   a. How hazardous are they? Can they cause allergic reactions?
3. Exposure
   a. Can the absorbed dose be sufficient to cause a clinical reaction?
4. Could there be other explanations for the symptom/reaction?
   a. Deviating laboratory tests?
   b. Simultaneous exposure to other allergens? Food?
   c. Drug side effect?
   d. Are medical and odontological differential diagnoses excluded?

Table 3
Tentative causality categories for adverse reactions related to dental materials[a].

Causality term	Assessment criteria*
Certain	• Abnormal reaction, with a probable time relation to dental treatment • Cannot be explained by disease or other exposure • Response to interrupted exposure / discontinuation plausible (toxicology / allergy / hypersensitivity) • Objective and specific reaction • Re-exposure (rechallenge) satisfactory
Probable/ Likely	• Abnormal reaction, with a reasonable time relation to dental treatment • The reaction is most likely not attributable to illness or other exposure • Response to interrupted exposure clinically reasonable • Re-exposure (rechallenge) not necessary
Possible	• Abnormal reaction, with a reasonable time relation to dental treatment • Can also be explained by illness or other exposure • Information on interrupted exposure may be incomplete or unclear
Unlikely	• Abnormal reactions, with an unclear temporal relationship to dental treatment that makes a relationship unlikely (but not impossible) • Disease or other exposure provide plausible explanations

a) Reactions caused by mechanical trauma (e.g., a removable denture causing traumatic ulcers) are not classified.
* All points should be reasonably complied with
Adapted from WHO-UMC Causality Categories for Pharmacovigilance (https://who-umc.org)

In summary, clinical examinations at a specialty clinic for patients referred for assessment regarding possible adverse reactions to dental biomaterials are complex and time consuming. Both medical and dental examinations are recommended. The examination should have a broad focus, and possible differential diagnoses should be considered [27]. Adverse reactions can be detected in some patients, but the diagnosis is often tentative since a certain diagnosis of an adverse reaction in most cases needs a re-exposure, which in many cases is not possible (Table 3).

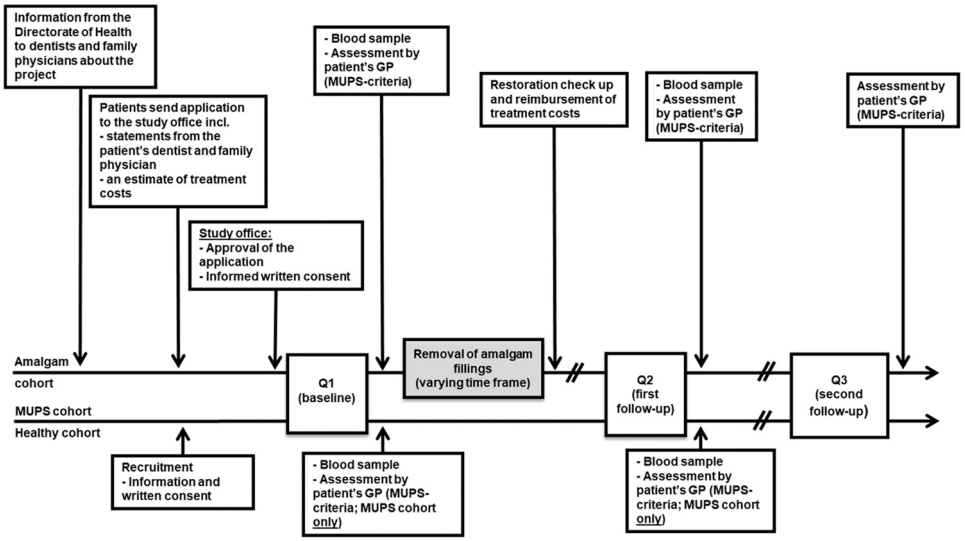

Fig. 9. Timeline of the study.
(adapted from reference 47).

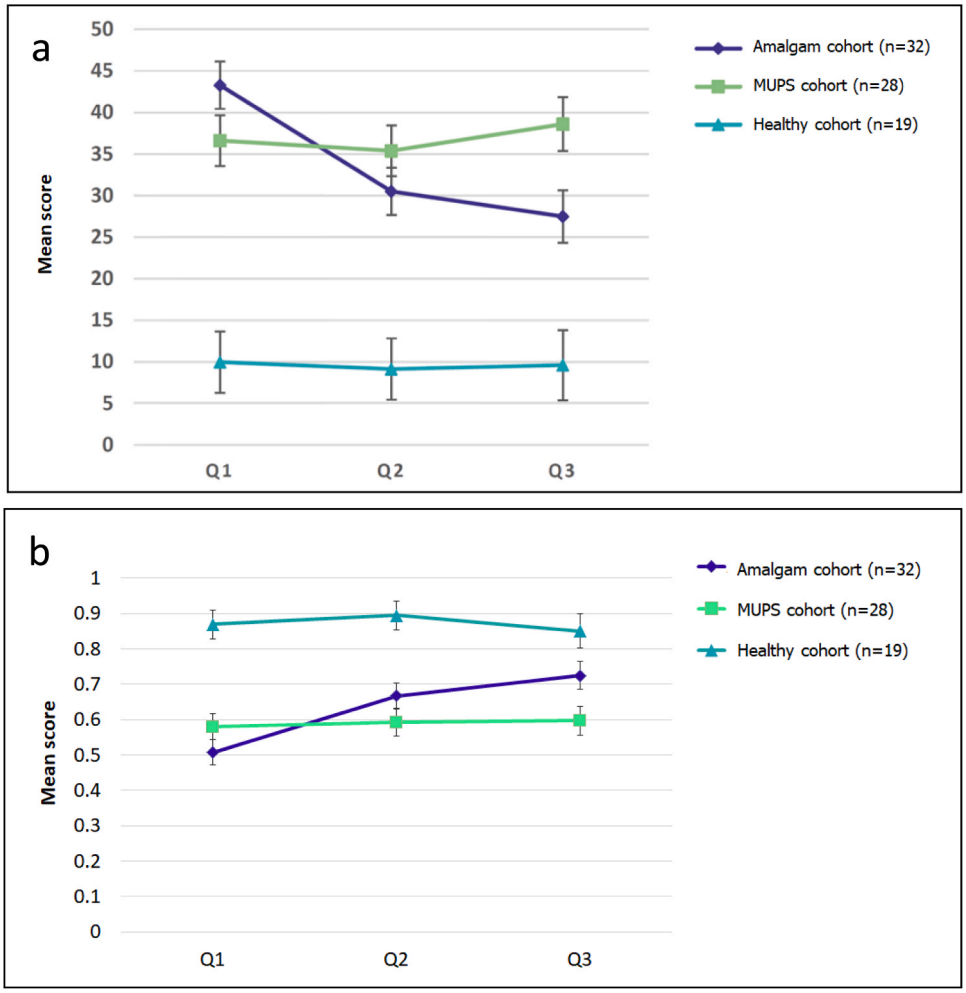

Fig. 10. Mean values (and standard error) for the General Health Complaints index score (panel a), General health and health-related quality of life (panel b) at baseline (Q1) and first (Q2) and second (Q3) follow-up.
(adapted from reference 47).

4. Experimental treatment

4.1. Background

As a part of the risk management strategy of the Norwegian health authorities, an experimental treatment project was funded for patients with health complaints attributed to dental amalgam [28]. In the White paper ("*Stortingsmelding*" number 35, 2006–2007) from the Norwegian government, it was mentioned that a project that could include removal of dental restorations in patients with suspected adverse reactions should be started. This was not primarily a research project, but an experimental treatment project with the aim of better health and quality of life for individuals with health problems attributed to amalgam [28].

4.2. Methods

The project was designed as a prospective cohort study and organized by the Dental Biomaterials Adverse Reaction Unit. Three cohorts were followed over time, an Amalgam cohort (treatment group), MUPS cohort, and a Healthy cohort, and data were collected both at baseline and follow-ups at one and five years [46].

The reason for not using a Randomized Controlled Trial (RCT) design was that the project was primarily a treatment project that included experimental treatment, and patients usually have preferences about treatment. Thus, there was a considerable risk that patients randomized to a control group would drop out of the study or remove their fillings on their own. In addition, a waiting list group design could also be associated with a considerable risk that patients drop out of the study.

The Amalgam cohort consisted of patients with health complaints attributed to amalgam fillings who wanted to have the fillings removed. They were examined according to the official guidelines [27], and in addition fulfilled criteria for *medically unexplained physical symptoms* ("MUPS") attributed to amalgam. The MUPS cohort, on the other hand, consisted of patients with *medically unexplained physical symptoms* (without attribution to amalgam), whereas the Healthy cohort consisted of a group of healthy individuals [46]. The project started in 2012, and patients in the Amalgam cohort were included from 2013 to 2015. The timeline for the study is given in Fig. 9.

There were several criteria for inclusion in the Amalgam cohort [46]. Among the most important criteria was that the patient's general practitioner/family physician and dentist should assess that the general and dental health of the patient would most likely not deteriorate due to participation in the project. Also, the patient's dentist assessed that there were no major risks for complications following amalgam removal (e.g., the need for root canal treatments or extractions). These criteria were important due to the ethical challenges associated with the project and have importance for the external validity of the project's results.

The primary outcome of the project was index score from the General Health Complaints [48] calculated from 12 items one year after treatment. General health and health-related quality of life were measured with the instrument EQ-5D-5L [49] one year after treatment was a secondary outcome. All participants completed questionnaires at Baseline (Q1), at one year follow-up after completed amalgam removal (Q2) and again four years later (Q3) (Fig. 9).

4.3. Results

The results of the study showed that the General Health Complaints index score decreased significantly in the Amalgam cohort after removal of the amalgam fillings ($p < 0.001$; Fig. 10). In the other cohorts there were no significant changes over time [46,47]. General health and health-related quality of life increased significantly one year after treatment ($p < 0.001$), and similar to the General Health Complaints index score, there were no significant changes over time in the other cohorts [47].

Health economy analyses indicated that amalgam removal was associated with a modest increase in costs and improved health outcomes, concluding that the removal of amalgam fillings in this group of patients was a highly cost-effective intervention [50].

The external validity of the results is limited to patients who have medically unexplained physical symptoms attributed to their amalgam fillings, fulfilling the criteria used in the study. Nevertheless, it was concluded that amalgam removal was followed by improved health and quality of life for individuals with health problems attributed to amalgam [47].

Table 4
Controlled studies of changes in health complaints after the removal of amalgam.

Study	Design	Primary outcome	Effect size
Nerdrum et al. [52]	Prospective quasi-experimental	General health complaints (measured by GBB-24)	1.4[a]
Melchart et al. [53]	Randomized controlled trial	Change of intensity for the three main complaints at baseline	1.6[b]
Sjursen et al. [48]	Before and after study	General health complaints (GHC-index score calculated from 12 'numeric rating scales')	0.76[b]
Zwicker et al. [54]	Longitudinal (retrospective)	Improvement of self-reported symptom scores	[odds ratio 1.6; $p < 0.05$]

a) Cohen's d: (Mean 1– Mean 2) / SD
b) Standardized response mean (mean difference divided by the standard deviation of the differences between the paired measurements)
Es < 0.2 small 0.5 medium > 0.8 large

Table 5
Bradford Hill criteria for causation applied to the issue regarding the relationship between the removal of amalgam restorations and an improvement in health.

Concept	Comment	References
Strength	Medium to large effect size for general health complaints	Melchart et al. [53], Nerdrum et al. [52], Sjursen et al. [48]
Consistency	Published studies show similar results	Weidenhammer et al. [16], Nerdrum et al. [52], Zwicker et al. [54], Sjursen et al. [48], Stenman and Grans [58]
Specificity	Mercury causes symptoms mainly from the CNS	Berlin et al. [59]
Temporality	Effect after treatment / exposure	Weidenhammer et al. [16], Nerdrum et al. [52], Zwicker et al. [54], Sjursen et al.[48], Stenman and Grans [58]
Biological gradient	Dose-response relationship	Björkman et al. [60], Weidenhammer et al. [16], Stenman and Grans [58]
Plausibility	Mercury is toxic	Berlin et al. [59]
Coherence	Mercury from dental amalgam is found in the brain and other organs	Nylander et al. [61], Björkman et al. [62]
Experiment	Removal of a potentially harmful exposure reduces symptoms	Weidenhammer et al. [16], Nerdrum et al. [52], Zwicker et al. [54], Sjursen et al. [48], Stenman and Grans [58]
Analogy	Other toxic metals cause toxic effects as well	Nordberg et al.[63]

4.4. Levels of evidence

Since the study was a cohort study, only limited scientific evidence could be provided. To provide a higher level of evidence, data from randomized controlled trials with blinding would be useful. Blinding of this kind of treatment is, however, not possible, and thus, placebo could

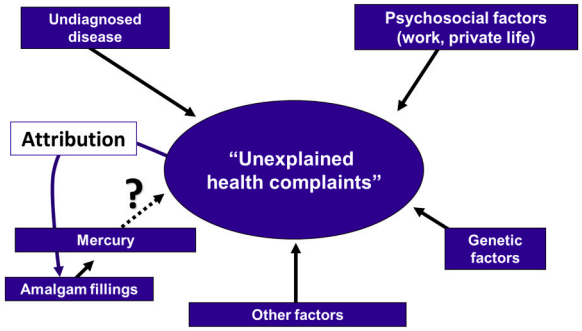

Fig. 11. Model of a hypothesis: Factors of potential importance for unexplained health complaints attributed to amalgam fillings. Several factors can be important simultaneously and to varying degrees.

be one of several factors influencing the results. Nevertheless, the improvement in the Amalgam cohort was consistent even at the 5-year follow-up, which provides evidence for a long-term improvement. The results should be interpreted and compared with other studies on the same topic. In addition, it should be noted that the common belief that only randomized controlled trials can provide trustworthy results, and that observational prospective cohort studies are misleading, has been challenged [51].

4.5. Other studies

Other controlled studies of changes in health complaints after the removal of amalgam show similar results and relatively large effect sizes (Table 4), which supports the findings and conclusions of the study.

4.6. Could there be a causal relationship?

Using the Bradford Hill criteria for causation [55,56] on the challenging issue regarding the possibility of a causal relationship between the removal of amalgam restorations in patients with health complaints attributed to amalgam and an improvement in health, reveals some support for a causal relationship (Table 5). However, the methodological issues associated with this research question should be considered. Future research focusing on individual variations in sensitivity to xenobiotics can hopefully bring more clarity [57].

4.7. Unexplained health complaints - a hypothesis

Patients with medically unexplained physical symptoms (MUPS) are common among patients in general practice [64]. A hypothesis including factors of potential importance for MUPS includes undiagnosed diseases, psychosocial factors (both at work and in private life), genetic factors, and other unknown factors. In addition, this hypothesis includes amalgam fillings and mercury as possible contributing factors. All these factors could be of importance simultaneously and to varying degrees (Fig. 11). The attribution of unexplained health complaints to amalgam restorations has been explored and described [65]. Both a temporal relationship between exposure to amalgam and episodes of ill health and feeling of agreement with descriptions of amalgam poisoning were found among other factors [65].

5. Final comment and conclusion

The Dental Biomaterials Adverse Reaction Unit was started as a response to the public concern regarding the safety of dental materials, and amalgam specifically. With a 30-years perspective, it could be discussed whether the action was successful and provide the intended support to patients, dentists, and physicians. An external evaluation of the Dental Biomaterials Adverse Reaction Unit was conducted in 2005. The conclusion was that the Dental Biomaterials Adverse Reaction Unit had - by and large - succeeded in fulfilling its mandate and carrying out its tasks in an efficient manner [66].

Finally, we need an increased awareness about adverse reactions to dental biomaterials in order to strengthen the safety of our patients. Information about all ingredients, including CAS numbers for unambiguous identification, should be made readily available. The reporting of adverse reactions should be encouraged, and adverse reaction reports should be systematically registered in order to provide essential information available to the users.

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