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In vivo/Ex vivo Mercury Release from Dental Amalgam Fillings in the Human Body and its Health Implications: An Overview of Clinical Studies

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Abstract

Mercury dental amalgam has a long history of ostensibly safe use despite its continuous release of elemental mercury vapor, inorganic mercury, metal ions and particles of amalgam. Mercury release from dental amalgam fillings implanted into the human body in dental/orthodontic surgery is becoming a major cause for concern on humans and environment. With the current ageing population, dental health is a major issue and current dental restorations still have shortcomings. Even though mercury is the most toxic non-radioactive material known to man, there has been an ongoing controversy about its safety since it was first introduced for use in dentistry. However, the health policies of different countries, world organizations and agencies have not reached a consensus on the use and safety of amalgam. This review has uncovered no convincing evidence pointing to any adverse health effects that are attributable to dental amalgam restorations besides hypersensitivity in some individuals. Finally, a collection of published clinical data on in vivo and ex vivo released mercury from dental amalgams in included.

Keywords: Dental Amalgam Fillings, Mercury, Health Implications, Human Biological Specimens, In vivo Ex vivo Quantifications

1. Introduction

Dental materials are among the most extensively employed materials for incorporation in the human body. In dentistry, metallic materials are used as implants in reconstructive oral surgery to replace a single tooth or an array of teeth, or in the fabrication of a dental prosthesis, such as metal plates for complete or partial dentures, crowns and bridges, and are particularly essential for patients requiring hypoallergenic materials. Depending on the different requirements for the wide range of applications, the dental material market offers a large variety of products; various inert metallic, alloy biomaterials and dental amalgams are used in these implant systems [1,2].

Dental amalgam is one of the most commonly used materials in restorative dentistry. Its physical and mechanical properties, stability, ease of the use and relatively low cost have made amalgam the preferred choice in many clinical situations when compared with other direct restorative materials such as composites and glass ionomers. However, one of its major components, mercury is of particular concern due to its potential adverse effects and clinical problems on human health and the environment. There are four possible harmful effects of dental amalgam: oral galvanism, toxicity, allergen city and ecological complaints. A primary concern with the use of dental materials is whether they are safe as these materials have the potential to cause a variety of adverse reactions such as local or general toxicity, hypersensitivity reactions or irritation [3].

This review has uncovered no convincing evidence pointing to any adverse health effects that are attributable to dental amalgam restorations besides hypersensitivity in some individuals. The author reports contribution to the health risk assessment of mercury use in dentistry, namely occupational exposure to mercury in dentists working with dental amalgam and exposure to mercury in patients treated with amalgam dental restorations.

1.1. Mercury Dental Amalgam

Dental amalgam is an alloy made of liquid mercury that was introduced over 150 years ago; amalgam is a dental filing material contains approximately 50% mercury by weight, as well as other metals, including silver, tin, copper, and zinc. Some alloys also contain indium, palladium or platinum. Elemental mercury (Hg^0) has been used in clinical dentistry since 1830th when it began to be used in filings. Amalgam is a dental filling material contains approximately 50%

mercury by weight, as well as other metals, including Ag, Sn, Cu and Zn. The final composition of dental amalgams typically contains 45 to 55% mercury, 35-45% silver, and about 15% tin. Silver, being the main component of the presently dominating alloy, has resulted in the name silver fillings of these restorations. Considering that mercury, not silver, is the dominating metal in the final filling, they should rather be termed mercury fillings.

It is well known that all dental materials release ions into the oral environment and have the potential to interact with the oral tissues and fluids. During the last 20 years, some remarkable changes in restorative dentistry have occurred. The employment of amalgam and different kinds of alloys has dropped dramatically. The main reasons were connected with the aesthetic aspects and the controversy over amalgam employment and metal toxicity, but also because of environmental pollution from mercury waste. However, there is no convincing evidence pointed out to adverse health effects due to dental amalgam restorations, except in rare instances of an allergic reaction, and can be used as a preferred restorative material where aesthetic is not a concern [4-16].

1.2. Current Status of National Reporting Systems for Adverse Reactions to Dental Amalgams

At present, research is being undertaken to evaluate the potential correlation between Hg release from dental amalgams, and a number of chronic and degenerative human diseases [17]. Mercury vapor (elemental mercury) released during amalgam removal or placement may be inhaled and absorbed into the bloodstream and can cross the placental barrier. In the past two decades, the safety of amalgam as restorative material in dentistry has been discussed controversially, and this has led to the result that several countries (Norway and Sweden) banned this type of dental filling material [18,19]. Germany and Canada advise against its use in pregnant women and children [20]. The American Dental Association (ADA) has opposed a complete ban on dental amalgams [21]. The World Dental Federation (FDI) is still in favor of the continued use of mercury dental amalgam [22]. The US Food and Drug Administration (FDA) have also considered the question of banning the use of Hg-containing dental materials; acknowledge that dental amalgam releases low levels of elemental mercury vapor [23]. The FDA says mercury from dental amalgam can bioaccumulations in bodily fluids, tissues, kidneys, and the brain, but then states that "studies have not shown that increased mercury levels and bioaccumulation due to dental amalgam result in detectable damage to target organs. On one side of the debate, the FDA and the ADA support amalgam as a safe and effective material for dental restorations and amalgam continues to play a major role in dentistry today [24-26]. Results from the only two randomized, controlled, clinical trials on dental amalgam, known as the Children's Amalgam Trials, were first reported in 2006 [27,28]. Both studies found no difference in neurobehavioral outcomes between the amalgam group and the composite (non-amalgam) group; although in both trials the amalgam group showed a statistically significant increase in urinary mercury levels. These two studies, in addition to being widely cited in the literature, are cited by the FDA and the ADA as providing evidence for the safety of amalgam [29,30]. However, indirect evidence for a link between Hg exposures from dental amalgams has been reported [31,32].

The World Health Organization (WHO) deemed the first route of mercury exposure to humans is from dental amalgam. The WHO estimates that the typical absorbed dose of mercury from amalgams is 1 - 22 μg/day, with most people incurring doses of less than 5 μg/day [33]. Considerable variation exists, with an upper range of 100 μg/day associated with gum chewing. Exposure variables include the total amalgam surface area, the physical and chemical composition of the amalgam, the mechanical stresses of chewing and bruxism, the proximity to other metals, and the oral conditions of temperature, pH, and negative air pressure. The FDA assumes and exposure of 1 - 5 μg/day in its current amalgam rule [33].

In November 2013, the Environmental Protection Agency (EPA) released a study of the National Health and Nutrition Examination Survey (NHANES) dataset claiming that mercury concentrations were decreasing in the human population over time [34]. In fact, the opposite conclusion is supported by their data. The unreported rise in blood inorganic mercury levels (IHg) indicates a rise of chronic mercury exposure in the population over time. Blood inorganic mercury level is the best biomarker available in the NHANES dataset to estimate chronic mercury exposure. It is clear that a significant increase in blood IHg has occurred. In fact it had more than doubled. The EPA study on mercury concentrations in NHANES is available for public analyses [35,36]. However, a date certain to ban mercury dental amalgam's use globally has not yet been achieved.

According to the Regulation (EU) 2017/852 of the European Parliament and of the Council of 17 May 2017 the use of mercury in dental amalgam is the largest use of mercury in the Union and a significant source of pollution. The use of dental amalgam should therefore be placed down and the Commission should assess and report of the feasibility of a phase out of the use of dental amalgam preferably by 2030 [37].

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) from the European Commission claimed that "... no risks of adverse systemic effects exist, the current use of dental amalgam does not pose a risk of systemic disease...". SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review [38]. But the real scientific data show that: (a) Dental amalgam is by far the main source of human total mercury body burden. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden. (b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys. (c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. (d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. (e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals. (f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

van Noort et al. [39] stated that "There is a need to raise the awareness among dental professionals of the potential for adverse reactions due to dental materials and to develop and internationally accepted system of data gathering that can produce the evidence that reflect the extent, severity and incidence of adverse reactions to dental materials".

1.3. In Vivo/Ex Vivo Mercury Release from Dental Amalgam Fillings in the Human Body

From a risk assessment point of view, it is of interest to reveal the impact of extensive dental treatment, i.e. amalgam removal, on the Hg levels in biological fluids, and to relate this to the influence of the daily Hg uptake from amalgam fillings. It is known that amalgam fillings release mercury; therefore, its concentrations increase in blood, urine, saliva, and intra-oral air of subjects with amalgam fillings [40-69].

Ekstrand summarized some reports on mercury release from amalgam fillings and resulting concentrations in biological fluids, development of antibiotic resistance, and kidney function [12]. In a series of studies of subjects with amalgam fillings, mercury levels were followed in saliva, feces, blood, plasma, and urine before and until 60 days after removal of all of the fillings. According to the conclusions of independent evaluations from different state health agencies, the release of mercury from dental amalgam does not present any non-acceptable risk to the general population.

Mercury levels in blood and in mouth air before and after chewing were measured in 47 persons with and 14 persons without dental amalgam restorations. Differences in the mouth air mercury levels before and after chewing were statistically significant in the group with amalgams, but not in the group without amalgams. Blood mercury concentrations were positively correlated with the number and surface area of amalgam restorations and were significantly lower in the group without dental amalgams [40]. It should be stressed that the elemental mercury found in dental amalgams is different from methyl mercury, a form of organic mercury from seafood that affects fetal brain.

Leistevuo studied differences in the amounts of organic and inorganic mercury in saliva samples between amalgam and no amalgam human study groups [41]. The amount of organic and inorganic mercury in whole saliva was measured in 187 adult study subjects. They reported that the levels of methyl-mercury in saliva ranged from 0 to 174 nmol/L (0-37.523 μg/L), with a mean methylmercury level estimate of 14.0 nmol/L (3.019 μg/L). The mercury contents were determined by cold-vapor atomic absorption spectrometry (CV-AAS). The amount of organic and inorganic mercury in paraffin-stimulated saliva was significantly higher ($p<0.001$) in subjects with dental amalgam fillings ($n=88$) compared to the non-amalgam study groups ($n = 43$ and $n = 56$). Authors discovered no significant difference in mercury content between those who did not have amalgam restorations and those who had them removed (mean time since last removal = 390 days). They found a correlation between the total amalgam surfaces and organic mercury - presumably as methylmercury (CH_3Hg^+) - in saliva. Their results are compatible with the hypothesis that amalgam fillings may be a continuous source of organic mercury, which is more toxic than inorganic mercury, and almost completely absorbed by the human intestine [41].

Ganss determined the relationship between mercury content of resting and stimulated saliva, and blood and urine [42]. Eighty subjects participated; 40 of them attributed their self-reported complaints to dental amalgam (patients), the others were matched with respect to age, sex and amalgam restorations (controls). Serum, 24-h urine, resting and chewing stimulated saliva were analyzed for mercury using the atomic absorption spectrometry technique (AAS). Median mercury levels in serum were 0.67 μg L^{-1} for patients and 0.60 μg L^{-1} for controls. In urine levels were found to be 0.77 μg L^{-1} and 0.94 μg L^{-1} creatinine, respectively. Resting saliva contained 2.97 μg L^{-1} in patients and 3.69 μg L^{-1} in controls. Chewing mobilized additional amount of 16.78 μg L^{-1} in patients and 49.49 μg L^{-1} in controls. Only a weak correlation was found between mobilized mercury in saliva and serum. Saliva testing is not an appropriate measure for estimating the mercury burden derived from dental amalgam.

Sandborgh-Englund have obtained data on changes in Hg levels in blood, plasma, and urine following removal of all amalgam fillings during one dental session in 12 healthy subjects [43]. Frequent blood sampling and 24-h urine collections were performed up to 115 days after amalgam removal and in 80 subject's additional samples of plasma and urine were collected up to three years after amalgam removal. A transient increase of Hg concentrations, determined by cold vapor atomic absorption spectrometry (CV-AAS), in blood and plasma was observed within 48 hours after amalgam removal. No increase in the urinary Hg excretion rate was apparent after amalgam removal. Sixty days after the amalgam removal, the Hg levels in blood, plasma, and urine had declined to 60% of the pre-removal levels. There was evidence that correlation between mercury levels in saliva, serum, and urine (i.e. the absorbed metal) is weak. Thus, saliva testing to estimate the mercury burden caused by amalgam restorations is also not appropriate.

Berglund and Molin performed a study to determine whether removal of all amalgam restorations might significantly affect mercury levels in plasma and urine and whether the use of rubber dams might reduce patient exposure to mercury during amalgam removal [44,45]. The measured the mercury concentrations in plasma and urine were performed by atomic absorption spectrometry (AAS). The study showed that dental amalgam had a statistically significant impact on the mercury levels found in plasma and urine in the patients tasted, and that the use of a rubber dam during removal of all amalgam restorations significantly reduced the peak of mercury in plasma following removal. Although the composition of saliva does not permit a reliable estimation of body burden of mercury and it is, therefore, far from being of the same importance of blood and urine as a diagnostic tool. A highly subjective and inter-subjective variability of results has been reported and there is evidence that some elements such as Hg may also occur in saliva in a particulate form [46,47].

Monaci assessment of a possible role of human saliva in the diagnosis of some physiological and pathological changes in oral and body functions [48]. He was determined by a flow injection mercury system and K, Na, Mg, P, and Ca by inductively coupled plasma optical emission spectrometry (ICP-OES). Total concentrations of major cations (Ca, K, Mg, and Na) and Hg in whole saliva from 33 healthy adults showed that concentrations of Hg were positively correlated to the number of amalgam fillings and increased at a rate of about 1.9 µg L^{-1} for each filling. No correlations were found between Hg concentrations and those of major elements. Data reported in this study, although preliminary, contribute to the assessment of levels of major cations and Hg in whole unstimulated human saliva.

Pesch measured Hg levels in urine, hair and saliva of 245 German children (8-10 years old) [49]. A basic medical examination was done, as well as a checkup by a dentist to determine the dental status (number of amalgam fillings, condition and age of the amalgam restorations and the number of amalgam filling surfaces). Atomic absorption spectrometry (AAS) and sodium borohydride were used to determine all forms of the Hg. Authors found a median salivary mercury concentration even lower than those of control group (no amalgams) in the present study (0.16 µg Hg L^{-1}). This difference may be due to the fact that the two studies used different techniques. The results showed that urine is suitable to estimate Hg exposure due to amalgam fillings. Mercury levels increased with the number of amalgam fillings and the number of amalgam filling surfaces but there was no significant difference. There was a weak correlation between the Hg levels in hair and urine. Saliva was not a suitable sample to monitor the Hg burden at low levels of exposure. Results showed that levels of Hg found in urine did not reveal health risks due to exposure to Hg when compared with human biological monitoring (HBM) values. Therefore, Hg analysis in urine is suitable to estimate mercury exposure due to amalgam fillings.

Exposure to static magnetic fields such as those generated by MRI, electromagnetic fields such as those produced by mobile phones, ionizing electromagnetic radiations such as X-rays and non-ionizing electromagnetic radiation such as lasers and light cure devices can significantly increase the release of mercury from dental amalgam restorations and/or cause micro leakage [50]. A report from Turkey showing ex vivo mercury release (increased) from dental amalgam fillings after high-powered MRI However, this research indicates that MRI is not completely devoid of any effects on amalgam restorations, and the primary risk of MRI systems arises from the effects of its strong magnetic field on objects containing ferromagnetic materials [51]. A study by Yilmaz and Adisen investigated 7T MRI's impact on mercury excretion from dental amalgam [52]. Authors evaluated the amount of mercury in artificial saliva; 60 caries-free molar or premolar teeth that had been extracted for clinical indications. Two-sided cavities were opened in each tooth and amalgam fillings applied. After 9 days, two groups of 20 randomly selected teeth were placed in 20 mL of artificial saliva immediately followed by 20 minutes of MRI exposure at 1.5 or 7.0 T. The teeth were removed from the artificial saliva 24 hours later, and the saliva was analyzed for mercury content by using inductively coupled plasma mass spectrometry (ICP-MS). The mean mercury content of the artificial saliva was 673 µL in the 7.0-T MRI group, 172 µL in the 1.5-T group, and 141 µL in the control group. The mercury content in the 7.0-T group was greater than that in both the 1.5-T group and the control group. In an ex vivo setting, mercury was released from amalgam fillings after exposure to 7.0-T MRI but not 1.5-T MRI. The results of that study showed elevated mercury excretion from MRI-scanned teeth and called into question the safety of scanning clinical patients, most notably at 7T.

Mortazavi and Mortazavi reported that the mercury release has been associational with RF fields of various sources, including wireless Internet networks, mobile phones, and MRI [53]. Burkett investigated the effects of MRI exposure on mercury excretion using fresh, lab-created dental amalgam restorations and extracted teeth with old, pre-existing restorations [54]. Donated, unfilled human teeth (n = 120) were restored with amalgam before being stored in saliva, artificial saliva, or a dry box prior to MRI scanning. The teeth were placed in individual tubes of fresh artificial and scanned at 1.5-T, 3-T, or 7-T or left unscanned as controls. Mercury concentrations were measured by using inductively coupled plasma mass spectrometry (ICP-MS) 24-30 h later. Donated teeth with pre-existing restorations (n = 40) were stored in artificial saliva, scanned at 7-T or left unscanned as controls, and mercury concentration tested. For teeth extracted and restored in a laboratory, no significant difference was found between mean mercury concentrations of unscanned teeth (13.72 µg/L and teeth scanned at 1.5-T (10.88 µg/L), 3-T (12.65 µg/L), or 7-T (8.88 µg/L). MRI of dental amalgam does not significantly increase mercury excretion at 1.5 -T, 3-T, or 7-T compared to unscanned teeth. The mercury concentrations in the experiments, however, were much lower than those reported by Yilmaz et al. at both 1.5 and 7T, by a factor of 15.8 and 75.8, respectively. The results of the study also contradict the Yilmaz group's main finding that 7T MRI causes increased mercury excretion from dental amalgam [52]. The discrepancy between the study and Yilmaz et al. could be due to multiple factors such as storage conditions, pH of the testing solution, the metal composition of the amalgam, and/or the MRI parameters.

Fakour estimated of mercury in saliva as well as scalp hair samples among Iranian women exposed to mercury-containing dental amalgam [55]. Hg concentration in saliva samples was analyzed by cold vapor atomic absorption spectrometry (CV-AAS). In amalgam restorations, the mercury released from the restoration is inconsistent for the first month, and it is only after 6 months or more that the mercury release reaches a consistent level. This showed that the amount of Hg0 lost from the amalgam capsules can be absorbed into the human body through inhaling, swallowing the saliva or through the dental pulp after the dentist places the fillings in the patient's teeth. They conclude that "mercury can be absorbed systematically upon swallowing and to be concentrated in different body tissues such as hair" [55].

Although mercury-containing dental amalgam is truly the most important source of vapor and inorganic mercury in the general population [55], it is possible that mercury forms (species) in oral cavity are not only inorganic, as the article by Leistevuo et al. cited by the authors points out [41]. Lorscheider confirmed that Hg is released into intra-oral air, and thus Hg0 can be inhale and swallowed through the nose and mouth and is distributed throughout the body [56]. The proximate cause of mercury alkylation in oral microbial communities - which occurs in dental plaque - appears to be associated with the presence of some bacteria [57]. Hence, when mercury vapor (Hg^0) is released from amalgams and dissolved into the saliva, it exists mainly as Hg^0 and partly as inorganic divalent mercury (Hg^{2+}). Having shown that both methyl and ethyl mercury are present in saliva samples of mercury amalgam bearers, it is now essential to determine whether organic mercury generated from dental amalgam may contribute to the levels of hair mercury in individuals who are exposed to mercury amalgam fillings, as seen in Fakour et al. work [55,58,59].

Organic mercury is formed in saliva owing to the presence of dental amalgams. A plausible biochemical explanation would involve mercury vapor (Hg^0) emitted from amalgams which is reduced to mercuric mercury (Hg^{2+}) and then transformed in mono-methylmercury (CH_3Hg^+) and ethyl mercury ($CH_3CH_2Hg^+$) by oral bacteria [57]. Furthemore, Guzzi investigation seems to support the work of Leistevuo suggesting evidence that subjects with dental amalgams have shown higher levels of methylmercury compared with controls [41,58]. In approximately 270 individuals with amalgams, they used inductively coupled plasma mass spectrometry (ICP-MS), to measure a wide range of possible values of total mercury in saliva. Mercury levels ranged from the limit of detection (LOD; 0.1 μg L^{-1}) to 780 μg L^{-1} in both salivary baseline flow rate in unstimulated condition and in post-chewing-gum test [58].

Exposure to Hg^0 from amalgam fillings, with potential negative health effects, has commonly been measured to happen either by erosion or evaporation directly from the surface of the filling, followed by ingestion X-ray fluorescence imaging has been used quantitatively to determine the spatial distribution of Hg^0 and Zn in sections of human teeth that had been filled with amalgam for more than 20 years. The results showed a significant releasing (leaching) of Hg^0 through the dentine and into the pulp, and migration of Hg^0 through the dentinal tubules of the tooth from where it could enter the blood supply through the pulp, while Zn was evenly distributed [59].

Dental amalgam restoration occupies a unique position in dentistry. One outdated member of the family of mercury containing filling materials is the copper amalgam. These amalgam alloys are broadly known as low-copper (5% or less copper) and high-copper alloys (13% to 30% copper). A study reported that through the increasing of their copper density, conventional dental amalgam alloys improved their micro structural and mechanical properties. Reports have also revealed the disappearance of the gamma-2 phase in copper content with more than 20 wt%. Both low and high copper amalgams undergo a transformation process for several years after placement, resulting in a substantial reduction in mercury content, but there exist no limit for maximum allowed emission of mercury from dental amalgams. These modern high copper amalgams are nowadays totally dominating the European, US and other markets, resulting in significant emissions of mercury, not considered when judging their suitability for dental restoration [60].

Elemental mercury (Hg^0) is the main type of metal in dental amalgam fillings and represents approximately 50% of the total number of metals found in these fillings. It can be combined with other metals such as silver, tin, copper, zinc and other trace metals [61]. It does not have any beneficial function in the human body and any amount of this toxic element could be harmful [56]. Saber-Tehrani studied 60 human permanent healthy teeth (without filling) and analyzed using flame atomic absorption spectrometry (FAAS), cold vapor atomic absorption spectrometry (CV-AAS), hydride generation atomic absorption spectrometry (HG-AAS), and electrothermal atomic absorption spectrometry OET-AAS) for the determination of Ca, Hg, Se, Cu, and Ag [62]. The concentration of these elements was assessed in carious and no carious teeth, different tooth groups, with age and with number of amalgam fillings. A negative correlation was found between Ca and the number of amalgam fillings, and significant negative correlations were found between Ca and three other metals (Hg, Ag, and Cu) that indicate the possibility of substitutions of Ca by three other metals. Significant positive correlations were found among the number of amalgam fillings and Hg, A, Cu and Se showed metal concentration in permanent healthy teeth were affected by the presence of the number of amalgam fillings. I addition, significant positive correlations between Hg and Ag, Hg and Cu, and Ag and Cu proved the suspicion that the Hg content in permanent healthy teeth was mainly found because of the influence of amalgam filling, not from other sources.

Consequently, the permanent healthy teeth would be considered as a bioindicator for the accumulation of long-term exposure of Hg and Ag. Saghiri evaluated the levels of mercury and tin in the dental pulp tissue of amalgam restored teeth and in the blood of patients possessing amalgam restoration [63]. 12 amalgams restored and 12 non-restored, sound teeth were chosen and access cavity preparation to the pulp chamber was made. The dental pulp tissue contents were transferred to a graphite furnace atomic absorption spectrometer (GF-AAS) to measure the levels of heavy metals. The blood samples of five patients in each group were randomly analyzed to determine the level of these heavy metals in the blood and if there were a correlation between these levels in blood and pulp. The long-term presence of dental amalgam (at least 5 years) resulted in no significant difference between the levels of Hg and Sn in pulp tissue; however, the blood analysis showed higher level of Hg amalgam group. The analysis between the pulp and blood samples showed positive correlations for both Hg and Sn elements in dental pulp and the blood.

Zimmer performed a study to determine the internal mercury exposure of two groups differing in their attitude towards possible health hazards by mercury from amalgam fillings [64]. Blood, urine and saliva samples were analyzed from 40 female subjects who claimed to suffer from serious health damage due to amalgam fillings. 43 female control subjects did not claim any association. Mercury was determined by means of cold vapor atomic absorption spectrometry (C V-AAS). Median (range) mercury levels in blood were 2.35 (0.25 - 13.40) µg L^{-1} for "amalgam sensitive subjects" and 2.40 (0.25 - 10.50) µg L^{-1} for "amalgam non-sensitive controls". In urine, the median mercury concentrations were 1.55 (0.06 - 14.70) µg L^{-1} and 1.88 (0.20 - 8.43) µg L^{-1} creatinine respectively. No significant differences could be found between the two groups. Stimulated saliva contained 76.4 (6.7 - 406.0) µg L^{-1} mercury in "amalgam sensitive subjects" and 57.0 (2.8 - 559.0) µg L^{-1} mercury controls (not significant). Mercury levels in saliva did not correlate with the concentrations in blood and urine, but merely with the number of amalgam fillings or of the filling surfaces. Mercury in saliva is therefore not recommended for a biological monitoring.

To determine whether patients complaining of oral and medical symptoms perceived to be associated with chronic mercury toxicity has elevated mercury levels in their blood and urine. [65]. The study group in this audit were 56 patients. Their symptoms and co-morbidity were charted and mercury levels in blood and urine were biochemically tested by cod vapor atomic absorption spectrometry (CV-AAS). None had elevated mercury levels in blood or urine above normal threshold level. Mercury levels in blood and urine of this cohort of patients with perceived chronic mercury toxicity were within the normal range in accordance with a national laboratory threshold value [65].

Hosseini and Vaziri performed a study to evaluate the concentration of mercury in saliva before and after amalgam fillings and its relation with numbers and surfaces of amalgam fillings [66]. Twenty-five patients who had no amalgam fillings were selected and the samples of saliva were collected before fillings. After that all posterior decayed teeth were filled in an appointment with amalgam and, 24 hours later, the second samples of saliva were collected. The amount of saliva mercury before and after filling was measured cold vapor atomic absorption spectrometry (CV-AAS). In this study the mean of mercury in saliva was 0.00896 µg mL^{-1} before and 0.16404 µg mL^{-1} after amalgam fillings. The mean of number of fillings was 1.96 and mean of size of surfaces was 76.43 mm^2 and mean of consumption amalgam was 4.1 units. There was no significant correlation between age, sex, number of fillings, number of surface of filling and size of surfaces of fillings, with mercury levels in saliva after amalgam fillings. There was a significant relation between mercury level in saliva after fillings and amalgam amount. Therefore, amalgam may be designating a significant source for mercury release in saliva.

Tercanli investigated the effect of amalgam restorations on mercury concentration in saliva, as well as the effect of restoration number, surface number, and chewing on this concentration [67]. A total of 86 participants were included in this study. Only unstimulated saliva was collected from the control group. The effect of chewing on mercury concentration was examined in the study group with unstimulated and stimulated saliva specimens using inductively coupled plasma mass spectrometry (ICP-MS) technique. In the present study, the mean amounts of mercury in unstimulated saliva (5.6 µg Hg L^{-1} in the study group 0.23 µg Hg L^{-1} in the controls) were consistent with the literature. Mercury concentration in the unstimulated saliva was found to be higher in the study group compared to the control group. The significantly higher level of salivary mercury in the study group of this current investigation is consistent with the results of Leistevuo but not with the results of Zimmer who found no significant difference between the groups [41,63]. As the number of amalgam restorations and the number of amalgam restoration surfaces increased, the mercury concentration in the saliva increased. There was no statistically significant difference between mercury levels in the unstimulated saliva and stimulated saliva. They find that the number of amalgam restorations and the number of restoration surfaces, is also consistent with the literature [41,55,63]. Chewing presented an insignificant difference in mercury concentration. Overall, most of the aforementioned studies suggest that amalgams impact salivary mercury levels.

Ryo investigated the possible relation between dental amalgam fillings and mercury concentration in hair, a suitable biomarker of mercury burden [68]. They measured the mercury concentrations, using inductively coupled plasma mass spectrometry (ICP-MS) technique, in scalp hair samples from 74 female Japanese subjects who had a dietary habit of little fish-consumption. The hair mercury concentrations in the subjects with multiple amalgam fillings were significantly higher than those in the subjects with no amalgam fillings and correlated with the number of amalgam fillings. These findings suggest that the dental amalgam fillings positively influence mercury accumulation in the hair and, probably, in the body.

Tuček report is a contribution to the health risk assessment of mercury use in dentistry, namely occupational exposure to mercury in dentists working with dental amalgam and exposure to mercury in person treated with amalgam dental restorations [69]. Determination of total mercury in samples of biological material (urine, hair) was performed in 50 persons by the AAS method using the mercury vapor generation technique. Current dental exposures based on the most recent findings do not exceed acceptable risk levels for dental personnel and are below the biological limit of mercury in urine valid for occupationally exposed persons (100 µg g-1 of creatinine). The results of the determination of total mercury in the urine have tendency to correlate with the number of amalgam fillings in the oral cavity, which supports the view that amalgam fillings are a permanent source of mercury exposure of such treated persons.

Ertaş investigated in autopsy cases whether exposure to Hg vapor from amalgams is associated with Hg deposition in the parietal lobe of the brain [70]. The Hg levels in the parietal lobes of the brains of 32 cadavers were analyzed with hydride generation atomic absorption spectrometry (HG-AAS). A total of 32 brain samples were tested; of these, 10 were from cadavers with amalgam fillings, while 22 of them were amalgam free. The average Hg level of the amalgam group was 0.97 µg g^{-1}, and in the amalgam-free group, it was 1.06 µg g^{-1}. The results of the study showed no correlation between the presence of amalgam fillings and brain Hg level and that dental amalgam is not a major contributor to brain Hg levels.

1.4. Instrumental Techniques for the Measurement of Mercury Release from Dental Amalgam Fillings

The main analytical problem is determining these ultratrace metals in clinical samples (human biological specimens) as they are present at extremely low (sub-µg/ng L^{-1}) concentrations in very complicated matrices: human saliva, biological fluids (blood, serum, urine) and tissues. The release of mercury has been mainly measured using atomic absorption spectrometry (AAS) - flame atomic absorption spectrometry (FAAS), cold vapor atomic absorption spectrometry (CV-AAS), and hydride generation atomic absorption spectrometry (HG-AAS), electrothermal atomic spectrometry (ET-AAS) also known as graphite furnace atomic absorption spectrometry (GF-AAS), inductively couple plasma optical emission spectrometry (ICP-OES), inductively coupled plasma mass spectrometry (ICP-MS) or X-ray absorption near-edge spectrometry (XANES).

Atomic absorption spectrometry (GF/ET-AAS) is still the dominant analytical technique used for mercury and trace metals analysis in clinical laboratories. Although GF/ET-AAS allows direct sample analysis, most of the works reported in the literature perform specimen's analysis after digestion of the sample. However, more clinical laboratories are transitioning away from graphite furnace AAS technique toward those based on ICP-MS, which is a form of inorganic MS measuring mercury and metal ions rather than molecular ions. ICP-MS is the method of choice for potentially toxic mercury and trace metal determination, in clinical specimen's analysis.

2. Conclusion

This review is not all-inclusive and presents only a small portion of the vast published literature on the subject of the health effects of mercury in dental amalgam restorations. It appears clear, however, that, despite a plethora of well-designed studies, no definitive evidence showing that dental amalgam is a hazard to patients. While further research will help to settle particular questions as to whether dental amalgam fillings or another material causes a specific adverse health effect, the broader question of whether a material is completely safe can never be fully answered. However, the health policies of different countries, agencies and world organizations have not reached a consensus on the use and safety of dental amalgam. The study showed that dental amalgam fillings had a statistically significant impact on the mercury, most toxic non-radioactive element, levels found in biological fluids and tissues in the patients tested. This overview aimed to investigate the effect of dental amalgam restorations on mercury concentration in human biological specimens. Research on the effects of mercury from dental amalgam fillings should continue in order to explore cause-and-effect sequences and deepen on understanding of the health implications. The search for an "ideal" restorative material for tooth tissue after dental treatment should be accelerated.

Bjørklund says "Despite this, many environmental toxicology researchers still question whether the adverse human health effects of dental amalgams have fully been considered and appropriately addressed by dentists, dental laboratories and government [71]. Although, very recently, Tibau and D Grube stated that "The latest significant findings on human exposure to mercury dental amalgam using the "Gold Standard National Health and Nutrition Examination Survey (NHANES) database, may finally be the catalyst that will achieve the goal and "Make Mercury History" in the dental sector" [72].

Finally, this review of the dental amalgam controversy outlines the debate over whether dental amalgam (the mercury alloy in dental fillings) should be used. Supporters claim that it is safe, effective and long-lasting while critics argue that amalgam in unsafe because it may cause mercury poisoning and other toxicity [7,73].

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