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Association of Dental Amalgam Restorations With Kidney Disease And Dysfunction: A Review Of Literature And Evidence From Randomized Clinical Trials

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Abstract:
Background: *Dental amalgam is a popular and cost-effective dental restorative material but in recent years concerns emerged over its potential adverse health effects because of its mercury content. The aim of this paper is to identify and review the available published literature and randomized clinical trials on the association of dental amalgam restorations with kidney disease and dysfunction. The secondary objective is to examine the weight of evidence from published literature and randomized clinical trials on the association of dental amalgam restorations with kidney disease and dysfunction.*
Materials and methods: *A systematic search for relevant published literature and randomized clinical trials on "association of dental amalgam restorations with kidney disease and dysfunction" was made using Google, Google Scholar, and HINARI search engines.*
Results*: Twenty studies were identified and reviewed. Twelve of them are cross-sectional, one study is retrospective and one other consecutive. There are two original randomized clinical trials (RCTs) with two additional studies each being products of each of the original RCTs giving a total of six RCTs.*
Conclusion*: Half of the studies in this review showed a positive correlation between exposure to dental amalgam and some degree of kidney dysfunction. Despite the positive correlation with urinary mercury excretion, the level of mercury exposure from amalgam fillings did not exceed the capacity for mercury elimination by the kidneys via urinary excretion in the children. Evidence from available randomized clinical trials employing biomarkers of renal glomerular and tubular damage are supportive of potential renal glomerular and proximal tubular dysfunction resulting from exposure to dental amalgam restorations in children. In terms of quality of evidence, randomized clinical trials are superior to cross-sectional studies. More randomized clinical trials are needed to further confirm the association between dental amalgam restorations and kidney dysfunction.*
Keywords*: Dental amalgam, urinary mercury, urinary albumin, nephrotoxic biomarkers, kidney disease, kidney dysfunction, randomized clinical trials.*

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I. Introduction

Dental amalgam contains about 50% mercury (500mg amalgam restoration contains approximately 200–250mg of Hg) and has been used for more than 165 years as restorative material in dentistry[1]. Its use has recently become controversial, particularly because it continually releases small amounts of mercury vapour[1]. In 2018, the World Dental Federation adopted the Minamata Convention recommendation of 2013 for the phase down or possible phase out of amalgam especially for dental lesions that are amenable to treatment with other restorative materials, more so with first restorative treatments and in young patients[2].

Mercury released from dental amalgam fillings can take several forms: mercury vapour, metallic ions and/or fine particles. Dental amalgam is also a source of elemental and inorganic mercury and the kidney is one of the primary target organs of inorganic mercury exposure, particularly at higher doses[3]. Dental amalgams have been correlated with disease outcomes, for instance, kidney dysfunction in children [4].

Kidney disease can be classified into two categories: acute kidney injury and chronic kidney disease (CKD) each of which represents a major public health problem worldwide[5, 6]. Could exposure to dental amalgam be contributory to the growing global burden of kidney disease? This paper reviews the available literature and the evidence from randomized clinical trials on the association of dental amalgam restorations with kidney disease and dysfunction.

II. Materials And Methods

A systematic literature search was carried out in Google**,** Google Scholar, and HINARI search engines with the aim of identifying relevant published literature and randomized clinical trials with information on the main terms "association of dental amalgam restorations with kidney disease and dysfunction". In addition, the search was made using different combinations of the key words. The articles are published in English language

III. Result

The search returned more than 150 articles relating to systemic health effects and safety issues associated with dental amalgam. Twenty (20) studies relevant to association of dental amalgam restorations with kidney disease and dysfunction were identified and reviewed. Table 1 summarizes the characteristics of the reviewed studies. Twelve of the reviewed articles are cross-sectional studies, one a retrospective study while another one is a consecutive study. Six studies are from randomized clinical trials (RCTs) of which there are two original randomized clinical trials and two additional studies as products of each of the two original randomized clinical trials (Table 1).

Table 1: Types of reviewed studies and the number of reviewed studies for each type

Type of Study reviewed	**No. of reviewed studies**
Cross-sectional	12
Randomized Clinical Trial	6
Retrospective	1
Consecutive	1
Total	**20**

The studies in this review involved all age categories (Table 2). Eight of the studies were done in adults while nine studies were carried out in children/adolescents Two studies had adolescents/young adults as study subjects and one study involved all the age categories.

Table 2: Types of reviewed studies and the age categories of subjects studied

Type of Study reviewed	**No. of adults studied**	**No. of children/adolescents studied**	**No. of adolescents/young adults studied**	**No. of all age category persons studied**
Cross-sectional	6	3	2	1
Randomized Clinical Trial	0	6	0	0
Retrospective	1	0	0	0
Consecutive	1	0	0	0
Total	**8**	**9**	**2**	**1**

Table 3 summarizes the reviewed studies and the type and number of markers of kidney disease and dysfunction employed in the studies as well as number of studies with positive correlation for kidney disease and dysfunction associated with exposure to dental amalgam restorations.

The markers for kidney disease and dysfunction were evaluated by monitoring the level of urinary mercury concentrations in the study subjects in fourteen studies (nine cross-sectional studies, four RCT studies and one consecutive study in this review). The presence of nephrotoxic biomarkers in the urine of study subjects was evaluated for in seven studies (four cross-sectional studies and three RCT studies). Similarly, in seven studies (four cross-sectional and three RCTs), the presence of significant protein in urine (albuminuria), a marker for glomerular dysfunction was evaluated for. One of the studies in this review is a two-year consecutive case series which evaluated study subjects for blood and urine mercury levels. The study subjects believed that their oral/medical symptoms or conditions were caused by mercury toxicity from amalgam fillings. In one other study, the subjects were evaluated for features of immunologic disease of the kidney associated with exposure to dental amalgam restoration by testing them for serum levels of antibodies to glomerular basement membrane (GBM-IgG). The only retrospective study in this review examined for clinical evidence of kidney disease associated with dental amalgam restorations from the clinical records data of the studied subjects.

Type 3: Types of reviewed studies and the type and number of markers of kidney disease and dysfunction employed as well as number of studies with positive correlation for kidney disease or dysfunction associated with dental amalgam restorations

Study type	Urinary mercury excretion	Nephrotoxic biomarkers	Albuminuria	Clinical kidney disease	Immunologic kidney disease	Number of studies with positive correlation for kidney disease or dysfunction
Cross-sectional	9	4	4	0	1	5
Randomized clinical trial	4	3	3	0	0	5
Retrospective	0	0	0	1	0	0
Consecutive	1	0	0	0	0	0
Total	**14**	**7**	**7**	**1**	**1**	**10**

Association of Dental Amalgam restorations with Kidney Disease and Dysfunction: Review of Literature

Boyd et al first demonstrated possible renal effects of dental amalgam mercury release in an animal study. Working with sheep, they demonstrated reduced inulin clearance by the kidneys and changes in urinary electrolyte patterns in six sheep, each of which was administered 12 occlusal fillings[7]. Their study however, clearly involved an unrealistic exposure scenario[7]. Nevertheless, some studies in humans have shown that people with amalgam restorations have higher kidney mercury concentrations than people without amalgams[8]. Nicholae et al[s3] in a population-based study determined the overall urinary mercury level in the Canadian general population in relation to the number of dental amalgam surfaces. The authors employed data from the 2007/2009 Canadian Health Measures Survey, which measured urinary mercury concentrations in a nationally representative sample of 5,418 Canadians aged 6–79 years. Urinary mercury concentrations were stratified by sex, age, and number of dental amalgam surfaces. The authors found that the mean urinary mercury concentrations in the study (general) population were significantly lower than the values considered to be associated with risk to health.

Other studies have investigated kidney function in relation to amalgam loading. For example, in one cross-sectional study involving 48 randomly selected healthy male students, aged 17–22 years, Herrstrom and colleagues[9] found no association between urinary proteins indicative of renal glomerular dysfunction and either number of dental amalgam restorations or urinary mercury levels. The study population in this study was small and this might have underpowered the observations.

In another study Eti et al in the United States detected a small increase in urinary N-acetyl-β-glucosaminidase (NAG) levels in people with amalgam fillings[10]. In this cross-sectional study, the authors sought to answer the question as to whether sufficient mercury was absorbed from dental amalgam fillings to cause renal damage. One hundred healthy adults (18–44 years old) who filled out health questionnaires and voided urine samples had their urine mercury concentration and urinary NAG measured. The subjects were grouped into those with amalgam fillings (N=66) and those without (N=34). People with mercury amalgam fillings excreted slightly more mercury than people without them, and had a very small increase in urinary NAG excretion that the authors considered probably of no clinical significance. They concluded that dose of mercury absorbed from amalgam appeared too little to be a public health hazard for renal injury. The authors conclusion appears inconsistent with their findings which showed statistically significant differences in the median urinary mercury concentration for those with and without amalgam fillings was 1 (1–2) and 0 (0–0.6) ng/ml ($P<0.01$) (95% Confidence Interval) and median urinary NAG concentration was 23 (18–27) and 16 (11–18) units ($P<0.05$) in the two groups respectively[10]. Moreover, although the authors considered their observation to probably have no clinical significance, this was a cross-sectional study and it is possible that a longer period of follow up of the study population might have revealed a more significant finding giving that kidney damage could be progressive. In this study there was significant disparity in the number of study subjects between the two study groups. The number treated with amalgam was almost double the number without amalgam treatment.

Al-Saleh et al[11] in Saudi Arabia examined the effect of mercury (Hg) associated with dental amalgam fillings on biomarkers of renal and oxidative stress in children age 5-15.5 years. Urine samples were analysed for *N*-acetyl-β-D-glucosaminidase (NAG), α_1-microglobulin (α_1-MG), β_2-microglobulin (β_2-MG), retinol binding protein (RBP), albumin (ALB), 8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA). The level of urinary mercury (UHg-C) was calculated as μg/g creatinine. Multiple regression analyses revealed that the excretion of urinary NAG was significantly associated with the presence of dental amalgam fillings[11]. Furthermore, the authors observed that mercury affected the excretion of urinary 8-OHdG in a dose-related pattern that was mostly associated with long-term exposure to low mercury levels[11]. The data from the study by

Al-Saleh et al provide evidence that low exposure to mercury from dental amalgam fillings exerts an adverse effect on kidney tubular functions in children. The authors suggested that oxidative stress may play a role in the process. They also suggested urinary NAG as the most sensitive of all the investigated renal biomarkers[11].

A retrospective cohort study[12] of 20,000 New Zealand military personnel (comprising 84% males) which covered the period 1977 to 1997 found no associations between an index of longitudinal dental amalgam exposure and any of a number of kidney diseases found in hospital discharge data[12]. Although this study had a large sample population, it was retrospective and there is the possibility that some relevant data might have been missing in the clinical records. The data consisted of yearly dental treatment histories, including amalgam filling placements compiled from individual patient records. To minimize amalgam exposure misclassification, the cohort was restricted to people who at New Zealand Defence Force entry were aged less than 26 years old and had all their posterior teeth. The cohort was linked with morbidity records in which disorders of the nervous system and the kidney were examined[12].

Ye X et al[13] evaluated impacts of low-level mercury exposure on kidney function as well as neurobehavioral and neuropsychological performance among 403 children aged 7–11 years from five schools in Xuhui, Shanghai, China based on dental histories of the children as checked by dentists. One hundred and ninety-eight (198) children had confirmed amalgam fillings while 205 children had never had dental amalgam treatment. Each child provided a urine sample for measurements of total mercury, *N*-acetyl-*β*-D-glucosaminidase (NAG) activity, microalbumin, and creatinine (Cr). Mean urinary mercury concentration was 1.6μg/g creatinine for children with amalgam fillings and 1.4μg/g creatinine for children without amalgam fillings. No differences were found between children with and without amalgam fillings for either microalbuminuria and the nephrotoxic biomarker, NAG.

However, the authors observed that urinary mercury concentration was slightly elevated among children with amalgam fillings, although they found no evidence of adverse effects on kidney function[13].

Guzi et al[14] studied a small group of 24 Caucasian adults aged between 18 and 75 years, three-quarters of whom were females. All the study subjects had a history of long-term exposure to mercury vapour from mercury-containing amalgam fillings and were showing adverse effects that were laboratory confirmed. Enzyme-linked immunosorbent assays (ELISAs) were used to evaluate serum levels of antibodies to glomerular basement membrane (GBM-IgG). None of the patients showed evidence of anti-GBM autoimmunity. The authors also found no evidence for the presence of circulating anti-GBM antibodies in subjects suffering from adverse events due to long-term exposure to mercury from dental amalgams[14]. The study was however limited its small size study population.

Eyeson et al[15] studied a group of 56 consecutive patients presenting to the Oral Medicine Unit at Guy's Hospital, London, UK over a period of two years from 2003-2004 who believed that their oral/medical symptoms or conditions were caused by mercury toxicity from amalgam fillings. Biochemical investigations that were carried out as part of the study include blood and urine mercury levels. Six healthy volunteers (three males, three females, mean age 45yrs) who had history of medical disorders and who were free of any amalgam restorations were used as controls for the study. The authors found that blood and urine levels were within the normal range in the study cohort. Furthermore, the authors noted that compared to the healthy control group, the symptomatic group had neither a higher estimated daily uptake of inhaled mercury vapour or a higher mercury concentration in blood and urine. The authors concluded that the study provided no scientific basis for the belief that the patients' symptoms were the result of mercury release from their amalgam restorations[15]. Despite the fact that all the subjects studied had urine mercury levels below the limit of normal level (50nmol/L or about 18μg/L), the study sample population was small and much more so the healthy control group which comprised just six volunteers.

Other studies have also investigated the effect of amalgam restorations on the levels of mercury in urine and other bodily fluids. One German study measured 24-hour urinary mercury levels in 703 adolescent/young adult subjects with amalgam restorations [16, 17]. The study found the mean urine mercury level was 0.75 μg/L and the mean level standardized for creatinine was 0.64μg mercury/g of creatinine in the study population[16, 17]. Furthermore, the mean 24-hour urinary mercury excretion was 0.48 micrograms in subjects younger than 18 years and 0.99 micrograms in subjects older than 18 years[16, 17]. The value standardized for creatinine reported in the study was lower than the minimum mean level (30μg mercury/g of creatinine) reported by the World Health Organization to be associated with adverse effects in sensitive people[16, 18]. Another study investigated urinary mercury levels in German children age 3-15 years with and without amalgam restorations[16, 19]. The mean urinary mercury concentration for the 93 children without amalgams was 0.17μg/L, compared to 0.70μg/L for the 86 children with amalgam restorations[16, 19]. A significant difference in urinary mercury levels was found between the two groups, as well as a positive correlation between the number of amalgam surfaces and urinary mercury levels[16, 19]. But despite the significant differences urinary mercury levels were well below the normal limit of 18μg/L.

From a nationally representative study sample in the United States, using household interview, dietary interview, dental examination, and laboratory data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES), Dye et al[20] al examined the association between urinary mercury concentrations and dental restorations in US women of reproductive age in whom approximately 13% of all posterior dental surfaces were restored with amalgams. They found that the average urinary mercury level in the women was low (1.34μg/L).

Again, Kingman and colleagues[21] from a cohort of United States adult military population of 1127 healthy males whose ages ranged from 40 to 78 years and had an average of 19.9 tooth surfaces exposed to amalgam, with amalgam exposure varying from 0 to 66 surfaces. Their average inorganic urinary mercury concentrations were 2.88μg/L. There was significant correlation between amalgam exposure and the total urinary mercury concentrations. Based on the cross-sectional data, it was estimated that, on average, each ten-surface increase in amalgam exposure is associated with an increase of 1μg/L mercury in urine concentration suggesting a potential for renal damage with increasing dental amalgam exposure.

Dutton et al[22] analysed data from 2,137 Canadian adult subjects mean age 49.3 years with and without dental amalgam who agreed to undergo a urinary six-hour challenge to determine their mercury levels from September 2010 through February 2013. Urinary mercury levels were statistically significantly higher in participants with amalgam surfaces, with an average difference of 0.55μg/g-creatinine. The authors also found a statistically significant linear relationship between urinary mercury levels and the number of amalgam surfaces. They estimated that an individual with seven or more dental amalgam surfaces has 30% to 50% higher urinary mercury levels than an individual without amalgams.

From Egypt, Mortada and colleagues[23] studied 101 healthy adults (80 males and 21 females) grouped into those with amalgam fillings (39 males and 10 females) and those without (41 males and 11 females). Exposure to mercury was assessed by determination of mercury levels in blood, urine, hair and nails. Urinary excretion of beta-2-microglobulin (beta2M), N-acetyl-beta-D-glucosaminidase (NAG), gamma-glutamyl transferase (gamma GT) and alkaline phosphatase (ALP) were evaluated as markers of tubular damage. Albuminuria was also assayed as an early indicator of glomerular dysfunction while serum creatinine, beta-2-microglobulin (beta2M) and blood urea nitrogen (BUN) were determined to assess glomerular filtration. The authors found that mercury levels in blood and urine were significantly higher in persons with dental amalgam than those without. Furthermore, in the dental amalgam group, blood and urine mercury levels significantly correlated with the number of dental amalgams. Again, urinary excretion of NAG, gamma GT and albumin was significantly higher in persons with dental amalgam than those without, and urinary excretion of NAG and albumin significantly correlated with the number of amalgam fillings. They concluded that kidney damage is possible with dental amalgam exposure conditions and may be assessed by urinary excretions of albumin, NAG, and gamma-GT [23].

Randomized Clinical Trials

Randomized clinical trials on the effects of dental amalgam on kidney disease and dysfunction have been very few and have been carried out in children. In one original randomized clinical trial, the New England Children's Amalgam Trial (NECAT) Bellinger et al[24] in the United States compared renal function (and neuropsychological function) in children whose dental caries were restored using amalgam or mercury-free materials. This was a two-group randomized clinical trial involving five community health dental clinics in Boston, Massachusetts, and one in Farmington, Maine, between September 1997 and March 2005. A total of 534 children aged 6 to 10 years at baseline with no prior amalgam restorations and two or more posterior teeth with caries were randomly assigned to receive dental restoration at baseline and incident caries during a five-year follow-up period using either amalgam (n=267) or resin composite (n =267) materials. Renal glomerular function was measured by creatinine-adjusted albumin in urine. The study subjects had two or more posterior teeth with dental caries such that restoration would include the occlusal surfaces and had a mean of 15 tooth surfaces (median, 14) restored during the five-year study period. They had no prior history of renal or immunosuppressive disease. The study initially attempted to collect timed overnight urine samples from the children, but switched to spot samples mid-trial due to challenges with collecting timed overnight samples from the children.

The authors found a statistically significant higher mean urinary mercury level (0.9 vs. 0.6 μg/g of creatinine at year 5, $P<.001$) in the amalgam group compared to the composite resin group. None of the children in the study had a urinary mercury level greater than 20 μg/g of creatinine at any time in the trial**.** There were 77 children with microalbuminuria (albumin >30 mg/g of creatinine) during the trial with no significant difference between treatment groups. There were also no statistically significant differences in adverse renal effects observed over the five-year period in children whose caries were restored using dental amalgam or composite materials

In another study derived from the NECAT trial by Barregard et al[25] which focused on renal effects of dental amalgam, indices of glomerular and tubular kidney function measured in the trial such as urinary albumin, alpha-1-microglobulin, gamma-glutamyl transpeptidase (g-GT) and N-acetyl-b-glucosaminidase (NAG) were analysed. Unlike in the composite group, children in the amalgam group had an elevated prevalence of microalbuminuria[25] (defined as urinary albumin >30 mg/g creatinine) in years 3 and 5 of the five-year follow-up. But there was no significant increase in the microalbuminuria associated with either the number of amalgam fillings or urinary mercury excretion levels. The authors considered the increased prevalence of microalbuminuria in children treated with dental amalgam might reflect a causal association or a chance finding. This analytic study of the NECAT randomized clinical trial also showed no effect of dental amalgam on renal tubular function with no significant urinary excretion of the renal biomarkers[25]. Furthermore, there was a lack of association between amalgam restorations and urinary NAG. However, the authors did acknowledge that a follow-up period beyond five years might be needed to demonstrate potential subtle toxic effects of exposure to mercury from dental amalgam, such as on renal proximal tubules.

In yet another study derived from the NECAT trial, Dunn et al[26] analysed a comparison of urinary mercury levels at various points of the New England Children's Amalgam Trial (NECAT) trial with baseline values from the children when they had no amalgam restorations. They observed that the number of amalgam restorations had a significant dose-response relationship with urinary mercury levels. Notably, they also found that daily gum chewing in patients with amalgam filling was associated with these elevated levels[26].

Another original randomized clinical trial is the Casa Pia 7-year longitudinal study[27] which was carried out in Portugal. In the study, Woods et al[27] evaluated urinary concentrations of glutathione S-transferases (GSTs) alpha and pi as biomarkers of renal proximal and distal tubular integrity, respectively, and albumin as a biomarker of glomerular integrity in children over a 7-year course of dental amalgam treatment. Five hundred and seven (507) children, aged 8-12 years at baseline, participated in the clinical trial to evaluate the renal (and neurobehavioural) effects of dental amalgam in children. The subjects had an average total of 19 amalgam surfaces and were randomized to either dental amalgam or resin composite treatment groups. Urinary GSTs alpha and pi, albumin, and creatinine concentrations were measured at baseline and annually in all subjects. Using linear regression analysis, the authors found that urinary GST-alpha concentrations were similar between treatment groups and in each sex and race (white vs. non-white) group in each follow-up year. GST-pi levels tended upward over the course of follow-up by four- to six-fold. This increase was seen in all groups irrespective of the treatment group, race, or gender. Females had GST-pi levels approximately twice those of males at all ages. Albumin concentrations were constant throughout the follow-up period and did not differ by treatment, although females had 39% higher albumin levels than males. Furthermore, they found no significant effects of amalgam treatment on the proportion of children with microalbuminuria (>30 mg/g creatinine).

But in a subsequent study derived from the Casa Pia children's dental amalgam trial, Geier and his colleagues[4] looked at urinary biomarkers of kidney integrity in children 8–18 years old, with and without dental amalgam fillings, from the completed parent study of the clinical trial. Their study determined whether there was a significant dose-dependent correlation between increasing mercury exposure from dental amalgams and glutathione S-transferase alpha (GST-α) and glutathione S-transferase pi (GST-π) as biomarkers of kidney proximal convoluted and distal convoluted tubular integrity respectively. Using a different and more sensitive statistical model than was used in the parent study, they found a statistically significant dose-dependent correlation between cumulative exposure to mercury from dental amalgams and urinary levels of GST-α**,** after covariate adjustment but a non-significant relationship was observed with urinary levels of GST-π. Furthermore, they observed that urinary GST-α levels increased by about 10% over the 8-year course of the study among individuals with an average exposure to amalgams in the amalgam group, compared to those with no exposure to dental amalgams. These findings suggest that dental amalgam does contribute to on-going kidney damage at the level of the proximal renal tubules in a dose-dependent fashion. It is noteworthy that this study involved some older children (age 8-18years)[4] compared to the original Casa Pia study by Woods et al (age 8-12years) [27] .

In yet another study, as part of the Casa Pia longitudinal study, Woods et al[28] performed annual measurements of urinary mercury concentrations in children between 8 and 18 years of age as an assessment of longitudinal exposure to mercury from amalgam fillings in relation to number of amalgam surfaces and time since placement over a 7-year course of amalgam treatment. In the study, the children were randomized to either dental amalgam or composite resin fillings. Urinary mercury and creatinine concentrations were measured at baseline and annually in all the participants. Baseline urinary mercury concentration (~ 1.5μg/L) was comparable in the two treatment groups. The mean urinary mercury concentrations in the amalgam group increased to a peak of ~ 3.2μg/L at year 2 and then declined to baseline levels by year 7 of follow-up consistent with a whole-body biological half-time of mercury in the order of 60–70 days. There was a strong, positive association between urinary mercury and both the number of amalgam surfaces and time since placement. Girls had significantly higher mean urinary mercury concentrations than boys throughout the course of study. This was not attributable to the amount of amalgam treatment received. There were no differences by race in urinary

mercury concentration associated with amalgam exposure. The authors thus concluded that urinary mercury concentrations are highly correlated with both number of amalgam fillings and time since placement in children. In addition, they suggested the existence of possible sex-related differences in mercury handling and susceptibility to mercury toxicity. However, the authors also observed a constant but quantifiable urinary mercury excretion among children in the study who did not receive amalgam restorations, most likely representing the systemic uptake of mercury from food, air, and other environmental sources. The latter observations implied that the level of mercury exposure from all sources including amalgam fillings did not exceed the capacity for mercury elimination by the kidneys via urinary excretion in the children.

IV. Discussion

There are a total of 20 studies in the current review that examined the association of dental amalgam restorations with kidney disease and dysfunction. Twelve of the studies are cross-sectional[3, 9, 10, 11, 13, 14, 17, 19, 20, 21, 22, 23]. One study is retrospective[12] while another one is a consecutive study[15]. Six studies are randomized controlled trials[4, 24, 25, 26, 27, 28] with two studies each being products of each of two original randomized clinical trials[24, 27]: the NECAT randomized clinical trial [25, 26] and the Casa Pia 7-year longitudinal study[4, 28] respectively.

The studies in this review covered all age categories. Eight of the studies were carried out in adult subjects[10,12,14,15,20,21,22,23]. Nine studies involved children/adolescents.[4,11,13,19,24,25,26,27,28] while adolescents/young adults were the subjects in two studies[9, 17]. One study involved all the age categories[3]. The studies were also spread across five continents; Africa (1), Asia (2), Europe (8) North America (8) and Oceania (1). Specific countries where the studies were carried out include Egypt (Africa), China and Saudi Arabia (Asia), Germany, Italy, Portugal, Sweden, United Kingdom (Europe) Canada and the United States (North America), New Zealand (Oceania).

The correlation of exposure to dental amalgam with kidney disease and dysfunction was evaluated by monitoring the level of urinary mercury concentration in study subjects in fourteen studies [3, 10, 13, 15, 17, 19, 20, 21, 22, 23, 24, 25, 26, 28]. Urinary mercury concentration has been widely used as a measure of mercury exposure from dental amalgam fillings[24, 25] and occupational exposures resulting in urinary mercury levels greater than 50 µg/L (18µg/g of creatinine) have been associated with renal and immunological impairments [18].

Findings in this review show that in four [19, 21, 22, 23] out of nine[3, 10, 13, 15, 17, 19, 20, 21, 22, 23] cross-sectional studies in which kidney dysfunction was evaluated by monitoring the level of urinary mercury concentration in study subjects, a significant positive correlation was shown between exposure to dental amalgam and levels of urinary mercury excretion. These four cross-sectional studies[19, 21, 22, 23] observed significant differences in urinary concentration of mercury between study subjects with and without exposure to dental amalgam, including a positive correlation between the number of amalgam surfaces and urinary mercury levels in two studies [**19, 21**]**.** The urinary mercury concentrations observed in the studies were however well below the minimum levels reported for normal health by the World Health Organization[18]. Moreover, typical urinary mercury levels in adults with amalgam fillings have been shown to be much lower than in those where renal effects have been demonstrated [20, 21, 22, 30, 31]. On the other hand, Kingman et al[21] suggested that each ten-surface increase in amalgam exposure is associated with an increase of 1µg/L mercury in urine concentration indicating a potential for renal damage with increasing dental amalgam surface exposure.

Again, in four of the cross-sectional studies [10, 11 13, 23,] the correlation between dental amalgam exposure and kidney dysfunction was evaluated for by the presence of nephrotoxic biomarkers in the urine of study subjects. Two of the four cross-sectional studies[11, 23] showed a positive correlation between exposure to dental amalgam and the nephrotoxic biomarker, N-acetyl-b-glucosaminidase (NAG). It was shown that excretion of the nephrotoxic biomarker was significantly associated with the presence of dental amalgam fillings[11]. Al-Saleh et al[11] also noted that low exposure to mercury from dental amalgam fillings exerts an adverse effect on kidney tubular functions in children and suggested that oxidative stress may play a role in the process. Mortada et al[23] showed urinary excretion of NAG, and gamma GT was significantly higher in persons with dental amalgam than those without, and urinary excretion of NAG was significantly correlated with the number of amalgam fillings. Al-Saleh et al suggested urinary NAG as the most sensitive of all the investigated renal biomarkers[11]

Also, in four cross-sectional studies, the presence of significant protein in urine (microalbuminuria), an indicator for glomerular dysfunction was evaluated for[9, 11, 13, 23]. Here again, two cross-sectional studies[11,23] showed significant positive correlation between exposure to dental amalgam and microalbuminuria. Mortada et al[,23] observed that urinary excretion of albumin was significantly higher in persons with dental amalgam than those without. Furthermore, in the amalgam group, urinary excretion of NAG and albumin significantly correlated with the number of fillings[23]. Mortada et al [23] note that in the context of dental amalgam exposure conditions, kidney damage is a possibility and may be assessed by urinary excretions of albumin and nephrotoxic biomarkers such as NAG, and gamma-GT.

The only retrospective study in this review examined for the presence of kidney disease in association with dental amalgam restorations from the clinical records data of the studied cohort. The authors found no

associations between an index of longitudinal dental amalgam exposure and any of a number of kidney diseases found in hospital discharge data[12]. Although this study had a fairly large sample population, the study population was limited to military personnel and a predominantly male gender.

Again, from the sole consecutive study in this review, there was no correlation between dental amalgam restorations and kidney dysfunction as evaluated by mercury levels in the blood and urine of study subjects[15.]

From the perspective of the randomized clinical trials, the correlation of urinary mercury excretion with dental amalgam exposure was evaluated in four studies [24, 25, 26, 28]. Three of the studies showed a positive correlation[24, 26, 28]. Bellinger et al [24] from the original NECAT study observed a statistically significant higher mean urinary mercury level (0.9 vs. 0.6 μg/g of creatinine at year 5, *P*<.001) in the amalgam group compared to the composite resin group.

Dunn et al [26] observed that the number of amalgam restorations had a significant dose-response relationship with urinary mercury levels. Notably, they also found that daily gum chewing in the presence of amalgam was associated with these elevated levels[26]. Woods et al[28] also observed a strong, positive correlation between urinary mercury excretion and both the number of amalgam surfaces and time since placement in children. But as with the cross-sectionals studies none of the children in the RCTs had a urinary mercury level greater than 20μg/g of creatinine during the trial which is well below 30μg mercury/g of creatinine minimum mean level reported by the World Health Organization[16, 18]. These observations would suggest that the level of mercury exposure from amalgam fillings did not exceed the capacity for mercury elimination by the kidneys via urinary excretion in the children[28]. Still the higher levels of urinary mercury excretion in subjects with dental amalgam fillings would suggest some degree of kidney dysfunction associated with exposure to dental amalgam even if overall renal excretion capacity of mercury remains adequate. Kingman et al[21] suggested that each ten-surface increase in amalgam exposure is associated with an increase of 1μg/L mercury in urine concentration indicating a potential for renal damage with increasing dental amalgam surface exposure.

The correlation of the nephrotoxic biomarkers with dental amalgam exposure was evaluated in three RCT studies[4, 25, 27]. Only one of the three RCT studies[4] demonstrated a positive correlation. This study was a further analysis of the original Casa Pia children's dental amalgam trial using a different and more sensitive statistical model than the original parent study[4]. The authors found a statistically significant dose-dependent correlation between cumulative exposure to mercury from dental amalgams and urinary levels of the nephrotoxic biomarker GST-α[4]. This observation suggests that dental amalgams contribute to on-going kidney damage in the proximal tubules of the kidney in a dose-dependent fashion[4, 32]. The original Portugal-based Casa Pia 7-year longitudinal study[27] observed no significant correlation between amalgam treatments and the urinary levels of the nephrotoxic biomarkers[27]. Similarly, in the original NECAT randomized clinical trial[24] there was no correlation between dental amalgam treatment and renal tubular dysfunction, with no significant urinary excretion of the nephrotoxic biomarkers. But the authors did acknowledge that a follow-up period beyond five years might be necessary in order to observe potential subtle toxic effects of exposure to mercury from dental amalgam, such as on renal proximal tubules[24].

With respect to microalbuminuria, Three RCT studies[24, 25, 27] examined for the correlation of this index of glomerular dysfunction with dental amalgam exposure. Only in one study[25] was an increased prevalence of microalbuminuria in the amalgam treatment group demonstrated in years 3 and 5 of the five-year follow-up. Unlike in the composite resin group, children in the amalgam group had an elevated prevalence of microalbuminuria[25] (defined as urinary albumin >30 mg/g creatinine) in years 3 and 5 of the five-year follow-up. The authors considered the increased prevalence of microalbuminuria in children treated with dental amalgam could reflect a causal association or might be a chance finding. None of the three studies from the Portugal-based Casa Pia 7-year longitudinal trial[4, 27, 28] observed a significant correlation between amalgam treatments and the presence of microalbuminuria in children.

V. Summary of findings in the current review

Half of the 20 studies in this review showed a positive correlation between exposure to dental amalgam and some degree of kidney dysfunction as evidenced by increased urinary mercury concentration[19, 21, 22, 23, 24, 26, 28], presence of nephrotoxic biomarkers' in urine[4, 11, 23] and presence of microalbuminuria [11, 23, 25]. Only two studies[12, 14] evaluated for association of kidney disease (one of which was immunologic renal disease[14]) with exposure to dental amalgam. The two studies showed a lack of correlation between dental amalgam exposure and kidney disease[12] or immunologic renal disease[14] respectively.

. Five of the studies with a positive correlation between dental amalgam exposure and some degree of kidney dysfunction are cross-sectional studies[11, 19, 21, 22, 23] and five are randomized clinical trials[4, 24, 25, 26, 28]. Again, while in four of the five cross-sectional studies, the correlation is with urinary mercury excretion[19, 21, 22, 23], in two studies, it is in the context of a nephrotoxic biomarker of tubular injury and urinary albumin excretion[11, 23].

From the perspective of the randomized clinical trials, the positive correlation is with urinary mercury excretion in three studies[24, 26, 28], nephrotoxic biomarkers of tubular injury in one[4] and with urinary albumin excretion in one other[25]. Moreover, in seven of the ten studies with positive correlations between exposure to dental amalgam and kidney dysfunction the study subjects were children[4, 11, 19, 24, 25, 26, 28].

Despite the positive correlation with urinary mercury excretion, the level of mercury exposure from amalgam fillings did not exceed the capacity for mercury elimination by the kidneys via urinary excretion in the children so that urinary mercury levels in those with amalgam fillings remained well below the limit of normal levels..

Evidence from the available randomized clinical trials employing biomarkers of renal tubular and glomerular dysfunction are supportive of potential renal glomerular and proximal tubular damage resulting from exposure to dental amalgam restorations in children.

The findings in this review agree with Minamata Convention recommendations as adopted by the World Dental Federation in 2018 to the effect that amalgam restorations should not be used for treatment of dental lesions where other suitable restorative materials are available especially in young patients. Children in particular are known to be vulnerable to mercury [25].

VI. Conclusion

There is a positive correlation between exposure to dental amalgam and some degree of kidney dysfunction. Despite the positive correlation with urinary mercury excretion, the level of mercury exposure from amalgam fillings did not exceed the capacity for mercury elimination by the kidneys via urinary excretion in the children. Evidence from available randomized clinical trials employing biomarkers of renal tubular and glomerular damage are supportive of potential renal glomerular and proximal tubular dysfunction resulting from exposure to dental amalgam restorations in children. In terms of quality of evidence, randomized clinical trials are superior to cross-sectional studies. More randomized clinical trials are needed to further confirm the association between dental amalgam restorations and kidney disease and dysfunction.

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