



Mercury and Atherosclerosis: Cell Biology, Pathophysiology, and Epidemiological Studies

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Abstract

Today atherosclerosis is considered as a main cause of death in the worldwide. There is a significant association between heavy metal exposure and atherosclerosis. In this study, we discussed the scientific literature about the effect of mercury on the pathogenesis of atherosclerosis. We also considered the epidemiological studies on mercury as a risk factor for atherosclerosis. Web of Science, Google Scholar, Medline, PubMed, and Scopus were searched by using the following keywords to 2019: (cardiovascular diseases OR atherosclerosis OR endothelial dysfunction) AND (mercury). Mercury has the potential to act as one of the novel risk factors for atherosclerosis development. The findings have indicated the role of mercury in the pathogenesis of atherosclerosis, vascular endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. Mercury can induce atherosclerosis indirectly via increasing the total cholesterol, triglycerides, and LDL-C levels as well as decreasing the HDL-C level. Mercury can be considered as a risk factor in the atherosclerosis progression. However, more studies are required to find the exact mechanisms involved in the pathogenesis of atherosclerosis induced by mercury.

Keywords Atherosclerosis · Dyslipidemia · Inflammation · Mercury · Oxidative stress

Introduction

Mercury is one of the major environmental pollutants that exerts toxic effects on the cardiovascular system [1]. The environmental health agencies identify mercury as a very toxic heavy metal that threatens public health. Mercury possesses toxic impacts on the ecosystem which widely spread in the

world [2]. Mercury triggers endothelium lining in the blood vessel wall. The outcome of mercury exposure on cardiovascular is myocardial infarction, heart rate variability, high blood pressure, and atherosclerosis [3]. Although mechanisms underlying mercury-induced cardiovascular diseases are not fully studied, however, several studies have indicated endothelial dysfunction due to mercury-induced oxidative stress may be responsible for cardiovascular disorders [4]. Mercury exposure leads to over-production of reactive oxygen species (ROS), resulting in low-density lipoprotein cholesterol (LDL-C) oxidation, which can induce atherosclerotic plaque formation and progression [4]. Epidemiological studies have indicated an association between mercury exposure and atherosclerosis which focused on vascular endothelial dysfunction [5]. Atherosclerosis is initiated by various risk factors such as genetics, behavioral, and environmental factors [6]. The traditional risk factors for atherosclerosis include abnormal lipid profile (high total cholesterol, high LDL-C, and low high-density lipoprotein cholesterol (HDL-C)), age, male gender, hypertension, diabetes mellitus, and smoking [6]. Furthermore, the novel risk factors have been identified to enhance our ability to assess and control the global risk profile of atherosclerosis [7]. Impaired fasting glucose, triglycerides (TG), lipoprotein (a), homocysteine, and high-sensitivity C-reactive protein (CRP) have been recognized as new risk

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factors of atherosclerosis [7]. According to several clinical and pre-clinical studies, mercury is one of the important risk factors for atherosclerosis [8]. The present study was designed to review several experimental and epidemiological studies that evaluate the relationship between mercury exposure and atherosclerosis. In addition, several mechanisms have been discussed in the current review to explain this link.

Method

All available scientific publications about mercury exposure and atherosclerosis were gathered by searching several databases including Web of Science, Google Scholar, Medline, PubMed, and Scopus. The studies were selected by using the following keywords: (cardiovascular diseases OR atherosclerosis OR endothelial dysfunction) AND (mercury). Only published English language articles from beginning to 2019 were selected for providing the present review.

History

Metallic mercury and its inorganic salts have been known to man since antiquity and medical application of this element. Compounds of mercury were used as a reliable germicide [9], antiseptic [10], and treatment of fungal infection, psoriasis [11], and ocular conditions [12]. The organic mercury compounds with covalent bonds were first described in the nineteenth century [13]. Methyl mercury is stored in the lipid portion of muscle tissue of aquatic life and may lead to bioaccumulation over time. A well-publicized case of mercury bioaccumulation occurred between the 1930s and the 1960s in Japan, where thousands of people in and around the Minamata town were poisoned by eating fish contaminated with mercury dumped by a chemical factory into Minamata Bay [14]. Another major historical outbreak of mercury poisoning was reported from Iraq in which high exposure occurred as a result of the use of homemade bread of seed wheat exposed with a methyl-mercurial fungicide [15, 16].

Chemical Properties of Mercury

Mercury is a heavy metal that usually known with Hg as a symbolic name [17]. Mercury is also called liquid silver due to its liquid state in room temperature [17]. This metal has been effective as a medicine and a poisoning agent from ancient days [18]. Nowadays, mercury is used in fluorescent lamps, batteries, felt production, barometers, thermometers, and dental amalgams [19]. Recently, this metal has been focused as an important environmental pollutant that threatens human health [20]. The chemical forms, sources of exposure, toxicokinetics,

and toxicity mechanism for mercury will be mentioned in the following.

Chemical Forms

There are three forms of mercury including metallic mercury (elemental mercury), inorganic mercury, and organic mercury [21]. Metallic mercury (Hg^0) is a pure form of mercury that is a liquid at 20 °C [22]. Metallic mercury is applied in thermometers, latex paint, some electrical switches, and dental amalgams [22]. Metallic mercury may evaporate and enter the atmosphere at room temperature [22]. This agent in the vapor state is colorless and odorless that quickly absorbed by the respiratory system [22]. Inorganic mercury (Hg salts) is formed when it reacts with elements such as sulfur, acetate, chlorine, and oxygen [23]. Most mercury salts are white powders; mercuric sulfide is red and turns black following exposure to light [23]. Inorganic mercury is used in cosmetic products, laxatives, teething powders, antiseptics, and diuretics [24]. The formation of organic mercury compounds occurs following the interaction between mercury and carbon [24]. Methyl mercury (MeHg) and ethyl mercury (EtHg) are two of abundance organic mercury compounds in the environment [24]. The other organic mercury compound is dimethylmercury that is also used in some chemical analysis as a reference standard [24]. Methyl mercury and ethyl mercury are white powder, and dimethylmercury is a colorless liquid [24]. The use of methyl mercury and ethyl mercury compounds in antifungal agents has been forbidden from 1991 [25]. The addition of thimerosal-containing ethyl mercury to vials of the vaccine has been eliminated or decreased according to the guideline of Public Health Service agencies in 1999 [25].

Sources of Mercury Exposure

Mercury may enter into the environment within some natural processes such as volcanic outgassing and human activities such as mining [26, 27]. Metallic mercury, mercuric chloride, mercuric sulfide, and methyl mercury are the most known environmental mercury [28]. World Health Organization reported that occupational exposure, dental amalgam, and consumption of contaminated fish are the main familiar sources of mercury for human poisoning [28]. Mercuric sulfide and elemental mercury are the primary forms of mercury in the earth's crust [29]. The mercury is released into the atmosphere through volcanic activity, coal combustion, mining, and solid waste [29]. Methyl and dimethylmercury are usually caused by the biological process [28]. Methyl mercury enters to human food chain when the organism containing methyl mercury is ingested by fish [28]. Dispersed mercury in water is

converted into methyl mercury by microorganisms [29]. Dimethylmercury is found at dangerous waste sites, and it is very detrimental for human and animals [29]. The general population is usually exposed to metallic mercury through mercury released from dental amalgam fillings [29].

Toxicokinetics of Mercury Exposure

Elemental Mercury or Metallic Mercury Compounds

A liquid form of metallic mercury absorption is minimal. In fact, it is not considered a threat to human health [21]. About 80% of metallic mercuric is absorbed through the respiratory system in vapor form [30]. Metallic mercury has high lipophilicity, and thus mercury rapidly crosses the cell membranes, the blood-brain barrier, and placenta. Therefore, it is deposited in most tissue [31]. The complex of mercury at sulfhydryl group in proteins leads to toxic effects on the various tissues including vessels [32]. Although metallic mercury is rapidly changed to mercuric mercury form in the blood, the accumulation of metallic form has been found in the central nervous system [32]. The half-life of mercury is reported from few days to several months, depending on the rate of accumulation in tissue, the organ of deposition, and oxidation state [33].

Mercurous Mercury and Mercuric Mercury Compounds

The absorption of mercurous mercury in the form of Hg_2Cl_2 is very low, although some absorption occurs during oxidation to more absorbable forms [34]. It was proposed that the mercurous mercury is modified to metallic mercury and mercuric mercury in the body [34]. Mercuric chloride (HgCl_2) has been considered as the most toxic and corrosive mercuric mercury compound which has been used as a preservative for the development of photographic film [34]. However, it results in death after accidental ingestion or eating for suicide purposes [34]. Similar to metallic mercury, mercuric mercury in the blood binds to sulfhydryl groups on glutathione, metallothionein, and erythrocytes [35]. Mercuric mercury does not pass the blood-brain barrier, but it can cross in the placenta and deposits in the fetal tissues [35]. Mercuric mercury is transported through amino acid transporters [35]. Its accumulation in the brain occurs via binding to cysteine [35]. Mercuric mercury is mainly deposited in the kidney and liver [35]. The cardiovascular toxicity has been reported after acute and chronic exposure to mercuric mercury [35]. It excretes through urine, stool, sweat, tears, breast milk, and saliva. Its effective half-life is 42 days for 80% of oral ingestion [35].

Organic Mercury Compounds

Among organic mercury compounds, methyl mercury is considered as a major threat to human health due to its consumption through polluted fish [36]. Methyl mercury is efficiently absorbed through lung, intestinal, and skin. This agent strongly binds to sulfhydryl-containing protein in the bloodstream [36]. The distribution of methyl mercury to peripheral tissues occurs through cysteine transporter [36]. It is distributed in the brain, kidney, liver, placenta, and fetus. The half-life of methyl mercury is about 70 days. It is usually excreted through stool and urine [36].

The Safety Levels for Human

The chemical form of mercury determines its toxic impact on several tissues [37]. Mercury compounds are classified in the neurotoxic agent groups [37]. Several studies have reported the safe recommended doses of different forms of mercury. FAO/WHO suggested that intake of 1.6 mg/kg of mercury did not cause neurological damage [38]. However, the neurotoxic effects of mercury at 1.6 mg/kg were found in the fetus. It was also reported that the blood mercury levels > 5 ng/mL are toxic for human [38]. The WHO confirmed the hair mercury levels < 6 $\mu\text{g/g}$ are safe [38]. However, ethyl mercury even at levels below allowable concentrations causes neurological and cardiovascular diseases in children [38].

Mechanism of Mercury Toxicity

Mercury compounds induce toxic damages in the body through several mechanisms. Researchers have shown that the toxic mechanisms of all forms of mercury have high similarities [39]. The interaction of mercury with sulfhydryl groups is recognized as essential mechanisms with which altering the structure of proteins, especially low molecular weight thiols such as cysteine [40]. It was suggested that the binding of mercury to sulfhydryl groups led to modified DNA, RNA, and ribosomal proteins [40]. In addition, mercury compounds, particularly methyl mercury, have a high affinity for binding to sulfhydryl groups of microtubules which may lead to disturbances in cellular structural maintenance [40]. Mercury also causes damage to glutathione/amino acid transports and disturbs energy metabolism, amino acid metabolism, and membrane phospholipid structure [40]. Indeed, the toxicity of mercury may be mediated by the content of sulfhydryl groups including reduced glutathione (GSH), metallothioneins (MTs), and other sulfhydryl-containing constituents [41]. It is suggested that differences in the cellular sulfhydryl content may be responsible for the different sensitivity of various cells to the mercury toxicity [41]. Over-

production of ROS is another important mechanism involved in the toxicity of mercury [41]. Mercury also decreases the activities of antioxidant enzymes by interacting with selenium (Se) [42]. Se is an essential element which mainly acts through selenoproteins such as glutathione peroxidase. Moreover, Se alleviates the toxicity of heavy metals. This element has been shown to react with Hg in the bloodstream by forming complexes containing the two elements at an equimolar ratio when selenite and mercuric chloride are co-administered. Se acts as a cofactor of the key antioxidant enzyme in which it contributes both catalytic activity and spatial conformation. Se also has the ability to protect the membrane lipids from oxidative damage. Se additionally increases the antioxidant status as indicated by the elevated glutathione peroxidase activities which will give protection against spontaneous lipid peroxidation [42]. Therefore, the outcomes of mercury-induced toxicity may be associated with a disturbed balance between the oxidant and antioxidant system [42]. The other mechanism which plays a main role in the toxicity induced by mercury is inflammation [33]. It was reported that mercury in the non-toxic levels induced proliferation and cytokine production from T lymphocytes [43]. Controversially, it has been shown that mercury inactivated nuclear factor B (NF- κ B) [43]. NF- κ B is the major transcription factor involved in the expression of several inflammatory and immunity components [43]. They suggested that the binding of mercury to sulfhydryl groups resulted in the inactivation of NF- κ B [43]. However, numerous studies indicated that the toxic effects of heavy metals on the cellular function are related to the absorbed dose, route, and duration of exposure [44].

Mercury and the Risk of Atherosclerosis: Epidemiological Observation

Numerous studies have indicated inconsistent results regarding the impact of mercury on the development of atherosclerosis. The relation between hair mercury levels and development of carotid atherosclerosis has been conducted by Salonen and coworkers (2000) on the 1014 men 40–60 years old from Kuopio Ischemic Heart Disease Risk Factor (KIHD) cohort study. The findings have indicated that there was an increase of 8 μ m for each microgram of methylmercury in the hair in the 4-year increment in the mean common carotid artery intima-media thickness (CCA-IMT). It was indicated that the mean CCA-IMT was higher in the men with the highest hair mercury content versus the other subjects after adjustment for relevant confounders. The significant association was seen between the mean CCA-IMT, high hair mercury content, and cigarette smoking in participants [45]. The data have shown that the accumulated mercury in organs is connected to the development of carotid atherosclerosis. The connection between the level of mercury in urine and the

thickness of carotid or the diameter of the intraventricular septum has been searched in 155 workers in the company with mercury production. The concentration of mercury in urine was 5.6 ± 12.2 μ g/g creatinine in men ($n = 125$) and 1.9 ± 2.7 μ g/g creatinine in women ($n = 29$). Additionally, the mercury concentration in the urine of smoker was higher than in the non-smokers. There was a positive relationship between the thickness of carotid and the concentration of mercury in urine, and also a negative linear correlation between the thickness of carotid and HDL-C. The negative dependence between the thickness of carotid and the antioxidant of serum ($r = -0.2142$; $p < 0.05$), and the positive relation between the antioxidant of serum and HDL-C were exposed to be reliable for the all concerned groups. The lipid profile was normal in women; however, the level of TG was upper than the normal range in men. Since the control group was not selected, the findings were compared to the normal range. The marked differences in the serum lipid profiles and total antioxidant were not observed between the smokers and non-smokers.

It showed that the long exposure to the vapor of mercury might cause atherosclerosis in carotid. The relation between thickness in carotid and the elimination of mercury as a marker for metallic mercury in urine is documented in the non-smoking subjects. The protective mechanisms for preventing atherosclerosis in the non-smokers are tightly connected to HDL; however, these protective mechanisms are impaired in smokers [46]. A study conducted by You and coworkers on 477 Koreans (2011) has indicated there is a significant correlation between blood mercury and LDL-C as well as HDL-C levels. The blood mercury concentration in males was higher than in females, and the relation between mercury and cardiovascular disease was seen in the male. However, smoking status has not been related to blood methyl mercury levels [47]. Hong et al. (2013) studied the relation between the modification of lipid profile and that of mercury in hair in 236 non-smoking and smoking subjects 16–75 years old who had visited the center of health in hospital from January 2004 to January 2007. The data have shown that the concentration of methylmercury had a positive connection to the raised levels of total cholesterol, TG, LDL-C, and the reduced level of HDL-C. Furthermore, there was a rise in the concentration of mercury in the group of smoking. It has been proposed that smoking is positively connected to the accumulation of mercury, and high concentration of mercury is connected to the abnormal of serum lipid [48].

Eom et al. (2014) showed the importance of the level of methylmercury in blood on the lipid concentration in 2114 normal people that have not been involved in mercury in their jobs. The data have shown that the average concentration of mercury in the serum was 3.90 μ g/L which was dramatically modified by residence area, alcoholic consumption, age, seafood intake, sex, and smoking [49]. Asgary and coworkers (2017) have indicated that mercury deteriorated lipid profile

modification in coronary artery disease patients versus normal people. In the study of case-control, 65 angiographically coronary artery disease patients (35 females) 50–70 years old and 65 normal people (43 female) adjusted for age, sex, and living place were managed. They have shown that the mercury concentration of coronary artery disease patients was dramatically higher versus control people. The similar data were obtained after matching for risk factors of cardiovascular such as hypertension, diabetes mellitus, dyslipidemia, and age. The average levels of HDL-C, TC, and TC/HDL-C ratio were dramatically higher in coronary artery disease patients. However, there was no dramatic connection between HDL-C, TC, and TC/HDL-C ratio with the mercury concentration in serum. The obtained data have indicated that the concentration of methylmercury in serum is connected with coronary artery disease. The authors did not determine the smoking and smoking status and their prevalence since the main goal of their study was to evaluate the relationship between mercury levels and CAD [50].

The continued involvement with mercury acts in the progression of plaques in coronary atherosclerosis. The connections between risk factors of cardiovascular disease and the concentration of mercury and methyl mercury in adults were examined using information from the Nutrition Examination Survey (NHANES) and National Health, 2011–2012. The result for 1129 adults 12–19 years old who attended in the US NHANES 2011–2012 was evaluated. The statistical analysis was done to study the connection between risk factors of coronary artery disease and concentrations of methylmercury in blood. The direct connection between methyl mercury and mercury in blood and TC in adult in the matched model was seen. There are no connections with other risk factors of coronary artery disease were explored in all people. The analyzed data with sex linear correlation models showed that the serum TC level of girls exposed to the highest levels of methyl mercury increased 4.22% higher versus girls with the lowest levels of methyl mercury. The findings show the serum cotinine levels, indicator of cigarette exposure, were not related to mercury or methyl mercury levels. The results proposed that methyl mercury in the blood may be directly connected with the total cholesterol in adult girls [51].

Using the cross-sectional analysis, they found the connections of dyslipidemia and its components with toenail mercury in the Yeungnam area in South Korea, including 269 women and 232 men. The average toenail methylmercury levels were 0.34 $\mu\text{g/g}$ for women and 0.47 $\mu\text{g/g}$ for men. After adjusting all the confounding including smoking status, subjects with the highest levels of toenail mercury had 2.24 times higher risk of dyslipidemia and 4.08 times higher risk of hyper-LDL-c than those in the lowest toenail mercury [52]. One cross-sectional study was conducted to evaluate the association between serum lipid profile (HDL-C, LDL-C, the ratio of APO B to APO-A, and TG levels), oxidized LDL (ox-LDL), and

heavy metal (HM) content (numerous arsenic and mercury) of seafood consumption in 81 adults without risk factors for CVD. The smokers were not included in this study. The study indicated that the moderate amount consumption of shellfish was related to a pro-atherogenic alteration in lipid profile. This link is affected by the estimated exposure to arsenic and mercury in shellfish [53]. Controversially, the association between mercury exposure and incidence of atherosclerosis was not observed in the study conducted by Yoshizawa and coworkers (2002) on 33,737 individuals [54]. It was observed that the weak correlation between methylmercury exposure and fish consumption caused an increase in the risk of coronary heart disease. The highest percentage of current smokers being parallel to the lowest mercury level may be related to the lifestyles of subjects, that smoker healthy men may consume more fish [54]. Furthermore, the marked association was not observed between the urine levels of mercury and coronary heart disease in patients. It was suggested that nutrition (fish and alcohol eat) and smoking are important sources of mercury. However, this metal has a weak role in the pathogenesis of CAD versus the impact of blood pressure, glucose, and lipid profile in the selected participants [55]. Table 1 shows the epidemiological research on the connections of mercury levels of tissues with the atherosclerotic risk factors.

Possible Mechanism of Mercury-Induced Atherosclerosis

The involved mechanisms in the mercury-induced atherosclerosis are not precise, but vascular endothelial dysfunction, oxidative stress, inflammation as well as lipid profile abnormalities are suggested to play the main role in the toxic effects of mercury on the cardiovascular system [1].

Mercury, Vascular Endothelial Cells, and Atherosclerosis

Several hypotheses describe the initiation and progression of cardiovascular diseases. According to the present literature, “response to injury hypothesis” is the main mechanism that is responsible for atherosclerosis induced by mercury. This hypothesis indicates that primary endothelial damage and/or functional disruption causes atherosclerosis [56]. Endothelial damage is caused following the release of vasoconstrictor, proinflammatory, and prothrombic mediators. Although several pathways are involved in endothelial dysfunction, the over-production of free radicals has a main role in this process. Furthermore, NO and superoxide anions interaction leads to the peroxynitrite production which deteriorates lipid peroxidation and platelet aggregation. Mercury can affect the regulation of cellular redox, transcription factor, and gene expression related to the dysfunction of an endothelial cell. Mercury

Table 1 Epidemiological studies on the association of tissue levels of mercury with the risk factors of atherosclerosis

References	Type of study	Nationality	Sex	No.	Mercury sample	Mean level	Main results
Salonen et al. (2000) [45]	Cohort prospective	Finnish	M	1014	Hair ($\mu\text{g/g}$)	1.8	Increased carotid intima-media thickness
Yoshizawa et al. (2002) [54]	Nested case-control	USA	M	33,737	Toenail ($\mu\text{g/g}$)	0.74 ± 1.21 0.72 ± 1.40	No association between mercury levels and coronary artery disease
Skoczynska et al. (2009) [46]	Cross-sectional	Netherlands	M = 29 F = 125	154	Urine ($\mu\text{g/g}$ creatinine)	5.6 ± 12.2 1.9 ± 2.7	Increased the blood levels of TG in men Increased carotid intima-media thickness
You et al. (2011) [47]	Cross-sectional	Korean	M	164	Blood ($\mu\text{g/L}$)	9.74	Increased blood levels of LDL-C and TC
Hong et al. (2013) [48]	Cross-sectional	Korean	M	313	Hair (ppm)	7.21	Decreased the blood levels of HDL-C
Eom et al. (2014) [49]	Cross-sectional	Korean	M	148	Blood ($\mu\text{g/L}$)	> 1.8	Increased blood levels of LDL-C, TG, and TC Decreased the blood levels of HDL-C
Sponder et al. (2014) [55]	Cross-sectional	German	M	920	Blood ($\mu\text{g/L}$)	3.9	Increased blood levels of TG and TC
Aranda et al. (2017) [53]	Cross-sectional	Spanish Mediterranean	M	1194	Blood ($\mu\text{g/L}$)	0.53	No association between mercury levels and coronary artery disease
Asgary et al. (2017) [50]	Cross-sectional	Iran	F	111	Blood ($\mu\text{g/L}$)	0.34	Increased blood levels of LDL-C, TG, TC, and ox-LDL-C Decreased the blood levels of HDL-C
Zhang et al. (2018) [51]	Cross-sectional	Mexican American	M	53	Blood ($\mu\text{g/L}$)	–	Increased the blood levels of TC, HDL-C, and TC/HDL-C ratio
Park & Seo (2017) [52]	Cross-sectional	Korean	M	22	Blood ($\mu\text{g/L}$)	8.12 ± 0.05	Increased blood levels of TC in adolescent female
			F	43	Toenail ($\mu\text{g/g}$)	0.55 ± 0.66	Increased the blood levels of LDL-C
			M	582		0.47	
			F	547		0.34	
			M	232			
			F	269			

toxicity may damage the vascular endothelium cells by inducing oxidative stress [57]. ROS over-production following mercury exposure causes endothelial cell damage and dysfunction. Mercury also increased the production of superoxide anion ($O_2^{\cdot-}$) by inducing NADPH oxidase, resulting in the disruption of the mitochondrial membrane, which leads to endothelial damage [57].

Mercury induces a modification in the function of the endothelial barrier by the impairment of endothelial cell-cell adhesions and by inducing apoptosis in endothelial cell, which has been indicated in vivo and in vitro [55]. According to the “response to injury hypothesis,” the endothelial damage leads to elevated permeability to inflammatory cells and lipoproteins, and accumulation of LDL-c in the vessel wall. In vivo studies have indicated that lipids accumulate in various tissues such as a vascular wall in mercury-exposed animals [56]. Additionally, over-production of ROS by mercury causes ox-LDL that leads to the progression of atherosclerotic plaque [4]. The levels of mercury may be used as a predictor of the ox-LDL-c levels [4]. Other involved mechanism in the toxic mercury impact on the vascular endothelium is inhibition of the “paraoxonase” activity [4]. Paraoxonase decreases LDL oxidation, resulting in the inhibition of atherosclerosis progression [4]. It was observed that extracellular cells and matrix below the endothelium are exposed to factors in the bloodstream in endothelial damage induced by mercury [56]. Additionally, due to mercury-induced endothelial cells death in the vessel wall, cellular debris is released [56]. All these events induce cellular stress leading to secretion of inflammatory cytokines. Endothelial cell damage, oxidative stress, and inflammation have the main role in the onset and progression of atherosclerosis [56].

Mercury, Inflammation, and Atherosclerosis

Inflammations have an important role in the pathogenesis of CVD induced by mercury [58]. The association between mercury and inflammation of the brain and also systemic inflammation has been found, but the link between mercury and vascular inflammation is not fully understood [59]. Inflammation associated with vascular tissue remodeling demonstrates the presence of inflammation phenomenon induced by mercury [59]. In vitro studies have confirmed this hypothesis by indicating cytokines release, and also an expression of adhesion molecules intercellular adhesion molecule-1 (ICAM1) in cells exposed to mercury [60]. However, the link of serum mercury levels and CRP levels in the serum of humans has not been reported [60]. Controversially, some studies have indicated that mercury might also act as an anti-inflammatory agent. Research has shown that the low dose of mercury down-regulates the NF- κ B expression [43]. One study indicated that the levels of IL-1 β and TNF- α reduced in the workers exposed to mercury [61]. Due to the pro- and

anti-inflammatory properties of mercury, more studies are needed to identify this issue [62]. It is suggested that the dose of mercury and duration of exposure are the major factors that cause the above “contradictory” findings [62].

Mercury, Oxidative Stress, and Atherosclerosis

Mercury exposure increases the generation of reactive ROS during atherosclerosis through mitochondrial electron transport uncoupling, induction of oxidative enzymes, and some inflammatory mediators. Methyl mercury binds to the glutathione peroxidase (GPx) through thiol (–SH) and/or selenol (–SeH) groups from macromolecules [63]. Mercury has a high affinity to the thiol groups. This binding reduces glutathione peroxidase selenium-dependent activity [62]. GPx reduces hydrogen peroxide to water and oxygen [64]. GPx also reduces lipid peroxides to alcohols and oxygen by using glutathione [65]. Altogether, these molecules are the primary antioxidant defense system in cells [66]. Catalase and superoxide dismutase are the two antioxidant enzymes which combat against oxidative stress induced by mercury [67]. The increase of ROS and decrease of the antioxidant activity lead to the progression of cardiovascular disease including atherosclerosis [67]. Free radicals induce lipid peroxidation which is an autocatalytic process [68]. During lipid peroxidation, polyunsaturated fatty acids such as phospholipids in LDL in cell membranes decrease via a chain reaction [68]. The presence of ox-LDL in the artery walls attracts monocytes into the vessel endothelium, where they change into macrophages [57]. Macrophages remove ox-LDL particles and accumulate intracellular lipids in vessel endothelium [57]. Then macrophages release proinflammatory cytokines which induce monocyte recruitment and formation of foam cells. These are the main cells that produce early atherosclerotic lesions [57]. Mercury has been indicated to induce lipid peroxidation and atherosclerosis in animals and humans [69]. Mercury also increased myeloperoxidase activity in oxidant-induced tissue damage [69]. Mercury inactivates paraoxonase, an important HDL-C-bound antioxidative enzyme, which has been related to the risk of atherosclerosis [70]. The chronic exposure to mercury leads to increase endothelial dysfunction in vessels, because of the reduced nitric oxide (NO) bioavailability due to the elevation of superoxide anion ($O_2^{\cdot-}$) generation from NADPH oxidase [71]. Inhibition of eNOS phosphorylation and expression by mercury are other mechanisms involved in the pathogenesis of atherosclerosis [71].

Mercury, Dyslipidemia, and Atherosclerosis

Several epidemiologic and experimental studies have indicated a link between dyslipidemia and progression of atherosclerosis [72]. Mercury has been found to increase the plasma levels of TC, TG, and phospholipids [72]. However, the

underlying mechanism of dyslipidemia induced by mercury is not clear. It was reported that mercury exposure might cause dyslipidemia via inducing damage to enzymes related to lipid metabolism [73]. Furthermore, mercury binds to glutathione, leading to increased ROS production, which promotes lipid peroxidation [73, 74].

Epidemiological evidences have also confirmed that occupational exposure to mercury increased the prevalence of dyslipidemia [75, 76]. Regarding the main role of dyslipidemia in the pathogenesis of atherosclerosis, the screening of the blood lipid profile is necessary for preventing cardiovascular diseases [77]. More studies should be done to investigate the mechanisms involved in dyslipidemia induced by mercury.

Conclusion

Mercury is substantially present in our world. The pro-atherogenic effects of mercury versus the other common risk factors could cause a severe impact on human health. In the animal models, the toxic effects of mercury, especially the pathophysiological aspects of mercury on the classes have been found. The numerous epidemiological evidences have also confirmed the association between mercury exposure and atherosclerosis. Vascular endothelial cells have high sensitivity to oxidative stress which leads to endothelial dysfunction seen in atherosclerosis. The dose, time, and route of exposure to mercury play main roles in its toxic effects on the vascular endothelial cell. The mechanism of vascular toxicity of mercury is not fully understood, but the induction of oxidative stress is suggested as a primary mechanism. Mercury induces the atherosclerosis progression through vascular endothelial dysfunction, oxidation of lipoprotein, aggregation of platelets, inflammation in the vessels, vascular smooth muscle cell proliferation, and dyslipidemia. Additionally, mercury exerts toxic impact by disrupting several cellular signaling pathways that cause vascular inflammation and platelet aggregation. Most findings of the present study have indicated the association between the mercury level of blood, hair, urine, toenail, and atherosclerosis risk factors such as dyslipidemia and also coronary artery diseases. The studies have suggested that mercury can induce atherosclerosis indirectly via increasing the TC, TG, and LDL-C levels as well as decreasing HDL-C level. However, some studies have not confirmed the association between the mercury levels in biological samples and atherosclerosis.

Since the methylmercury form has suitable absorption in the gut and accumulates in epithelial tissues, this form of mercury was very common in the selected articles. Urinary mercury is the best index of exposure to elemental and inorganic mercury, while blood mercury has been focused on human studies as an index for methylmercury exposure through food in populations.

Limitation Due to a low number of conducted studies on this field and also low scale size of intervention groups, the present review could not introduce mercury as one of the main risk factors of atherosclerosis. Additionally, the present study has other limitation: the confounding factors including age, gender, and smoking were different in the included studies. Most of the studies had reported various cigarette smoking in their participants. Interestingly, the studies have shown an association between cigarette smoking and blood mercury levels. Therefore, more research is needed to thoroughly understand the involved mechanisms in the mercury effects on the cardiovascular system.

Compliance with Ethical Standards

Conflict of Interest All the authors declared no conflict of interests.

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