

The Role of Mercury in Cardiovascular Disease

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Abstract

Mercury toxicity is highly correlated with hypertension, coronary heart disease (CHD), myocardial infarction (MI), stroke and other cardiovascular disease. Mercury has a high affinity for sulfhydryl (-SH) groups, which inactivates numerous enzymatic reactions, amino acids, and sulfur-containing antioxidants [NAC (n-acetyl cysteine, ALA (alpha lipoic acid), GSH (glutathione)], with subsequent decreased oxidant defense and increased oxidative stress. Mercury binds to metallothionein and substitutes for zinc, copper, and other trace metals reducing the effectiveness of metalloenzymes. Mercury induces mitochondrial dysfunction with reduction in ATP, depletion of glutathione, and increased lipid peroxidation. Selenium and fish containing omega 3 fatty acids or omega 3 fatty acids supplements with DHA and EPA antagonize mercury toxicity. The overall vascular effects of mercury include increased oxidative stress, inflammation, reduced oxidative defense, thrombosis, vascular smooth muscle dysfunction and hypertrophy, endothelial dysfunction, dyslipidemia, immune and mitochondrial dysfunction. The clinical consequences of mercury toxicity include hypertension, CHD, MI, cardiac arrhythmias, reduced heart rate variability, increased carotid IMT and carotid artery obstruction, CVA, generalized atherosclerosis, renal dysfunction, renal insufficiency and proteinuria. Pathological and biochemical findings correlate with the clinical manifestations of mercury toxicity. Mercury diminishes the protective effect of fish and omega-3 fatty acids. Mercury inactivates COMT (catecholamine O methyl transferase), which increases serum and urinary epinephrine, norepinephrine, and dopamine. This effect will increase blood pressure and may be a clinical clue to mercury- induced heavy metal toxicity. Mercury toxicity should be evaluated in any patient with hypertension, CHD, MI, CVD, CVA or other vascular disease. Specific testing for acute and chronic toxicity and total body burden using hair, toenail, urine and serum should be done with both baseline and provocation methods.

Keywords: Mercury toxicity; Hypertension; Cardiovascular disease; Coronary heart disease; Stroke; Renal disease; Oxidative stress; Inflammation

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. The overall health effects of chronic exposure to various heavy metals in the environment is a serious issue that has not received proper medical attention, especially as it relates to cardiovascular disease. This is particularly true of mercury but also with other heavy metals such as cadmium, lead, aluminum, iron and arsenic [1-5]. The cardiovascular consequences of mercury toxicity and the correlation of environmental pollution and the development of CVD have been well documented in the literature [1-80]. CERLA (The Comprehensive Environment Response, Compensation and Liability Act) has prepared a list of substances that are most commonly pose the most significant potential threat to human health due to their known or suspected toxicity and potential for human exposure [6-8]. These include arsenic, lead and mercury in the top three. This paper will critically review the cardiovascular consequences of mercury toxicity in humans as it relates to hypertension, generalized atherosclerosis, coronary heart disease (CHD), myocardial infarction (MI), cardiac arrhythmias, heart rate variability (HRV), sudden cardiac death (SCD), cerebrovascular accidents (CVA), carotid artery disease, renal dysfunction, renal failure and total mortality.

Types of mercury

Mercury exists in three basic forms: elemental, inorganic and organic (Table 1) [1-5]. Dental amalgams are the most common source for elemental mercury vapor, a stable monoatomic gas. Inorganic mercury, a divalent compound, is the toxic species found in human tissue after conversion from the other forms. Organic mercury in the

form of methyl and ethyl mercury is primarily from fish, sea mammals and thimersol vaccines. Although dental amalgams have historically been the major source of human exposure, fish and sea mammals are becoming an increasing environment source of potential mercury toxicity [1,2,4,5].

Mercury biotransformation and biomethylation

Mercury exposure is from numerous sources. These include elemental mercury from earth sources or inhaled mercury vapor, methyl and ethyl mercury which are converted by biomethylation

| | | | |
|---|-----------|--|--|
| 1 | Elemental | Mercury Vapor (Hg ⁰) | Dental Amalgams |
| | | Stable Monoatomic Gas | |
| 2 | Inorganic | Divalent Mercury (Hg ²⁺) | Toxic species in human tissue after conversion |
| 3 | Organic | Methyl Mercury (CH ₃ Hg ⁺) | Fish, sea mammals |
| | | Ethyl Mercury (CH ₃ CH ₃ Hg ⁺) | Thimersol vaccines |

Table 1: Mercury types.

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Received July 15, 2014; Accepted August 27, 2014; Published September 03, 2014

Citation: Houston MC (2014) The Role of Mercury in Cardiovascular Disease. J Cardiovasc Dis Diagn 2: 170. doi:10.4172/2329-9517.1000170

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to inorganic divalent mercury, the toxic form in human organs and tissues (Figure 1) [4]. Divalent mercury is soluble and stable in water, undergoes biomethylation to methyl mercury, which is found in high concentrations in certain fish and sea mammals. This is now the major source of human exposure to mercury.

The Environmental Protection Agency (EPA) has proposed that the safe daily intake of mercury is less than 0.1 microgram/kg/day [6]. However any amount of mercury may have health consequences. Also, 12% of women have hair mercury above the level at which stopping consumption of highly contaminated fish would be advisable (1.0 ug/g) [7]. It is estimated that one dental amalgam filling releases about 3-17 micrograms of mercury vapor per day. The typical amalgam is composed of 50% mercury, 25% silver and 25% tin, copper and nickels [7-10].

Fish and sea mammals provide about 2-3 micrograms per day depending on the type and amount consumed [1,2,4,5]. The long-lived large predatory fish such as swordfish, tilefish, shark and king mackerel contain about one microgram of methyl mercury per gram and should probably be avoided in the human diet. Pike, whale, bass, tuna and trout are about 0.1-0.5 micrograms of mercury per gram. Nine vaccines that contain thimerosal (50% mercury) as a preservative would give an estimated exposure of 62 micrograms of organic mercury [1,2,4,5]. All other sources of mercury provide about 0.3 micrograms per day [1,2,4,5].

Important Facts about Mercury

Mercury is the most dangerous of all the heavy metals [11]. It will modify the distribution, toxicity and retention of other heavy metals [12-14]. Mercury has no known physiological role in human metabolism and there are no mechanisms to metabolize or to excrete mercury acutely or chronically [15]. Mercury will accumulate during life. The average 70 kg person has a total body burden of over 13 mg of mercury [11]. Mercury has a high affinity for sulfhydryl groups (-SH), various enzymes and amino acids, alpha lipoic acid (ALA), N-acetyl cysteine (NAC), and glutathione (GSH), which provide between 10-

50% of the plasma protein antioxidant defense and capacity [11,15,16]. Both NAC and ALA, as well as cysteine, are precursors for glutathione, which is the most potent intracellular anti-oxidant and protects against oxidative stress, inflammation, immune dysfunction, infections, carcinoma and cardiovascular disease [3-5,11,12,15]. This mercury-induced reduction in oxidant defense and increase in oxidative stress increase the risk for CHD, MI, CVD and CVA. Selenium antagonizes some of the adverse effects of mercury by forming a seleno-mercury complex in tissue that is less toxic [12,18-24]. Higher intake of selenium reduces mercury related CHD, MI, CVD and CVA. Selenium in supplemental form should not exceed 200 micrograms per day.

Physiological basis of mercury toxicity

Mercury induces mitochondrial dysfunction, decreases ATP production and energy and increases oxidative stress [25-27]. The primary mitochondrial dysfunction occurs at the ubiquinone-cytochrome B region and with NADH dehydrogenase causing displacement of Fe²⁺ and Cu⁺ ions in the a3Cub center of cytochrome C (Figure 2). The depolarization and auto-oxidation of the inner mitochondrial membrane with lipid peroxidation lead to severe mitochondrial dysfunction. Physiologic consequences include increased hydrogen peroxide (H₂O₂), depletion of mitochondrial glutathione by 50% or more, increased lipid peroxidation markers such as TBARS by over 70%, oxidation of pyridine nucleotides such as NAD(p)H and altered calcium homeostasis [25-27]. Increase in the intracellular calcium results in cell apoptosis and death. This severe mitochondrial dysfunction increases oxidant stress and reduces oxidant defenses that increase the risk of cardiovascular disease.

The three primary sources of mercury- induced lipid peroxidation include the affinity for sulfhydryl groups, selenium deficiency and the Fenton reaction [11]. Mercury's high affinity for sulfhydryl groups (-SH), such as glutathione, NAC and ALA, which comprise much of the antioxidant capacity of plasma, reduces both membrane and plasma antioxidant defense. Mercury is a direct catalyst in Fenton-type reactions and as an indirect catalyst via iron stimulation, which increases the production of radical oxygen species (ROS) and superoxide anion [11]. Insoluble complexes of mercury with selenium reduce selenium availability, which is a necessary co-factor for glutathione peroxidase (GPx) activity to break down hydrogen peroxides and various other toxic peroxidation products. A reduced GPx and low GSH levels are associated with increased risk for CHD and MI. Plasma and intracellular antioxidant capacity are both reduced as GSH levels fall [11].

Vascular biological effects of mercury

In vitro, animal and human studies have demonstrated numerous toxic effects of mercury (Table 2). Mercury increases free radical production and ROS and damages DNA inactivates antioxidant defenses and depletes vitamin C and E, binds to thiol-containing molecules, binds to selenium forming seleno-mercury complexes lowering selenium availability for GPx activity inactivates glutathione, catalase and superoxide dismutase increases lipid peroxidation, increases oxidation of LDL (oxLDL) and increases plasma oxLDL complexes inducing an immune reaction [3,28-39]. Thrombosis is potentiated by increased platelet aggregation, change in platelet shape, abnormal erythrocyte shape and microvesicle generation increases in Factor VIII platelet factor-4 and thrombin with reduction in protein C [28,40,41]. Endothelial cell formation and migration are reduced from endothelial progenitor cells (EPCs) which reduce vascular endothelial repair; nitric oxide (NO) bioavailability is decreased with subsequent endothelial dysfunction which is one of

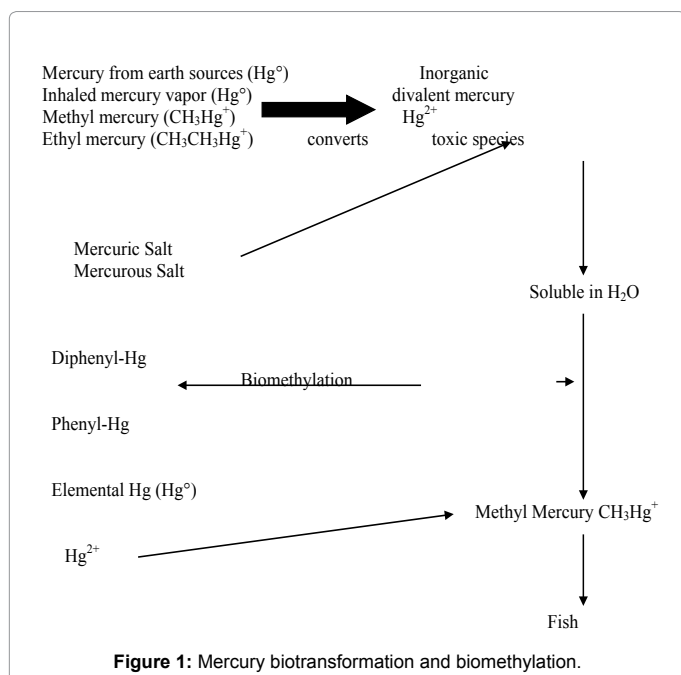


Figure 1: Mercury biotransformation and biomethylation.

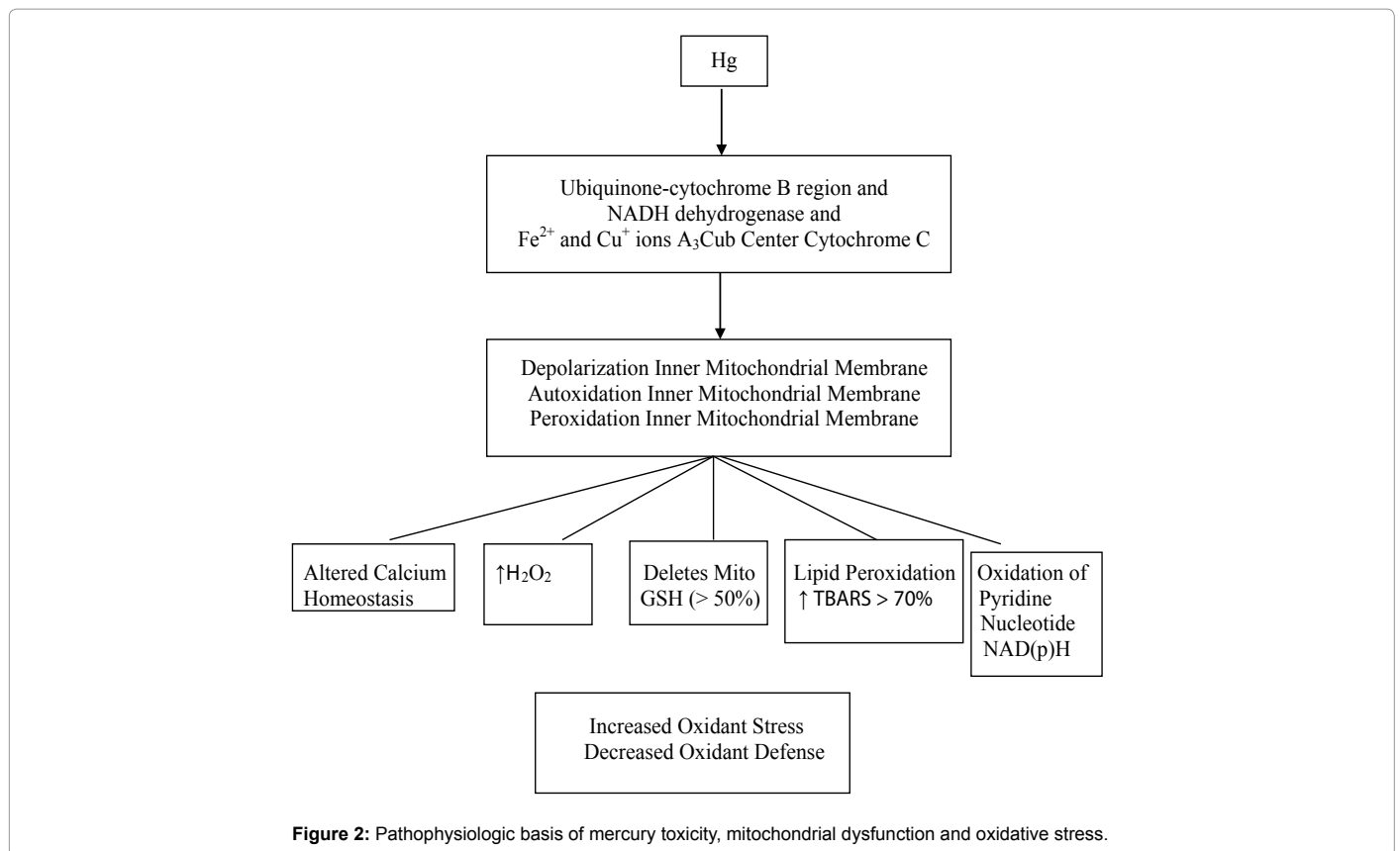


Figure 2: Pathophysiologic basis of mercury toxicity, mitochondrial dysfunction and oxidative stress.

| | |
|----|---|
| 1 | Increased free radical production and increase in oxidative stress |
| 2 | Inactivation of antioxidant defenses |
| 3 | Mitochondrial dysfunction |
| 4 | Binds to thiol-containing molecules (sulfhydryl groups) |
| 5 | Binds to SE forming Se-Hg complex-mercury selenide which decreases Se available for cofactor with GPx |
| 6 | Inactivates glutathione, catalase, SOD |
| 7 | Increases lipid peroxidation in all organs |
| 8 | Increases oxLDL and oxLDL immune complexes |
| 9 | Increased platelet aggregation and thrombosis |
| 10 | Increased coagulation and thrombosis: increases Factor VIII, PF4, thrombin and reduces protein C |
| 11 | Inhibit endothelial cell formation and migration and decreases endothelial repair |
| 12 | Decreases nitric oxide bioavailability |
| 13 | Endothelial dysfunction |
| 14 | Increase apoptosis |
| 15 | Reduced monocyte function and phagocytosis |
| 16 | Immune function is impaired |
| 17 | Increased vascular inflammation with increase TNF – alpha and IL-6 |
| 18 | Stimulation of vascular smooth muscle cells |
| 19 | Inactivation of paroxonase and other HDL proteins and enzymes |
| 20 | Translocaion of membrane phosphytidyl serine |
| 21 | Activates phospholipase A2 |
| 22 | Activates phospholipase D. |

Table 2: Vascular biological effects of mercury.

the earliest predictors of future CV events [42]. Apoptosis is increased, monocyte function and phagocytosis are impaired immune function is reduced and vascular inflammation is increased with elevations of HS CRP (High sensitivity C reactive protein) TNF alpha (tumor necrosis alpha) and IL-6 (interleukin 6) [30]. There is an increased production and release of superoxide anion from human neutrophils

and monocytes depolarization of the inner mitochondrial membrane with severe mitochondrial dysfunction and disruption of plasma membrane lipid integrity by translocation of phosphytidyl serine (PS) which will increase procoagulant activity [25-30]. Mercury stimulates proliferation of vascular smooth muscle (VSMC) cells and inactivates paroxonase (PON 1 and 2), an extracellular antioxidative enzyme

related to HDL, CHD and MI risk [43-45]. The reduction in PON will make the HDL dysfunctional, reduces reverse cholesterol transport and increase the risk of CHD, MI and CVD. The clinical consequences of these and other pathophysiologic mechanisms explains the wide variety of cardiovascular diseases caused by mercury including CHD, MI, arrhythmias abnormal heart rate variability (HRV), generalized atherosclerosis, sudden cardiac death, CVA, carotid artery stenosis, renal dysfunction, renal failure, proteinuria and hypertension. [4,5,9,10-12,16,19,23,32,46-80]. Mercury activates phospholipase A2 (PLA-2) which increases the risk for coronary artery and cerebral plaque rupture with MI and CVA. In addition, mercury induces formation of arachidonic acid metabolites such as total prostaglandins, thromboxane B2 and 8 isoprostane in vascular endothelial cells and activates vascular endothelial cell phospholipase D [59-63]. Even very low levels of chronic mercury exposure promote endothelial dysfunction (ED) as a result of increased inflammation, oxidative stress, immune dysfunction, reduced oxidative defense, reduction in nitric oxide (NO) bioavailability. Many of the cardiovascular consequences of mercury are mitigated by concomitant intake of fish containing omega 3 fatty acids and by the intake of selenium [11,53-58]. All of these pathobiological findings will increase the risk of hypertension, CHD, MI, CVD and CVA [27].

In summary, the overall vascular effects of mercury include oxidative stress, decreased oxidative defense, increased inflammation, immune dysfunction, VSM proliferation, hypertrophy and migration, endothelial dysfunction, reduced NO bioavailability, dyslipidemia and mitochondrial dysfunction and thrombosis. All of these abnormalities have the potential to increase the risk for hypertension, CHD, MI, CVD and CVA.

Clinical vascular consequences of mercury toxicity

The clinical consequences of mercury toxicity related to cardiovascular disease include hypertension, CHD, MI, reduction in heart rate variability increase in sudden cardiac death increase in carotid intimal medial thickness (IMT) and carotid obstruction, CVA, generalized atherosclerosis, renal dysfunction, renal failure and proteinuria⁴ and an overall increase in total and cardiovascular mortality [4,5,16-19,23,32,46-49,19,48,64-70,73,80]. In a study of Faroese whaling men, both toenail and hair mercury levels were significantly associated with increased carotid IMT and hypertension [78]. Gomez et al. followed 3,998 workers in mercury mines exposed to inorganic mercury from 1895 to 1994 and found a 2.78x increase incidence of hypertension, 1.17x increase risk of stroke and 1.51x increase risk in total cardiovascular mortality, but no increase in CHD [78]. Evidence from these and other epidemiologic and clinical studies suggest that people with high levels of urine, hair, blood and toenail mercury have an increased risk of cardiovascular diseases [5,11,16,58,65,68,69,80].

Coronary heart disease and myocardial infarction

The cardiovascular and cardiac pathology in rabbits exposed to inhaled mercury vapor are clinically manifest as endothelial proliferation with inflammatory foci and focal edema, bradycardia, thrombosis in small and medium caliber arteries, papillary muscles and valves, focal necrosis with thickening of the endocardium of the perivalvular regions, inflammation and fibrosis of the ascending aorta [49].

A nine country case control study of 684 men with their first MI, demonstrate a significant association of toenail mercury content, adipose tissue DHA and first MI [5]. A 15% higher toenail mercury

content as assessed by neutron activation analysis (NAA) was found in the men with their first MI compared to the control group (95% CI; 5-25%). The OR, risk adjusted, for MI was 2.16 in highest versus the lowest quintile ($p=0.006$, 95% CI; 1.09-4.29). The adipose DHA was directly proportional to the mercury toenail content ($p<0.001$) and the DHA content was inversely correlated to MI with an OR of 0.59 in the highest versus the lowest quintile ($p=0.02$, 95% CI; 0.30-1.19). They concluded that there exists a positive, monotonic increase in the risk of MI with mercury toenail content above the 0.25 microgram/gram level. This association was even more pronounced when adjusted for the DHA adipose tissue content. Mercury diminishes the cardiovascular protection of fish consumption and omega 3 fatty acids. Another study substantiated these results in which the highest quartile of DHA with the lowest quartile of mercury was associated with a 67% reduction in CHD ($p<0.016$) [50]. In the Finish Kuopio Ischaemic Heart Disease Risk Factor Study a cohort of 1871 Finnish men age 42-60 years free of previous coronary heart disease or stroke at baseline found a direct relationship of mercury hair content and CVD, CHD and all-cause mortality. Mercury also attenuated the protective effects of fish on cardiovascular health [51].

However, in another large nested case control study of 33,733 male healthcare professionals between the ages of 40-75 years (Health Professionals Follow-Up Study, HCPFUS), no association between mercury toenail content assessed by NAA and CHD was found [12]. However, if dentists were included, there was a nonsignificant correlation of toenail mercury and CHD. Also, subjects with the highest tertile of mercury and the lowest serum selenium level had a significant increase in CHD.

Other human studies have shown mixed results [9,11,46,47,52]. Mercury miners had no relationship between CHD and serum mercury levels [32]. However, another study of European mercury miners over 90 years (6784 males and 265 females from Spain, Slovenia, Italy and the Ukraine) showed a significant relationship of mercury exposure to total mortality (increase 8%), CHD (increase 36%), myocarditis, hypertension (increase 46%), renal disease (increase 55%) and CVA (increase 36%) [46]. The incidence of CVD correlated with the time of onset of the first exposure to mercury. A Finnish study found a significant relationship between hair mercury, 24-hour urine mercury and cardiovascular events [11]. In patients with hair mercury in the highest tertile, over 2.0 micrograms/gram, and increased 24-hour urinary mercury, CHD and MI risk were increased two-fold ($p=0.005$), cardiovascular death increased by 2.9 times ($p=0.014$) and circulating oxLDL and immune complexes to oxLDL increased significantly ($p=0.01$). The National Health and Nutrition Examination Survey from 1999-2002 found levels of DHA and EPA and other nutrients in fish, even with elevated mercury levels, helped to offset the risk of CHD and MI [71]. The fish intake resulted in lower levels of CRP and higher serum HDL cholesterol as well [71]. The Gothenburg Study showed no relationship between serum mercury content and the number of amalgam fillings and CHD or MI [9]. Exposure to methylmercury in a Finnish and Swedish population was associated with increased risk of MI and higher PUFA concentrations were associated with a decreased risk of MI [72]. In this study, hair mercury had a significant correlation with MI at $p=0.005$. A change of 1 percent omega 3 fatty acids in fish consumption was associated with a 7% reduction in MI. High exposure to mercury reduced the benefits of long chain n-3 PUFA in the 20 year follow-up of the Kuopio Heart Disease Risk Factor Study of 1857 men [73]. For each .5 percentage unit increase in serum long-chain n-3 PUFA was associated with HR of .77 for sudden cardiac death, based on hair mercury content [73]. The DHA level was most strongly

correlated. In a US cohort of 51,529 men and 121,700 women, there was no association of toenail mercury content (neutron activation analysis, NAA) and risk of CHD, CVA or total CVD in the 3427 participants that were prospectively studied [74]. The toenail mercury content was .23 ug/gram in the case participants and .25 ug/gram in the controls. A study of 274 children from South Korea found a significant correlation of urine mercury levels and serum cholesterol which would increase the risk of CHD [75].

Stroke and carotid atherosclerosis

High hair mercury content increases carotid IMT and carotid atherosclerosis [16]. An increase in mean carotid IMT during a four year follow-up was related directly to hair mercury content ($p=0.0007$), in a study of 1,014 men between the ages of 42-60 years [16]. Each increase of one microgram in hair mercury content correlated with a 0.008 mm increase in carotid IMT, a 7.3% increase over the mean. There was a 0.042 mm/4 years increase in carotid IMT in the highest quintile versus the lowest quintile, which correlated to a 32% greater increase ($p<0.05$). In addition, mercury hair content was proportional to blood pressure levels, waist hip ratio, fibrinogen and low HDL cholesterol; all significant at $p=0.0002$. Other studies have shown a direct relationship between mercury vapor exposure and urinary mercury and early increase in carotid IMT, asymptomatic carotid atherosclerosis, and low HDL cholesterol and reduced total antioxidant capacity [17]. Many studies on the risk of fish intake, mercury and stroke have been inconclusive. In addition, the various types of stroke have often not been separated or well defined. In a population-based cohort, mercury levels and relative content of fatty acids were determined in erythrocyte membranes in the population consuming one meal per week as fish [77]. In women, there was a non-significant decrease in stroke risk with increasing fish intake with OR of .90. The risk in men for stroke rose with increasing fish intake with OR of 1.24. The corresponding risk in men for mercury was 0.99 and for the sum of proportions of EPA and DHA was 1.08. This study suggested that the risk for stroke between genders differs with increasing fish intake, EPA and DHA consumption, but there was no association between stroke risk and mercury at these lower levels of one meal of fish per week. There are many basic mechanisms by which mercury can increase the risk for stroke as discussed earlier in this paper. The increases in blood pressure, pulse pressure, increased augmentation index, arterial stiffness increased thrombotic risk related to increased platelet aggregation, increase in Factor VIII, thrombin and platelet factor 4 and reduction in protein C as well as endothelial dysfunction from reduced NO bioavailability may account for much of the observed elevation in CVA risk with mercury [16,40-42,46,47,52,64-66,76,68-80]. One recent study showed that mercury increases thrombotic risk by enhancement of procoagulant activity in erythrocytes by protein thiol depletion-mediated phosphatidyl serine exposure and microvesical generation [78].

Hypertension

The association of mercury toxicity and hypertension in humans is well documented and convincing [16,32,46,47,52,64-80]. Mercury miners have significant increases in systolic blood pressure ($p<0.01$) that correlated with oxidative stress, reduced oxidative defense and lipid peroxidation ($p<0.01$) [32]. European mercury miners had a 46% greater incidence of hypertension vs. aged-matched controls. The Wisconsin Sleep Cohort study of over 100 subjects found that those in the upper quartile of blood mercury were 1.9 times more likely to be hypertensive ($p=0.023$) [66]. The subjects in the upper quartile of hair mercury were 4 times more likely to be hypertensive than those

in the lowest quartile ($p=0.02$). There was no change in brachial artery flow mediated vasodilation or the middle cerebral artery reactivity to CO_2 [66]. Other studies have shown significant correlations with hair mercury content, hypertension, diastolic dysfunction, LVH and carotid IMT [16]. Over 250 subjects in the Brazilian Amazon were found to have significant increases in BP associated with total hair mercury levels. The OR for elevated SBP with total hair mercury over 10 mcg/g was 2.91 (1.26-7.28) [65]. Inuit adults had blood mercury levels that were correlated with pulse pressure ($p=0.0004$), SBP ($p<0.0001$) and DBP ($p=0.069$) [67]. In a comparative population study of 833 subjects, long term methyl mercury exposure, as measured by hair mercury levels, was associated with a risk of hypertension of 1.4 to 1.6 times in [68]. In a sample of 1240 women age 16-49 who participated in the National Health and Nutrition Examination Survey 1999-2000 a significant increase in SBP with increasing levels of blood total mercury was demonstrated, but only among non-fish consumers [69]. There was a 1.83 mm Hg increase in SBP for each 1.3 ug/L increase in blood total mercury (95% CI: 0.36, 3.30; interaction $p=0.02$). The risk of hypertension over ten years was highly correlated in a group of chemical factory workers exposed to mercury vapor [76].

Pederson et al. [77] found an increase in pulse pressure using 24 hour ambulatory blood pressure monitoring (54 mm Hg vs 50 mm Hg with $p<0.0001$) that was related to blood mercury levels ($\rho=0.272$, $p<0.01$) in a group of Greenlanders consuming more fish than a group of Danes. Mercury is also significantly associated with reduced heart rate variability (HRV) in addition to the increased pulse pressure and hypertension [77]. A reduced HRV may predispose to ventricular fibrillation and sudden cardiac death, as well as being associated with angina, MI, CHD, CHF and all-cause mortality [77].

In acute and chronic mercury intoxication, mercury binds to the sulfhydryl group S-adenosyl methionine (SAM) and inactivates this enzyme, which is a necessary cofactor for catecholamine-0-methyl transferase (COMT), the enzyme needed to metabolize norepinephrine, epinephrine and dopamine by methoxylation [47]. This results in a clinical syndrome that resembles a pheochromocytoma crisis with malignant hypertension in acute mercury intoxication and significant increases in urinary catecholamines in chronic mercury toxicity. This can be a very helpful clinical clue to mercury-induced hypertension. It would be important to measure baseline and provoked 24 hour urine mercury levels in patients with hypertension and a history or evidence clinically of possible mercury exposure. Mercury also induces renal dysfunction and proteinuria, which contribute to sodium retention and hypertension [31,46,47,53]. In such cases, it is important to evaluate both potassium and magnesium balance, as hyperkalemia and hyper-magnesemia are common metabolic problems with renal dysfunction. This is especially common with renal tubular disease (renal tubular acidosis-RTA) and the inability to adequately secrete potassium. As the GFR drops below about 20 cc per minute the risk of hyperkalemia increases. Studies have shown an increase in renal insufficiency in mercury miners by 55% [46]. Mercury concentrates in the renal tubules and in the glomerulus and results in proteinuria, interstitial and glomerular fibrosis, chronic renal dysfunction and renal insufficiency [31,52].

The most effective means to reduce mercury toxicity is to decrease the mercury load from the offending source and treat with either oral or intravenous chelation therapy. Chelation therapy is beyond the scope of this paper but the reader is referred to the prolific literature on this topic (Table 3).

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|---|--|
| 1 | Oxidative Stress |
| 2 | Inflammation |
| 3 | Thrombosis |
| 4 | Vascular Smooth Muscle (VSM) Proliferation and Migration |
| 5 | Endothelial Dysfunction |
| 6 | Dyslipidemia (oxHDL and paroxonase) |
| 7 | Immune Dysfunction |
| 8 | Mitochondrial Dsfunction |

Table 3: Summary of the overall vascular biologic effects of mercury.

Summary

1. Mercury has a high affinity for sulfhydryl(-SH) groups, which inactivate numerous enzymatic reactions, amino acids and sulfur-containing antioxidants (NAC, ALA, GSH) with decreased oxidant defense and increased oxidative stress. Mercury binds to metallothionein and substitutes for zinc, copper and other trace metals reducing the effectiveness of metalloenzymes.

2. Mercury induces mitochondrial dysfunction, lowers ATP production, depletes glutathione and increases lipid peroxidation.

3. Selenium and fish high in omega 3 fatty acid content antagonize mercury toxicity.

4. The overall vascular effects of mercury include increases in oxidative stress, immune dysfunction and inflammation, reduction in oxidant defense, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia, thrombosis, and mitochondrial dysfunction.

5. The clinical consequences of mercury toxicity include hypertension, CHD, MI, cardiac arrhythmias, LVH, diastolic dysfunction, sudden cardiac death, reduced HRV, increased carotid IMT and carotid artery obstruction, CVA, generalized atherosclerosis and renal dysfunction, renal failure, insufficiency and proteinuria. Pathological and biochemical findings correlate significantly with the clinical CV manifestations.

6. Mercury diminishes the protective effect of fish and omega 3 fatty acids.

7. Mercury inactivates COMT (catecholamine-0-methyl transferase), which increases serum and urinary epinephrine, norepinephrine and dopamine. This effect will increase blood pressure and may be a clinical clue to mercury toxicity.

8. Mercury toxicity should be evaluated in any patient with hypertension, CVD, CHD, CVA or other vascular disease that have a clinical history of exposure or clinical evidence on examination of mercury overload. Specific testing for acute and chronic toxicity and total body burden using hair, toenail, urine and serum should be done. The 24 hour urine measurements should be done with baseline and provoked samples.

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Citation: Houston MC (2014) The Role of Mercury in Cardiovascular Disease. J Cardiovasc Dis Diagn 2: 170. doi:10.4172/2329-9517.1000170

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