BioChemMed

Technium BioChemMed Vol. 1, Issue 1 pp.18-30 (2020)
ISSN: 2734-7990
www.techniumscience.com

Mercury in the diet, absorption and bio accessibility

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Abstract:

The human body is exposed to significant amounts of the potent inorganic mercury (Hg^{+2}) or methylmercury (Me-Hg). The diet is the main route for this exposure; the fish consumption may result with confusion for the crucial benefits of the fish consumption beside the hazardous side of their content of mercuric compounds. The mercuric compounds have different routes of absorption, mostly by the gut through the diet, causing severe health problems via the oxidative stress mechanisms. The diet complexity regarding ingredients and cooking type may affect the bioaccessibility of the present mercuric compounds by several mechanisms, in addition to the protective role of gut microbiota.

The aim of this review is to explore the available data and researches, about the mercuric present forms, absorption pathways, toxicity mechanisms and dietary components that negatively affect the mercuric compounds bioaccessibility (absorption) including the cooking type, fat content, omega-3 fatty acids, selenium, glutathione, gut microflora, ethanol content, garlic, onion, tea, coffee, and fruits.

Introduction:

Historical accidents resulted from inappropriate use of mercury, caused several disasters. The main rout of mercury exposure is the fish based diet, fish diet is recommended due to its unique nutritional composition of proteins and significant amounts of the essential omega-3 α-linolenic acid (ALA 18:3 n-3) fatty acids, the precursors of the eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), the important Prostaglandins and leukotrienes for anti-oxidation mechanisms [1], that have a role to lessen of rate of the cardiovascular diseases and other oxidative stress diseases.

On the other hand, fish contain significant amounts of the toxic heavy metal mercury after marine environment contamination of mercu+ric compounds. Mercury in its different forms: inorganic (Hg^{+2}), elemental mercury (Hg^{0}), or organic mercury (methylmercury and ethyl mercury)[2].

Exposure to mercuric compounds results with adverse health problems; affect the cardiometabolic syndrome (CMS) biomarkers [3], accumulation in brain [4], liver and kidneys [5], caused by oxidative stress due to its strong ability to bind to the sulfhydryl cysteine terminal in the vital proteins and enzymes [6-7], mainly disrupt the anti-oxidizing glutathione proteins [4,8].

All types can be absorbed via the gastrointestinal tract at different rates and different mechanisms [9], simple, facilitated and active diffusion [10-12], the neutral amino acid L-type transporters (LAT) and the organic anionic transporters (OAT) [5,9].

Diet complexities have a protection effect for mercury absorption. In vivo animal studies, showed the lower blood mercury level after exposure to defined dose of the mercuric compounds, several studies investigate the factors that may affect the mercury bioaccessibility in the gastrointestinal gut including; the cooking effects [13-15], fat content [16-18], the omega-3 fatty acids content [19,20], presence the divalent metals, mainly the selenium [21-23], the protein and glutathione content [4,8,

19,21, 24], the dietary fibers effect [25-27], the gut microflora [28-31], the biochemical compounds in garlic and onion [32-36], ethanol content [37-39], the fruits effect and the antioxidants [40-43], green tea, black tea and coffee effect [14-15,44-45].

In conclusion, even though human body exposed by trace toxic amounts of mercury, its absorption depend on several factors including the ethnic, age, physiological status, also its bioaccessibility to absorption may diminish in the presence by several dietary factors present in the diet.

Mercury is a heavy metal with known toxicity, several historical accidents for mercury toxicity took place, due to inappropriate use of mercury in construction of mercury rivers in mausoleum of Chinese Emperor Qin Shi Huang at (260-210 BC), this result with sudden premature death after mercuric dose consumption [46], the First Japan Minamata disease (1956), the Second Niigata Minamata Disease (1965), result with severe neurological symptoms after eating fish contaminated from water by mercury waste [47], and the same symptoms was detected in the Iraq poison grain disaster (1971) after eating bread from wheat treated with mercuric fungicide [48].
Mercury present mainly in three forms: **1-Elemental mercury** ($^{203}Hg^{0}$): It's liquid at room temperature, used in dental amalgams, thermometers, lights and other processes. It's volatile and mainly absorbed through the respiratory tract (80%), whereas its absorption through the gastrointestinal tract is negligible. **2-Inorganic mercury (Hg^{+2})**: Gastrointestinal absorption of inorganic mercury is relatively poor compared to the organic form (10-30%). Distributes mainly in the kidneys (by 60-90%) and, to a lesser extent, to the liver. The critical effect of inorganic mercury is renal damage**. 3-Organic mercury (methylmercury MeHg and ethyl mercury),** which bio-accumulates and biomagnifies along the food chain, particularly in the aquatic food chain; long lived carnivorous fish and marine mammals exhibiting the highest contents [49,50].

Absorption mechanism: Exposure to Hg^{+2} and MeHg occurs mainly through diet. Bioaccumulation and magnification of the mercury compounds to several folds more than the source [5,9]
Several suggested absorption processes through the mammalian intestinal epithelial tissues including:

- Inorganic mercury Hg^{+2} enter the cells by simple diffusion or through voltage-gated $Na^{+}K$ pump cotransporter and Ca^{+2} [10].
- Passive simple diffusion of neutral mercury amino acid complexes mainly the methylmercury cysteine complexes (CH_3Hg-Cys)[11].
- Facilitated diffusion [9].
- Active transport [12].
- Amino acid transporters, the MeHg-Cys pass through epithelial cells by L-type transporters (LAT) that are energy consumers. Beside the organic anionic transporters (OAT)[5].

The specific absorption mechanisms in different body tissues can be summarized:

The gastrointestinal enterocytes (GIE): the inorganic mercury may be transported by simple passive and active diffusion [10, 51-52], also as the diet rich in amino acids, and the mercuric ion has high affinity to sulfhydryl terminals making amino acid complexes, that can be mediated by organic transporters [5]. Even though the methylmercury transportation is the more efficient, thus more dangerous. The methylmercury bind to the sulfurous part of glutathione (GSH) inside the

Technium BioChemMed Vol. 1, Issue 1 pp.18-30 (2020)
ISSN: 2734-7990
www.techniumscience.com

lumen forming methylmercury glutathione complex (MeHg-SG), that is transported by γ-glutamyltransferase (GGT) and cysteinylglycinase (CGase) [53], they are members of OAT found several cell membranes including the gut lumen, then (CH_3Hg-SG) complex pass into the circulation [9]. While in the **Blood brain barrier (BBB):** the transportable form is (MeHg-S-G) via LAT system [4]. In the **Kidney** mercury accumulates in the cortex and outer medulla of the kidney by 50% of exposure [54], that take place by OAT (γ-glutamyltransferase and cysteinylglycinase), while MeHg transported after conjugation to the sulfur of the glutathione to form CH_3Hg-S-G and to the cysteine molecule CH_3Hg-S-Cys [53], the laters considered the most transportable forms of organic mercury by the OAT [5]. The **Liver** absorbs methylmercury molecules via the circulation, that will reach the bile as CH_3Hg-S-G, this part will be reabsorbed by the enterocytes making the MeHg enterohepatic cycle [5] but most of it well be excreted with feces 4 (Clarkson et al., 2007).
Placenta: the organic MeHg compounds is transported through the placenta as cysteine conjugates (CH_3Hg-S-Cys) mainly by the LAT members [5,55].

Toxicity mechanisms: Mercury has a major role to induce oxidative stress by inducing several protein disturbances at different levels including; starting with mitochondrial dysfunction 56(Berntssen *et al.,* 2003), that increase the hydrogen peroxides and lipid peroxidation [57].
The high affinity of methylmercury to bind to the sulfhydryl terminal of the proteins, results with block of active sites of functional proteins, transporters, enzymes, receptors, and others [7].
At the same time, mercury causes reduction in the defense mechanisms, by induction of apoptosis in human T cells and monocytes [58]. Also, by binding to the GSH molecules, and lipid peroxidation, that result with rise risk of cardiovascular risk factors, increase LDL-C molecules, dysfunctional HDL-C [59], beta cell dysfunction and insulin resistance [57, 60], has a role of hypertension by listening of the nitric oxide (NO) and angiotensin converting enzymes activity (ACE) [7], and obesity related problems by interruption pre-adipocyte differentiation [58].

Factors affect the Hg compounds bio accessibility:
The term bio accessibility is referred to the part of ingested nutrient that is solubilized into the gastrointestinal tract become available for intestinal absorption, any factor affect the bio accessibility well change the amount of Hg absorbed to blood and other body organs [41, 61, 62].

Cooking effect: Cooking cause increase concentration of the metal in the food portion due to loss of fluids relative to the fresh food, by cooking less bio accessibility of Hg ordered in descending manner as (highest concentration of raw food, then steamed or boiled, next become the grilled, and finally fried with at last) by (26-85%) lower bio accessibility [13-15]. This reduction of bio-accessibility was proposed by Afonso et al, (2015) [63] to the protein denaturation by cooking, that disrupt the tertiary and quaternary structure, that decrease protease action, so that less Hg bio accessibility, as tuna consider important source of Hg in human diet [13]. Ouédraogo et al., (2011) proposed reduction of tuna Hg content by 40%. The heat used in cooking and canning process mostly reduces the Hg bio accessibility [14, 63].

Selenium: It's is essential metal for several physiological processes, the selenocystein and selenomethionine are the main selenoproteins, that incorporate in the redox enzymes including; antioxidant glutathione peroxidase (GSH-Px), beside the selenoenzymes; iodothyronine deiodinases, 5,5'-monodeiodination that activate the thyroid hormone, also the thioredoxin reductases [22-23].

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Selenium is known as natural protective agents against mercury induced toxicity due to its ability counteracts the adverse influences of methyl mercury by the antagonism effect to Hg and other heavy metals when they administered simultaneously [21]. The seleno-cysteine act as ROS scavenger making detoxifying effect [21-23], at the same time mercury selenium insoluble complex well be formed bis-methylmercuric selenide (BMS), this compound is considered inert, high molecular weight, large complex, stable, non-diffusible, long retention in the blood and low accumulation in the kidneys and liver [64], that will reflect positively on methylmercury toxicity.

Glutathione: Glutathione is a tripeptide (γ-glutamylcysteinyl-glycine), synthesized in the liver, provides about (30–40%) of the plasma antioxidant capacity, and is the most potent intracellular and mitochondrial antioxidant for protecting against oxidative stress, inflammation, and cardiovascular diseases [19, 21, 24].

Mercury binds to glutathione via the sulfhydryl terminal as in a comparable form of the oxidized glutathione (GS-SG), so that transport freely via glutathione endogenous carrier across the liver cell membrane into bile [4]. Then it will be hydrolyzed by enzymes (γ-glutamyl transpeptidase and dipeptidase) to glutathione constituents and CH_3-Hg-Cys complex, that well be reabsorped to the circulation, and the CH_3-Hg form the glutathione complex in the liver, and reabsorption by the gallbladder making the enterhaepatic cycle [4,7, 8].

High fat diet: Højbjerg, et al., (1992) in animal experiment, demonstrate that the high fat diet (50%) result with lower absorption of methylmercury and mercuric chloride than the low fat diet (5.0%), it was explained by increase satiety and lower food intake, on the other hand the high fat diet effect of saponification[18].

At the same time, the type of the fat used in the diet cause variations in the amount of methyl mercury retained in the body, the coconut oil retained higher amount of than the cod liver fat type, even though the higher content of cod liver oil in the diet result with lower retention of methyl mercury and mercury chloride than the lower content diets [16-18].

Modulation of mercury toxicity by fish oil took place by the Inuit people; fish oil is known to contain substantial amounts of omega-3 a-lionleic acid [65]. On the other hand, lower incidence of mortality in people who used to consume fish based diets, or their oil supplements regardless the level of contamination [66].

Insignificant but lower whole body total mercury retention and higher fecal excretion between the fish based diets and lard diets, which reflect the protective role of fish based diets methylmercury toxicity modulation [17].

Omega-3 PUFA: Appropriate amounts of omega-3 polyunsaturated fatty acids attained mainly from reasonable consumption of fish diets, this well also provide appreciable amounts of selenium. The n-3 fatty acids well antagonize some of the adverse effects of this mercury exposure [19], the n-3 long chain poly unsaturated fatty acids (n-LCPUFA) contain two important essential components (eicosapentaenoic -EPA- and docosahexaenoic –DHA). Several researches approve the antioxidant effect of n-3 in fighting the reactive oxygen species, lipid peroxides, free radicals, and scavenge the superoxide onion [20]. These process alienate any oxidation effect discussed above may produce by the mercury exposure.

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Dietary Fibers: No significant decrease in Hg bioaccessibility was observed for mackerel and shark after addition of corn starch. For tuna a decrease of up to 20% of Hg bioaccessibility was reported after the addition of 50 mg of corn starch, but no further decrease occurred after the addition of more corn starch [15]. While Shim et al. (2009) [16] evidenced that the presence of insoluble fibers, such as those from wheat, decreases Hg bio-accessibility, since these compounds can bond and diminish Hg solubility. This fact might explain the low Hg bioaccessibility in fried black scabbard fish, as wheat flour was added during the culinary preparation [16].

The dietary fibers may have adsorbent effects, that may reduce the metal bioaccessibility in contaminated food [26], due to their non-toxic and non-degradable nature [16]. This theory was investigated by [25], by applying a natural dietary factor to chelate the heavy metals in the contaminated food. They found a reduction of mercury bio accessibility by (34%-85%) in a dose dependent manner, when used the cassava pulp tubers, that is rich starch (60%) and rich fiber (30%) tubers [25].

On the other hand, wheat bran had a great effect on mercury binding capacity by (72%-84%) much more than oat bran and psyllium, this due to higher content of insoluble fiber content in the wheat brane than the others [16]. Consistent results with Rowland et al. (1986) [27], he found that wheat bran consumption with the mercury food resulted in increased fecal excretion, and reduce the methyl-mercury level in the blood and brain of experimental animals by (10-30%) [27].

Garlic and Onion: The garlic (Alium sativum) contains organosulfur compounds (OSC) as a cysteine derivatives. The garlic exhibits a numerous beneficial biological activities, by having oxidative stress reduction and apoptotic effects [67-68]. It was believed that garlic have metal binding capacity or chelating agents which can increase mercury excretion [35, 69]. This may be explained to the high affinity of the mercuric compounds to the sulfur compounds [7], so by binding to –SH terminal in the chelating agent provide protection to the active site of functional proteins [35-36].

The same mechanism proposed by [33], that the binding of the Hg to the sulfhydryl groups in the cell wall of the green onion, and react to reduce Se availability and make the Se-Hg complex [32-34].

Ethanol role in mercury retention: Ethanol consumption associated with lower retention of mercury in the serum and the erythrocytes in a dose dependent manner [37], both human and animal experiments confirm the same results [38-39].

One of the proposed mechanisms for ethanol role is the inhibition of mercury oxidation in the presence of ethanol even at very low concentration (0.2%), beside the mercury may mobilize and reduce in the accumulated inorganic mercury in the tissues [39]. Although taking in consideration the diuretic effect of the ethanol consumption that result with excretion and mobilization of body mercury [37]. Sumathi and Chritinal, (2015) [70] revealed in their research the normalization effect of ethanol derivatives against histopathological alteration of the mercury induced toxicity

Gut Flora: Microbes have been known to modulate a wide range of heavy metals toxicity including MeHg, the remediation of contaminates environments using microbes are effective process [30,71-75].

The demethylation process is accomplished via two steps: first the reduction of MeHg to produce Hg^0 and CH_4, second the oxidation which results with (Hg^{+2} + CO2) [28-29]. Other several detoxification mechanisms was proposed that decrease mercury bioaccessibility, they comprise mercury resistant gram positive and gram negative bacteria including the biosorption, biotransformation, bioaccumulation, and biovolatilization, these organisms contain large surface to volume with active cell wall, the functional phosphate, sulfonate, hydroxyl, carboxyl and amide groups act as chemisorption sites [76].

Five strains from Enterobacter, Bacillus, and Pseudomonas bacteria was isolated and demonstrated to be effective in adsorption and accumulation of 99% of mercury from the surrounds [74], beside a commensal methanogenic archaea bacterial types contain gene clusters required for mercury metabolism was isolated from human feces [30-31].

In vitro experiments, mice showed increase methyl mercury fecal excretion with prolonged antibiotic treatments, due to demethylation of the methylmercury to the inorganic mercury, which is less absorbable form by the gut [27]. Comparable results from experiment constructed on neonatal rats with sterile gut, compared to older weaned rats, after giving oral dose of methylmercury, longer time of suckling rats was needed to eliminate the mercury dose [27].

Lower blood mercury concentration was in the Tanzanian pregnant women who used to consume yoghurt (contain probiotic *Lactobacillus rhamnosus* GR-1), when compared to control [77].

Fruit: As fresh fruits very rich in mineral, antioxidents, vitamins especially vitamin E and vitamin C, beside substantial amounts of the fibers, that may modulate the mercury absorption. Several studies took place in the Brazilian region, due to the highest level of blood mercury concentration among the Amazon population, owed to large dependence on fish diet [41-43].

Inverse relationship was found between the fresh fruit intake in the Amazon region and blood mercury concentrations [41,78], the fruit was the only material that modulates the mercury exposure and blood concentration among all the dietary items studied [79].

Also Jacob and colleague [40], demonstrated the protective effect of the bioactive flavonoid (fisetin), which is a coloring polyphenols found in many fruits such as strawberries and grapes. Fisetin protect the offspring after maternal exposure to MeHg exposure, by decreasing the level of oxidative stress biomarkers [40].

Tea and coffee: Flavonoids in black tea is type of polyphenols, known by its chelating capacity for the redox active metals such as non heme iron that may result with anemia. [79]. The same scenario was applied to the inorganic mercury. As well, tea reveal diuretic effect, that participate in Hg excretion by urine, and mobilization of it from liver and kidney [14,15, 45], result with significant reduction of blood mercury level.

Ouédraogo et al., (2011) [15] reported a reduction of Hg bioaccessibility by more than 50% after addition of 40 mg of green or black tea. However 14 He and Wang, (2011) reported a reduction of the bioaccessibility with addition of green and black tea extract, with greater reduction in the green tea by more than 72% in different fish types. They proposed the presence of the flavonoids polyphenols beside the catechins and the flavins, these compounds act as good natural scavengers of metals [14,15].

Controversy, results obtained by Janle *et al*., (2015) [44], were surprised to found significant increase of mercury bioavailability rather than reduction, by the addition of green tea after administration of fish meat as bolus to experimental rats [14]. Similar results attained by Canuel et al., (2006) after three days of 6 cups tea consumption and 150g fish meals for 6 times, to consumers and compare them with non-tea drinkers with fish meals of Canadian aboriginal populations, the results showed 40% higher than those consume fish without tea[45]. The hypothesized mechanism by Canuel the amplification of mercury due to enterohepatic circulation and release of Hg from the liver stores, and secretion into bile as MeHg-G complex, that well be reabsorbed by the intestine [45].

Few studies investigate the coffee consumption effects on mercury bioavailability, Ouédraogo revealed that the co-ingestion of coffee had a lesser effect on Hg bioavailability, leaving about 50% of Hg bioaccessible, after the addition of 40 mg instant coffee [15, 16].

Summary:

Toxic effect of the mercury was documented in several historical accidents that revealed by neurological symptoms, the cardio metabolic syndrome, liver and renal diseases via the oxidative stress mechanisms, due to the strong ability of the mercuric compounds to bind to the sulfhydryl terminal of vital proteins and enzymes. The diet, especially the fish based ones accumulate significant amounts of the methylmercury, which threaten the human body.

Fortunately, the diet complexity result with decreasing the mercuric bioaccessibility within the human gut, although the gut microflora plays a crucial role for decreasing the available amounts of mercury in the gut.

In vivo studies, detect the cooking effect, the high fat content diet, presence of divalent cations like selenium, dietary fibers, protein content that affect the glutathione concentration, the organosulfur compounds present in the garlic and onion, ethanol consumption, antioxidants and fruits intake, beside the gut microbiota that plays a appreciable role in the detoxification of mercuric compounds.

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