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Review Paper： Dietary Lead Metal: Content And Body Toxicity

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Abstract: Lead exposure is achieved through various environmental issues including diet and marine food intake. It exist in several forms that varies in their toxicity degrees and rate of absorption. Lead change the body homeostasis by several oxidative stress mechanisms that affect the whole body, mainly the mitochondria and red blood cells, resulting with anemia and several degrees of toxicity. This review search the available literature, to shed the light on lead contamination sources, Pb chemical forms, absorption routs, and attempts to elucidate the mechanism of action of lead and consequent haematological manifestations of lead toxicity and the factors that affect it, mainly the dietary factors that may be a source of contamination or an approach for treatments. In conclusion the chronic exposure to lead can result in a severe alterations that may be reduced by consuming healthy diets, rich in fiber, vitamins, antioxidants, sufficient calcium and iron which can decrease lead absorption or manage the cell injury result from its toxicity.

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I) Introduction:

Lead (Pb) is considered multi-target toxicants, it has favorite applicable physical characteristics, let its used since several centuries in industries including paints, mining, ceramics, batteries, plastics, children toys and jewelries and the high use of car gasoline [1,2].

The food contamination part include mainly the contaminated drinking water, water transporting pipes, fruits and vegetables plants in contaminated soil or irrigated by contaminated water, animals dependents on such feed, fish and sea food from contaminated water [3].

On the other hand, the growing increase of fish consumption, beside the canned types of them, marine food considered good indicators of heavy metals including Pb contamination in aquatic systems, due to Pb accumulation in the fish flesh; consequently the sea food dependent consumers may be at the danger zone of Pb toxicity [4,2].

Pb exist in several forms; varied in their toxicity levels, and absorption degrees, including; i) **elemental lead ($Pb^{82})^0$**; that account 0.002% of earth crust as lead ore [5], ii) **inorganic Pb:** as Pb salts, that contribute to (50-70%) of ocean Pb content [6], iii) **organic Pb**: produced in thousands tons as tetraethyl lead [Pb $(CH_2CH_3)_4$], and methyl lead, in forms added to leaded gasoline, and released to environment after combustion, this type considered more toxic, due to higher absorption by the enterocytes [7].

II) Absorption routs:

1- **Inhalation by lungs**: the primary way of exposure, 30-40% of the exposed organic lead will be inhaled by the lung, mostly totally absorbed to circulation [8].

2- **Skin absorption**: from lead containing paints, cosmetics, traditional remedies, and gasoline. Inorganic & organic lead mainly the tetraethyl-lead or alkyl-lead that can pass transcutaneous to the systematic circulation if exposed directly to intact skin [9].

3- **Direct ingestion**: by ingestion of contaminated food and repetitive hand -to- mouth activity [10].

The lead toxicity was described by Hippocrates (370 BC) as inhalation of pernicious dust that causes constipation and colic [11]. Several lead crises took place through history, recent lead toxicity poisoning outbreak took place in 2010 in the Zamfara state in Nigeria, as a result of soil contamination from the gold mining industry [12], that affects few hundreds of children, with BLL >400 mcg/dl [13]. Another lead crisis happened in Michigan, Florida, affect thousands of children, after chlorination of tap water to get rid of E.coli and coliform bacteria, this result of lead leaching from the water pipes [14].

Molecular mechanism for lead toxicity: The major mechanisms that of lead toxicity at different levels of BLL can be summarized in three main routes, which may cause severe consequences on different body organs:

a- **Oxidative stress (OS):** it's the increase of ROS underlying lead toxicity, more than the antioxidant capacity against free radicals derived from hydrogen peroxide (H_2O_2), superoxide anions (O^{2-}) and hydroxyl radicals (OH^-) [15,16,17]. OS occurrence ROS generation and suppression of antioxidant mechanisms. It may induce subsequent adverse health problems resulting with hypertension, cardiovascular, neurotoxicity, erythorolysis, nephrotoxicity, gastrointestinal, immune and hormonal disruption [18,17].

b- **Binding to electron donor** enriched sulfhydryl containing metalloenzymes and metal transporters which are essential for the process of oxidative phosphorylation (OXPHOS). Sulfhydryl containing proteins are targets for heavy metals (Zn^{+2}, Fe^{+2}, and Ca^{+2}). Mitochondrial dysfunction is one of the earliest events, beside impairment of a multitude of enzymatic processes. So that impair the activities of antioxidant enzymes (i.e., superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), and decrease the antioxidant molecules such as glutathione [15, 16, 19].

c- **Ca^{+2} hypothesis**: lead exposure trigger cell membrane (CM) and endoplasmic reticulum (ER) impairments. Through modulation of ion channels that maintain the Ca^{+2} homeostasis in brain, skeletal muscles and cardiomyocytes, by inhibiting the inositol trisphosphate receptors [18]. Resulting in cytosol Ca^{+2} free, that work as second messenger for the neuron signaling, membrane excitability. This inhibit phospholrylation of cell signals including calmodulin-dependent protein kinase II (CaMKII), cyclic adenosine 3',5' -monophosphate (cAMP), response element binding protein (CREB) the anti-apoptotic protein B-cell lymphoma 2 (Bcl2) [18, 20].

In Mitochondria which is the site of H_2O_2 production, Pb cause significant mitochondrial evolution lipid peroxidation, ATP consumption, glutathione oxidation, block of electron transport chain (ETC) via destabilization of calcium homeostasis, and mitochondrial permeability transition pore, result with direct damage to the mitochondria function. Beside more susceptibility to the mitochondrial DNA damage, with lower ability to repair, as a result of OS [17, 21].

While in red blood cells lead cause anemia in a dose dependent manner as more than 95% of absorbed lead found in the RBCs. Pb reduce the heme synthesis in the frank anemia and hemolytic anemia after acute and prolonged exposure to lead, by inhibiting three enzymes, i) mainly the cytosolic delta-aminolevulinic acid dehydratase (ALAD) that is responsible for convertion of δ-aminolevulinic acid (ALA) to porphobilinogen, that has been used clinically to measure lead poisoning, ii) the mitochondrial aminolevulinic acid synthetase (ALAS) that is responsible for aminolevulinic acid (ALA) formation, iii) and the mitochondrial ferrochelatase enzyme, responsible iron insertion in the protoporphyrin in heme synthesis, inhibition of this enzyme result to formation of zinc protoporphyrin (ZPP).

Another anemia factor is the increase of erythrophagocytosis by spleen sequestering effect via phosphatidylserine (PS) [22]. Kempe *et al*., (2005) [23] suggest the PS exposure that may take place when eleviation of BLL, that lead to K^+ loss, through activation of K^+ channels, result with RBCs shrinkage and PS exposure at the RBC surface, end with spleen erythrophagocytosis [23, 15].

V) Factors affect Pb absorption: the diet and food habits have been studied by several scientists for a long time, several issues were proposed to influence of diet on lead absorption, and these includes the following:

1- **Fasting**: Lead that is swallowed at fasting is absorbed to a high level as compared to the condition with ingested food. It has been stated that Pb absorbed during fasting was 35%, while it was 10% absorbed in food [24, 25].

2- Meal time and absorption: evidences for the drop of absorption from 60% of oral administration of lead after prolonged fasting, to near 4% if taken mixed with healthy balanced diet [26, 27].

3- **Gastrointestinal disorders**: BLL in children suffering gastrointestinal disorders were significantly higher when compared to healthier children [28]. Shah et al., (2015) [29] found that healthy children have lower BLL than the WHO permissible BLL (10µg/dL), while children with gastrointestinal disorders have higher concentrations of the BLL [29].

4- **Environmental exposure**: several studies demonstrated higher BLL for citizens in contaminated areas of lead, as what happened Nigeria and Michigan [30, 14], battery recycling workers, and those with different socio-economic conditions [31].

5- **Age:** children have doubled ability of lead absorption more than adults [32, 33], beside the higher rate of intake the hand -to-mouth behaviors after exposure to lead sources [24], beside children have lower rate of excretion [34].

6- **Drinking water:** the Pb content in drinking tap water still underestimated source of Pb exposure, since great Florida Pb leaching in water pipes [14], mainly the old type lead-solders plumbing types. Also, children in Washington D.C. have elevated BLL, due to consumption of tap water, with Pb levels higher than the U.S. EPA levels of 15 part per billion (PPb).

7- **Dietary Factors:**

Divalent cations: it's one of the proton-coupled metal ion transporter group, present in the duodenal, enterocytes, kidney, and erythroid precursor cells, has a role to transport the divalent cations mainly iron (Fe+2), beside zinc (Zn^{+2}) and calcium (Ca^{+2}), the availability of these cations competes with lead on the same divalent metal transporter 1(DMT1) in the gastrointestinal absorption [2, 10, 24, 35].

- **Iron**: Strong inverse relationship between iron intake and BLL have been documented in several researches, this is also applied on meat consumption, as a source of heme iron [2, 10].

- **Zinc** also compete on the DMT1, it has another zinc transporters (ZnT), although it was found that higher bone lead in rats with marginal Zn^{+2} rats compared to controls $Zn^{+}2$ [10], Zn-thiamine or Zn-methionine combinations was used to prevent and treat lead toxicity [24].

- **Selenium**: negative association among the blood levels of Pb and Se was demonstrated in human and animal experiments [36]. Explanation for Se effect on BLL involves its formation of complexes that decrease Pb bioavailability, and the absorption competition. Beside Se is part of the antioxidant enzymes; glutathione peroxidase (GPx), glutathione (GSH), Superoxide dismutase (SOD), glutathione reductase (GR) so that sufficient Se inhibit the possible oxidative damage result from lead [37].

- **Calcium**: Presence of insufficient amount of Ca^{+2} ions, enhance Pb^{+2} absorption via DMT1, thus increase storage in bones [34]. The remobilization of the long term bone storage in case of pregnancy and lactation result to lead transfer to fetus and infants, as well increase BLL in case of osteoporosis [24]. [38] Kim *et al*., (2017), showed inverse relation between milk and yoghurt consumption and BLL. The same results documented by Kordas *et al*., and Ahamed *et al*., [10, 38].

5.2 Dietary ascorbic acid: vitamin C enhance the absorption of non heme iron by conversion from ferric (Fe^{+3}) to the transportable form by DMT1 ferrous (Fe^{+2}), improving the iron status in the body [10]. In addition to the antioxidant role of ascorbic acid, which lessen the damage resulted of lead toxicity oxidation. [10, 24].

5.3 Dietary fiber:

Kim and Lee (1990) [39] showed lower growth rate for SD rats fed different dietary fibers types (non-fibre cellulose, pectin, guar gum, or carboxymethylcellulose (CMC), with lowest values in pectin added group [39].

Dietary fibers considered good adsorbents that help in the detoxification mechanism for the heavy metals contamination. The consumption for example of pectin-rich fruits in the diet contributes to improve digestion and owing to it high capability of pectin in binding heavy metals. After ingestion pectin passes directly the stomach and intestine and reaches the colon. As negatively charged compounds, pectin fibers tend to attract the ions of heavy metals. Pectins reach out with their carboxylic groups and grab heavy metals, radionuclides, and bile acids to bind and carry these items out of our bodies, which help reduce our toxic load [40].

Tap water: the lead in tap water, consider more serious source of contamination, especially if increased as a result of chlorine leaching from the pipes as the Mitchigan child elevated BLL [14]. Several studies approve the same phenomenon, mainly if water lead levels above 5µg/L after 1 minute flush [41, 42]. Lead in tap water is also increased by leaching from lead-bearing materials in premise plumbing (PP), such as lead-tin solders containing up to 50% lead [43], and brass materials containing up to 8% lead [42].

Nonetheless, the rise in lead levels in tap water significantly increased the number of children with elevated BLLs in many studies [42, 44]. Also reported that water lead levels above 5 mg/L after 1 min of flushing significantly increase the BLLs of children aged 6-24 months. Finally, recent cases of lead intoxication in children have been related to solder particle ingestion [45].

Fruits: The fruits and vegetables have high contribution of human energy intake [46]. Leafy vegetables could be considered high accumulators of lead [47]. Tomatoes, spinach and other vegetable in our pattern, have also been shown to be contaminated by lead [47, 10, 46].

Pb registered the second highest contamination ratio in fruits, and the second highest potential health risk as a result from fruits consumption, and has been another important risk contributor [49].

6) **Dietary managements**: several therapeutic strategies may be recommended in case of lead toxicities, that may minimizes it's effects, that includes;

1- Health balanced diet: Ding and his Colleagues (2019) [50], demonstrated in their research the protective role of prudent diet in reducing the precipitated lead in bones [50]. Other evidences and mechanisms support the same theory. By decreasing the bioavailability of the heavy metals in the gut [10,27].

2- α-tocopherol and ascorbic acid act to counteract the toxic effects of lead poisoning, by increasing the antioxidant capacity, they act as free radicals scavengers so decreasing the ROS [10, 51]. On the other hand, ascorbic acid enhance absorption of non-heme iron, which can in turn influence the lead

absorption, by competing the gut transporters [10, 50]. Garlic is traditional herb, contain potent pharmacological organosulfer components, including; allin, allicin, myrosinase and others. These compounds have a role in declining the absorption of lead b chelating mechanisms and enhancing the antioxidant capacity [50,52].

3- Ginger that is used as spices in the diet. It has several beneficial medical applications. Its potent Zingerone (vanillyl acetone) component, reported to ameliorating the anti-oxidative stress proteins by scavenging the ROS resulted from lead toxicity [48].

4- Mineral supplements mainly the calcium and phosphorus, have a role in reducing lead and other heavy metals adsorption [27, 53]. This can be accomplished by insuring intake of 2 servings of dairy products or calcium rich foods [10]. Also, sufficient zinc and iron in the diet insure lower Pb absorption rate. Zinc intake trigger synthesis of detoxifying metallothionein protein, maintain activity of δ-aminolevulinic acid dehydratase enzyme [52, 53].

5- Insuring intake of high dietary fiber polysaccharides and pectin items; cereals, legumes, vegetables and fruits, which have high sorption abilities of heavy metals. Since these fibers persist digesting enzymes, and adsorb the available metal ions, and reducing their toxic effect [54].

6- Medical chelating leaching process: chelation therapy is used to promote metal excretion, by using less toxic metal complexes, taking into consideration safety issues for critical cases. Chelators such as calcium disodium versenate (CaNa2EDTA) and meso-2,3-dimercaptosuccinic acid (DMSA) are water soluble, stable and have high Pb+2 affinity in the blood pH, so that can used against Pb toxicity [1, 52].

7- Probiotics use: the use of commercial probiotics strands including Lactobacillus, Bacillus, Bifidobacterium and yeast (Saccharomyces boulardii) as functional foods supplements, have an effect on adsorbing to the gut available Pb to their cell membrane, beside their antioxidants properties [52].

8- Other food items rich in antioxidants compounds and ma b rich in dietary fiber; royal jelly, ginseng, liquorice, tomato, berries, grapes, onion and grapefruits [27, 53].

Conclusion:

The human body considered an open environment to be contaminated with lead by environmental and nutritional routs, which have an obvious influence on its absorption from the gastrointestinal tract. The chronic lead absorption can result in a severe negative amendments to the human. This changes may be reduced by consuming healthy diets, rich in fiber, vitamins, antioxidants, sufficient calcium and iron which can decrease lead absorption or manage the cell injury result from its toxicity.

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