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Review Article

Lead-Induced Hepatorenal Injury: Ameliorative and Protective Antidotes

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ABSTRACT

Lead is a multi-organ toxicant implicated in various cancers, diseases of the hepatic, renal, and reproductive systems etc. Lead constitutes an integral source of poisoning to the ecosystem. It primarily affects the central nervous system, hematopoietic, hepatic and renal system, producing serious disorders. Lead exposure also causes anemia, immunotoxicity and toxicity to the reproductive organs. Excessive dietary intake of lead has been linked with cancers of stomach, small intestine, large intestine, ovary, kidney, lungs, myeloma, all lymphomas, and all leukemia. Developing nations are particularly of high risk to lead poisoning and carry the highest burden of this hazard. Many antidotes are biological products and their cost, methods of production, potential for eliciting immunogenic responses, the time needed to generate them, and stability issues contribute to their limited availability and effectiveness. These factors exacerbate a world-wide challenge for providing treatment. The present study seeks to add to the fund of knowledge for the clarification of the usefulness in the management of the hepato-renal complications of chronic lead exposure since available data so far have focused on acute lead exposure.

Keywords: Heavy metal; Neurological damage; Pathophysiology; Kidney cells; Antioxidants

INTRODUCTION

Lead, denoted by Pb is characterized as soft, high malleable, ductile and toxic heavy metal with low melting point [1,2]. It is widely used in some industries such as gasoline (residual emissions), batteries production, paint, ceramics and plastics [2,3]. Lead poisoning, formally referred to as plumbism, colica, picatorum, saturnism, devon colic, or painter's colic is an ancient health problem recognized and reported as early as 2000 BC [2-4]. Till date, lead poisoning is one of the oldest and most extensively studied occupational hazard, because, many workers are still exposed to lead in their workplace [4]. However, environmental contamination by lead generated from human activities has become an evident problem during the last decades due to contamination of soil and water from mining and/or lead pipes [5]. Apart from occupational hazard and environment risks (soil/drinking water), lead exposure can be acquired accidentally from the daily consumption of lead containing food/items e. g meat killed with lead bullet, lip sticks, vegetables from lead containing soil etc. [6,7]. Recently, findings have revealed that ayurvedic medicines are heavily contaminated with heavy metals, such that patient taking some traditional remedies were reported to suffer from dysplastic changes in erythroid precursors due to lead poisoning [7].

Lead accumulation beyond normal threshold is a multisystemic disease that may be asymptomatic, mild, moderate or severe/life threatening in both old and young [8]. One in three children worldwide are exposed to lead poisoning. Short term effects (acute toxicity) dependent on amount ingested or circulated into the blood within a short period, while long term effects dependent on frequency of exposure overtime and consequences of short-term effects (Chronic/sub chronic toxicity). Lead poisoning due to accidental exposure has contributed deleterious effect on children's health, especially neurological damage and behavioural problems because lead easily crosses blood brain barrier at any detectable level [8]. Consequently, abnormal testicular development and steroidogenesis during prenatal and postnatal life have been recently documented to be an aftermath of lead poisoning among male children affected by lead exposure or male babies delivered by lead exposed pregnant women [8,9]. However, in adults, acute lead poisoning is a noticeable medical emergency that can be easily diagnosed while chronic lead exposure remains underdiagnosed and emerging cause of liver, kidney and cardiovascular damage, especially among those in low socio-economic environments.

LITERATURE REVIEW

Pathophysiology and mechanism of lead exposure (Oxidative stress and inflammatory response)

According to Centres for Disease Control and Prevention (USA),

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elevated blood lead level for children and adults is 5 μg/dL and 10 μg/dL respectively [8]. High to low lead (Pb) concentrations transfer via lactational and during prenatal and postnatal life respectively [8,9]. Lead can be Inhaled but commonest routes of entry of into vital metabolic organ (liver and kidney) in childhood/adulthood is via oral ingestion [10,11]. Although rate of transmission via skin is low, it could also contribute to perturbation of some biological events [12]. However, lead easily diffuses into the blood and primarily store in soft tissues for long period (as long as 30 years in bone) [8-12].

Lead is regarded as hepatotoxic, nephrogenic and carcinogenic (genotoxic) agents [12,13]. Lead as a compound affect various organs at cellular, intracellular and molecular level. Lead inducts oxidative stress to intensify apoptosis of hepatocytes and kidney cells [14,15]. It causes inflammation and also interferes with Ca (2+) dependent enzyme like nitric oxide synthase [16]. However, the main mechanism of lead toxicity is the generation of reactive oxygen species (ROS) and interference with generation of antioxidants (both enzymatic and non-enzymatic) [16,17].

Oxidative stress plays important role in pathogenesis of lead-induced toxicity and pathogenesis of coupled diseases. ROS are stabilized by glutathione in the body. Lead has high ability to bind high ability to bind with SH group of GSH and lead-induced oxidative stress [7,17]. Low blood lead level is capable of causes the generation of ROS like hydroperoxide, hydrogen peroxide, and singlet oxygen by inhibiting the activity of the enzyme/antioxidants such as heme synthesis enzymes, thiol-containing antioxidants, notably, cellular thiols have been modulated for protection against reactive oxygen species (ROS) as well as a therapeutic strategy against lead poisoning. Other enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, glucose 6-phosphate dehydrogenase and antioxidant molecules like GSH [18-20]. Decreased SOD concentration reduces the disposal of superoxide radical, whereas reduction in CAT impairs scavenging of superoxide radical (O_2^-) [17,21]. Lead also attack cell membrane to cause lipid peroxidation (LPO). The generated free radical captures electrons from the lipids present inside the cell membranes and damages the cell. Malondialdehyde (MDA) is another biomarker of oxidative stress, formed as a product of primary and secondary lipid peroxidation products. Wang and colleagues reported that lead induce hepatorenal injury by cascade of reactions that result to oxidative stress [18]. Their findings revealed that hesperetin attenuates oxidative stress by increasing and decreasing level of GSH and MDA respectively. Thus, suggest that lipid peroxidation observed in their study may be due to high ability of lead to bind with SH group of GSH. However, other toxicity studies involving lead have also shown that proportionate amount of vitamin C (ascorbic acid) and Vitamin E (tocopherol) also attenuate lipid peroxidation associated with lead induced cellular damage [3,19,20].

Apart from targeting the sulfhydryl groups and glutathione, lead induces an iron-deficiency-like response in developing erythrocytes (Bone marrow defects). Thus, result to formation of free radicals. It also replaces the zinc ions that serve as important co-factors for these antioxidant enzymes and inactivates them [19]. Lead interferes with the enzymes that help in the synthesis of vitamin D and with enzymes that maintain the integrity of the cell membrane. In blood cells, lead accumulation significantly downregulate three key enzymes involved in the heme synthesis. These enzymes include, **δ-aminolevulinic acid dehydratase (ALAD)**, a cytosolic enzyme that catalyzes the formation of porphobilinogen from δ-aminolevulinic acid (ALA), **aminolevulinic acid synthetase (ALAS)**, a mitochondrial enzyme that catalyzes the formation of aminolevulinic acid (ALA) and the mitochondrial enzyme **ferrochelatase** that catalyzes the insertion of iron into protoporphyrin to form heme [3,7,16]. Therefore, inhibition of ALAD causes hemolysis, which results in an increased concentration of substrate ALA in both blood and urine. These elevated ALA levels generate hydrogen peroxide and superoxide radical and also interact with oxyhemoglobin, resulting in the generation of hydroxyl radicals [3,21].

Furthermore, Lead affects vasoactive function of endothelium through the increased production of reactive oxygen species, inactivation of endogenous nitric oxide and downregulation of soluble guanylate cyclase by reactive oxygen species, leading to a limiting nitric oxide availability, impairing nitric oxide signalling. Nitric oxide (NO) seems to be involved in lead-induced cellular and impairment of DNA transcription [20,21].

Meanwhile, the influence of Pb on inflammatory processes is multifaceted, Pb affects both humoral and cellular. Exposure to lead can result to significant decrease in IFNγ, IL-4, IgA, IgG and increase TNF-α, IL-1b, 2,6,8 production. In response to proinflammatory factors (IL-1, IL-6), creative reactive protein (CRP) is produced in the liver and fat cells [21,22]. In human study, elevated levels of CRP and a strong positive correlation between blood Pb and CRP levels have been observed in workers exposed to lead [23-26]. In addition, significant effect of Pb on the expression of TGF-β1 and IL-6 has been found in the whole studied brain tissue.

Lipopolysaccharide (LPS) is a potent inducer of proinflammatory cytokines especially TNF-α. LPS binding to CD14 receptor and TLR4 receptor trigger multiple signalling pathways that activate NF-κβ and p42/44 mitogen-activated protein kinase (MAPK), leading to the expression of proinflammatory cytokines [17,25]. Using peritoneal macrophages and murine macrophage cell line, Cheng et al. reported that adult mice treated with lipopolysaccharide (LPS) and Pb produced excess TNF-α. Their study revealed that p42/44 is involved in MAPK signalling pathway which increased TNFα expression. Likewise, Pb exposure increases mRNA and IL-6 protein levels in the brains of adult mice treated with lipopolysaccharide (LPS) while IFNγ production was significantly reduced in mice that were co exposed to LPS and lead, thus, interferes with cellular immunity.

Pb stimulates IL-8 synthesis and secretion in a mechanism dependent on Nrf2 (nuclear factor erythroid 2 [NF-E2]. Nrf2 is responsible for the induction of xenobiotic-metabolizing enzymes (XMEs), Nrf2 protects cells and tissues from a variety of toxicants and carcinogens by increasing the expression of a number of cytoprotective genes. It functions as a sensor protein against ROS [17,23]. Lead exposure activates Nrf2, this may result in a dissociation from Keap1 (Kelch-like erythroid cell-derived protein with CNC homology [ECH]-associated protein 1) and migration to the cell nucleus, where it forms a heterodimer with a small Maf protein and binds to the antioxidant response element (ARE) of nuclear DNA via the leucine zipper [23,24].

Vascular endothelium is now regarded as the main target organ for the toxic lead effect. Lead predisposes decreases individuals to increased inflammatory diseases vascular smooth muscle cells (VSMC) and cancers [20,25]. A study by Simões et al. incubated

primary culture of vascular smooth muscle cells from thoracic aorta with 20 μg/dL solution of Pb acetate for 48 hr, the result showed increased level of COX-2 mRNA and increased expression of COX-2 protein with no changes in the expression of COX-1 protein [26,27]. The study concluded that observed changes in Pb-induced COX-2 mRNA expression in VSMC could be as a result of activation of p53 and p42/44 mitogen-activated protein kinase (MAPK). Moreover, activation of endothelin B receptor (ET_BR) activation by Pb induced endothelin-1/endothelin 3 (ET-1/ET-3) have been documented as an enhancer of vascular endothelial growth factor (VEGF) up-regulation, cyclooxygenase (COX)-1/COX-2 protein expression and promoter of COX-2 activity [28]. However, effects of lead on COX-2 activation and endothelin activity are yet to be fully elucidated.

Some other studies have confirmed that lead signalling pathways and its carcinogenic effect are related to activation of mainly redox-sensitive transcription factors, involving SP1, NF-kappaB, AP-1 and p53 [21,27-29]. Therefore, inactivation of these signalling pathways can be a therapeutic target for management of lead poisoning and its complications (Figures 1 and 2).

Lead induced hepatorenal injury and complications

In human studies, pathological analysis of lead-exposed patients revealed that a large amount (approximately 33%) of the absorbed Pb in stored in liver. Clinically, chronic cases of lead poisoning are usually asymptomatic, that is, no symptoms of lead poisoning with elevated levels of lead in the body but histologically, lead may culminate a potent toxic effect on histoarchitecture of liver cells which may further result to glycogen depletion, cholesterol metabolism and initiation of periportal fibrosis/liver cirrhosis and hepatic hyperplasia. With blood lead concentration between of 30 to 80 mg/dl, patient with severe gastrointestinal effects may present with vomiting, loss of appetite, malaise, abdominal pain, obstinate constipation and intestinal paralysis [30,31]. However, low level environmental lead exposure (blood lead levels below 5 μg/dl) contributes to nephrotoxicity [32]. Renal biopsy from the study of chronic lead nephropathy revealed moderate focal atrophy, loss of proximal tubules and interstitial fibrosis as a result of prolonged lead exposure. Lead deposition may result to an increased high molecular weight proteinuria, hyperuricemia, azotemia, decreased 24-hr urinary output and creatinine clearance [32-35]. These culminate to series of events in lead induced nephropathy which range from glomerulonephritis to other complications such as acute renal failure, gout, nephrotic syndrome and Fanconi syndrome. In addition, number of human studies have shown that low level environmental lead exposure may accelerated or deterioration

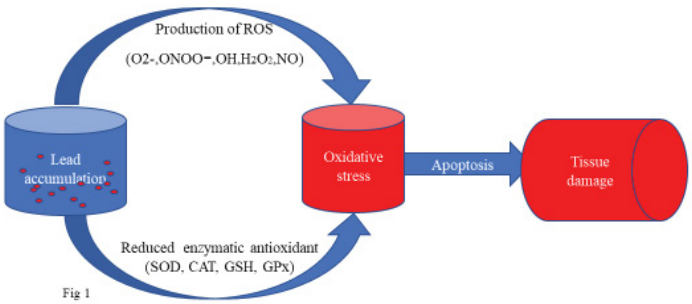

Figure 1: Lead as a toxicant causes production of reactive oxygen species (ROS) and reduction of enzymatic antioxidants which culminate to increase oxidative stress.

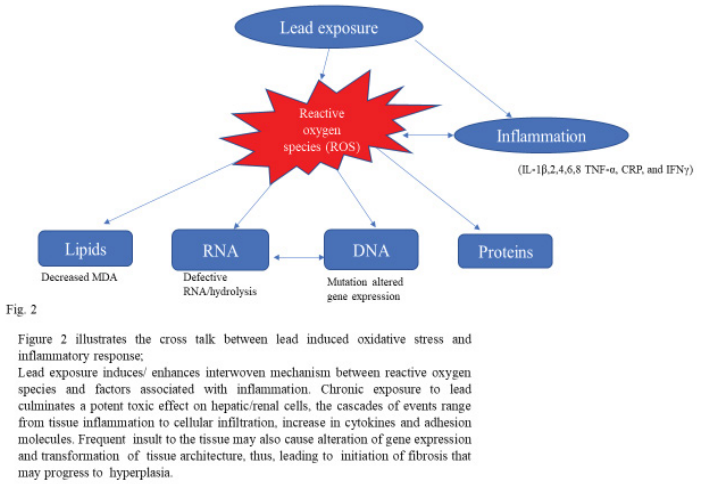

Figure 2: Illustrates the cross talk between lead induced oxidative stress and inflammatory response.

chronic renal insufficiency in patients with or without diabetes who have chronic renal disease [21,29,35]. Notably, interwoven mechanisms and pathogenesis of lead induced hepatorenal injury are strongly linked to hepatic encephalopathy, hypertension, coronary heart disease and stroke [2,5,11]. Although, neuronal encephalopathy may occur as the earliest manifestation of acute lead toxicity. This is characterized by headache (increased in intracranial pressure), vomiting, delirium, seizures and coma [3,35].

Therapeutic management and further considerations

Chelation therapy is a clinically acceptable definitive modality in the management of lead poisoning [36,37]. The aim is to trap and prevent lead compound from binding to the tissue. as chelation therapy is usually initiated when the BLL is > 80 μ g/dL in asymptomatic and > 50 μ g/dL in symptomatic adults [38]. This treatment is given until the blood level falls below 50 μ g/dL. In acute condition, DMSA was initially recognized as the first line drug. It is an orally active metal chelating agent with two sulfhydryl (SH) groups that form stable water-soluble complexes with lead [32-34]. DMSA regimen is given orally as 1050 mg/m^2/day in three divided doses. Considering lead mobilisation test, WHO has recognized and registered intravenous edetate calcium disodium ($CaNa_2EDTA$) as the mainstay of treatment of lead poisoning. $CaNa_2EDTA$ regimen (500 mg/m^2/day as a one-hour infusion) [39]. However, in comparison to the recent development, DMSA has been documented to be of greater advantage when reducing blood lead levels and mobilization of lead in the tissue is required. The main set back of the common chelating agents elevate liver enzyme. In addition, DMSA may cause rash, fever, palpitations, sweating, unpleasant smell of urine and decreased libido during the first three days of treatment. All the adverse effects are less common aside the unpleasant odour it gives during administration and passing out of faeces. However, adverse effect common to both drugs is transient elevation of hepatic enzymes. Taking into account that over 80% of the lead is stored in bones of an adult while about 70% in children, larger proportion of these accumulated lead can be released into the blood in adults, therefore, O'Flaherty model has suggested evaluation of chelation therapy on lead kinetics [40].

Till date, there is no safe lead level and ideal chelation therapy [39,40]. Meanwhile, most of Africa plants used as culinary possess

constituents that are medicinal for management various diseases and lead poisoning [4,37,41]. Flavonoids found in some of these plants possess both antioxidant and diuretic properties that may mitigate the activity of heavy metal [42-45]. Possibly, its synergistic effect with other antioxidants such as vitamin C may suppress the deleterious effect of lead induced free radicals. Interestingly, antioxidants such as N-acetylcysteine, α-lipoic acid, vitamin C, vitamin E, melatonin, quercetin and a few herbal extracts have shown prophylactic activity against the majority of lead mediated injury [46]. Several animal studies have shown that ascorbate acts as an antioxidant that prevents lipid peroxidation and does not promote protein oxidation in humans in vitro [37]. Few studies have also reported the efficacy of combination of DMSA and antioxidants especially vitamin C [36-39]. According to studies by Eluwole et al., there was appreciable improvement in experimental animals in both monotherapy and combination therapy, that is, experimental animals treated with either DMSA or *Launaea Taraxacifolia* (LT) or Vitamin C or combination therapy [20,47]. In another study by Adejuwon et al., leaf of LT has been found to reverse the cisplastin induced hepatorenal injury [48]. These studies speculated that, rich phytochemical activities particularly antioxidant, antidiuretic, and anti-inflammatory properties of LT may be responsible for its ameliorative and protective role [46-48]. Thus, the availability of these plants and their activities require further preclinical studies (molecular studies) and clinical trials.

Health education (Lead awareness and advocacy)

Environmental lead exposure continues to be a public health problem. Prevention has always been better than cure; therefore, protection against accidental or deliberate accumulation is essential. In 1980, Environment Protection Agency issued the regulation and presently, there is collaboration between several organizations such as WHO, UN Environment Programme (UNEP), governments, civil society organizations, health partners, industry to initiate Global Alliance to Eliminate Lead Paint (the Lead Paint Alliance), which is jointly led by UNEP and WHO [49]. The primary goal of the Alliance is to promote the global phase-out of lead paint through the establishment of appropriate legally binding measures to stop the manufacture, import, export, distribution, sale and use of lead paints in every country. Likewise, over 30 countries have phased out lead gasoline. Still focusing on lead poisoning as future public health risk, WHO now tagged last week of October (October 25-31) of every year as International Lead Poisoning Prevention Week [49].

DISCUSSION AND CONCLUSION

The awareness week gives an opportunity to draw attention to the need for action on lead paint and other sources of lead exposure. Similarly, each year, National Lead Poisoning Prevention Week (NLPPW) is a call by some countries to bring together individuals, organizations, industry, and different arms of governments to increase lead poisoning prevention awareness in an effort to reduce childhood exposure to lead because of their vulnerability to lead, regarding to lead-induced neurological defects. However, it is equally necessary to educate adults on major sources of lead poisoning (industrial products and mining) and prevention because, lead-related hepatorenal toxicity may be most significant as cause or complication of target organ damage due to frequent and accidental exposure to lead among lead workers (mining and other industries where lead is been used as raw material) and individuals from low socioeconomic class living in lead-exposed environment. Moreover, in developing countries, lead poisoning is underdiagnosed and there is little or no access to standard antidotes. Therefore, global efforts to reduce lead exposure in all age groups in developing countries remain important.

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