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A comprehensive review of environmental exposure of toxicity of lead

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Abstract

Lead toxicity has been recognized as a major public health risk, particularly in developing countries. This is primarily because lead bears unique physical and chemical properties that make it suitable for a large number of applications for which humans have exploited its benefits from historical times and thus, it has become a common environmental pollutant. Lead is highly persistent in the environment and because of its continuous use its levels rise in almost every country, posing serious threats. Though various occupational and public health measures have been undertaken in order to control lead exposure, cases of lead poisoning are still reported. Exposure to lead produces various deleterious effects on the hematopoietic, renal, reproductive and central nervous system, mainly through increased oxidative stress. These alterations play a prominent role in disease manifestations. Modulation of cellular thiols for protection against Reactive Oxygen Species (ROS) has been used as a therapeutic strategy against lead poisoning. N-acetylcysteine, α -lipoic acid, vitamin E, and a few herbal extracts show prophylaxis against the majority of lead mediated injury in both in vitro and in vivo studies. This review provides a comprehensive account of recent updates describing health effects of lead exposure, relevant biomarkers and mechanisms involved in lead toxicity and also focus on toxic effects of lead on the renal, reproductive and nervous system. It also updates the readers about recent advances in chelation therapy and newer therapeutic strategies, like nanoencapsulation, to treat lead induced toxic manifestations.

Keywords: antioxidants; reactive oxygen species; lead toxicity

Introduction

Lead is a heavy, bluish-gray metal that has a low melting point. It occurs naturally in the Earth's crust, but it is not a particularly abundant element. Inorganic lead is undoubtedly one of the oldest occupational toxins and evidence of lead poisoning can be found dating back to Roman times. Lead (Pb) is ubiquitous and one of the earliest metals discovered by the human race. Unique properties of lead, like softness, high malleability, ductility, and resistance to corrosion, have resulted in its widespread usage. On a global scale, 60% of lead is used for the manufacturing of batteries; 13% is used in pigments and 27% is used in the production of alloys such as solder, plastics, ammunition and a variety of other extruded products like ceramic glazes, antique-molded ornaments, storage batteries and shielding from radiation sources. In different industries like automobiles, paint, ceramics, plastics, etc. This in turn has led to a manifold rise in the occurrence of free lead in biological systems and the inert environment. Lead is regarded as a potent occupational toxin and its toxicological manifestations are well known. The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment. Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelting and coal combustion, lead-based paints, lead containing pipes or lead-based solder in water supply systems, battery recycling, grids and bearings, etc. Although lead toxicity is a highly explored and comprehensively published topic, complete control and prevention over lead exposure is still far from being achieved. There is no such level of lead that appears to be necessary or beneficial to the body and no "safe" level of exposure to lead has been found. Lead toxicity is a particularly insidious hazard with the potential of causing irreversible health effects.

Children aged 9 months to about 5 years are most at risk because they crawl on the floor, breathe in a zone nearest the floor, get lead on their hands during floor contact activities, and engage in hand-mouth activities (pica) most commonly. Moreover, children inhale a greater volume of air in relation to body mass than adults. The rate of deposition of lead in children is considerably greater than in adults. It is known to interfere with a number of body functions and it is primarily affecting the central nervous, hematopoietic, hepatic and renal system producing serious disorders (Kalia & Flora, 2005) [14].

Adults consume approximately 30 microgram of lead each day, of which only 10% is absorbed. The daily respiratory intake is probably about 15 to 20 microgram. Unlike adults,

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children absorb about 50% of ingested lead. A single chip of paint the size of a thumbnail can contain 50 to 200 mg of lead; the consumption of a few such chips a day equals 1000 times the allowable intake for an adult. Humans may develop a significant body burden from inhaling airborne lead. Inhaled lead aerosols, like other particles, are deposited in the lung by diffusion, sedimentation and impaction. About 20 to 60 percent of inhaled lead particles are deposited in the adult human respiratory tract. The amount of deposition varies with rate and depth of respiration, age and sex of the person, which determines the size of the airways. Acute toxicity is related to occupational exposure and is quite uncommon. Chronic toxicity on the other hand is much more common and occurs at blood lead levels of about 40–60 µg/dL. It can be much more severe if not treated in time and is characterized by persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma (Flora *et al.*, 2006; Pearce, 2007) ^[19, 22].

Effect on the nervous system

Compared to other organ systems, the nervous system appears to be the most sensitive and chief target for lead induced toxicity (Cory-Slechta, 1996) ^[18]. Both the central nervous system and the peripheral nervous system become affected on lead exposure. The effects on the peripheral nervous system are more pronounced in adults while the central nervous system is more prominently affected in children (Brent, 2006; Bellinger, 2004) ^[6]. Encephalopathy (a progressive degeneration of certain parts of the brain) is a direct consequence of lead exposure and the major symptoms include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory and hallucinations. More severe manifestations occur at very high exposures and include delirium, lack of coordination, convulsions, paralysis, coma and ataxia (Flora *et al.*, 2006) ^[9]. Foetus and young children are especially vulnerable to the neurological effects of lead as the developing nervous system absorbs a higher fraction of lead. The proportion of systemically circulating lead gaining access to the brain of children is significantly higher as compared to adults (Needleman *et al.*, 2004) ^[20]. Children may appear inattentive, hyperactive and irritable even at low lead exposure. Children with greater lead levels may be affected with delayed growth, decreased intelligence, short-term memory and hearing loss. At higher levels, lead can cause permanent brain damage and even death. There is evidence suggesting that low level lead exposure significantly affects IQs along with behaviour, concentration ability and attentiveness of the child. Repercussions of lead exposure on the peripheral nervous system have also been observed in the form of peripheral neuropathy, involving reduced motor activity due to loss of myelin sheath which insulates the nerves, thus seriously impairing the transduction of nerve impulses, causing muscular weakness, especially of the exterior muscles, fatigue and lack of muscular coordination (Sanders *et al.*, 2009) ^[27].

Effect on the hematopoietic system

Lead directly affects the hematopoietic system through restraining the synthesis of haemoglobin by inhibiting various key enzymes involved in the heme synthesis pathway. It also reduces the life span of circulating erythrocytes by increasing the fragility of cell membranes. The combined aftermath of these two processes leads to anaemia (Guidotti *et al.*, 2008; Cornelis, 2005) ^[12]. Anaemia caused on account of lead poisoning can be of two types: haemolytic anemia, which is associated with acute high-level lead exposure, and frank

anemia, which is caused only when the blood lead level is significantly elevated for prolonged periods (Vij, 2009) ^[36]. Lead significantly affects the heme synthesis pathway in a dose dependent manner by down regulating three key enzymes involved in the synthesis of heme. 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 finally, the mitochondrial enzyme ferrochelatase that catalyzes the insertion of iron into protoporphyrin to form heme (Piomelli, 2002) ^[23]. The initial and final steps of heme synthesis take place in the mitochondria, whereas the intermediate steps take place in the cytoplasm. Lead inhibits the three aforementioned vital enzymes of this pathway but its effect on ALAD is more profound and its inhibition has been used clinically to gauge the degree of lead poisoning. Inhibition of ALAD results in the accumulation of aminolevulinic acid, detectable in the plasma and urine even at blood lead levels of less than 10 µg/dl. Although ALAD inhibition is first noted at blood lead levels of 10–20 µg/dl, heme biosynthesis does not decrease until the activity of ALAD is inhibited by 80–90%, which occurs at a much higher blood lead concentration of about 55 µg/dl (Ahamed *et al.*, 2005) ^[2]. Inhibition of ferrochelatase results in increased excretion of coproporphyrin in urine and accumulation of protoporphyrin in erythrocytes (EP). Moreover, inhibition of this enzyme results in the substitution of iron by zinc in the porphyrin ring forming zinc protoporphyrin (ZPP). The concentration of ZPP thus gets increased, which can also be used as an indicator to monitor the level of lead exposure (Jangid *et al.*, 2012) ^[13]. Thus, the collective inhibition of these three key enzymes blocks the heme production via the heme synthesis pathway. The mechanism responsible for shortening the life cycle of erythrocytes is not well understood. One of the earliest observed hematological effects of lead revealed basophilic stipplings of red blood cells (presence of dense material in red blood cells), which is also a potential biomarker for the detection of lead poisoning. These aggregates are degradation products of ribonucleic acid (Patrick, 2006) ^[21].

Renal effects

Renal dysfunction occurs mostly at high levels of lead exposure (>60 µg/dL) but damage at lower levels has also been reported (~10 µg/dL) (Grant, 2008) ^[11]. Renal functional abnormality can be of two types: acute nephropathy and chronic nephropathy. Acute nephropathy is characterized functionally by an impaired tubular transport mechanism and morphologically by the appearance of degenerative changes in the tubular epithelium along with the occurrence of nuclear inclusion bodies containing lead protein complexes. It does not cause protein to appear in the urine but can give rise to abnormal excretion of glucose, phosphates and amino acids, a combination referred to as Fanconi's syndrome. Chronic nephropathy on the other hand, is much more severe and can lead to irreversible functional and morphological changes. It is characterized by glomerular and tubulointerstitial changes, resulting in renal breakdown, hypertension and hyperuricemia (Rastogi, 2008) ^[26].

Cardiovascular Effects

Both chronic and acute lead poisoning causes cardiac and vascular damage with potentially lethal consequences including hypertension and cardiovascular disease (Navas-

Acien *et al.*, 2007)^[19]. Low level lead exposure can contribute to hypertension in both animals and humans (ATSDR, 2005). Other major disorders include ischemic coronary heart disease, cerebrovascular accidents and peripheral vascular disease. Although evidence of causal relationship of lead exposure and hypertension was reported, it applies only in cases of cardiovascular out- comes of lead toxicity (Navas Acien *et al.*, 2007)^[19].

Reproductive Health Effects

Lead causes a number of adverse effects on the reproductive system in both men and women. Common effects seen in men include: reduced libido, abnormal spermatogenesis (reduced motility and number), chromosomal damage, infertility, abnormal prostatic function and changes in serum testosterone. Women on the other hand, are more susceptible to infertility, miscarriage, premature membrane rupture, preeclampsia, pregnancy hypertension and premature delivery (Flora *et al.*, 2011)^[10]. Moreover, during the gestation period, direct influence of lead on the developmental stages of the foetus has also been reported (Saleh *et al.*, 2009)^[29].

Effects on the liver

Disruption of the normal anatomical organisation of hepatic lobules, loss of the distinctive cord-like structure of functional liver cells, hyperchromatic hepatocytes with occasional vacuolations and congestion of sinusoids occur in lead poisoning (Bukola *et al.*, 2015). Abdel Moneim (2016) reported that at histology, lead acetate induced focal hepatic necrosis, accompanied by dilated blood sinusoids and congested central veins, infiltration of acute inflammatory cells, mainly in the central zone, derangement of hepatocyte cords with pyknotic and karyolytic nuclei, vacuolisation of hepatocytes and fatty change (steatosis), which include the intracellular accumulation of fats. Significant increase in free radical generation, activities of liver transaminase (alanine aminotransferase and aspartate aminotransferase) and total bilirubin in experimental lead-induced toxicity in male Wistar rats was reported by Abdel Moneim (2016) and Shatha *et al.*, (2016). The elevated plasma ALT and AST activity was complemented with high liver microsomal membrane fluidity, ROS production, and variation in the hepatocyte histogram moneim (2016).

Dietary management

Antioxidants are effective in alleviating and treating the oxidative stress-induced toxicity of lead. By interacting with generated reactive oxygen species (ROS), antioxidants prevent radical chain reactions. By chelating with lead ions, ROS generation is blocked, preventing and alleviating lead's toxicity. While chelating agents can remove lead from the body, their effectiveness in treating lead's neurological toxicity is unclear, and thus, they are not used in treatment for children with low blood lead concentrations (McKay, 2012). Additionally, as chelating agents have a rebound effect, they cannot be used in instances where lead exposure cannot be suspended. However, anti-oxidants can be used in such instances where lead exposure cannot be suspended or in cases of low blood lead levels. Antioxidants used in the alleviation of lead toxicity include vitamins, flavonoids, and herbs.

Vitamin B (Pyridoxine and Thiamine)

Vitamins Vitamin B6 (pyridoxine) and B1 (thiamine) are effective in alleviating health problems caused by lead poi-

soning (Gurer2007). Vitamin B6 produces antioxidant effects by promoting GSH generation. In an animal study using rats as subjects, vitamin B1 was effective in alleviating lead-induced lipid peroxidation (McKay, 2013). Lee *et al.*, (2012) found blood lead levels and homocysteine to have a proportional relationship in adults in the U.S., but as this showed different patterns depending on the vitamin B6, they suggested that an appropriate concentration of B6 in the body be maintained in order to block the effects of lead exposure.

Vitamin C (ascorbic acid)

Vitamin C (ascorbic acid) is the most widely studied antioxidant capable of removing free radicals. Unsurpassed in its ability to bind to and remove lead, vitamin C is highly effective at alleviating lead toxicity (Chang BJ, *et al.*, 2012). Through its antioxidant activity, vitamin C improves the lead-induced impairments in synaptic plasticity. The combined administration of vitamin C with silymarin can alleviate lead-induced hepatotoxicity (Shalan *et al.*, 2005)^[32]. In a study by lead-poisoned patients were administered 250 mg of vitamin C two times daily for a month, which resulted in a reduction in blood lead levels and an increase in blood ALAD activity. One study found that administering 250–500 mg of vitamin C daily to children was effective in removing free radicals and in treating lead-induced health problems (Tariq *et al.*, 2007)^[35].

Vitamin E (α -tocopherol)

Vitamin E (α -tocopherol) is a fat-soluble vitamin, it exhibits powerful antioxidant effects. With its neuro-protective effect and antioxidant effect, vitamin E improves cognitive impairment caused by aging. Sajitha *et al.* reported an improvement in lipid levels and the alleviation of lipid peroxidation-induced liver, heart, and kidney impairment in rats that had been administered vitamin E. As vitamin E improves lead-induced memory impairment, it has been recommended as good for preventing lead-induced health problems with appropriate dosing. Effect of vitamin E in combination with other antioxidants has been found to be more pronounced than its individual administration. Flora *et al.* (2003)^[9] reported that co-administration of vitamin E with monoisoamyl derivative (MiADMSA), which is a thiol chelator, exerts an elevated recovery from lead burden in rats. Interestingly, α -tocopherol is capable of reducing ferric iron to ferrous iron (i.e. to act as a pro-oxidant).

Herbal antioxidants

The ability of herbal antioxidants to act as useful clinical medicine is due to their low cost and few side effects. However, actual implementation of herbal antioxidants as potential medicines has been highly limited. This is due to the longer treatment durations associated with it, which makes it a preventive rather than therapeutic measure. Apart from this, herbal drugs also suffer from a serious drawback of poor bioavailability in the body and require much higher and repetitive doses to maintain the therapeutic threshold in the body. A few herbal antioxidants that have been reported to provide protection against lead induced oxidative stress will be discussed.

Garlic

Garlic is a medicinal plant that has been an inseparable part of Indian culinary for over 5000 years. Besides its use as a condiment, it is credited to have remarkable therapeutic and pharmacological properties. Its active agent is allicin, which

imparts its characteristic odor as well as medicinal properties (Sharma *et al.*, 2010). Garlic can prevent oxidative stress by chelating lead ions and scavenging free radicals. Senapati *et al.*, (2001) reported the prophylactic efficacy of garlic extract in reducing the lead burden from soft tissues. In another study, Pourjafar *et al.*, (2007) further confirmed the ability of garlic to reduce the lead burden from the liver, kidney, blood and bone. The protective efficacy of aqueous garlic extract was studied against lead induced hepatic injury in rats. The results clearly indicated the ameliorative ability of garlic towards hepatic injury caused by lead due to generated oxidative stress (Kilikdar *et al.*, 2011) ^[15].

Curcumin

Sethi *et al.*, 2009 reported that Curcumin is a yellow-colored polyphenolic compound and the principal active component of turmeric, which is obtained from the plant *Curcuma longa*. There are reports of antioxidant, radical scavenging and metal chelating effects of curcumin in metal toxicity. Shukla *et al.* (2003) reported for the first time the protective effect of curcumin against lead-induced neurotoxicity in rats by showing significant improvement in the levels

Conclusions

Many studies have been conducted on the occupational exposure and impact of lead toxicity on health, and the various efforts to prevent health problems caused by lead resulted in the significant decrease in the number of cases of occupational lead poisoning. As interest has grown in lead's carcinogenicity and the health problems of environmental lead exposure and exposure to low concentrations of lead, efforts are underway to reduce the concentrations of lead in the environment. Recently, studies have been conducted on health problems caused by low-level lead exposure, and reports on long-term low-level lead exposure and a variety of health problems are being continuously published. In this study we examined the toxicity and health impact of lead, and reviewed recent literature on the observation and treatment of lead exposure. We expect that this study can be usefully applied to the observation and management of environmental lead exposure.

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