An Overview of Lead -induced Neurotoxicity

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ABSTRACT

Lead (Pb) is among the most frequently encountered heavy metals that pollutes the environment. Lead buildup in body is very common in humans. The general public's health, particularly children, is also damaged in addition to that of occupationally exposed persons. Because lead poisoning can impact the body's hematologic, hepatic, cardiovascular, reproductive, gastrointestinal, and neurological systems, it is known to alter how the body functions. Pb exposure is connected to atypical social behavior, alterations in executive function, and cognitive impairment. Pb poisoning is particularly detrimental to the CNS. Lead's neurotoxic effects may stem from its capacity to mimic or impede the function of calcium and imbalance between oxidative stress and antioxidant processes. This review focuses on the lead's detrimental consequences on the neurological, and hematological systems. It also explains the neurotoxic mechanisms. The review offers a conceptual framework and future research paths for lead-induced neurological illness prevention, diagnosis, and therapy.

Keywords: heavy metals, lead poisoning, cognition, neurotoxicity.

1. INTRODUCTION

Lead (Pb) is among the most significant hazardous heavy metal in the environment. Its historical use may be traced back to historical times as a result of its significant physicochemical features. It is a globally dispersed, significant, yet hazardous environmental chemical. Resistance to corrosion, malleability, ductility, softness, and low conductivity are all critical features that render it challenging to abandon its use. The environment is exposed to an increasing number of risks as its concentration increases as a result of its non-biodegradable nature and continued use (1).

1. AIM OF THE WORK

This review discusses the neurotoxicological effects of lead (pb). It also describes the neurotoxic mechanism. The review focuses on preventing, diagnosing, and treating lead-induced neurological illnesses.

Physical and Chemical Properties of Pb: It is flexible, corrosion-resistant, and an inadequate conductor of electricity, sound, and vibration. Despite its resistance to phosphoric and sulfuric acids, lead metal is susceptible to nitric acids (HNO3) and hydrochloric acids. Pb compounds possess two unique oxidation states that undergo gradual dissolution in water and the majority of cold acids (2).

Sources of Exposure: The primary concern and the primary cause of Pb toxicity is occupational exposure. Pb poisoning may be a risk to both adults and children due to a range

of vocations and hobbies. Metal welding, battery production and recycling, bullet salvage, and Pb smelting and refining are among the most hazardous jobs.
(1).

Pb Toxicokinetics: Differential absorption, distribution, metabolism, and elimination of Pb in early children in contrast to adults is a critical aspect of its toxicokinetics. The primary path of Pb absorption in both adults and children is through the GI (ingestion). and the lung (inhalation) Although pulmonary absorption in both age ranges is highly effective (about 40%), children breath a greater volume of air in relation to their body size than adults, which places them at a proportionally larger risk. In general, children absorb approximately 40 to 50 % of Pb they consume, but adults only absorb approximately 10 to 15 %. The GI absorption of Pb is also increased in individuals accompanied by zinc, calcium, or iron deficiencies, which is more prevalent in young children than in adults. In rare instances, Pb absorption could arise from the soft tissues in the presence of lodged Pb foreign materials, such as retained Pb bullets. It is important to mention that Pb is easily transported across the placenta (3).

Upon absorption, Pb attaches to RBCs and is distributed into two primary compartments: soft tissues and bone. In contrast to the more sturdy bone compartment, the soft tissue compartment comprises the bone marrow, brain, kidneys, liver, and is very flexible. In adults, the stable bone compartment stores practically the whole-body burden of Pb, which is around 85 to 95 %. In contrast, only 70 % of body burden of Pb storage is in bone in children (4).

Therefore, children are once more at an elevated risk of experiencing symptoms of Pb toxicity due to the fact that a bigger portion of their Pb body load is kept in regions that are actively involved in metabolism rather than the comparatively inactive bone. Part of the absorbed Pb is excreted through the bile and urine since it is not absorbed into either of these compartments. Children are more susceptible to poisoning because adults excrete a larger fraction of the substance than do children (5).

Mechanism of Toxicity: Pb is likely the greatest thoroughly researched heavy metal. In this subject, research has revealed the toxicological effects of Pb in the body are caused via a number of different cellular, intracellular, and molecular routes (6).

1. Oxidative Stress:

It is indicative of an imbalance between biological system's capacity to promptly neutralize reactive intermediates or rectify the resulting harm and the creation of free radicals. It has been identified as a significant mechanism of toxicity generated by lead. The onset of oxidative stress is a result of the simultaneous operation of two distinct pathways under the influence of Pb. Firstly, the generation of reactive oxygen species (ROS) such as hydrogen peroxide (H2O2), singlet oxygen, and hydroperoxides (HO2•) occurs, and subsequently, the antioxidant reserves are depleted. (7).as shown in **Fig.1**

Pb binds to the sulfhydryl groups in GSH, hence inactivating it. Typically, the γ-glutamyl cycle is ineffective in replenishing the GSH supply, as a consequence of the production of GSH from cysteine. Enzymes such as glutathione-S-transferase, GSH reductase (GR), δ-amino levulinic acid dehydrates (ALAD), and GSH peroxidase (GPX) are inactivated by lead, which further decreases GSH levels (9).

Super oxide dismutase (SOD) and catalase are two further antioxidant enzymes that are made inactive by lead. The scavenging of superoxide radical (O2 – •) is impaired with a

reduction in SOD concentration, while the disposal of superoxide radical is reduced with a reduction in CAT. Pb has the ability to substitute zinc ions that function as critical co-factors for these antioxidant enzymes, in addition to targeting the sulfhydryl groups, so inactivating them (10).

One of the most well researched effects of ROS on lipid membranes is lipid peroxidation, which is a biomarker of oxidative stress. The cell is damaged as a result of the free radical's ability to take electrons from the lipids within the cell membranes. In addition to lipid peroxidation, Pb also induces hemoglobin oxidation, which results in the direct hemolysis of red blood cells. This is a consequence of ALAD inhibition, which leads to an elevated concentration of the substrate ALA in both blood and urine. Hydrogen peroxide and superoxide radicals are produced by these high ALA levels, which also engage in interaction with oxyhemoglobin, leading to the production of hydroxyl radicals. The cell is greatly susceptible to oxidative stress and may succumb to cell death as a result of the progression of all the aforementioned processes (11).

2. Ionic Mechanism of Pb Toxicity:

The primary explanation for the ionic mechanism of action of Pb is its ability to replace other bivalent cations, including Ca2+, Mg2+, and Fe2+, as well as monovalent cations, like Na+ (although bivalent cations are more easily substituted). This substitution process impacts a variety of fundamental biological processes in the body. Numerous key physiological functions, including Cell adhesion, apoptosis, ionic transportation, enzyme regulation, neurotransmitter release, protein folding and maturation, and intra and intercellular communication have all been profoundly affected (12).

The ionic pathway is the most major factor contributing to neurological deficits, as Pb is capable of penetrating the blood-brain barrier (BBB) at a high rate after replacing calcium ions. Pb accumulates in astroglial cells subsequent to its passage across BBB (containing Pb binding proteins). The toxic effects of Pb are particularly obvious in the developing nervous system, which is composed of young astroglial cells that lack Pb binding proteins. The juvenile astroglial cells are easily damaged by Pb, and the growth of the myelin sheath is impeded, both of which are key components of the BBB (13).

Pb has the ability to replace calcium, even at picomolar amounts, so affecting important neurotransmitters like protein kinase C, which is essential for long-term brain excitation and memory storage. In addition, it affects the concentration of sodium ions, which are crucial for a variety of biological processes, such as the regulation of the uptake and retention of calcium by synaptosomes, the generation of action potentials in excitatory tissues for the purpose of cell-to-cell communication, and the uptake of neurotransmitters (choline, dopamine, and GABA). Because of this interaction between Pb and sodium, the sodium-dependent systems indicated above are considerably hindered in their normal operation (14).

Signs and Symptoms: The quick repercussions of organic Pb's lipid-soluble nature may render it more hazardous than inorganic Pb. Nevertheless, the Pb levels at which signs and symptoms manifest are subject to significant variation, as they are contingent upon the unknown characteristics of each individual (15).

Neuropsychiatric symptoms, including irritation, slowed reaction times, difficulty concentrating, as well as slower motor nerve conduction and headache, are induced by blood Pb levels between 25 and 60 μg/dL.

High blood lead levels, which surpass 100 μg/dL, result in severe symptoms, including delirium, coma, seizures, headache, and encephalopathy signs (a disorder characterised by brain swelling) that are followed by a rise in pressure within the skull. Nevertheless, such signs are observed in children at Pb levels of 70 μg/dL or more (16).

Chronic Pb exposure typically results in the development of symptoms and signs within weeks to months; however, acute symptoms and signs may also emerge as a result of brief, intensive exposures. Intense exposure typically leads to neuromuscular symptoms and the central nervous system. Nausea, abdominal pain, coordination impairment, depression, numbness and tingling in limbs, and short-term memory impairment or focus are all symptoms of chronic exposure to lead. Chronic lead poisoning is also associated with fatigue, sleep disturbances, headaches, stupor, slurred speech, and anemia (17).

The conduct of children with chronic poisoning is typically characterized by aggression and a refusal to engage in play. Nervous system is the most frequently afflicted organ in children with lead exposure. Nevertheless, the toxicity in youngsters has a more significant effect than in adults. This is due to the fact that their tissues, both internal and exterior, are more delicate than those of adults. Adults may experience diminished cognitive performance in certain cognitive performance assessments that evaluate nervous system functioning as a consequence of prolonged exposure. Behavioral issues, learning difficulties, and a decreased IQ may be exacerbated by even low levels of Pb, which are particularly sensitive to infants and young children (18).

Pathophysiology: Pb is believed to impede the typical synaptic pruning process in early brains, which is likely the cause of the cognitive and behavioral deficits observed in young children with excessive Pb exposure, from a neurologic standpoint. Peripheral neuropathy is a prevalent symptom of chronic Pb toxicity in adults; nevertheless, the mechanism that underpins its development is still not well understood. Acute Pb encephalopathy is responsible for the most serious neurological effects of lead poisoning, such as coma and convulsions. This condition is believed to be at least partially the result of microvascular alterations in the brain caused byPb, which lead to cerebral edema and an increase in intracranial pressure(19).

Pb Toxicodynamics: Pb's toxicity is likely because of its affinity for cell membranes and mitochondria, which causes it to interfere with sodium, potassium, and calcium ATPases and mitochondrial oxidative phosphorylation. As a result, it is toxic. The activity of brain protein kinase C and calcium-dependent intracellular messengers is impaired by Pb. Furthermore, Pb induces the creation of inclusion bodies, which have the potential to move the metal into the nuclei of cells and alter the expression of certain genes (20).

Pb poisoning is caused by the metal's interaction with biological electron-donor groups, like sulfhydryl groups, which disrupts a variety of enzyme functions. Additionally, Pb interacts with important cations, specifically calcium, iron, and zinc; it modifies cellular and mitochondrial membranes, increasing cellular fragility; and it obstructs the sodium-potassium-adenosine triphosphate (Na+/K+-ATP) pump (21).

In addition, Pb modulates the activities of other nucleotides and inhibits pyrimidine-5'-nucleotidase. The operation of nearly every organ is impacted by Pb's interference with numerous enzyme systems in the body. Symptoms of Pb toxicity that are clinically evident include those that pertain to CNS, peripheral neurological system, hematological system, digestive system, and kidney system.

Devastating repercussions may result for children who are exposed to lead due to its detrimental effects on the growing brain (22).

Diagnosis: Proper diagnosis is a critical and key concern in the prevention of Pb poisoning and toxicity. It is imperative to investigate the potential pathways of exposure in order to get an accurate diagnosis. The investigation should encompass the assessment of clinical symptoms and the review of medical history. The establishment of an accurate diagnosis and treatment can be facilitated by the participation of qualified personnel, such as clinical toxicologists and medical professionals (23).

Basophilic stripping is a critical indicator of lead toxicity. This process of stripping renders the spots in RBCs visible under a microscope. Therefore, detection of Pb poisoning might be made easier by the screening of blood film for the presence of such indications. A lack of iron in the body is typical comorbidity of lead poisoning. Erythrocyte protoporphyrin (EP) measurements in blood samples can also be employed to assess lead toxicity. EP is recognized to rise with a delay of a few weeks when concentration of Pb in blood is great. Nevertheless, EP level alone is insufficiently sensitive to detect high blood Pb levels below roughly 35μg/dL (24).

1. Detection of Pb poisoning

The level of Pb in the blood can be determined by a variety of methods. The existence of alterations in blood cells that are evident under a microscope or elimination of thick lines in bones of youngsters that are observed on an X-ray are frequently used to diagnose Pb poisoning. Although the primary method for detecting heightened levels of body Pb is the detection of Pb in blood samples, this method is limited in its ability to perceive circulating Pb levels and not the quantity of Pb contained in body. Pb poisoning is indicated by blood levels of 10 μg/dL for adults and 5 μg/dL for children in whole blood (8).

2. Biomarkers of Pb exposure in humans

I. Blood and urine Pb levels as biomarkers of Pb exposure

The mechanistic relationship between Pb and the cascade of enzymatic pathways involved in heme synthesis has been elucidated in numerous literatures. Pb directly inhibits the cytoplasmic enzyme ð-aminolevulenic acid dehydrogenase (ALA-D), resulting in a negative exponential connection between ALA-D and blood-Pb. The most often used biological fluid for the measurement of Pb exposure in individuals, both for diagnostic and screening reasons, in recent years has been whole blood (25).

II. Hepatorenal indices as biomarkers of Pb exposure

Pb exposure at elevated levels (60 μg/dL) is the primary cause of renal impairment; however, damage has been documented at lower levels (~10 μg/dL). Acute nephropathy and chronic nephropathy are the two types of renal functional abnormality that are produced by Pb. The morphological manifestation of degenerative defects in the tubular epithelium, the appearance of nuclear inclusion bodies, which consist of Pb protein complexes, and the impairment of the functional mechanism of tubular transport are the primary defining features of acute nephropathy. (8).

III. Hematological indices as biomarkers of Pb exposure

One of the hematological signs of Pb poisoning that was initially recognized is the basophilic stippling of erythrocytes, which is a potential biomarker for the detection of Pb toxicity. This aggregates as a result of the

breakdown of ribonucleic acid. Pb directly influences the hematological system by blocking a variety of critical enzymes that are engaged in heme production pathway, hence restricting the synthesis of hemoglobin. Additionally, it diminishes the lifespan of circulating erythrocytes by enhancing fragility of cell membranes (26).

Pb poisoning can lead to two types of anemia: hemolytic anemia, which is associated with acute high-level Pb exposure, and iron deficiency anemia, which is only apparent when the blood Pb level remains significantly higher for an extended period. Other significant hematological changes that are associated with Pb-induced damage include anemia, which is defined by anisocytosis and RBC lipoperoxidation, which leads to an increase in Thrombocytopenia, leucopenia, and RBC fragility (24).

IV. Oxidative stress markers (GSH, SOD, MT) as biomarkers of Pb exposure in humans

In a previous study, the relationship between oxidative stress biomarker and blood Pb levels was investigated. The MDA levels (9.64 µmol/L) and blood Pb levels (5.28 µg/dL) of Pb-exposed hypertension participants were significantly higher than those of control group (8.23 µmol/L and 4.41 µg/dL). Additionally, a favorable connection was seen between blood Pb levels and antioxidant indicators (GPx, CAT, SOD, and GSH). In comparison to people with normotension, the antioxidant levels in subjects with Pb-induced hypertension are decreased (27).

3. Laboratory profile intoxication

Pb poisoning should be considered in patients who present with multisystem disease due to its multiorgan toxic properties. The preservation of blood PB levels at or under 1.9 µmol/L and the regular measurement of blood Pb in Pb-exposed workers are recommended. Pb-connected anemia is typically normochromic and normocytic, It could be accompanied with stippling that is basophilic. Peripheral demyelination caused by Pb is characterized by a prolonged nerve conduction time and eventual paralysis, usually of the extensor muscles of the hands and feet (28).

A metaphysical plate of expanding long bones ("Pblines") can develop an elevated density in youngsters, which is similar to the density observed in rickets. Fanconi's syndrome, pyuria, and azotemia are occasionally observed in children who have experienced elevated Pb exposure. Chronic exposure to Pb in adults can lead to the development of chronic alterations and intranuclear inclusion bodies, as well as higher blood creatinine levels and decreased creatinine clearance rates (detected at renal biopsy) (29).

Toxicological effect of Pb

1. Effect of Pb on nervous system

The organ most vulnerable to Pb exposure is the brain. Pb significantly influences the creation of synapses in the cerebral cortex of a child who is still in the process of developing. Pb also disrupts the architecture of ion channels and the synthesis of neurochemicals, such as neurotransmitters. Pb poisoning also results in the loss of the myelin sheath of neurons, a reduction in the quantity of neurons, interference with neurotransmission, and a reduction in neuronal growth (30).

MRI images of people who were exposed to elevated Pb levels throughout their youth also demonstrate a reduction in brain volume, particularly in the prefrontal cortex. Pb can cross BBB's endothelial cells and interfere with the formation of synapses because it can act as a calcium ion substitute and be absorbed by calcium-ATPase pumps. Developmental impairments are more prevalent in children

with a blood Pb content exceeding 10 µg/dL. It is at extremely low concentrations that lead has an impact on the cognitive capacities of youngsters. It seems that there is not a dose-response relationship lower threshold that is deemed safe for lead exposure. It was found that lower blood lead levels (5 µg/dL) were associated with worse academic performance (31).

Lower IQ and behavioral issues, including aggression, were observed to be connected with blood Pb levels under 10 µg/dL, in proportion to given blood lead level. An IQ decline of 2-4 points was noted in children for every µg/dL increase in blood lead levels between 5 and 35 µg/dL. Elevations in blood lead levels have also been connected to cognitive impairment and several psychiatric issues like sadness and anxiety. An increase in blood lead levels from 50 to about 100 µg/dL in adults was found to be linked to more serious issues, like chronic impairment of CNS function (32).

An additional investigation demonstrated a robust correlation between the levels of lead in preschool blood and the later developments in crime rates over the course of several decades in nine nations. Pb also interferes with the release of neurotransmitters. Neurotransmitters are substances that neurons employ to relay signals to other cells. The interruption of communication between cells is the result of this interference. Pb typically disrupts the neurotransmitter glutamate, which is essential for numerous processes, including learning. It functions by inhibiting NMDA receptors. Blocking these receptors is believed to be the primary objective of Pb toxicity. In addition to inhibiting the NMDA receptor, a study discovered that Pb exposure also reduced the quantity of the gene encoding this receptor in a specific region of the brain. In animal research, Pb was also discovered to be involved in the apoptosis of brain cells (33).

2. Effect of Pb on the skeletal system-bone

It was discovered that Pb increases the risk of osteoporosis and affects osteoblasts, osteoclasts, and chondrocytes. Osteoporosis is more prevalent among women who are experiencing menopause. Additionally, persons who are exposed to lead experience a severe fracture and recover at a significantly slower pace than those who are not (34).

3. Effect of Pb on the hematopoietic system

At BPb levels as minimal as 10 µg/dL, Pb has an immediate effect on the hematological system. It inhibits the manufacture of hemoglobin by blocking important heme synthesis-related enzymes, and it shortens erythrocyte life spans by making their cell membranes more fragile. For more information about destabilization, visit ScienceDirect's AI-generated Topic Pages. Frank's anemia is directly caused by this, which also leads to elevated blood lead levels (iron deficiency anemia). The red blood cells are destroyed at the same rate as they are produced, resulting in hemolytic anemia as a result of acute Pb exposure. δ-aminolevulinic acid dehydrates is a critical enzyme for the production of heme (ALAD). The enzyme responsible in order to synthesize porphobilinogen from δ-aminolevulinic acid is δ-ALAD, a cytoplasmic enzyme that is abundant in SH groups (ALA) (35).

Dehari-Zeka et al. demonstrated in their research that δ-ALAD is suppressed at BPb levels as minimal as 5 µg/dL, resulting in behavioral abnormalities and childhood Pb encephalopathy. The suppression of δ-ALAD leads to the buildup of δ-ALA in the plasma, which in turn causes severe neurological consequences (36).

δ- The presence of ALA in urine is also utilized as a sign of Pb exposure in industrial workers. Another mitochondrial enzyme, ferrochelatase, catalyzes the incorporation of iron (Fe2+) into ring. Zn2+ is substituted in the event of low Fe2+ availability, and Pb poisoning inhibits this enzyme. Additionally, it impedes the trans-mitochondrial transfer of iron. Over 90 % of the Pb in blood is still linked to the RBC, therefore even at BPb values of 10–150 µg/dL, plasma Pb concentrations stay stable at 2-3 µg/dL. Human hemoglobin levels dropping, anemia, weight loss, pregnancy complications, kidney failure, and in extreme situations, the emergence of cancer are some of the acute effects of these Pb (37).

4. Effects on children

Pb poisoning is more prevalent in children during their developmental stages than in adults. Pb toxicity in children is predominantly asymptomatic; nevertheless, children under the age of five may exhibit symptoms such as weariness, cramping in the abdomen, nausea, agitation, and loss of appetite. Epidemiological research indicates that children with a blood lead level of B Pb (BPb) of less than 10 µg/dL are significantly impacted. The word "biomarker" refers to interactions between biological system and an external environmental agent. The extracellular matrix, neurons, and astrocytes, which are a type of glial cell in brain, comprise the physical BBB. Pb2+ ions rapidly cross BBB and accumulate in brain cells, as they readily replace Ca2+ ions (38).

Prevention and treatment of Pb accumulation in human beings

The primary objective of the preventive medicine strategy is to monitor blood levels of children who are at a great risk of exposure to lead. Medical intervention is implemented to mitigate adverse effects of poisoning and limit the accumulation of Pb in the bloodstream after Pb is identified (39).

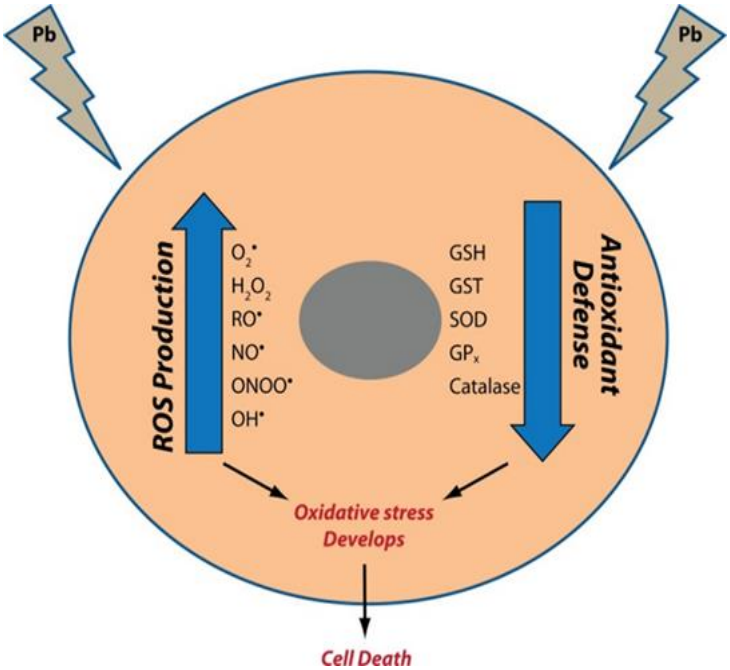

Figure 1: Mechanism underlying the development of oxidative stress in a cell on Pb exposure (6)

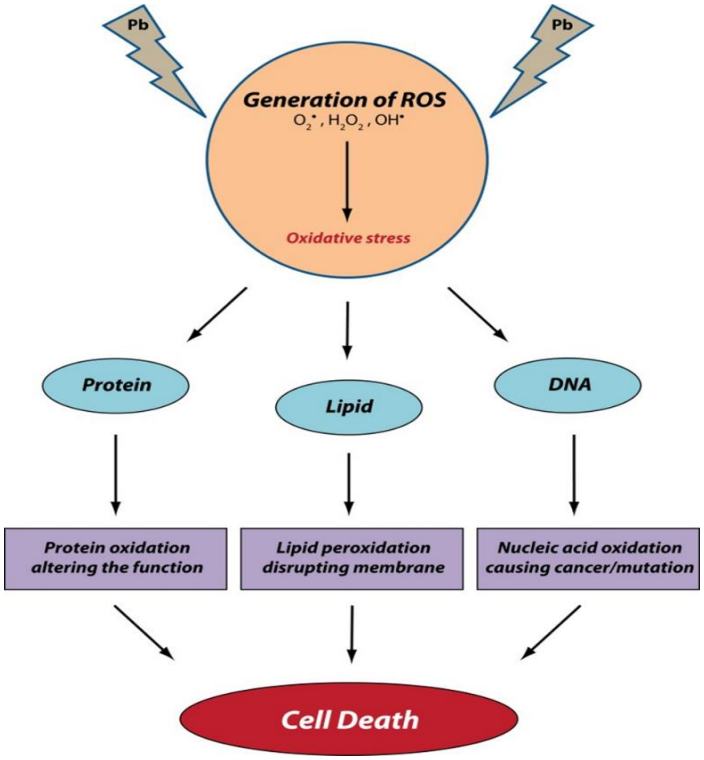

Figure 2: Possible mechanism and targets for lead-induced oxidative stress (6)

1. **Role of antioxidants in protecting Pb induced oxidative stress:**

Pb-stimulated oxidative stress is a condition in which biological system is unable to counteract the resultant effects due to the depletion of antioxidant reserves and the creation of free radicals above acceptable limits. Formation of free radicals initiates a chain reaction that leads to the oxidation of nucleic acids such as DNA and RNA, cell membrane breakdown, protein oxidation, and lipid peroxidation, ultimately resulting in the development of cancer. Research has indicated that the injection of a variety of antioxidants can stop or mitigate the harmful consequences of Pb, particularly the formation of oxidative stress. (40).

Numerous antioxidants are considered to lessen the toxicity of substances such as Pb and its associated compounds. The solubilization of poorly soluble medicines may result in enhanced biodistribution and bioavailability by a novel approach known as nano-encapsulation of antioxidants. Curcumin encapsulated in a pluronic block copolymer showed anticancer efficaciousness similar to free curcumin, along with a delayed and sustained release of curcumin. These novel methods may demonstrate potential for the treatment of numerous human ailments. A recent study revealed that puerarin stimulated the phosphorylation of Akt and GSK-3β in PC12 cells that were exposed to Pb acetate (41).

It was determined that puerarin, a phytoestrogen, could be a promising drug to cure and prevent chronic illnesses associated with Pb neurotoxicity. In yet another recent finding, betacarotene was discovered to have an antioxidant impact and exert some therapeutic benefits in lead poisoning, irrespective of chelation. Additionally, the scientists discovered that the injection of betacarotene to Pb-exposed workers resulted in a substantial reduction in homocysteine levels. N-acetylcysteine (NAC) was found to significantly reduce blood Pb levels in a group of workers who were occupationally exposed to Pb, according to a recent study (42).

Furthermore, it was demonstrated that glutamate dehydrogenase activity was greatly increased in NAC. Additionally, the treatment with NAC was shown to have normalized level of homocysteine and reduced oxidative stress. It was concluded as a result that NAC might be suggested as a different kind of treatment for chronic Pb poisoning in humans (43).

1. Natural antioxidants and the present status

It has been an important topic of research to investigate the role of naturally occurring antioxidants in quenching free radicals produced within the body under diverse pathologic situations. Research has demonstrated that antioxidants have the capacity to prevent and repair the damage caused by the production of free radicals in the body (44).

It has been discovered that vitamins, especially B, C, and E, play a very important and competitive role in preventing the toxicological signs and symptoms of lead poisoning. These vitamins have the potential to restore the pro/antioxidant balance and chelate lead out of the tissues. It has been noted how some well-known vitamins can help avoid lead toxicity:

I. Vitamin B (Pyridoxine and Thiamine)

It has been shown that vitamin B1 (thiamine) and vitamin B6 (pyridoxine)

have essential properties that can be used to cure the negative consequences of lead poisoning. An essential co-factor, pyridoxine is required for the metabolic trans-sulfuration process, which converts dietary methionine into cysteine. By encouraging the synthesis of GSH, vitamin B6 has both moderate chelating and antioxidant properties. Lead chelation by vitamin B6 may be caused by the presence of a ring in the nitrogen atom or by vitamin B6 interfering with lead absorption. Additionally, it has been noted that thiamine, or vitamin B1, protects against the immediate negative effects of lead poisoning (45).

II. Ascorbic acid (vitamin C)

Ascorbic acid is perhaps the vitamin that has been studied the most in terms of protecting against lead-induced oxidative stress. Because of its capacity to stifle ROS and metal chelation, it may function as a lead detoxifying agent 46).

III. Vitamin E (α-tocopherol)

Vitamin E is a fat-soluble vitamin that serves a variety of biological activities. It has potent anti-oxidative capabilities that block free radical chain reaction in membrane, hence stopping the peroxidation of lipids (47).

2. Recent strategies

The primary limitation of antioxidants is their inadequate bioavailability, which is a consequence of their quick clearance and limited solubility. A key barrier to clinical development is the relatively low bioavailability of most medications, even if their pharmacological safety suggests that they have great potential for the treatment and prevention of a wide range of disorders. The development of innovative strategies to address the issue of low bioavailability of these antioxidants is underway. These methods encompass enhanced formulations that facilitate improved distribution, including liposomes, micelles, phospholipid complexes, and nanoparticles (48).

A. Liposomal nanoparticles

Lipid-based nanoencapsulation methods improve effectiveness of antioxidants by minimizing undesirable interactions with other food components, increasing their bioavailability, and increasing their solubility. To deliver nutraceuticals, the main lipid-based nanoencapsulation technologies that can be used are nanoliposomes, nanocochleates, and archaeosomes. Food engineers can benefit from the exciting potential that nanoliposome technology offers, including enhanced bioavailability, stability, and shelf-life of sensitive components as well as the encapsulation and controlled release of antioxidants. A report was published regarding the utilization of nanoliposomes as carrier vehicles for food additives, food antimicrobials, enzymes, nutraceuticals, and nutrients. Liposomes are comprised of phospholipid bilayers that have contracted to create a minute bubble or vesicle(49).

B. Nanoencapsulation

Through solubilization, nanoencapsulation of antioxidants enhances the biodistribution and bioavailability of treatments that are not readily soluble. Solid nanoparticles, micelles, lipid polymer vesicles (polymersomes), and nanohydrogels are among the several vehicles that have been developed for the encapsulation and delivery of medicines. Biodegradable polymeric nanoparticles have garnered significant interest in recent years. Despite the proliferation of

synthetic and semi-synthetic polymers, natural polymers continue to be extensively employed. Among them are gums (such as guar and acacia), chitosan, gelatin, sodium alginate, and albumin. The literature has described the development of polymeric nanoparticles for the controlled release and targeted administration of functional chemicals. Polymers and surfactants are employed to synthesise them, which include chitosan, polylactic-co-glycolic acid, and alginic acid (50).

Dimercaprol and succimer are the primary treatments for lead poisoning. Given the recurrent findings about cognitive deficiencies induced by lead poisoning, particularly in youngsters, it is imperative to implement a widespread reduction in exposure. The chelating salt disodium calcium edentate, which is the calcium chelate of disodium salt of ethylene-diamine-tetracetic acid, is the standard treatment for lead poisoning (EDTA). These chelating agents exhibit a high affinity for the removal agent (51).

The lead chelate is created through exchange, as chelating agent for Pb has a higher affinity for Pb than calcium. This is subsequently eliminated by urine, resulting in the retention of innocuous calcium. In order to enhance the cognitive development of children who have been exposed to Pb, succimer was demonstrated to reduce blood Pb levels using chelation therapy. Nevertheless, succimer was discovered to be successful in lowering blood Pb levels; yet, it was unable to enhance the scores of cognitive tests (52).

Chelation therapy is sought after due to its ability to significantly reduce blood lead levels and the ease with which Pb2+ ions can be eliminated from the body through urine. Nevertheless, the use of chelating medicines is restricted to severe cases of heavy metal overexposure due to their potential adverse effects (53).

for quantitative data. The student's t-test was employed for comparing the mean of two numerical (parametric) groups. The Mann-Whitney U-test was employed for continuous non-parametric data. The significance threshold for this study was determined at 0.05.

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Sources of Exposure: The primary concern and the primary cause of Pb toxicity is occupational exposure. Pb poisoning may be a risk to both adults and children due to a range of vocations and hobbies. Metal welding, battery production and recycling, bullet salvage, and Pb smelting and refining are among the most hazardous jobs.
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Therefore, children are once more at an elevated risk of experiencing symptoms of Pb toxicity due to the fact that a bigger portion of their Pb body load is kept in regions that are actively involved in metabolism rather than the comparatively inactive bone. Part of the absorbed Pb is excreted through the bile and urine since it is not absorbed into either of these compartments. Children are more susceptible to poisoning because adults excrete a larger fraction of the substance than do children (5).

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It is indicative of an imbalance between biological system's capacity to promptly neutralize reactive intermediates or rectify the resulting harm and the creation of free radicals. It has been identified as a significant mechanism of toxicity generated by lead. The onset of oxidative stress is a result of the simultaneous operation of two distinct pathways under the influence of Pb. Firstly, the generation of reactive oxygen species (ROS) such as hydrogen peroxide (H2O2), singlet oxygen, and hydroperoxides (HO2•)

occurs, and subsequently, the antioxidant reserves are depleted. (7).as shown in **Fig.1**

Pb binds to the sulfhydryl groups in GSH, hence inactivating it. Typically, the γ-glutamyl cycle is ineffective in replenishing the GSH supply, as a consequence of the production of GSH from cysteine. Enzymes such as glutathione-S-transferase, GSH reductase (GR), δ-amino levulinic acid dehydrates (ALAD), and GSH peroxidase (GPX) are inactivated by lead, which further decreases GSH levels (9).

Super oxide dismutase (SOD) and catalase are two further antioxidant enzymes that are made inactive by lead. The scavenging of superoxide radical (O2 – •) is impaired with a reduction in SOD concentration, while the disposal of superoxide radical is reduced with a reduction in CAT. Pb has the ability to substitute zinc ions that function as critical co-factors for these antioxidant enzymes, in addition to targeting the sulfhydryl groups, so inactivating them (10).

One of the most well researched effects of ROS on lipid membranes is lipid peroxidation, which is a biomarker of oxidative stress. The cell is damaged as a result of the free radical's ability to take electrons from the lipids within the cell membranes. In addition to lipid peroxidation, Pb also induces hemoglobin oxidation, which results in the direct hemolysis of red blood cells. This is a consequence of ALAD inhibition, which leads to an elevated concentration of the substrate ALA in both blood and urine. Hydrogen peroxide and superoxide radicals are produced by these high ALA levels, which also engage in interaction with oxyhemoglobin, leading to the production of hydroxyl radicals. The cell is greatly susceptible to oxidative stress and may succumb to cell death as a result of the progression of all the aforementioned processes (11).

4. Ionic Mechanism of Pb Toxicity:

The primary explanation for the ionic mechanism of action of Pb is its ability to replace other bivalent cations, including Ca2+, Mg2+, and Fe2+, as well as monovalent cations, like Na+ (although bivalent cations are more easily substituted). This substitution process impacts a variety of fundamental biological processes in the body. Numerous key physiological functions, including Cell adhesion, apoptosis, ionic transportation, enzyme regulation, neurotransmitter release, protein folding and maturation, and intra and intercellular communication have all been profoundly affected (12).

The ionic pathway is the most major factor contributing to neurological deficits, as Pb is capable of penetrating the blood-brain barrier (BBB) at a high rate after replacing calcium ions. Pb accumulates in astroglial cells subsequent to its passage across BBB (containing Pb binding proteins). The toxic effects of Pb are particularly obvious in the developing nervous system, which is composed of young astroglial cells that lack Pb binding proteins. The juvenile astroglial cells are easily damaged by Pb, and the growth of the myelin sheath is impeded, both of which are key components of the BBB (13).

Pb has the ability to replace calcium, even at picomolar amounts, so affecting important neurotransmitters like protein kinase C, which is essential for long-term brain excitation and memory storage. In addition, it affects the concentration of sodium ions, which are crucial for a variety of biological processes, such as the regulation of the uptake and retention of calcium by synaptosomes, the generation of action potentials in excitatory tissues for the purpose of cell-to-cell communication, and the uptake of neurotransmitters (choline, dopamine, and GABA). Because of this interaction between

Pb and sodium, the sodium-dependent systems indicated above are considerably hindered in their normal operation (14).

Signs and Symptoms: The quick repercussions of organic Pb's lipid-soluble nature may render it more hazardous than inorganic Pb. Nevertheless, the Pb levels at which signs and symptoms manifest are subject to significant variation, as they are contingent upon the unknown characteristics of each individual (15).

Neuropsychiatric symptoms, including irritation, slowed reaction times, difficulty concentrating, as well as slower motor nerve conduction and headache, are induced by blood Pb levels between 25 and 60 μg/dL. High blood lead levels, which surpass 100 μg/dL, result in severe symptoms, including delirium, coma, seizures, headache, and encephalopathy signs (a disorder characterised by brain swelling) that are followed by a rise in pressure within the skull. Nevertheless, such signs are observed in children at Pb levels of 70 μg/dL or more (16).

Chronic Pb exposure typically results in the development of symptoms and signs within weeks to months; however, acute symptoms and signs may also emerge as a result of brief, intensive exposures. Intense exposure typically leads to neuromuscular symptoms and the central nervous system. Nausea, abdominal pain, coordination impairment, depression, numbness and tingling in limbs, and short-term memory impairment or focus are all symptoms of chronic exposure to lead. Chronic lead poisoning is also associated with fatigue, sleep disturbances, headaches, stupor, slurred speech, and anemia (17).

The conduct of children with chronic poisoning is typically characterized by aggression and a refusal to engage in play. Nervous system is the most frequently afflicted organ in children with lead exposure. Nevertheless, the toxicity in youngsters has a more significant effect than in adults. This is due to the fact that their tissues, both internal and exterior, are more delicate than those of adults. Adults may experience diminished cognitive performance in certain cognitive performance assessments that evaluate nervous system functioning as a consequence of prolonged exposure. Behavioral issues, learning difficulties, and a decreased IQ may be exacerbated by even low levels of Pb, which are particularly sensitive to infants and young children (18).

Pathophysiology: Pb is believed to impede the typical synaptic pruning process in early brains, which is likely the cause of the cognitive and behavioral deficits observed in young children with excessive Pb exposure, from a neurologic standpoint. Peripheral neuropathy is a prevalent symptom of chronic Pb toxicity in adults; nevertheless, the mechanism that underpins its development is still not well understood. Acute Pb encephalopathy is responsible for the most serious neurological effects of lead poisoning, such as coma and convulsions. This condition is believed to be at least partially the result of microvascular alterations in the brain caused byPb, which lead to cerebral edema and an increase in intracranial pressure(19).

Pb Toxicodynamics: Pb's toxicity is likely because of its affinity for cell membranes and mitochondria, which causes it to interfere with sodium, potassium, and calcium ATPases and mitochondrial oxidative phosphorylation. As a result, it is toxic. The activity of brain protein kinase C and calcium-dependent intracellular messengers is impaired by Pb. Furthermore, Pb induces the creation of inclusion bodies, which have the potential to move the metal into the nuclei of cells and alter the expression of certain genes (20).

Pb poisoning is caused by the metal's interaction with biological electron-donor groups, like sulfhydryl groups, which disrupts

a variety of enzyme functions. Additionally, Pb interacts with important cations, specifically calcium, iron, and zinc; it modifies cellular and mitochondrial membranes, increasing cellular fragility; and it obstructs the sodium-potassium-adenosine triphosphate (Na+/K+-ATP) pump (21).

In addition, Pb modulates the activities of other nucleotides and inhibits pyrimidine-5'-nucleotidase. The operation of nearly every organ is impacted by Pb's interference with numerous enzyme systems in the body. Symptoms of Pb toxicity that are clinically evident include those that pertain to CNS, peripheral neurological system, hematological system, digestive system, and kidney system. Devastating repercussions may result for children who are exposed to lead due to its detrimental effects on the growing brain (22).

Diagnosis: Proper diagnosis is a critical and key concern in the prevention of Pb poisoning and toxicity. It is imperative to investigate the potential pathways of exposure in order to get an accurate diagnosis. The investigation should encompass the assessment of clinical symptoms and the review of medical history. The establishment of an accurate diagnosis and treatment can be facilitated by the participation of qualified personnel, such as clinical toxicologists and medical professionals (23).

Basophilic stripping is a critical indicator of lead toxicity. This process of stripping renders the spots in RBCs visible under a microscope. Therefore, detection of Pb poisoning might be made easier by the screening of blood film for the presence of such indications. A lack of iron in the body is typical comorbidity of lead poisoning. Erythrocyte protoporphyrin (EP) measurements in blood samples can also be employed to assess lead toxicity. EP is recognized to rise with a delay of a few weeks when concentration of Pb in blood is great. Nevertheless, EP level alone is insufficiently sensitive to detect high blood Pb levels below roughly 35μg/dL (24).

4. Detection of Pb poisoning

The level of Pb in the blood can be determined by a variety of methods. The existence of alterations in blood cells that are evident under a microscope or elimination of thick lines in bones of youngsters that are observed on an X-ray are frequently used to diagnose Pb poisoning. Although the primary method for detecting heightened levels of body Pb is the detection of Pb in blood samples, this method is limited in its ability to perceive circulating Pb levels and not the quantity of Pb contained in body. Pb poisoning is indicated by blood levels of 10 μg/dL for adults and 5 μg/dL for children in whole blood (8).

5. Biomarkers of Pb exposure in humans

V. Blood and urine Pb levels as biomarkers of Pb exposure

The mechanistic relationship between Pb and the cascade of enzymatic pathways involved in heme synthesis has been elucidated in numerous literatures. Pb directly inhibits the cytoplasmic enzyme ð-aminolevulenic acid dehydrogenase (ALA-D), resulting in a negative exponential connection between ALA-D and blood-Pb. The most often used biological fluid for the measurement of Pb exposure in individuals, both for diagnostic and screening reasons, in recent years has been whole blood (25).

VI. Hepatorenal indices as biomarkers of Pb exposure

Pb exposure at elevated levels (60 μg/dL) is the primary cause of renal impairment; however, damage has been documented at lower levels (~10 μg/dL). Acute nephropathy and chronic nephropathy are the two types of renal functional abnormality that are produced by Pb. The morphological manifestation of degenerative defects in the tubular epithelium,

the appearance of nuclear inclusion bodies, which consist of Pb protein complexes, and the impairment of the functional mechanism of tubular transport are the primary defining features of acute nephropathy. (8).

VII. Hematological indices as biomarkers of Pb exposure

One of the hematological signs of Pb poisoning that was initially recognized is the basophilic stippling of erythrocytes, which is a potential biomarker for the detection of Pb toxicity. This aggregates as a result of the breakdown of ribonucleic acid. Pb directly influences the hematological system by blocking a variety of critical enzymes that are engaged in heme production pathway, hence restricting the synthesis of hemoglobin. Additionally, it diminishes the lifespan of circulating erythrocytes by enhancing fragility of cell membranes (26).

Pb poisoning can lead to two types of anemia: hemolytic anemia, which is associated with acute high-level Pb exposure, and iron deficiency anemia, which is only apparent when the blood Pb level remains significantly higher for an extended period. Other significant hematological changes that are associated with Pb-induced damage include anemia, which is defined by anisocytosis and RBC lipoperoxidation, which leads to an increase in Thrombocytopenia, leucopenia, and RBC fragility (24).

VIII. Oxidative stress markers (GSH, SOD, MT) as biomarkers of Pb exposure in humans

In a previous study, the relationship between oxidative stress biomarker and blood Pb levels was investigated. The MDA levels (9.64 µmol/L) and blood Pb levels (5.28 µg/dL) of Pb-exposed hypertension participants were significantly higher than those of control group (8.23 µmol/L and 4.41 µg/dL). Additionally, a favorable connection was seen between blood Pb levels and antioxidant indicators (GPx, CAT, SOD, and GSH). In comparison to people with normotension, the antioxidant levels in subjects with Pb-induced hypertension are decreased (27).

6. Laboratory profile intoxication

Pb poisoning should be considered in patients who present with multisystem disease due to its multiorgan toxic properties. The preservation of blood PB levels at or under 1.9 µmol/L and the regular measurement of blood Pb in Pb-exposed workers are recommended. Pb-connected anemia is typically normochromic and normocytic, It could be accompanied with stippling that is basophilic. Peripheral demyelination caused by Pb is characterized by a prolonged nerve conduction time and eventual paralysis, usually of the extensor muscles of the hands and feet (28).

A metaphysical plate of expanding long bones ("Pblines") can develop an elevated density in youngsters, which is similar to the density observed in rickets. Fanconi's syndrome, pyuria, and azotemia are occasionally observed in children who have experienced elevated Pb exposure. Chronic exposure to Pb in adults can lead to the development of chronic alterations and intranuclear inclusion bodies, as well as higher blood creatinine levels and decreased creatinine clearance rates (detected at renal biopsy) (29).

Toxicological effect of Pb

5. Effect of Pb on nervous system

The organ most vulnerable to Pb exposure is the brain. Pb significantly influences the creation of synapses in the cerebral cortex of a child who is still in the process of developing. Pb also disrupts the architecture of ion channels and the synthesis of neurochemicals, such as neurotransmitters. Pb poisoning also results in the loss of the myelin sheath of neurons, a reduction in the quantity of neurons, interference with neurotransmission, and a reduction in neuronal growth (30).

MRI images of people who were exposed to elevated Pb levels throughout their youth also demonstrate a reduction in brain volume, particularly in the prefrontal cortex. Pb can cross BBB's endothelial cells and interfere with the formation of synapses because it can act as a calcium ion substitute and be absorbed by calcium-ATPase pumps. Developmental impairments are more prevalent in children with a blood Pb content exceeding 10 µg/dL. It is at extremely low concentrations that lead has an impact on the cognitive capacities of youngsters. It seems that there is not a dose-response relationship lower threshold that is deemed safe for lead exposure. It was found that lower blood lead levels (5 µg/dL) were associated with worse academic performance (31).

Lower IQ and behavioral issues, including aggression, were observed to be connected with blood Pb levels under 10 µg/dL, in proportion to given blood lead level. An IQ decline of 2-4 points was noted in children for every µg/dL increase in blood lead levels between 5 and 35 µg/dL. Elevations in blood lead levels have also been connected to cognitive impairment and several psychiatric issues like sadness and anxiety. An increase in blood lead levels from 50 to about 100 µg/dL in adults was found to be linked to more serious issues, like chronic impairment of CNS function (32).

An additional investigation demonstrated a robust correlation between the levels of lead in preschool blood and the later developments in crime rates over the course of several decades in nine nations. Pb also interferes with the release of neurotransmitters. Neurotransmitters are substances that neurons employ to relay signals to other cells. The interruption of communication between cells is the result of this interference. Pb typically disrupts the neurotransmitter glutamate, which is essential for numerous processes, including learning. It functions by inhibiting NMDA receptors. Blocking these receptors is believed to be the primary objective of Pb toxicity. In addition to inhibiting the NMDA receptor, a study discovered that Pb exposure also reduced the quantity of the gene encoding this receptor in a specific region of the brain. In animal research, Pb was also discovered to be involved in the apoptosis of brain cells (33).

6. Effect of Pb on the skeletal system-bone

It was discovered that Pb increases the risk of osteoporosis and affects osteoblasts, osteoclasts, and chondrocytes. Osteoporosis is more prevalent among women who are experiencing menopause. Additionally, persons who are exposed to lead experience a severe fracture and recover at a significantly slower pace than those who are not (34).

7. Effect of Pb on the hematopoietic system

At BPb levels as minimal as 10 µg/dL, Pb has an immediate effect on the hematological system. It inhibits the manufacture of hemoglobin by blocking important heme synthesis-related enzymes, and it shortens erythrocyte life spans by making their cell membranes more fragile. For more information about destabilization, visit ScienceDirect's AI-generated Topic Pages. Frank's anemia is directly caused by this, which also leads to elevated blood lead levels (iron deficiency anemia). The red blood cells are destroyed at the same rate as they are produced, resulting in hemolytic anemia as a result of acute Pb exposure. δ-aminolevulinic acid dehydrates is a critical enzyme for the production of heme (ALAD). The enzyme responsible in order to synthesize porphobilinogen from δ-aminolevulinic acid is δ-ALAD, a cytoplasmic enzyme that is abundant in SH groups (ALA) (35).

Dehari-Zeka et al. demonstrated in their research that δ-ALAD is suppressed at BPb levels as minimal as 5 µg/dL, resulting in behavioral abnormalities and childhood Pb encephalopathy. The suppression of δ-ALAD leads to the buildup of δ-ALA in the plasma, which in turn causes severe neurological consequences (36).

δ- The presence of ALA in urine is also utilized as a sign of Pb exposure in industrial workers. Another mitochondrial enzyme, ferrochelatase, catalyzes the incorporation of iron (Fe^{2+}) into ring. Zn^{2+} is substituted in the event of low Fe^{2+} availability, and Pb poisoning inhibits this enzyme. Additionally, it impedes the trans-mitochondrial transfer of iron. Over 90 % of the Pb in blood is still linked to the RBC, therefore even at BPb values of 10–150 µg/dL, plasma Pb concentrations stay stable at 2-3 µg/dL. Human hemoglobin levels dropping, anemia, weight loss, pregnancy complications, kidney failure, and in extreme situations, the emergence of cancer are some of the acute effects of these Pb (37).

8. Effects on children

Pb poisoning is more prevalent in children during their developmental stages than in adults. Pb toxicity in children is predominantly asymptomatic; nevertheless, children under the age of five may exhibit symptoms such as weariness, cramping in the abdomen, nausea, agitation, and loss of appetite. Epidemiological research indicates that children with a blood lead level of B Pb (BPb) of less than 10 µg/dL are significantly impacted. The word "biomarker" refers to interactions between biological system and an external environmental agent. The extracellular matrix, neurons, and astrocytes, which are a type of glial cell in brain, comprise the physical BBB. Pb^{2+} ions rapidly cross BBB and accumulate in brain cells, as they readily replace Ca^{2+} ions (38).

Prevention and treatment of Pb accumulation in human beings

The primary objective of the preventive medicine strategy is to monitor blood levels of children who are at a great risk of exposure to lead. Medical intervention is implemented to mitigate adverse effects of poisoning and limit the accumulation of Pb in the bloodstream after Pb is identified (39).

3. Role of antioxidants in protecting Pb induced oxidative stress

Pb-stimulated oxidative stress is a condition in which biological system is unable to counteract the resultant effects due to the depletion of antioxidant reserves and the creation of free radicals above acceptable limits. Formation of free radicals initiates a chain reaction that leads to the oxidation of nucleic acids such as DNA and RNA, cell membrane breakdown, protein oxidation, and lipid peroxidation, ultimately resulting in the development of cancer. Research has indicated that the injection of a variety of antioxidants can stop or mitigate the harmful consequences of Pb, particularly the formation of oxidative stress. (40). As shown in **fig.5.**

Numerous antioxidants are considered to lessen the toxicity of substances such as Pb and its associated compounds. The solubilization of poorly soluble medicines may result in enhanced biodistribution and bioavailability by a novel approach known as nano-encapsulation of antioxidants. Curcumin encapsulated in a pluronic block copolymer showed anticancer efficaciousness similar to free curcumin, along with a delayed and sustained release of curcumin. These novel methods may demonstrate potential for the treatment of numerous human ailments. A recent study revealed that puerarin stimulated the phosphorylation of Akt and GSK-3β in PC12 cells that were exposed to Pb acetate (41).

It was determined that puerarin, a phytoestrogen, could be a promising drug to cure and prevent chronic illnesses associated with Pb neurotoxicity. In yet another recent finding, betacarotene was discovered to have an antioxidant impact and exert some therapeutic benefits in lead poisoning, irrespective of chelation. Additionally, the scientists discovered that the injection of betacarotene to Pb-exposed workers resulted in a substantial reduction in homocysteine levels. N-acetylcysteine (NAC) was found to significantly reduce blood Pb levels in a group of workers who were occupationally exposed to Pb, according to a recent study (42).

Furthermore, it was demonstrated that glutamate dehydrogenase activity was greatly increased in NAC. Additionally, the treatment with NAC was shown to have normalized level of homocysteine and reduced oxidative stress. It was concluded as a result that NAC might be suggested as a different kind of treatment for chronic Pb poisoning in humans (43).

4. Natural antioxidants and the present status

It has been an important topic of research to investigate the role of naturally occurring antioxidants in quenching free radicals produced within the body under diverse pathologic situations. Research has demonstrated that antioxidants have the capacity to prevent and repair the damage caused by the production of free radicals in the body (*44)*.

It has been discovered that vitamins, especially B, C, and E, play a very important and competitive role in preventing the toxicological signs and symptoms of lead poisoning. These vitamins have the potential to restore the pro/antioxidant balance and chelate lead out of the tissues. It has been noted how some well-known vitamins can help avoid lead toxicity:

IV. Vitamin B (Pyridoxine and Thiamine)

It has been shown that vitamin B1 (thiamine) and vitamin B6 (pyridoxine) have essential properties that can be used to cure the negative consequences of lead poisoning. An essential co-factor,

pyridoxine is required for the metabolic trans-sulfuration process, which converts dietary methionine into cysteine. By encouraging the synthesis of GSH, vitamin B6 has both moderate chelating and antioxidant properties. Lead chelation by vitamin B6 may be caused by the presence of a ring in the nitrogen atom or by vitamin B6 interfering with lead absorption. Additionally, it has been noted that thiamine, or vitamin B1, protects against the immediate negative effects of lead poisoning (45).

V. Ascorbic acid (vitamin C)

Ascorbic acid is perhaps the vitamin that has been studied the most in terms of protecting against lead-induced oxidative stress. Because of its capacity to stifle ROS and metal chelation, it may function as a lead detoxifying agent 46).

VI. Vitamin E (α-tocopherol)

Vitamin E is a fat-soluble vitamin that serves a variety of biological activities. It has potent anti-oxidative capabilities that block free radical chain reaction in membrane, hence stopping the peroxidation of lipids (47).

5. Recent strategies

The primary limitation of antioxidants is their inadequate bioavailability, which is a consequence of their quick clearance and limited solubility. A key barrier to clinical development is the relatively low bioavailability of most medications, even if their pharmacological safety suggests that they have great potential for the treatment and prevention of a wide range of disorders. The development of innovative strategies to address the issue of low bioavailability of these antioxidants is underway. These methods encompass enhanced formulations that facilitate improved distribution, including liposomes, micelles, phospholipid complexes, and nanoparticles (48).

C. Liposomal nanoparticles

Lipid-based nanoencapsulation methods improve effectiveness of antioxidants by minimizing undesirable interactions with other food components, increasing their bioavailability, and increasing their solubility. To deliver nutraceuticals, the main lipid-based nanoencapsulation technologies that can be used are nanoliposomes, nanocochleates, and archaeosomes. Food engineers can benefit from the exciting potential that nanoliposome technology offers, including enhanced bioavailability, stability, and shelf-life of sensitive components as well as the encapsulation and controlled release of antioxidants. A report was published regarding the utilization of nanoliposomes as carrier vehicles for food additives, food antimicrobials, enzymes, nutraceuticals, and nutrients. Liposomes are comprised of phospholipid bilayers that have contracted to create a minute bubble or vesicle(49).

D. Nanoencapsulation

Through solubilization, nanoencapsulation of antioxidants enhances the biodistribution and bioavailability of treatments that are not readily soluble. Solid nanoparticles, micelles, lipid polymer vesicles (polymerases), and nanohydrogels are among the several vehicles that have been developed for the encapsulation and delivery of medicines. Biodegradable polymeric nanoparticles have garnered significant interest in recent years. Despite the proliferation of synthetic and semi-synthetic polymers, natural polymers continue to be extensively employed. Among them are gums (such as guar and acacia), chitosan, gelatin, sodium alginate, and albumin. The literature has described the development of

polymeric nanoparticles for the controlled release and targeted administration of functional chemicals. Polymers and surfactants are employed to synthesize them, which include chitosan, polylactic-co-glycolic acid, and alginic acid (50).

Dimercaprol and succimer are the primary treatments for lead poisoning. Given the recurrent findings about cognitive deficiencies induced by lead poisoning, particularly in youngsters, it is imperative to implement a widespread reduction in exposure. The chelating salt disodium calcium edentate, which is the calcium chelate of disodium salt of ethylene-diamine-tetracetic acid, is the standard treatment for lead poisoning (EDTA). These chelating agents exhibit a high affinity for the removal agent (51).

The lead chelate is created through exchange, as chelating agent for Pb has a higher affinity for Pb than calcium. This is subsequently eliminated by urine, resulting in the retention of innocuous calcium. In order to enhance the cognitive development of children who have been exposed to Pb, succimer was demonstrated to reduce blood Pb levels using chelation therapy. Nevertheless, succimer was discovered to be successful in lowering blood Pb levels; yet, it was unable to enhance the scores of cognitive tests (52).

Chelation therapy is sought after due to its ability to significantly reduce blood lead levels and the ease with which Pb2+ ions can be eliminated from the body through urine. Nevertheless, the use of chelating medicines is restricted to severe cases of heavy metal overexposure due to their potential adverse effects (53).

CONCLUSION

Lead (Pb) is a highly toxic heavy metal that poses a threat to people's physical health worldwide. The central nervous system (CNS) is the most vulnerable to lead toxicity. the mechanisms of lead-induced neurological disorders, are oxidative stress and ion dyshomeoistasis. Chelation therapy is the primary therapeutic method for lead poisoning. It includes removing lead from various body sites through urine. Natural antioxidants, such as vitamins, have been shown to prevent and treat lead-induced neurological disorders. Nanoencapsulation or liposome-mediated medication administration is a recent addition to preventive regimens to address low systemic bioavailability of natural hydrophobic antioxidants.

RECOMMENDATIONS

Pb exposure can have a variety of toxicological effects, particularly on the central nervous system. To provide appropriate management, physicians must be aware of the toxicological effects of lead.Additional molecular and pathophysiological research is needed to understand the mechanisms of Pb-induced neurotoxicity.

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