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Lead Exposure and Cardiovascular Dysfunction: Molecular Insights and Clinical Evidence

Muhammad Irfan Shahzad Anjum (Corresponding Author)
PGR Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan. dralishahzad567@gmail.com

Muhammad Imran Sajid
PGR Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan.

Maham Riaz
PGR Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan.

Muhammad Ayaz Arshad
PGR Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan.

Aasim Ali Sajid
Department of Medicine, CMH, Multan Institute of Medical Sciences, Pakistan.

Author Details

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Corresponding E-mail & Author*:

Muhammad Irfan Shahzad Anjum
PGR Cardiology, Faisalabad Institute of Cardiology, Faisalabad, Pakistan. dralishahzad567@gmail.com

Abstract

Exposure to lead (Pb) continues to be a significant environmental health problem and is now known to play a significant role in cardiovascular disease (CVD). The aim of this review is to highlight the current knowledge regarding the molecular mechanisms and clinical implications of cardiovascular toxicity of lead. The main routes of exposure to lead are inhalation and ingestion, it is a long-term source of internal exposure because it is bioaccumulated in soft tissues and bone. Lead can cause oxidative stress, endothelial dysfunction, disruption of calcium signaling, chronic inflammation, mitochondrial impairment, and epigenetic changes all of which lead to vascular and myocardial injury. Lead exposure has been consistently associated with increased cardiovascular mortality, heart failure, stroke, coronary artery disease, and hypertension in epidemiological studies. Interestingly, there is no safe threshold for blood lead levels (BLL) since adverse CV effects have been reported at levels < 5µg/dl. In order to implement effective prevention strategies, to better define the risk of cardiovascular dysfunction, and to diminish the burden of cardiovascular dysfunction caused by environmental exposure, the complex relationship between the exposure to lead and cardiovascular dysfunction has to be understood.

1. INTRODUCTION

Globally, cardiovascular diseases (CVDs) are the leading cause of death, and they cause significant proportion of premature death and disability in the world (Lababidi et al. 2023). Although hypertension, dyslipidemia, diabetes mellitus, smoking, and obesity are classic risk factors, environmental toxicants are now known to have a significant,

and underrecognized, role in cardiovascular pathophysiology. Of these, one of the most persistent and relevant cardiovascular toxicants at low environmental concentrations is lead (Pb) exposure (Vaduganathan et al., 2022). Although lead levels in the atmosphere have dropped worldwide since the 1990s due to reduced emissions from industries and consumption of lead-based paints and pipes, the presence of lead in soil, water supplies, workplaces, and older homes and buildings remains one of the greatest public health challenges (Li et al., 2021).

Lead is a heavy metal that is highly toxic and has no known physiological function in the human body. It is bio accumulative, highly persistent in biological systems and has a multi-organ toxic effect with special reference to the nervous, renal, haematopoietic and cardiovascular systems (Bibi et al., 2023). Notably, new epidemiological and toxicological research has shown that there is no safe level for lead exposure; even low BLLs have been linked to higher cardiovascular morbidity and mortality (Nucera et al., 2024). Chronic exposures to lead have been shown in large-scale population studies to be associated with dose-related increases in risk of hypertension, coronary artery disease, stroke, and heart failure, and thus are considered a non-traditional, but important, cardiovascular risk factor (Bhattacharya, 2022).

The mechanism of cardiovascular dysfunction induced by lead is multifaceted and complicated, including oxidative stress, endothelial damage, inflammatory response, calcium signalling alteration, and mitochondrial dysfunction (Generalova et al., 2025). A major pathway is the overproduction of reactive oxygen species (ROS) and reduction of endogenous antioxidant systems causing vascular endothelial cell oxidative damage and smooth muscle dysfunction. This oxidative imbalance can lead to endothelial dysfunction, one of the early stages of atherogenesis and vascular remodelling. In addition, lead is capable of mimicking or interfering with two divalent cations, calcium (Ca^{2+}) and zinc (Zn^{2+}), thus affecting intracellular signaling pathways, which influence the vascular tone, myocardial contractility, and electrophysiological stability (Doligalska-Dolina et al., 2025; Samanth, 2024).

Lead exposure at the cellular level has been found to alter endothelial nitric oxide (NO) bioavailability which leads to vasoconstriction, increased peripheral vascular resistance, and hypertension (Fiorim et al., 2020). At the same time, lead disturbs lipid metabolism and stimulates low-density lipoprotein (LDL) oxidation, leading to the development of foam cells and atherosclerotic plaques. Recent experimental studies also indicate direct effects of lead on cardiac myocytes, including changes of calcium-dependent excitation–contraction coupling, modification of myosin kinetics, and changes of myocardial structure (Rajpoot et al., 2024). In addition, in recent molecular studies, it has been shown that lead can affect the bioenergetics of mitochondria, causing ATP depletion and the activation of apoptotic signalling pathways in cardiomyocytes (Chlubek and Baranowska-Bosiacka, 2024).

Lead exposure triggers direct vascular and myocardial toxicity as well as is strongly linked to systemic inflammation and immune dysfunction. Chronic exposure leads to upregulation of pro-inflammatory cytokines and adhesion molecules, which promotes adhesion of leukocytes to the endothelium and increases vascular damage (Harshitha et al., 2024). These processes all promote a pro-atherogenic environment. In addition, oxidative stress caused by lead has been linked to the activation of redox-sensitive transcription factors such as NF-κB that further exacerbates inflammatory cascades within the cardiovascular system (Wang et al., 2020).

Cardiovascular outcomes of lead exposure are becoming more apparent in the clinic. Blood lead levels (BLL) have been consistently linked with high blood pressure, coronary heart disease (CHD) risk, and subclinical cardiovascular injury markers like elevated high-sensitivity cardiac troponins and natriuretic peptides (Lamas et al., 2021). Significantly, the cardiovascular risk measured in populations with “acceptable” environmental exposure levels is also measurable, further supporting the notion that

lead is a continual cardiovascular stressor throughout the lifespan (Blaustein et al., 2024).

Although considerable progress has been made in the knowledge of the toxicology of lead, there are some gaps that still need to be addressed. There is still a lag time between molecular mechanisms and clinical cardiovascular endpoints, especially regarding the long-term cardiac remodelling and low dose chronic exposure (Lind et al., 2021). Furthermore, little is known about the synergism between lead and other environmental contaminants and metabolic risk factors. Hence, a thorough integration of available data is needed to connect mechanistic toxicology and clinical cardiology (Liu et al., 2023; Zong et al., 2025).

The purpose of this review is to carefully summarize and critically discuss the available scientific data regarding the molecular and cellular mechanisms underlying the cardiovascular dysfunction caused by lead, including oxidative stress, endothelial dysfunction, mitochondrial dysfunction and disruption of calcium signaling, and to relate these mechanisms to the epidemiological and clinical effects. This book aims to combine the experimental and clinical data and create a comprehensive picture of the role of chronic lead exposure in progression of cardiovascular diseases, and to emphasize future directions for prevention and therapeutic intervention strategies.

2. SOURCES AND PATHWAYS OF LEAD EXPOSURE

Despite the regulatory efforts to reduce lead (Pb) use, exposure to lead remains a large global health burden. It is persistent in the environment and susceptible to bioaccumulation, producing chronic toxicity, especially in the cardiovascular system, continually (Collin et al., 2022). The major environmental source of lead is contaminated soil and dust, which are largely from the use of leaded gasoline, industrial pollution and decay of lead-based paints (Kumar et al., 2020). These residues persist for decades and are involved in exposure by inhalation and ingestion of the resuspended dust, particularly in urban and industrial settings. An important pathway is drinking water contamination through corrosion of lead pipes, solder and plumbing systems. Low levels of lead in water can substantially contribute to chronic exposure, especially for populations lacking effective water treatment systems (Roy et al., 2024).

Another source of lead exposure is contaminated food crops that are grown in polluted soil or water. Additionally, the use of inadequate containers for food processing and storage can contribute to higher lead exposure levels, especially in areas with limited resources (Hamoud et al., 2024). Occupational exposure is still an important risk factor. Exposure primarily occurs through inhalation of the lead fumes and dust among workers engaged in battery manufacturing, smelting, welding, construction and informal e-waste recycling (Ali et al., 2022). This risk is further exacerbated by a lack of sufficient safety measures and poor regulation in developing areas. In addition, new sources like e-waste recycling, traditional medicines, and artisanal industries are increasingly being recognized as important sources of exposure in LMC states (Lebbie et al., 2021).

Once inhaled or ingested, lead enters the blood and is free to bind to the erythrocyte,as well as to soft tissues and bone where it is stored for many years. The skeletal reservoir is a long-term internal source that releases lead back into circulation upon aging, pregnancy or physiological stress, resulting in chronic exposure (Aktepe et al., 2022). Lead is ubiquitous in environmental, dietary, and occupational sources, and its long biological persistence means that exposure is continuous and at low doses, and is strongly associated with long-term cardiovascular dysfunction (Generalova et al., 2025).

3. ABSORPTION, DISTRIBUTION AND TOXICOKINETICS OF LEAD

The toxicokinetics of lead (Pb) is complex, with high absorption efficiency, extensive systemic distribution and long biological half-life, which imparts persistence as a cardiovascular toxicant (Ali et al., 2024). The main pathways for human exposure are inhalation (which can be very efficient in an occupational environment) and ingestion (via food, water, and dust) (Generalova et al., 2025). The gastrointestinal absorption of

lead is very variable and age and nutritional status are important factors affecting absorption. The absorption of lead is 40-50% in children and 10-15% in adults; thus, children are more susceptible to systemic toxicity, even at low exposures. The combined action of deficiencies in calcium, iron, and zinc also increases gastrointestinal uptake, thereby adding to the systemic lead burden (Del Rio, 2021).

Lead is quickly carried to other tissues in the blood; over 95% of it is bound to hemoglobin associated proteins and erythrocytes. This strong affinity for red blood cells allows systemic circulation and enhances the duration of exposure of vascular and cardiac tissues (Michel and Martin-Ventura, 2020). The smaller fraction is located in plasma, which is thought to be the biologically active fraction and is responsible for tissue toxicity. The lead then migrates to other soft tissues such as liver, kidneys, brain, and cardiovascular system, but most will eventually settle in bone tissue, the major long-term repository of lead in body, where more than 90% of body lead is stored in chronically exposed persons. Lead is stored in bone for decades, substituting calcium in the hydroxyapatite matrix of bone (Balali-Mood et al., 2021; Sani and Amanabo, 2021).

One of the most important toxicological properties of lead is that it can be remobilized into the bloodstream when there is increased bone turnover, as occurs during pregnancy, lactation, ageing, osteoporosis, and in individuals with chronic diseases (Widestrom, 2022). This endogenous release provides a secondary source of exposure even if the environmental exposure is not continuing. In general, lead can be considered as "time-bomb toxicant" as the effects of the initial exposures may be experienced years later due to slow elimination and continual internal recycling (Aslam et al., 2021). The long biological half-life and bone storage system are key to its chronic toxicity to the cardiovascular system, resulting in persistent vascular endothelial damage, vascular dysfunction, and development of progressive cardiovascular disease (Ortega et al., 2021).

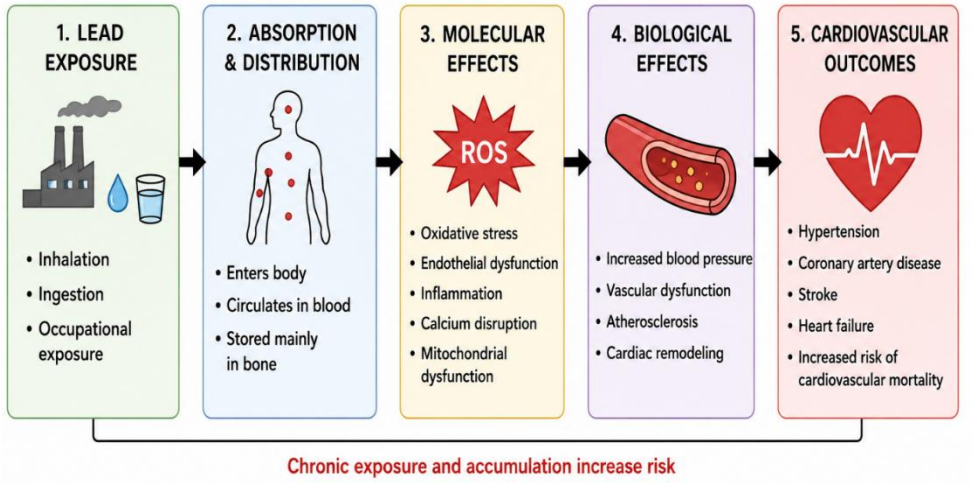

Figure 1. ***Overview of the progression from lead exposure to cardiovascular disease. Lead enters the body through inhalation or ingestion, undergoes systemic distribution and bone storage, triggers molecular and biological alterations, and ultimately contributes to hypertension, coronary artery disease, stroke, and heart failure.***

4. MOLECULAR MECHANISMS OF CARDIOVASCULAR TOXICITY

Cardiovascular toxicity caused by lead (Pb) can be attributed to a complex network of molecular and cellular disruptions. Lead has a multi-faceted action, disrupting redox balance, endothelial signaling, ionic balance, inflammation control and mitochondrial function. All of these mechanisms work together to contribute to vascular dysfunction,

myocardial injury, and the progressive cardiovascular disease (Dzugkoev et al., 2022; Wu et al., 2025).

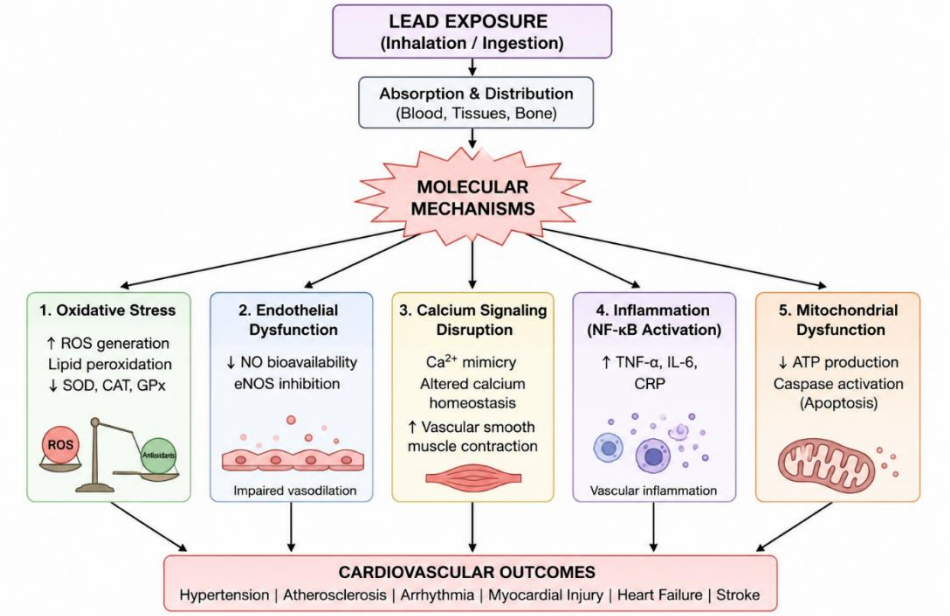

Figure 2. ***Integrated molecular mechanisms of lead-induced cardiovascular toxicity, highlighting oxidative stress, endothelial dysfunction, calcium dysregulation, inflammation, and mitochondrial injury leading to major cardiovascular outcomes.***

4.1. Oxidative Stress and ROS Generation

Oxidative stress is one of the main mechanisms of the cardiovascular effects of lead. Lead exposure increases the production of ROS such as superoxide anions and hydrogen peroxide and at the same time reduces the activity of the endogenous antioxidant defense mechanism (Vaziri and Sica, 2004). This imbalance causes lipid peroxidation of cellular membranes, protein oxidation and DNA damage in vascular endothelial and smooth muscle cells. An important effect of lead toxicity is the reduction of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). This decrease of these enzymatic defenses enhances the oxidative injury and increases the endothelial cell dysfunction. Oxidative stress also leads to an increase in the degradation of nitric oxide (NO) in vascular tissues, thus directly connecting oxidative stress to impaired vasodilation and hypertension (Navabpour et al., 2020; Turkington et al., 2025).

4.2. Endothelial Dysfunction

A major feature of lead induced cardiovascular disease is endothelial dysfunction. High exposure to lead markedly decreases nitric oxide (NO) generation and bioavailability, which plays a crucial role in regulating vascular tone, platelet aggregation and smooth muscle proliferation (Tubsakul et al., 2021). The mechanism of action is oxidative inactivation of endothelial nitric oxide synthase (eNOS) or by interfering with calcium dependent signaling necessary to generate NO (Pourbagher-Shahri et al., 2021). This leads to NO deficiency, which causes vasoconstriction, an increase in peripheral vascular resistance and early atherogenic changes. Endothelial injury also increases the expression of adhesion molecules that promotes the adhesion of leukocytes and vascular inflammation (Aleksandrowicz et al., 2025).

4.3. Calcium Signalling Disruption

The toxicological effects of lead are high, because it can mimic and compete with calcium ions (Ca^{2+}) because of their close physico-chemical properties. This calcium mimicking, interferes with the intracellular signalling pathways in vascular smooth muscle cells and cardiomyocytes (Park, 2025). Lead interferes with calcium channels and calcium dependent enzymes to disrupt the excitation contraction coupling in cardiac muscle and cause the abnormal contraction of vascular smooth muscle. This

leads to greater vascular tone, hypertension and decreased cardiac electrophysiological stability. Thus, alteration in calcium homeostasis is an important mechanism by which lead is associated with vascular and myocardial dysfunction (Dai and Khalil, 2025; Shah et al., 2022).

4.4 Inflammation and NF-κB Activation

Chronic lead exposure leads to a chronic pro-inflammatory response by activation of redox sensitive transcription factors, especially the nuclear factor kappa B (NF-κB). This activation leads to increased expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (Parchwani et al., 2025). These inflammatory mediators are involved in endothelial activation, vascular remodelling and accelerating the process of atherosclerotic plaque formation. In addition, inflammation can compound the oxidative stress and thus promote a vicious cycle of vascular injury. It is now known that persistent low-grade inflammation is one of the factors involved in cardiovascular risk from lead exposure (Kostenko et al., 2023).

4.5. Mitochondrial Dysfunction and Apoptosis

Chronic lead exposure leads to a chronic pro-inflammatory response by activation of redox sensitive transcription factors, especially the nuclear factor kappa B (NF-κB). This activation leads to increased expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (Parchwani et al., 2025). These inflammatory mediators are involved in endothelial activation, vascular remodelling and accelerating the process of atherosclerotic plaque formation. In addition, inflammation can compound the oxidative stress and thus promote a vicious cycle of vascular injury. It is now known that persistent low-grade inflammation is one of the factors involved in cardiovascular risk from lead exposure (Kostenko et al., 2023).

Table 1. Molecular mechanisms involved in lead-induced cardiovascular dysfunction

Mechanistic Pathway	Molecular Targets / Changes	Cardiovascular Outcome
Oxidative Stress	↑ ROS, ↓ SOD, ↓ CAT, ↓ GPx, lipid peroxidation	Endothelial injury, hypertension
Endothelial Dysfunction	↓ eNOS activity, ↓ NO bioavailability	Vasoconstriction, atherosclerosis
Calcium Signalling Disruption	Ca^{2+} mimicry, altered ion channel function	Arrhythmia, vascular hyperreactivity
Inflammation (NF-κB pathway)	↑ TNF-α, IL-6, CRP	Vascular inflammation, plaque formation
Mitochondrial Dysfunction	↓ ATP production, cytochrome c release	Cardiomyocyte apoptosis, heart failure

4.6. Integrated Mechanistic Perspective

These are all interconnected processes of oxidative stress, endothelial dysfunction, calcium signaling disruption, inflammation and mitochondrial injury. Lead toxicity is a cumulative and progressive process of lead-induced molecular abnormalities and eventually causes chronic cardiovascular dysfunction, vascular stiffness, and hypertension, atherosclerosis, and cardiac failure (Pang et al., 2024; Roy, 2025).

5. CLINICAL AND EPIDEMIOLOGICAL EVIDENCE

The link between lead exposure and harmful cardiovascular events in humans is consistently supported by a large body of epidemiological studies, consistent with the mechanistic studies in experimental models (Joffre and Hellman, 2021). This is consistently shown by large population-based cohorts and meta-analyses, and even at

low level environmental exposure, lead is shown to be an independent risk factor for cardiovascular disease (Liu et al., 2025).

5.1. Hypertension (Dose-Dependent Association)

The cardiovascular outcome that is most consistently reported as associated with lead exposure is hypertension. There have been several epidemiological studies showing positive dose–response relationships between blood lead levels and both systolic and diastolic blood pressure. Endothelial dysfunction, oxidative stress and impaired nitric oxide signaling are involved in the mechanism of increased vascular resistance due to lead exposure. Importantly, evidence suggests that there is no safe threshold for lead exposure, as there are measurable increases in blood pressure at low blood lead concentrations (Chen et al., 2021).

5.2. Coronary Artery Disease

Increased risk for coronary artery disease (CAD) has also been associated with lead exposure. Endothelial injury, lipid oxidation and chronic low-grade inflammation are mechanisms by which chronic exposure leads to atherosclerosis. These processes promote the formation of plaque and plaque instability and, therefore, myocardial ischemia. CAD prevalence and mortality rate were higher in people who have a higher cumulative lead burden, especially among occupational groups, as reported in population studies (Jani, 2024; Podkowińska and Formanowicz, 2020).

5.3. Stroke Risk

There are several large-scale epidemiological analyses that show that there is a significant relationship between lead exposure and stroke rates including both ischemic and haemorrhagic types. These mechanisms are vascular stiffness, hypertension and accelerated atherosclerotic process in cerebral vessels. Endothelial dysfunction adds to the vulnerability of the cerebrovascular system and poor autoregulation (Deng et al., 2024; Harshfield et al., 2020)..

5.4. Heart Failure Risk

There is emerging evidence of the relationship between chronic lead exposure and the development of heart failure. Progressive myocardial remodelling and impaired myocardial contractility is associated with lead related myocardial toxicity, mitochondrial dysfunction, and oxidative injury. Possible subclinical myocardial injury due to chronic exposure can culminate in clinical heart failure, especially in those with concurrent cardiovascular risk factors (Chen et al., 2021).

5.5. Biomarkers and Subclinical Cardiovascular Injury

Clinical studies have demonstrated changes in a number of cardiovascular markers with exposure to lead such as elevated C-reactive protein (CRP), increased oxidative stress markers, and subtle changes in cardiac injury markers like high-sensitivity troponins. Moreover, elevated both systolic and diastolic blood pressure are early functional markers for vascular impairment. Such biomarker alterations align with the notion that lead exposure triggers subclinical cardiovascular damage prior to the onset of disease symptoms (Garady et al., 2024; Xu et al., 2025).

Table 2. Clinical outcomes and biomarkers associated with lead exposure

Cardiovascular Outcome	Epidemiological Evidence	Associated Biomarkers / Indicators
Hypertension	Strong dose-dependent association even at low BLL	↑ SBP, ↑ DBP
Coronary Artery Disease	Increased risk in chronic exposure cohorts	↑ CRP, lipid oxidation markers
Stroke	Elevated risk (ischemic & hemorrhagic)	Endothelial dysfunction markers
Heart Failure	Linked with long-term exposure and remodeling	↑ Troponin, BNP changes

Subclinical Injury	Observed even at BLL <5 µg/dL	↑ oxidative stress markers

5.6. Critical Perspective

One of the most consistent findings in the epidemiological literature is that even low levels of blood lead (<5 µg/dL) are connected to elevated cardiovascular risk, a risk previously attributed to only high blood lead levels. This presents a paradigm shift in how to consider lead as a no threshold cardiovascular toxicant, and challenges conventional toxicological thresholds. Combined with mechanistic and clinical data, the role of chronic low dose exposure in the global burden of cardiovascular disease appears to be a significant one, especially among vulnerable populations (Lamas et al., 2021; Wang et al., 2023).

6. GENE–ENVIRONMENT AND EPIGENETIC EFFECTS

In addition to the classical toxicological pathways, there is growing evidence of gene–environment interactions and epigenetic modifications induced by exposure to lead (Pb) that may account for the increased susceptibility to cardiovascular outcomes after cessation of exposure. These mechanisms are now known to be a key link between environment and long-term disease phenotypes (Thakur et al. 2025; Cuomo et al. 2022).

6.1 DNA Methylation Changes

DNA methylation changes have been seen in genes related to oxidative stress regulation, inflammation and vascular homeostasis, and are associated with lead exposure. Disordered methylation may result in the inactivation of protective genes or the activation of pro-inflammatory pathways, and be involved in endothelial dysfunction and vascular remodelling. Importantly, the epigenetic changes could last long after the exposure, pointing to a "molecular memory" effect of lead toxicity (Meng et al., 2022).

6.2 Histone Modifications

The influence of lead on chromatin structure can also be mediated by histone modification such as changes in the acetylation and methylation status of histones. The changes include changes in gene transcription for antioxidant defense systems, nitric oxide signaling, and inflammatory responses. Therefore, the disruption of the regulation of histone can further enhance the oxidative stress and endothelial damage, thereby reinforcing the transcriptional level cardiovascular dysfunctions (Shvedunova and Akhtar, 2022; Zhang et al., 2020).

6.3 microRNA (miRNA) Regulation

The mechanism of dysregulation of microRNAs (miRNAs) is another important epigenetic mechanism which plays a pivotal role among the factors involved in the regulation of gene expression in post-transcriptional level. Disruption of miRNA signaling pathways related to endothelial function, lipid metabolism, and inflammatory signaling has been found in association with lead exposure. These miRNA alterations could play a role in endothelial activation, vascular inflammation, and atherogenesis, further supporting the mechanism that lead exposure is associated with cardiovascular disease (Tumolo et al., 2022; Wallace et al., 2020).

6.4 Transgenerational and Developmental Effects

Especially important is the possibility of transgenerational epigenetic inheritance. Epigenetic changes caused by lead in germ cells may be passed on to future generations, raising the risk for cardiovascular and metabolic diseases in future generations. Moreover, prenatal exposure and early life exposure can permanently alter cardiovascular regulatory pathways, having a long-term impact on blood pressure regulation and vascular structure in adulthood (Cuomo et al., 2022).

6.5. Integrated Perspective

Collectively, epigenetic mechanisms provide a deeper understanding of how lead exposure translates environmental insult into long-lasting biological effects. These changes have the potential to exacerbate oxidative stress and inflammation and also add a genetic and chronic cardiovascular risk component to lead exposure, making it a real

"environmental programming toxicant." The growing body of evidence is a strong argument for the need for more stringent exposure limits and early preventative measures (Sarigiannis et al., 2025; Tamagno and Freeman, 2025).

7. PUBLIC HEALTH AND PREVENTIVE STRATEGIES

Lead (Pb) is a persistent environmental contaminant with cumulative toxicity impacts that require a multifaceted public health strategy to address cardiovascular risk at the population level. The best method of action is prevention, since once systemic lead accumulations occur, they are generally irreversible (Zafar et al., 2025). One of the critical interventions is to phase out lead sources with policies and regulations. This involves enforcing restrictions on leaded gas, control of industrial emissions, and elimination of lead-based paints and water pipes (Sullivan and Green, 2020). Additionally, contaminated soil and water systems must be cleaned up, to minimize long-term exposure in high-risk areas. Blood lead level (BLL) screening programs are critical for early detection especially in occupationally exposed populations and children. Regular monitoring allows early detection of high levels of exposure and helps to implement intervention measures in time before irreversible cardiovascular damage is done (Chen, 2022; Schmits-Earley, 2024).

Ca, Fe and Zn have a protective effect when it comes to nutrition, as they will compete with gastrointestinal absorption of lead, by acting as competitive inhibitors (Katimba et al., 2024). Nutrient deficiencies in populations can increase their risk of systemic lead exposure, underscoring the role of nutrition interventions as a cost-effective and preventative measure, particularly in low-income countries (Shenoy et al., 2023). Moreover, the use of occupational safety measures plays an important role in minimising exposure for high-risk workers. These range from PPE usage, to the improvement of industrial ventilation, to workplace hygiene and the monitoring of compliance with regulations. It is especially vital to strengthen occupational health policies in developing countries where informal industries are a major source of lead exposure (Poudel et al., 2024)..

8. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite the large body of evidence that has shown the association between lead exposure and cardiovascular dysfunction, there remains a number of critical areas of missing knowledge and understanding that impede full mechanistic and clinical understanding of this association. One of the drawbacks is the absence of large-scale, long-term cohorts in developing countries where exposure is still relatively high and environmental monitoring is limited. The available evidence is largely from cross-sectional or retrospective studies, so there is limited ability to draw causal conclusions about long-term cardiovascular outcomes. Another unresolved question is what is the threshold for BLL that is safe. New evidence indicates that exposure levels as low as <5 μg/dL are linked to cardiovascular risk, especially in the context of the current regulatory framework that fails to incorporate contemporary epidemiological evidence, which suggests the need for a new, contemporary framework for exposures. Little is known about the interaction between lead exposure and other comorbidities like chronic kidney disease (CKD) or diabetes mellitus (DM) and smoking. These conditions can interactively exacerbate the effects of oxidative stress and vascular injury, which could further amplify lead-induced cardiovascular toxicity.

There is also a strong demand to develop the biomarkers based early detection strategies such as oxidative stress markers, inflammatory cytokines, and epigenetic signatures to detect subclinical CV injury before the onset of clinical disease. These would have huge impact on risk stratification and early intervention. There is potential to better understand individual susceptibility and the gene–environment interactions and mechanistic pathways of lead toxicity through advances in precision toxicology and the multi-omics (genomics, epigenomics, proteomics and metabolomics) approaches. These strategies could be integrated in the future, which may help to deliver future personalized risk assessment and targeted preventive strategies.

CONCLUSION

Lead is also a major but underappreciated risk factor for cardiovascular diseases globally. Experimental, clinical, and epidemiological studies have led to the accumulation of evidence supporting a range of interconnected mechanisms that explain the adverse cardiovascular effects of exposure to lead: oxidative stress, endothelial dysfunction, disruption of calcium signalling, chronic inflammation, mitochondrial impairment, and epigenetic modifications. These molecular changes lead to cardiovascular injury, hyper tension, atherosclerosis, myocardial damage and heart failure, which in turn lead to cardiovascular morbidity/mortality. Importantly, recent evidence suggests that cardiovascular risks are seen at BLL's previously thought to be safe, highlighting the lack of a completely safe level for lead exposure. The chronic toxic effects of lead are enhanced by its tendency to become mobilized slowly from the bone, with a long-term accumulation. While significant strides have been made in the knowledge and understanding of the cardiovascular toxicity associated with lead, there are still significant gaps in knowledge about low dose exposure, gene environment interactions, and susceptibility in vulnerable populations. This review will benefit for future studies that combine the longitudinal, biomarker discovery, and precision toxicology methods to enhance risk assessment and targeted preventive strategies. Prevention of environmental and occupational lead exposure should continue to be a worldwide concern for reducing the burden of cardiovascular disease.

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