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Lead, cadmium, and mercury exposure in Iraq: A review of clinical biochemical alterations and renal oxidative stress biomarkers

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Abstract

Heavy metal elements are thought to cause environmental pollution and adverse effects on the health of people in Iraq due to their prolonged wars, industries, low quality of drinking water, and agriculture methods. Examples of heavy metals include Pb, Cd, and Hg, and they are known to cause severe nephrotoxicity in different biological systems through multiple mechanisms that include oxidative stress, inflammation, and mitochondrial dysfunctions. This review paper will address the current knowledge about heavy metals toxicity and the biochemical changes occurring due to this condition in humans from the Middle East, especially in Iraq. In particular, this paper will be centered around the biochemistry of oxidative stress concerning nephrotoxicity and the changes in the levels of different biomarkers, including ROS, GSH, SOD, TAC, MDAs, and some inflammatory cytokines including TNF- α , IL-6, and CRP.

Keywords: Heavy metals, lead, cadmium, mercury, renal oxidative stress, kidney function biomarkers, Iraq, environmental toxicology, clinical biochemistry, mitochondrial dysfunction

1. Introduction

The issue of contamination with heavy metals is considered one of the most serious environmental problems around the globe, with Iraq and the Middle East being especially affected because of the geopolitical situation, industry development, and resource extraction processes taking place there ^[1]. Three of the most dangerous heavy metals namely lead, cadmium, and mercury, which are identified by health authorities as the most toxic are found in dangerously high concentrations in Iraq's soil, waters, and even human biological materials ^[2]. Among all body tissues, the kidneys rank second in terms of aerobic ability and the number of mitochondria; therefore, they are especially sensitive to toxic effects ^[3]. After the Gulf War of 1991 and invasion of 2003, Iraq has faced environmental pollution due to the usage of weapons containing depleted uranium, pollution due to industries, destruction of oil fields, and lack of proper waste disposal systems ^[1]. This has led to a continuous toxic exposure to many people living in Iraq. Symptoms of exposure to heavy metals may go unnoticed until damage occurs. Biomarker studies have therefore become crucial to detect early signs of toxicity ^[4].

It is crucial to understand that the state of oxidative stress, described as an imbalance between the production of reactive free radicals and their scavenging ability, is considered the main mechanism of nephrotoxicity caused by heavy metals ^[5]. The excess free radicals produced by the kidneys cause oxidative damage, which includes lipids, proteins, DNA, and mitochondria changes, which leads to cell death and eventually results in glomerulosclerosis and kidney failure ^[6]. This study gives a general view of current scientific knowledge about the mechanism of toxicity of lead, cadmium and mercury in combination with oxidative stress biomarkers in Iraq and the Middle East.

2. Sources of Heavy Metal Exposure in Iraq

2.1 Depleted Uranium and Warfare Residues

Iraq's environment has changed profoundly as a result of military conflicts spanning three decades. The 1991 Gulf War saw the deployment of approximately 300 tons of DU

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munitions, while the 2003-2011 invasion resulted in additional widespread DU contamination [2]. DU remains poorly soluble in soil but becomes bioavailable through dust inhalation, groundwater seepage, and biomagnification in the food chain. Fallujah, a city central to major combat operations, has documented uranium concentrations in hair samples of residents exposed to uranium that significantly exceed international reference values [2].

The chemical toxicity of uranium parallels the radiation risk, with primary renal manifestations including proximal tubular dysfunction and glomerular hyperfiltration [7]. Evidence from weaponized uranium research shows associations with increased birth defects, cancer incidence, and chronic kidney disease within affected areas [1]. Environmental surveys have identified enriched isotopic fingerprints of uranium in Iraqi water supplies, confirming the presence of armed rather than natural sources [2].

2.2 Industrial and Agricultural Contamination

The geographic position of Iraq in the region of the Tigris and Euphrates rivers, coupled with past and present industrialization in Baghdad and Basra, has resulted in extensive pollution with heavy metals in soils and water used for irrigation [8]. Lead in the soil found beside the major roads is an indication of the decades of emissions from leaded gasoline while the presence of cadmium and mercury in agricultural land is due to the use of contaminated phosphorus fertilizer and fungicides and sewage sludge [9].

Khuzestan province of southwestern Iran, adjacent to the Iraqi agricultural lands, undergoes dust storms seasonally which bring pollution with heavy metals to drinkable water and food products in southern Iraq [10]. Metal pollutants have been emitted by mining and oil extraction processes in oil-rich southern provinces of Iran [11].

2.3 Contaminated Water and Drinking Water Sources

The pollution of the water source is the key exposure route for Iraqis. Systematic surveys have shown that there is an increased presence of lead (about 20-50 µg/L), cadmium (2-10 µg/L), and mercury (1-5 µg/L) in city water, which greatly exceeds WHO guidelines (Lead: 10 µg/L; Cadmium: 3 µg/L; Mercury: 1 µg/L) [8]. The rural population using wells for their source of water experiences a higher level of contamination with reports of contamination increasing by a factor of 3 to 5 times in certain studies [8].

3. Lead Toxicity and Biochemical Alterations

3.1 Lead Metabolism and Renal Accumulation

Lead has a bi-phasic distribution with fast uptake into blood and soft tissues followed by gradual build-up in bones where 90% of lead is stored in the adult body [3]. However, lead concentration in renal cortex in chronic exposure cases may range from 10 to 100 µmol/kg tissue making the kidney an important target organ [3]. Lead accumulation in the kidney is achieved through the process of filtration in the glomerulus and then subsequent reuptake into proximal tubule cells where it binds with metallothionein and related metal binding protein [13].

The ability of lead to affect calcium (Ca^{2+}) homeostasis by interfering with the activity of voltage gated Ca^{2+} channels and Ca^{2+} dependent movement of proteins interferes with the process of voltage gated Ca^{2+} signaling that regulates glomerular filtration and tubular reabsorption [14]. Moreover,

lead affects the function of aminolevulinic acid dehydratase and ferrochelatase, two enzymes that regulate heme biosynthesis [15].

3.2 Lead-Induced Glomerular and Tubular Dysfunction

Several epidemiological studies in the United States have shown that chronic exposure to lead is associated with a progressive decrease in glomerular filtration rate (GFR), with higher blood lead levels associated with a decrease in estimated glomerular filtration rate (eGFR) [3]. Populations with chronic kidney disease, the association becomes more pronounced, suggesting that impaired lead excretion leads to amplification of circulating levels and renal accumulation [3].

Lead nephropathy usually manifests itself in chronic interstitial nephritis along with impaired function of glomeruli and tubules. Recently, urinary kidney injury molecule-1 (KIM-1) has become a marker of early and more sensitive changes in renal parenchyma associated with lead nephrotoxicity, as compared to classical biochemical parameters like serum creatinine and urinary albumin [16]. In occupational lead-exposed individuals, urine KIM-1 is more correlated with blood lead levels, as compared to traditional biomarkers, and ROC analysis shows that the cut-off value is 16.59 ng/g creatinine [16].

3.3 Oxidative Stress Mechanisms and Antioxidant Depletion:

Lead causes oxidative stress via three mechanisms, which include:

(i) interaction with -SH groups of antioxidant enzymes, which causes enzyme inhibition; (ii) disruption of transition metals (Fe^{2+} , Cu^{2+}) involved in redox reaction by regulatory protein, thus causing dangerous Fenton reactions; and (iii) inhibition of $\text{NO}\cdot$ production, thus producing vascular dysfunction and high blood pressure [14]. All these mechanisms cause significant loss in antioxidant system function in cells. Studies of communities exposed to lead contamination show significant reduction in serum and urine activities of SOD, CAT, and GPx as antioxidant enzymes. Conversely, malondialdehyde (MDA) levels are significantly increased, which is indicative of lipid peroxidation. There is also an imbalance in the GSH/GSSG ratio, indicating poor cellular reducing activity [13]. It has been observed that restoration of Nrf2/HO-1 signaling, which regulates the antioxidant enzymes' transcriptional expression, produces protective effects against oxidative stress [13].

4. Cadmium Toxicity and Renal Oxidative Stress

4.1 Cadmium Nephrotoxicity Mechanisms

Cadmium is one of the most toxic heavy metals that have a biological half-life of 10-35 years in renal tissue. Unlike lead, cadmium preferentially targets the kidney, where it binds MT and other proteins. Proximal tubular cells are especially loaded with cadmium, where the amount of this element can reach up to 1000 times the concentration present in the bloodstream [17]. Cadmium accumulation is accomplished due to its internalization through divalent metal transporter-1 (DMT1) and cation channels and subsequent compartmentalization in cellular compartments. There are three key mechanisms of cadmium toxicity, including: (1) induction of oxidative stress due to mitochondrial ROS formation; (2) induction of endoplasmic reticulum (ER) stress and alteration in Ca^{2+} signaling; and

(3) initiation of apoptosis and necrosis ^[18]. Cadmium blocks mitochondrial respiratory chain complexes, causing energy shortage and ROS accumulation. At the same time, ER stress induced by cadmium activates the transcription factor ATF4-CHOP pathway, promoting apoptosis ^[18].

4.2 Clinical Biochemical Alterations in Cadmium Nephropathy: High exposure to cadmium has been shown to result in increased serum creatinine and blood urea nitrogen (BUN) levels, in addition to a decreased eGFR ^[19]. The co-exposure to lead and cadmium results in synergistic effects on the kidneys based on the odds ratio for high urinary NAG, which is 7.7 (95% CI: 4.0-14.7) ^[19]. There is also an increase in the levels of biomarkers indicative of advanced renal injury, including NGAL and KIM-1, before the increase in the levels of conventional biomarkers ^[20]. After cadmium exposure, there is a sharp increase in NGAL levels, about 3- to 5-fold, in the 24-72 hours time span. Cystatin C, a cysteine protease inhibitor that is independent of muscle mass and age, has been identified as the most sensitive biomarker of reduced eGFR ^[21].

4.3 Mitochondrial Dysfunction and Ferroptosis

Studies have recently shown that cadmium-induced nephrotoxicity is prominently demonstrated during the process of ferroptosis, which is a programmed cell death that is different from apoptosis and results from oxidative stress due to the process of lipid peroxidation dependent on iron. Cadmium causes nephrotoxicity through its action through Nrf2, whose activation increases the production of heme oxygenase-1 (HO-1). The product of HO-1 is free iron, which is obtained from degradation of heme. Meanwhile, the expression of ferritin heavy chain 1 (FTH1), which stores iron, is inhibited, resulting in increased iron content inside cells and activation of Fenton reaction, which leads to formation of hydroxyl radicals ($\bullet\text{OH}$). This process results in lipid peroxidation and damage to mitochondria. The features of mitochondria damage by cadmium include abnormalities in cristae membrane structure, inhibition of ATP synthase activity and oxidative phosphorylation (OXPHOS), and increase in the amounts of SIRT1, SIRT3, and PGC-1 α that cause mitochondrial unfolded protein response (UPRmt). While UPRmt is the protective response of the body, it may lead to mitochondrial phagocytosis and mitochondrial dysfunction ^[22], ^[23].

5. Mercury-Induced Biochemical Dysfunction

5.1 Mercury Speciation and Renal Bioaccumulation

Mercury can be found in three main forms: elemental mercury (Hg^0), inorganic mercury (Hg^{2+}), and organic mercury (methylmercury, CH_3Hg^+). In Iraq's freshwater aquatic environments and on land, methylmercury is dominant because of the bacterial methylation of mercury in anoxic soils and sediments, especially in rice paddies and marshlands of the Tigris-Euphrates delta ^[24]. This compound is highly bioavailable and crosses the biological cell membrane by LAT1, which detects methylmercury-cysteine analogues to methionine ^[25]. The renal retention of mercury takes place by glomerular filtration and proximal tubule reabsorption. Unlike cadmium that accumulates inside tubular cells, mercury exists in glomerular and tubular pools affecting both glomerular and tubular functions ^[24]. The approximate half-life period for mercury in the kidneys is 40-70 days, less than half-life periods of lead and cadmium, and allows quick elimination of mercury from the body while also implying tubular secretion of the substance ^[24].

5.2 Mercury Toxicity Pathways and ROS Generation

Mercury is the second most toxic element only to plutonium due to its strong reactivity with sulfhydryl group as well as its capacity of generating reactive oxygen species. For example, mercury binds to cysteine residues in selenoproteins including glutathione peroxidase-4 (GPx-4), thioredoxin reductase (TrxR), and iodothyronine deiodinase and inhibits their enzymatic activity, resulting in increased oxidative stress ^[25]. Mercury was also identified to act as a competitive inhibitor of HSF1 and Nrf2, ^[14].

5.3 Mercury's Effects on Renal Function Biomarkers

Decreased glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) have had modest but persistent positive associations with high blood mercury levels in cohort studies. However, mediation analysis shows that changes in serum α -klotho, a protective factor for renal function, partially mediate the Hg-eGFR connection ^[27]. Mercury primarily affects glomerular structures, as seen by the much lower levels of α 1-microglobulin and N-acetyl- β -D-glucosaminidase (NAG), two urine markers of tubular dysfunction, in mercury nephropathy compared to cadmium nephropathy ^[27].

Table 1: Major Heavy Metals, Sources of Exposure, and Target Organs in Iraq and the Middle East

Heavy Metal	Primary Environmental Sources	Major Exposure Routes	Target Organs (Priority)	Renal Manifestations	Clinical Significance
Lead (Pb)	Depleted uranium munitions, vehicular emissions (leaded petrol legacy), industrial smelting, contaminated fertilizers	Drinking water (10-50 $\mu\text{g/L}$), food crops, dust inhalation, occupational	Brain, kidney, bone marrow, heart	Chronic interstitial nephritis, tubular dysfunction, glomerulosclerosis	Cumulative toxin; delayed manifestation; reversible if early
Cadmium (Cd)	Phosphate fertilizers, metal plating, batteries, pigments, oil refining	Contaminated drinking water (2-10 $\mu\text{g/L}$), agricultural crops, occupational	Kidney (95% accumulation), bone, prostate	Proximal tubular necrosis, proteinuria, progressive CKD	Most nephrotoxic metal; irreversible at high exposure
Mercury (Hg)	Riverine methylation (wetlands), dental amalgam (legacy), industrial chlor-alkali plants, waste incineration	Methylmercury in fish/aquatic foods, drinking water (1-5 $\mu\text{g/L}$), inhalation	Central nervous system (methylmercury), kidney, thyroid	Glomerulonephritis-like pattern, immune complex deposition	Neurotoxicity primary; renal effects secondary
Uranium (natural + enriched DU)	Depleted uranium weapons, natural geologic sources, phosphate rock	Dust inhalation, drinking water, food bioaccumulation	Kidney (primary chemical toxicity), bone	Acute tubular necrosis, chronic interstitial disease	Dual chemical and radiological toxicity; post-conflict hotspot

6. Oxidative Stress Mechanisms and Kidney Damage

6.1 Reactive Oxygen Species Generation and Mitochondrial Involvement

The kidney is particularly sensitive to heavy metals because of the high mitochondrial density required for ATP production and active solute transport [28]. There are several ways that heavy metals exert effects on mitochondrial function (1) direct inhibition of ETC complexes, (2) uncoupling oxidative phosphorylation (OXPHOS), (3) induction of MPT and/or (4) suppression of mitochondrial dynamics (fusion/fission) [28].

Lead, cadmium, and mercury lead to collapse of mitochondrial membrane potential and formation of superoxide radicals ($O_2^{\bullet-}$) as a result of impaired OXPHOS and increased proton leak. Mitochondrial calcium influx becomes compromised, leading to elevated cytoplasmic calcium and activation of calcium-dependent proteases (calpains), phospholipases, and endonucleases [29, 30].

6.2 Antioxidant Enzyme Systems and Their Suppression

The antioxidant defenses of the kidney are very strong and composed of both enzymatic (SOD, CAT, GPx, thioredoxin reductase) and non-enzymatic components (GSH, α -tocopherol and vitamin C) [5]. Metal ions suppress the synthesis of antioxidant enzymes through a variety of mechanisms, including direct catalytic site inhibition, enhanced degradation by the proteasome, and competitive displacement for zinc and selenium [14]. Consequently, the levels of MDA and protein carbonyl increase upon exposure to heavy metals, whereas total antioxidant capacity (TAC), an integrated measure of both enzymatic and non-enzymatic systems, continue to fall [31]. Additionally, GSH depletion and GSSG buildup are reflected in a change from normal adult values in the ratio of reduced glutathione to oxidized glutathione (GSH/GSSG) [5].

6.3 Inflammatory Amplification and Cytokine Activation

The presence of heavy metals leads to oxidative stress, which triggers signaling through MAPK and NF- κ B pathways and also causes a considerable release of pro-inflammatory cytokines. The presence of oxidative stress-induced DAMPs causes signaling in TLR4, resulting in greater NF- κ B activation. Due to an increase in the concentration of TNF- α , IL-1 β , IL-6, and MCP-1, T-cells and macrophages get attracted toward the kidney. Autoregulatory loops develop when resident cells in the kidney such as podocytes, tubular epithelial cells, and mesangial cells begin to release more cytokines due to pro-inflammatory mediators. At the same time, anti-inflammatory cytokines like IL-10 and TGF- β fail to be secreted. In lead nephropathy and cadmium nephropathy, the secretion of TNF- α and IL-6 increases by around three- to tenfold, respectively [23].

7. Clinical Biochemical Biomarkers and Their Clinical Utility

7.1 Traditional Markers: Creatinine, Urea, and eGFR

Serum creatinine is the most widely used marker of glomerular function due to its simplicity and low cost, but it suffers from several limitations as creatinine production depends on muscle mass, age, diet, and metabolism, factors that are not related to kidney function [35]. In elderly people who suffer from malnutrition, creatinine remains within the normal range despite the significant decrease in glomerular

filtration rate. Likewise, a severe decline in glomerular filtration rate <50% may sometimes not lead to a detectable rise in creatinine due to the narrow functional range of creatinine as an influential biomarker [36]. Creatinine-based glomerular filtration rate equations frequently overestimate real glomerular filtration rate in South Asian populations by 10-20%. This restriction applies to Middle Eastern cultures with comparable genetic heritage and muscle mass characteristics [37]. Creatinine-based glomerular filtration rate equations frequently overestimate real glomerular filtration rate in South Asian populations by 10-20%. This restriction applies to Middle Eastern cultures with comparable genetic heritage and muscle mass characteristics [37].

7.2 Cystatin C as an Alternative GFR Marker

Cystatin C, a 13 kDa inhibitor of cysteine proteases secreted at relatively constant rates from all nucleated cells, provides potential benefits over creatinine [36]. Cystatin C undergoes free filtration by the glomerulus followed by complete absorption and metabolism in the proximal tubules, resulting in virtually no urinary excretion. The serum concentration of cystatin C is not dependent on muscle mass, age (>4 years), and sex, which might be advantageous for the assessment of GFR decline in people with differing muscle mass [21]. Studies have shown that there is an increase in serum cystatin C independent of creatinine concentration upon exposure to cadmium, indicating that cystatin C measures early tubulopathy before any decrease in GFR occurs, leading to an increase in creatinine [21]. According to mediation analysis, serum α -klotho partly mediated the association between cadmium and cystatin C, and therefore cadmium inhibits α -klotho, an antinuretic protein, promoting an increase in serum cystatin C concentration [21]. Combining estimations using both creatinine-based and cystatin C-based eGFR equations can improve the ability to detect early kidney problems [37]. Cystatin C-based equations (for example, EKFC equation) provide a better performance compared with creatinine-based ones for South Asian and probably Middle Eastern populations [37].

7.3 Tubular Injury Biomarkers: KIM-1 and NGAL

Kidney injury molecule-1 (KIM-1) is a receptor for phosphatidylserine on dedifferentiated proximal tubular epithelial cells. KIM-1 acts as a highly specific marker of stress and injury to tubular epithelial cells [38]. After tubular injury, there is marked upregulation (10 to 100 fold increase) of KIM-1 expression, and the ectodomain gets secreted in the urine. Urinary KIM-1 appears in the urine soon after the injury and before increased concentrations of creatinine [16]. In occupational exposure to lead, urinary KIM-1 has been found to provide more discriminating ability than traditional biomarkers in identifying sub-clinical tubular injury [16].

The third biomarker is neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa iron binding protein secreted by neutrophils and renal tubules [38]. NGAL is used as a biomarker for acute tubular injury associated with sepsis, ischemia-reperfusion injury, and nephrotoxicity. Urinary and serum NGAL is associated with the severity of histological damage in cadmium and lead nephropathies [20] and also predicts progression to chronic kidney diseases. The combination of KIM-1 and NGAL increases the sensitivity and specificity of diagnosing AKI compared to

using either KIM-1 or NGAL alone. In chronic kidney disease of unknown origin (CKDu) population, the combined analysis of urinary KIM-1 and NGAL gives a sensitivity of 82.3% - 87.2% and specificity of 73.9% - 67.4% for identifying active CKDu patients [38].

7.4 Inflammatory Biomarkers: TNF- α , IL-6, and CRP

As a pro-inflammatory cytokine and a marker of systemic inflammation, tumor necrosis factor alpha (TNF- α) can be used to diagnose renal injury before any morphological changes occur as well as to predict the course of chronic kidney disease [39]. In the case of cadmium-associated nephropathy, levels of circulating TNF- α increase 3- to 5-fold in individuals exposed to heavy metals depending on the degree of proteinuria and reduced eGFR [30]. Another pro-inflammatory cytokine that plays a dual role in pathogenesis (depending on context) and is constantly

elevated in heavy metal nephropathy is IL-6 [34]. IL-6 stimulates production of several acute-phase proteins (C-reactive protein and serum amyloid A in the liver), increases blood vessel permeability, and recruits pro-inflammatory immune cells. Higher baseline levels of IL-6 are associated with the development of chronic kidney disease independent of traditional risk factors like eGFR and proteinuria [40]. C-reactive protein (CRP) and highly sensitive C-reactive protein (hsCRP) - a product of hepatocytes' reaction to IL-6 - mark increased risk of developing cardiovascular diseases and rapid progression of kidney disease in epidemiological studies [41]. Higher levels of hsCRP (>3 mg/L) correlate with faster development of cardiovascular and kidney diseases. An increase of about 0.5-1 mg/L per quartile of exposure to lead or cadmium has been noted in population studies [3].

7.5 Oxidative Stress Biomarkers

Table 2: Oxidative stress biomarkers in nephrotoxicity

Biomarker	Definition and Production	Clinical Utility in Heavy Metal Nephropathy	Advantages	Limitations
Malondialdehyde (MDA)	Terminal product of arachidonic acid peroxidation; reactive aldehyde	Reflects acute lipid peroxidation; early indicator of oxidative stress	Sensitive, rapid response to toxicant exposure	Lacks specificity; multiple endogenous sources
Glutathione (GSH)	Tripeptide antioxidant; primary cellular reducing agent	Depletion indicates antioxidant system exhaustion	Fundamental marker of cellular redox state	Requires specialized assays; rapid oxidation <i>ex vivo</i>
Superoxide Dismutase (SOD)	Converts O ₂ ^{•-} to H ₂ O ₂ ; ubiquitous antioxidant enzyme	Suppression indicates Nrf2 pathway inactivation	Direct measure of antioxidant capacity	Multiple isoforms; tissue-specific regulation
Catalase (CAT)	Converts H ₂ O ₂ to H ₂ O and O ₂ ; peroxisomal enzyme	Consistent suppression in all heavy metals	Specific for H ₂ O ₂ detoxification	Primarily intracellular; limited serum utility
Total Antioxidant Capacity (TAC)	Cumulative measurement of all antioxidant systems	Holistic assessment of antioxidant reserve	Integrates enzymatic and non-enzymatic defenses	Less specific; influenced by multiple factors
8-Hydroxy-2'-deoxyguanosine (8-OHdG)	DNA base oxidation product; stable marker	Indicates DNA oxidative damage; correlates with kidney fibrosis	Stable biomarker; specific for DNA damage	Influenced by renal clearance; age-dependent

Table 3: Clinical Biochemical and Oxidative Stress Biomarkers Affected by Lead, Cadmium, and Mercury

Biomarker Category	Specific Biomarker	Lead Exposure Pattern
Cadmium Exposure Pattern	Mercury Exposure Pattern	Early/Late Indicator
Clinical Utility	Renal Function	Serum Creatinine
↑ (late marker; delayed rise)	↑↑ (progressive increase)	↑ (modest increase)
Late	Poor sensitivity <50% GFR loss	Blood Urea Nitrogen (BUN)
↑ (late, variable)	↑↑ (marked increase)	↑ (mild increase)
Late	Nonspecific; influenced by protein intake	eGFR (creatinine-based)
↓ (10-30% decline in chronic exposure)	↓↓ (marked decline)	↓ (modest decline)
Late	Accuracy limited in non-Europeans	eGFR (cystatin C-based)
↓ (early detection)	↓↓↓ (most sensitive)	↓ (early detection)
Early	Superior for Middle Eastern populations	Cystatin C (serum)
↑ (early elevation)	↑↑↑ (marked elevation)	↑ (modest elevation)
Early	Detects GFR decline before creatinine change	Tubular Injury Markers
KIM-1 (urinary)	↑↑↑ (highly sensitive)	↑↑↑↑ (most elevated)
↑↑ (moderate elevation)	Very Early	Best early marker; rises within hours
NGAL (serum/urinary)	↑↑ (moderate)	↑↑↑ (marked)
↑↑ (moderate)	Early	Validates KIM-1; complementary utility

8. Public Health Challenges in Iraq and the Middle East

8.1 Environmental and Occupational Exposure Surveillance

There are no well-developed national biomonitoring programs in Iraq that could measure the degree of exposure of populations to heavy metals and monitor changes over time. The results of regional monitoring carried out by WHO and UN agencies reveal information about heavy

contamination but fail to provide the resources and structures necessary for regular monitoring [1]. Lack of monitoring of the water quality, especially during the periods of war (1991-1993, 2003-2011, 2014-2017), led to significant data gaps and prevented the reconstruction of exposure history [8]. There are virtually no biomonitoring programs aimed at evaluating occupational exposures in industries, such as oil refining, metal smelting and waste

recycling. Workers and their families lack knowledge about the nature of potential dangers, which leads to continuous but not monitored exposure^[12].

8.2 Vulnerable Populations and Equity Considerations

Internally displaced persons (IDPs) housed in the camps are exposed to various toxicants due to poor water quality, poor sanitation practices, living near the industrial area, and insufficient antioxidants because of malnutrition^[42]. In a cross-sectional study of kidney function in Duhok camps, increased microalbuminuria (5.3% compared to 2% in controls), decreased serum albumin, and high albumin/creatinine ratios have been reported among internally displaced persons^[42]. These biomarkers point toward chronic kidney disease development; however, follow-up and therapy for such conditions are lacking. Exposure to toxicants is more pronounced in female agricultural workers because of irrigation with contaminated water and traditional medicine preparation from such water sources^[9]. Women exposed to lead and mercury during pregnancy are at greater risk of developing fetal neurotoxicity and congenital disabilities; this risk may be even greater for Iraqi women whose mothers were exposed to lead, and congenital abnormalities were observed^[2].

8.3 Healthcare System Capacity and Diagnostic Challenges:

The healthcare system of Iraq, which has been severely compromised by ongoing wars, still lacks the adequate ability to perform biomarker analyses and provide services for nephrology. Many of the hospitals in Iraq are unable to conduct the analysis of biomarkers of oxidative stress (such as SOD, CAT, MDA, GSH), as well as novel markers for kidney injury such as KIM-1, NGAL. In many places, kidney function has been assessed only through serum creatinine levels and urinalysis^[42].

9. Future Perspectives and Research Gaps

9.1 Mechanistic Research Priorities

Despite many improvements in the understanding of mechanisms of heavy metal toxicity, a number of important research areas have yet to be explored. There is a lack of research on the combined effect of exposure to lead, cadmium, and mercury in populations exposed to all three metals, although it appears that additive interactions do not occur; there are only synergic or antagonistic interactions; however, adequate predictive models are still lacking^[43]. Mechanisms related to epigenetic changes in populations exposed to heavy metals, including DNA hypomethylation, hypermethylation, changes in histone acetylation, as well as non-coding RNA dysregulation, are important for future research in the region^[44]. Moreover, a mechanism of mitophagy (autophagic clearance of mitochondrial damage) in heavy metal-induced nephropathies needs to be elucidated. Current studies indicate that mitophagy plays a protective role in acute exposures, but may cause pathogenesis when the process becomes dysregulated^[28].

9.2 Biomarker Development and Validation

Biomarkers that should be validated among Middle Eastern populations include microRNAs that have been found to be deregulated by metal exposure, urinary exosomal markers, and metabolites that reflect the presence of oxidative stress^[31]. While such biomarkers could prove more specific and

sensitive than existing markers, the feasibility of using them in the context of Iraq has yet to be established due to cost considerations.

Nrf2 pathway activation status represents another promising area of research. Studies show that polymorphisms in the Nrf2 gene resulting in high expression of the protein are correlated with better prognosis in patients with cadmium nephropathy^[22].

9.3 Therapeutic Development

The utilization of antioxidant interventions among the population of Iraq requires thorough validation via clinical trials. While preclinical studies have shown promising results regarding the effectiveness of compounds aimed at modulating Nrf2/HO-1 pathway, inhibition of NF- κ B signaling, and mitochondria biogenesis, its clinical application is yet to be achieved^[28]. Research on compounds such as activators of Nrf2 (dimethyl fumarate), natural antioxidants (curcumin), as well as mitochondria-targeted antioxidants (MitoQ, SS-31) is justified among those exposed to heavy metals in Iraq. Chelation treatment is still under debate but can be applied in certain cases. Chelating agents DMSA (dimercaptosuccinic acid) and DMPS (dimercaptopropane sulfonic acid) are efficient in lowering the body burden of lead and cadmium among occupational exposures.

10. Conclusion

The exposure to lead, cadmium, and mercury is currently becoming an increasing and persistent health threat to the kidneys in Iraq and the entire Middle Eastern region because of many years of conflict, industrial pollution, and lack of remediation measures. Mechanistically, nephrotoxicity for lead, cadmium and mercury is linked to the activation of many overlapping pathways such as oxidative stress, inflammatory response activation, mitochondrial toxicity and metabolic pathology. More sophisticated biomarkers for oxidative stress (MDA, GSH, SOD, CAT, TAC) and novel renal damage biomarkers (KIM-1/NGAL) provide an objective index of kidney pathology and risk of its progression. Comparative to creatinine, there are strong rationale for a shift towards cystatin C as biomarker for eGFR calculation within Middle Eastern populations and the employment of KIM-1 and NGAL in urine should be implemented routinely to reveal tubulotoxic effects of heavy metals.

Key issues are

(1) implementation of national monitoring systems to assess population exposure to heavy metals over time; (2) development and validation of culturally tailored preventive strategies; (3) investigation of antioxidant and anti-inflammatory drugs through randomized clinical trials in Iraq's population; and (4) improving diagnostics capabilities in peripheral healthcare institutions via biomarker point-of-care testing.

As long as no serious measures of environmental remediation and source reduction take place, vulnerable populations of Iraq will suffer from chronic heavy metal exposure. A rational strategy should involve the use of biomarkers and evidence-based treatment and prevention methods.

References

1. Surdyk S, *et al.* Weaponised uranium and adverse health outcomes in Iraq: A systematic review. *BMJ Global Health*. 2021;6(2):e004166. DOI:10.1136/bmjgh-2020-004166.
2. Alaani S, Tafash M, Busby C, Hamdan M, Blaurock-Busch E. Uranium and other contaminants in hair from the parents of children with congenital anomalies in Fallujah, Iraq. *Conflict and Health*. 2011;5:15. DOI:10.1186/1752-1505-5-15.
3. Danziger J, Dodge L, Hu H, Mukamal K. Susceptibility to environmental heavy metal toxicity among Americans with kidney disease. *Kidney360*. 2022;3(4):678-687. DOI:10.34067/KID.0006782021.
4. Ahamad R, *et al.* Oxidative stress-driven mechanisms and biomarkers of drug-induced nephrotoxicity: Translational insights and therapeutic implications. *Antioxidants*. 2026;15(4):412. DOI:10.3390/antiox15040412.
5. Jomová K, *et al.* Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. *Archives of Toxicology*. 2023;97(8):2033-2056. DOI:10.1007/s00204-023-03562-9.
6. Kandel R, Roy P, Singh KP. Molecular basis of oxidative stress-induced acute kidney injury, kidney fibrosis, chronic kidney disease, and clinical significance of targeting reactive oxygen species-regulated pathways to treat kidney disease. *Frontiers in Bioscience-Scholar*. 2025;17(3):389-405. DOI:10.31083/fbs38963.
7. Patočka J. Human health and environmental uranium. *Military Medical Science Letters*. 2014;83(3):112-124. DOI:10.31482/mmml.2014.022.
8. Lindén O, Jerneloef A, Egerup J. The environmental impacts of the Gulf War 1991. IIASA PURE (International Institute of Applied Systems Analysis). 2004. Report No.: IR-04-015.
9. Milanković V, *et al.* Metals on the menu analyzing the presence, importance, and consequences. *Foods*. 2024;13(12):1890. DOI:10.3390/foods13121890.
10. Broomandi P, Dabir B, Bonakdarpour B, Rashidi Y. Identification of dust storm origin in south-west of Iran. *Journal of Environmental Health Science and Engineering*. 2017;15:18. DOI:10.1186/s40201-017-0280-4.
11. Al-Ansari N, Pusch R, Knutsson S. Suggested landfill sites for hazardous waste in Iraq. *Natural Science*. 2013;5(4):460-472. DOI:10.4236/ns.2013.54060.
12. Tarkhani H. Guns, bombs, and pollution: Unraveling the nexus between warfare, terrorism, and ecological devastation in Iraq. *The Journal of Social Encounters*. 2024;8(1):124-140. DOI:10.69755/2995-2212.1240.
13. Shi Y, *et al.* Protective effects of *Smilax glabra* Roxb. against lead-induced renal oxidative stress, inflammation and apoptosis in weaning rats and HEK-293 cells. *Frontiers in Pharmacology*. 2020;11:556248. DOI:10.3389/fphar.2020.556248.
14. Jomová K, Alomar SY, Nepovimová E, Kuča K, Valko M. Heavy metals: Toxicity and human health effects. *Archives of Toxicology*. 2024;98(11):3393-3420. DOI:10.1007/s00204-024-03903-2.
15. Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic mechanisms of five heavy metals: Mercury, lead, chromium, cadmium, and arsenic. *Frontiers in Pharmacology*. 2021;12:643972. DOI:10.3389/fphar.2021.643972.
16. Abdullah AH. Evaluation and study the effect of asymmetric dimethylarginine in chronic renal failure patients treated by hemodialysis. *Journal of Kerbala University*. 2011;9(2):4-8.
17. Yan L, Allen D. Cadmium-induced kidney injury: Oxidative damage as a unifying mechanism. *Biomolecules*. 2021;11(11):1575. DOI:10.3390/biom11111575.
18. Saleem MAU, *et al.* Cadmium disrupted homeostasis of proximal renal tubular cells via targeting ATF4-CHOP complex into the nucleus. *Poultry Science*. 2025;104(3):105059. DOI:10.1016/j.psj.2025.105059.
19. Chen X, *et al.* The association between lead and cadmium co-exposure and renal dysfunction. *Ecotoxicology and Environmental Safety*. 2019;172:121-128. DOI:10.1016/j.ecoenv.2019.01.121.
20. Ebhohon SO, Asoya EV, Okwor LO, Ezeokeke CB. Nephroprotective effects of aqueous extract of *Loranthus micranthus* Linn. leaf against cadmium-induced kidney toxicity in male rats. *Journal of Basics and Applied Sciences Research*. 2024;14(1):21-30. DOI:10.33003/jobasr-2023-v1i1-3.
21. Fang Y, Chen C, Su T, Lin C. Cadmium exposure, epigenetic modifications, and serum cystatin C: Insights into mediated pathways and mortality risks in U.S. adults. *Clinical Epigenetics*. 2025;17:88. DOI:10.1186/s13148-025-01888-y.
22. Luo T, *et al.* Mechanistic insights into cadmium-induced nephrotoxicity: NRF2-driven HO-1 activation promotes ferroptosis via iron overload and oxidative stress *in vitro*. *Free Radical Biology and Medicine*. 2025;231:47-59. DOI:10.1016/j.freeradbiomed.2025.04.047.
23. Ge J, *et al.* Cadmium exposure triggers mitochondrial dysfunction and oxidative stress in chicken (*Gallus gallus*) kidney via mitochondrial UPR inhibition and Nrf2-mediated antioxidant defense activation. *Science of the Total Environment*. 2019;689:405-414. DOI:10.1016/j.scitotenv.2019.06.405.
24. Kumar S, Sharma A, Sedha S. Occupational and environmental mercury exposure and human reproductive health: A review. *Journal of the Turkish-German Gynecological Association*. 2022;23(3):202-213. DOI:10.4274/jtgga.galenos.2022.2022-2-6.
25. Wu YS, *et al.* The toxicity of mercury and its chemical compounds: Molecular mechanisms and environmental and human health implications: A comprehensive review. *ACS Omega*. 2024;9(3):3112-3135. DOI:10.1021/acsomega.3c07047.
26. Roustas AM, *et al.* Protective effect of sesamin in lipopolysaccharide-induced mouse model of acute kidney injury via attenuation of oxidative stress, inflammation, and apoptosis. *Immunopharmacology and Immunotoxicology*. 2018;40(6):523-529. DOI:10.1080/08923973.2018.1523926.
27. Jiang L, Guo T, Zhong X, Cai Y, Yang W, Zhang J. Serum protein α -klotho mediates the association between lead, mercury, and kidney function in middle-aged and elderly populations. *Environmental Health and Preventive Medicine*. 2025;30:29. DOI:10.1265/ehpm.24-00296.

28. Pavlović N, Križanac M, Kumrić M, Vukojević K, Božić J. Mitochondrial dysfunction: The silent catalyst of kidney disease progression. *Cells*. 2025;14(11):794. DOI:10.3390/cells14110794.
29. Ince S, *et al.* Magnolin alleviates cyclophosphamide-induced oxidative stress, inflammation, and apoptosis via Nrf2/HO-1 signaling pathway. *Toxicological Research*. 2024;40(3):129-138. DOI:10.1093/toxres/tfae129.
30. Ijaz M, *et al.* Alleviative effects of pinostrobin against cadmium-induced renal toxicity in rats by reducing oxidative stress, apoptosis, inflammation, and mitochondrial dysfunction. *Frontiers in Nutrition*. 2023;10:1175008. DOI:10.3389/fnut.2023.1175008.
31. Chakif D, Furrer J. Heavy metal toxicity in clinical and environmental health: Sources, mechanisms, diagnostics, and evidence-based management of mercury, lead, cadmium, and arsenic. *International Journal of Molecular Sciences*. 2026;27(8):3513. DOI:10.3390/ijms27083513.
32. Yuan Q, Tang B, Zhang C. Signaling pathways of chronic kidney diseases: Implications for therapeutics. *Signal Transduction and Targeted Therapy*. 2022;7:182. DOI:10.1038/s41392-022-01036-5.
33. Hu X, *et al.* Inhibition of myeloid differentiation protein 2 attenuates renal ischemia/reperfusion-induced oxidative stress and inflammation via suppressing TLR4/TRAF6/NF- κ B pathway. *Life Sciences*. 2020;250:117864. DOI:10.1016/j.lfs.2020.117864.
34. Amri J, Emadi A, Rezaei N, Salemi Z. Cerium oxide nanoparticles attenuate diabetic nephropathy in rats by reducing oxidative stress, improving dyslipidemia, and modulating PKM2 and KIM-1. *Acta Biochimica Iranica*. 2025;2(4):185-193. DOI:10.18502/abi.v2i4.19107.
35. Hapsari PPH, Suryantoro S. The role of neutrophil gelatinase-associated lipocalin (NGAL) in the early detection of nephrotoxicity caused by chemotherapy for breast cancer. *Journal of Medical and Health Studies*. 2025;6(9):12-19. DOI:10.32996/jmhs.2025.6.9.2.
36. López-Giacoman S. Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World Journal of Nephrology*. 2015;4(1):57-73. DOI:10.5527/wjn.v4.i1.57.
37. Sinha A, Sarnowski A, Dalrymple K, Delanaye P, Bramham K, Gama R. Nephrology Dialysis Transplantation. 2025;40(Suppl 1):gfaf116.1351. DOI:10.1093/ndt/gfaf116.1351.
38. Rajyalakshmi N, Rajagopalan V, Sivanesan S, Sabhavatu V. Comparison of biomarkers to differentiate chronic kidney disease and chronic kidney disease of unknown etiology. *International Journal of Life Science and Pharma Research*. 2022;12(5):L40-L48. DOI:10.22376/ijpbs/lpr.2022.12.5.l40-48.
39. Küçükler S, Çomaklı S, Özdemir S, Caglayan C, Kandemir F. Hesperidin protects against the chlorpyrifos-induced chronic hepato-renal toxicity in rats associated with oxidative stress, inflammation, apoptosis, autophagy, and up-regulation of PARP-1/VEGF. *Environmental Toxicology*. 2021;36(4):475-490. DOI:10.1002/tox.23156.
40. Fernández-Fernández B, Hasegawa T, Saruta Y, Guan YL, Sánchez-Rodríguez J, Ortiz A. Nephrology Dialysis Transplantation. 2025;40(Suppl 1):gfaf116.1924. DOI:10.1093/ndt/gfaf116.1924.
41. Powell TC, Powell SL, Allen B, Griffin R, Warnock DG, Wang HE. Association of inflammatory and endothelial cell activation biomarkers with acute kidney injury after sepsis. *SpringerPlus*. 2014;3:207. DOI:10.1186/2193-1801-3-207.
42. Yousif BS, Al-Kass SY. Renal health status in individuals living in camps of Duhok, Kurdistan Region, Iraq. *AL-Kindy College Medical Journal*. 2026;22(1):73-81. DOI:10.47723/h73rdn81.
43. Yin G, *et al.* Complex interplay of heavy metals and renal injury: New perspectives from longitudinal epidemiological evidence. *Ecotoxicology and Environmental Safety*. 2024;275:116424. DOI:10.1016/j.ecoenv.2024.116424.
44. Alkahtani LM, Alharbi YA, Alharbi NT, Almuhammadi G, Al-Harbi R, Mohaini MA. Mitochondrial biomarker-enhanced diagnostic framework for assessing chronic kidney disease prevalence in hypertensive populations: A cross-sectional study integrating urinary mitochondrial DNA and oxidative stress indices. *Journal of Advanced Trends in Medical Research*. 2026;3(1):120-125. DOI:10.4103/atmr.atmr_120_25.