Review Paper

Heavy Metal Intoxication: A Key-Player in Chronic Kidney Disease (A Review)

ABSTRACT

Heavy metals gain entry into biological systems mainly via inhalation and ingestion, and also via radiation or radio-therapeutic measures. The accumulation of these heavy metals in biological systems overtime may cause several deleterious health challenges such as liver, kidney and brain damages amongst others. Intoxication with heavy metals may either be acute or chronic, and because the kidney has the ability to reabsorb and accumulate divalent metals, it happens to be the primary target organ for heavy metal toxicity, inducing renal damage. The extent of this damage depends on the dose, nature, route and duration of exposure to the metal. Chronic kidney disease (CKD) is characterized by a permanent loss of nephrons accompanied by an eventual decline in glomerular filtration rate (GFR); this (to a greater extent) maybe due to heavy metal intoxication and the renal reabsorption of these heavy metals. Although 70 percent of the heavy metals are reabsorbed in the proximal tubule, all segments of the nephrons are involved in the reabsorption of these metals, where several transporters such as the Divalent Metal Transporter (DMT)-1, Na^+/amino acid co-transporter, Zinc Transporter (ZnT)-1 and stretch-activated cation channels (SAC) facilitate the reabsorption. In the nephrons of each kidney, heavy metals are primarily reabsorbed via the apical membrane and accumulate at the basolateral membrane; these heavy metals do not readily exit the basolateral membrane, which overtime may result in chronic inflammation of the nephrons, fibrosis and kidney failure. However, the loss of nephrons and decline in GFR in CKD are compensated by certain changes (glomerular and cellular, enhanced renal blood flow, enhanced single nephron glomerular filtration rate and tubular hypertrophy) in the remaining functional nephrons. These changes help to deliver solutes to the remaining

functional nephrons for uptake by the epithelial cells of the renal tubules. Also, because the luminal and basolateral surfaces of tubular epithelial cells of the remaining healthy nephrons are also potentially exposed to higher levels of metabolic wastes, xenobiotics, heavy metals and other nephrotoxicants, renal injury, tubular or glomerulosclerosis, and death of these nephrons occur. These compensatory changes become insufficient once about 75 percent of the nephrons are no longer functional and incapable of maintaining homeostasis and renal function. This results in the accumulation of metabolic wastes in the blood, and induction of metabolic disturbances and/or organ intoxication.

Keywords: Heavy metal intoxication, chronic kidney disease, accumulation, biological system, nephrons, basolateral.

1.0 INTRODUCTION

Heavy metals are those metals with higher atomic number and weight. They constitute different groups of elements with variations in their biological functions and chemical properties. They are a large group of elements with an atomic density of greater than six grams per cubic centimetre, and are both biologically and industrially important (Alloway, 1995). They are natural components of the environment discovered mainly in rock formations, soil, plants and animals (Ezejiofor *et al.,* 2013), and are at least five times denser than water; as such, are said to be stable elements.

The largest of its proportion occur in oil and aquatic ecosystems, while its smaller proportion occur as particulate or vapours in the atmosphere (Ezejiofor *et al.,* 2013). Some heavy metals such as iron, copper and zinc are important trace elements to humans; these trace elements play a significant role in cell homeostasis by acting either as cofactors or activators of enzyme reactions, and are also involved in the regulation of various physiological functions

including the synthesis of nucleic acid and protein, stabilization of the membrane, oxidative phosphorylation, and involvement in antioxidant defence system. At very low concentration, they are effective, and their concentration in body fluids must be tightly regulated to prevent their deficiency or excess. On the other hand, some heavy metals are non-essential, and are thus toxic even at very low doses, and non-biodegradable with a very long biological half-life; some of which include platinum, cadmium, lead, chromium, mercury and lead (Barbier *et al.,* 2005).

Over twenty different heavy metals are released into the surroundings naturally and anthropogenically (Ezejiofor *et al.,* 2013), and gain access into biological systems either through inhalation or ingestion, where they cause the cells to malfunction, by displacing original metals from their natural binding sites, and binding to such sites which are not originally made for them (Jaishankar *et al.,* 2014).

After the absorption of heavy metals, they are distributed into organs and tissues, and are excreted mainly via the kidneys and digestive tract. However, they persist in some storage organs, such as the liver, bones, and kidneys, and bio-accumulate for several years. Due to the potential of the kidney to reabsorb and accumulate divalent metals, it happens to be the first target organ of heavy metal toxicity inducing renal damage; the extent of which is dependent on the dose, nature, route and duration of exposure to the metal (Barbier *et al.,* 2005).

Chronic kidney disease (CKD) also called chronic kidney failure refers to a slow and progressive loss of kidney over a long period. It is characterized by a permanent loss of nephrons and an eventual decline in glomerular filtration rate (GFR) (Diamond and Zalups 1998). Price (1982) reported that CKD is seriously on the increase worldwide, with prevalence estimate of 8–16% of the world's population. Patients with CKD usually find it

difficult to produce ample volume of urine, and thus have a reduced ability to eliminate metabolic wastes, xenobiotics, and toxicants (Bridges, 2017).

2.0 SOURCES OF EXPOSURE TO HEAVY METAL INTOXICATION

2.1 Food and Drinking Water

Food is a major mode or source of heavy metal intoxication, which is due to the contamination of the food with these heavy metals during processing, packaging or preparation.

Cadmium enters and contaminates groundwater supplies, soil and lakes, crops, and different animal species and fishes through its application in some chemical fertilizers (Binns *et al.,* 2003); toxicity due to this heavy metal was reported in Japan as it was consumed through contaminated rice (Hashemi *et al.,* 2017). Lead, cadmium and arsenic contaminates soil and agricultural products through the use of herbicides, insecticides and chemical fertilizers; constant application of these fertilizers, herbicides or insecticides overtime, may lead to their absorption and accumulation by the plants, which can directly exert a deleterious effect to the food chain. During sewage treatment, if the water is acidic in pH, it will absorb lead while passing through the water pipes (Shahryari and Mollasadeghi, 2011). Ebrahimi and Taherianfard (2010) reported that individuals, who consume rice, are exposed to significant concentration of heavy metals.

Sea foods are rich in nutrients, but could be contaminated with toxic heavy metals, which may be attributed to the entry of wastewater containing chemical fertilizers and agricultural toxins into the rivers, which in turn, may impact a deleterious effect on freshwater ecosystems and water species habitats (Hashemi *et al.,* 2017). Sea foods may also get contaminated with toxic heavy metals through oil spillage and waste disposal in the water

body. Fyneface *et al.,* (2018) reported that the concentration of nickel in periwinkles obtained from Eagle Island River was above the tolerable limit. In a study carried out by Iweala *et al.,* (2014) in Nigeria, they discovered the presence of various heavy metals above the WHO tolerable limits in different kinds of foods; nickel was present in roasted meat (also called suya), roasted plantain (also called bole), cassava flour (also called fufu), beans, roasted fish and yam flour (also called amala). Mercury was also present in roasted plantains above the tolerable limits.

Most spices and seasonings, cooking oil, bread, noodles, tea, vegetables and snacks may also be contaminated with heavy metals through handling them with contaminated hands or through other means. Binns *et al.,* (2003) reported that vegetables irrigated by contaminated water elevate the possibility of the presence of heavy metals in the vegetables. Khan *et al.,* (2014) also reported that significant amounts of heavy metals have been detected in natural food spices mainly due to heavy metal contamination.

2.2 Soft and Alcoholic Drinks

Soft drinks are consumed daily due to its characteristic taste, affordability, and potential to quench thirst, and are thus on a high demand by the populace; this level of demand however, may compromise the quality of production with possible contamination of heavy metals (Godwill *et al.,* 2015).

From a study conducted in Nigeria, which assessed the concentrations of heavy metals in some beverages, Ogunlana *et al.,* (2015) stated that 60 percent of the beverages contained either (or both) lead and arsenic levels above the WHO-recommended levels, while 10 percent of the beverages had both lead and cadmium levels above the recommended levels.

Godwill *et al.,* (2015) carried out a study to determine the constituents of some soft drinks and contamination by some heavy metals in Nigeria, and stated that cadmium, lead and mercury were found to be present in most of the soft drinks, and that the values were above the tolerable limits for consumption.

In a study carried out by Kemasuode *et al.,* (2013), they assessed the concentrations of heavy metals in three popular local drinks (burukutu, kunu and zobo) consumed in Benue State, Nigeria. They stated that the levels of lead and iron in burukutu and kunu drinks were higher than the WHO-recommended limits. They also stated that, the reason for the higher lead levels was due to the source of water used, and that the elevated iron levels in burukutu and kunu drinks were attributed to use of rusting metal drums and vessels used to prepare both drinks.

Also, Maigari *et al.,* (2016) carried out a study to assess the heavy metal contamination in two popular local drinks (zobo and kunu) consumed in Northern Nigeria. They stated that the levels of chromium, lead and iron in these drinks were above the WHO-recommended levels.

About 68.9 percent of uncanned beverages and 76.2 percent of canned beverages in Nigeria had chromium levels greater than the acceptable level of 0.10 mg/L. Also, about 33.3 percent of uncanned beverages and 55.2 percent of canned beverages in Nigeria had arsenic levels greater than the maximum contaminant level of 0.01 mg/L (Maduabuchi *et al.,* 2007).

2.3 Cigarette Smoking

Smoking of cigarettes or shisha is a major means of heavy metal intoxication. Cigarettes contain tobacco, which in turn, contains some toxic substances, which may directly affect the kidney. Tobacco plants take up heavy metals from the soil and concentrate them in leaves, thus the heavy metal concentration in tobacco may vary across countries (Pappas, 2011).

Tsuchiyama *et al.,* (1997) reported that the concentrations of chromium were significantly higher in smokers' lungs than in non-smokers' lungs. Chromium is naturally present in tobacco (Pappas, 2011), as such when it is consumed (through cigarette smoking), it may accumulate in the lung and enter the bloodstream, resulting in their elevation. Stojanovic *et al.,* (2004) reported that nickel content in the blood of smokers was higher than in the blood of non-smokers; nickel in burning cigarettes might form nickel tetracarbonyl (a volatile and gaseous compound), which may then enter the respiratory tract (Torjussen *et al.,* 2003), and then into the blood.

2.4 Inhalation

Heavy metal intoxication may also occur as a result of occupational exposure through the frequent inhalation of heavy metals in vapours, fumes and dust in workplaces. Ibama and Amadi (2018) reported that the serum levels of the heavy metals chromium, nickel and arsenic in carpenters exposed to wood dust were significantly higher than those of non-smokers; this occupational exposure may however predispose carpenters to nephrotoxicity (Ibama *et al.,* 2018). Passive smoking also called second-hand smoke or environmental tobacco smoke is also a means of heavy metal intoxication.

3.0 THE CHEMICAL FORMS OF HEAVY METAL FILTERED BY THE GLOMERULUS AND TRANSPORTED IN THE KIDNEY

Chronic heavy metal intoxication in humans may occur through food and water intake, inhalation or skin contact of vapours, fumes and dust in workplaces, while acute intoxication occur from inhalation, skin contact or an inappropriate use of some therapeutic measures (Lentini *et al.,* 2017).

The kidney has the ability to reabsorb and accumulate divalent metals (cations), which are present in the plasma as non-diffusible (protein-bound) and diffusible (complexed/ionized) forms, with the ionized form of the heavy metals being relatively more toxic.

During acute heavy metal intoxication, the heavy metal ions bind rapidly to albumin (at the free sulfhydryl group of terminal cysteine and histidine residues) in the plasma (Ferguson *et al.,* 2001), with usually a small fraction of the heavy metals escaping this binding. Thus, in this type of intoxication, the plasma contains both the free (ionized) and bound forms of the heavy metal, and are both filtered by the glomerulus into the proximal tubule (Barbier *et al.,* 2005).

During chronic heavy metal intoxication however, the free (ionized) form of the heavy metal induces the increased synthesis of metal-binding proteins such as metallothioneins and glutathione in renal and liver tissues; these proteins prevent heavy metal-induced toxicities in the liver and kidneys by trapping the metals inside the cells through the formation of complexes (heavy metal-protein complexes) (Zalups, 2000). Normally in chronic intoxication, the heavy metals are rapidly cleared off the plasma and sequestered in tissues mainly the liver. However, when the capacity of the liver to sequester ionized (free) forms of metals is exceeded, liver damage ensues, which in turn induces the release of the bound forms (metal-metallothionein and metal-glutathione) in the liver into the blood, and then transported to the kidneys and filtered by the glomerulus (Thevenod, 2003). Thus, in chronic intoxication, the plasma, as well as the ultrafiltrate contains mainly the complexed forms of the heavy metals.

4.0 RENAL REABSORPTION OF HEAVY METALS

4.1 In acute intoxication

As earlier stated, both albumin-bound and ionized heavy metals are filtered by the glomerulus. The divalent heavy metal cations (ionized form) present in the ultrafiltrate are reabsorbed in the various segments of the nephrons (proximal tubule, loop of Henle, distal tubule, and collecting ducts), although 70 percent of them are reabsorbed in the proximal convoluted tubule (Felley-Bosco and Diezi, 1987).

In the proximal tubule, reabsorption of heavy metals occur; this reabsorption is an active process made possible by several transporters (thus transcellular pathway is involved in the transport of heavy metals in this segment), one of which, is the Divalent Metals Transporter (DMT) 1; this transporter was first discovered in the GIT, where it functions in the transport of trace elements (such as ferrous, zinc and manganese ions), and is also greatly expressed in renal tissues (Ferguson *et al.,* 2001), where it also functions in the transport of trace elements and some highly toxic divalent heavy metal cations such as cadmium, lead, cobalt, nickel and platinum ions (Barbier *et al.,* 2005). The presence of these cations in the ultrafiltrate causes a decrease in the levels of essential trace elements being reabsorbed due to competition with the heavy metal cations.

Another type of renal transporter in the proximal tubule is the sodium ion-amino acid cotransporter, which functions in the transport of zinc ion (Zn^{2+}) complexed with cysteine or histidine in the proximal tubule (Gachot *et al.,* 1991). However, toxic divalent heavy metals such as mercuric and cadmium ions may also get transported by this cotransporter, by binding to the amino acid moiety of the cotransporter to form cysteine conjugates (Barbier *et al.,* 2005).

Also existing, is the Zinc Transporter (ZnT) 1 located in the basolateral membrane of the nephron, which also transports cadmium and cuprous ions with a low degree of affinity.

Stretch-activated cation channels (SAC) could also be involved in the uptake of divalent heavy metals (Barbier *et al.*, 2005).

In the loop of Henle, ferrous, cadmium, zinc and other divalent heavy metal cations are reabsorbed probably through both paracellular and transcellular pathways (Barbier *et al.*, 2004); the paracellular passive reabsorption of cations being propelled by a positive voltage in the lumen generated by $Na^{+}K^{+}2Cl^{-}$ cotransport and K^{+} recycling in the apical membrane; with this membrane the DMT1 transporter (Ferguson *et al.*, 2001).

4.2 In chronic intoxication

As earlier stated, in chronic intoxication, mainly complexed forms of the heavy metals such as metal-metallothionein and metal-glutathione are present in the ultrafiltrate, and these complexed heavy metals are reabsorbed in the proximal tubule through a process of endocytosis. Also, some of the metal-glutathione complexes are broken down by the enzyme glutamyltransferase (GGT) to produce the metal bound to cysteine residues (Cysteine-metal conjugates) to be transported by the sodium ion-amino acid cotransporter (Barbier *et al.*, 2005).

5.0 HEAVY METALS-INDUCED RENOPATHIES

In the nephrons of each kidney, heavy metals are primarily absorbed through the apical membrane and accumulate at the basolateral membrane; these heavy metals do not readily exit from this membrane, and overtime, can cause chronic inflammation, fibrosis and renal failure (Sabolić, 2006).

The degree of damage to the kidneys depends on the mode of exposure to the heavy metal (whether acute or toxic), the concentration and the nature of the heavy metal. In chronic heavy metals intoxication, a Fanconi syndrome is usually induced, and this syndrome is characterized by a decrease in the GFR, an increase in the rate of urine outflow, proteinuria, glycosuria, aminoaciduria and excessive loss of major ions (Barbier *et al.,* 2005).

Heavy metals interact with some renal transporters; for example, cadmium ion decreases phosphate and glucose transport by inhibiting the NaPi and the Na/glucose cotransporters. In the loop of Henle, distal tubule and collecting duct, cadmium ions block the effect of ion channels such as the epithelial calcium channel and the renal outer medullary potassium ion (Barbier *et al.,* 2005). Sulphate transporter 1 may also be blocked by mercuric, lead and chromium ions.

Ionized heavy metals induce rupturing of the outer membrane and an uncoupling of mitochondrial respiration; cadmium ions inhibit the transfer of electrons and oxidative phosphorylation, leading to the release of reactive oxygen species, which in turn induce oxidative damage resulting into several disease conditions.

Deficiency in plasma essential trace elements may also be another problem due to heavy metal toxicity, in that the heavy metals compete with these trace elements for carriers, thereby decreasing the reabsorption of the trace elements; this is the case for anaemia induced by cadmium ions intoxication, in which cadmium ions compete with ferrous for the Divalent Metal Transporter-1 leading to a decrease in the intestinal absorption of ferrous.

6.0 COMPENSATORY ACTIONS OF THE KIDNEYS TO HEAVY METAL-INDUCED CKD

As a form of compensation to the loss of nephrons and decline in GFR in CKD, certain changes (glomerular, cellular and tubular hypertrophy, enhanced renal blood flow, and enhanced single nephron glomerular filtration rate) occur in the remaining functional nephrons (Zalups and Diamond, 1987). There is also an enhanced transcription and translation of RNA, leading to an increased expression of the messenger RNA, and thus the amount of proteins. These changes help to deliver solutes to the remaining structurally and functionally normal nephrons for uptake by the epithelial cells of the renal tubules (Magos and Stoytchev, 1969). Due to these compensatory actions (enhanced renal blood flow and single nephron glomerular filtration rate), the luminal and basolateral surfaces of tubular epithelial cells of the remaining healthy nephrons are potentially exposed to higher levels of metabolic wastes, xenobiotics, heavy metals and other nephrotoxicants, which may in turn, cause renal injury, tubular or glomerulosclerosis, and death of these nephrons. These metals may also be taken up by the hypertrophied tubular cells due to elevations in the expression of certain cellular transport mechanisms (Miller *et al.,* 2013); increased exposure and uptake of which may adversely affect these hypertrophied tubular cells (Vanholder *et al.,* 1982), reducing the functional renal mass. A reduced functional renal mass is directly related to a decreased urinary excretion of metabolic wastes and toxicants.

However, these compensatory changes become insufficient once about 75 percent of the nephrons are no longer functional, and incapable of maintaining homeostasis and renal function. This results in the accumulation of metabolic wastes in the blood, and induction of metabolic disturbances and/or organ intoxication (Hall *et al.,* 1986).

7.0 CONCLUSION

There is a strong relationship between heavy metal intoxication and chronic kidney disease such that the higher the intoxication, the higher the possibility of chronic kidney disease to occur.

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