

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

ABSTRACT

Heavy metals are released into the environment by natural and anthropogenic means; they 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) is induced by 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. CKD begins with loss of some nephrons accompanied by a decline in GFR; these are compensated by certain changes (glomerular, cellular and tubular hypertrophy, enhanced renal blood flow and enhanced single nephron glomerular filtration

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

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

38

39 **1.0 INTRODUCTION**

40 Heavy metals are those metals with higher atomic number and weight. They constitute
41 different groups of elements with variations in their biological functions and chemical
42 properties. They are a large group of elements with an atomic density of greater than six
43 grams per cubic centimetre, and are both biologically and industrially important (Alloway,
44 1995). They are natural components of the environment discovered mainly in rock
45 formations, soil, plants and animals (Ezejiolor *et al.*, 2013), and are at least five times denser
46 than water; as such, are said to be stable elements.

47 The largest of its proportion occur in oil and aquatic ecosystems, while its smaller proportion
48 occur as particulate or vapours in the atmosphere (Ezejiolor *et al.*, 2013). Some heavy metals
49 such as iron, copper and zinc are important trace elements to humans; these trace elements
50 play a significant role in cell homeostasis by acting either as cofactors or activators of

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

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

64 After the absorption of heavy metals, they are distributed into organs and tissues, and are
65 excreted mainly via the kidneys and digestive tract. However, they persist in some storage
66 organs, such as the liver, bones, and kidneys, and bio-accumulate for several years. Due to
67 the potential of the kidney to reabsorb and accumulate divalent metals, it happens to be the
68 first target organ of heavy metal toxicity inducing renal damage; the extent of which is
69 dependent on the dose, nature, route and duration of exposure to the metal (Barbier *et al.*,
70 2005).

71 Chronic kidney disease (CKD) also called chronic kidney failure refers to a slow and
72 progressive loss of kidney over a long period. It is characterized by a permanent loss of
73 nephrons and an eventual decline in glomerular filtration rate (GFR) (Diamond and Zalups
74 1998). Price (1982) reported that CKD is seriously on the increase worldwide, with

75 prevalence estimate of 8–16% of the world’s population. Patients with CKD usually find it
76 difficult to produce ample volume of urine, and thus have a reduced ability to eliminate
77 metabolic wastes, xenobiotics, and toxicants (Bridges, 2017).

78 **2.0 SOURCES OF EXPOSURE TO HEAVY METAL INTOXICATION**

79 **2.1 Food and Drinking Water**

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

83 Cadmium enters and contaminates groundwater supplies, soil and lakes, crops, and different
84 animal species and fishes through its application in some chemical fertilizers (Binns *et al.*,
85 2003); toxicity due to this heavy metal was reported in Japan as it was consumed through
86 contaminated rice (Hashemi *et al.*, 2017). Lead, cadmium and arsenic contaminates soil and
87 agricultural products through the use of herbicides, insecticides and chemical fertilizers;
88 constant application of these fertilizers, herbicides or insecticides overtime, may lead to their
89 absorption and accumulation by the plants, which can directly exert a deleterious effect to the
90 food chain. During sewage treatment, if the water is acidic in pH, it will absorb lead while
91 passing through the water pipes (Shahryari and Mollasadeghi, 2011). Ebrahimi and
92 Taherianfard (2010) reported that individuals, who consume rice, are exposed to significant
93 concentration of heavy metals.

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

98 contaminated with toxic heavy metals through oil spillage and waste disposal in the water
99 body. Fyनेface *et al.*, (2018) reported that the concentration of nickel in periwinkles obtained
100 from Eagle Island River was above the tolerable limit. In a study carried out by Iweala *et al.*,
101 (2014) in Nigeria, they discovered the presence of various heavy metals above the WHO
102 tolerable limits in different kinds of foods; nickel was present in roasted meat (also called
103 suya), roasted plantain (also called bole), cassava flour (also called fufu), beans, roasted fish
104 and yam flour (also called amala). Mercury was also present in roasted plantains above the
105 tolerable limits.

106 Most spices and seasonings, cooking oil, bread, noodles, tea, vegetables and snacks may also
107 be contaminated with heavy metals through handling them with contaminated hands or
108 through other means. Binns *et al.*, (2003) reported that vegetables irrigated by contaminated
109 water elevate the possibility of the presence of heavy metals in the vegetables. Khan *et al.*,
110 (2014) also reported that significant amounts of heavy metals have been detected in natural
111 food spices mainly due to heavy metal contamination.

112 **2.2 Soft and Alcoholic Drinks**

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

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

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

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

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

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

139 **2.3 Cigarette Smoking**

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

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

152 **2.4 Inhalation**

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

160 **3.0 THE CHEMICAL FORMS OF HEAVY METAL FILTERED BY THE** 161 **GLOMERULUS AND TRANSPORTED IN THE KIDNEY**

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

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

169 During acute heavy metal intoxication, the heavy metal ions bind rapidly to albumin (at the
170 free sulfhydryl group of terminal cysteine and histidine residues) in the plasma (Ferguson *et*
171 *al.*, 2001), with usually a small fraction of the heavy metals escaping this binding. Thus, in
172 this type of intoxication, the plasma contains both the free (ionized) and bound forms of the
173 heavy metal, and are both filtered by the glomerulus into the proximal tubule (Barbier *et al.*,
174 2005).

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

187 **4.0 RENAL REABSORPTION OF HEAVY METALS**

188 **4.1 In acute intoxication**

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

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

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

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

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

214 In the loop of Henle, ferrous, cadmium, zinc and other divalent heavy metal cations are
215 reabsorbed probably through both paracellular and transcellular pathways (Barbier *et al.*,
216 2004); the paracellular passive reabsorption of cations being propelled by a positive voltage
217 in the lumen generated by $\text{Na}^+\text{K}^+\text{2Cl}^-$ cotransport and K^+ recycling in the apical membrane;
218 with this membrane the DMT1 transporter (Ferguson *et al.*, 2001).

219

220 **4.2 In chronic intoxication**

221 As earlier stated, in chronic intoxication, mainly complexed forms of the heavy metals such
222 as metal-metallothionein and metal-glutathione are present in the ultrafiltrate, and these
223 complexed heavy metals are reabsorbed in the proximal tubule through a process of
224 endocytosis. Also, some of the metal-glutathione complexes are broken down by the enzyme
225 glutamyltransferase (GGT) to produce the metal bound to cysteine residues (Cysteine-metal
226 conjugates) to be transported by the sodium ion-amino acid cotransporter (Barbier *et al.*,
227 2005).

228 **5.0 HEAVY METALS-INDUCED RENOPATHIES**

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

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

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

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

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

253 **6.0 COMPENSATORY ACTIONS OF THE KIDNEYS TO HEAVY METAL-** 254 **INDUCED CKD**

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

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

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278 **7.0 CONCLUSION**

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

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