Heavy metals as environmental risk factors for cardiovascular diseases: from the perspective of the renin angiotensin aldosterone system and oxidative stress

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ABSTRACT

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels. CVDs were responsible for approximately 31% of all global deaths in 2016, and 85% of all CVD deaths are due to heart attack and stroke. The underlying process in the blood vessels that results in heart attack and stroke is atherosclerosis. A recent study indicated that exposure to environmental toxic heavy metals is associated with an increased risk of CVDs. In this review, we focus on several heavy metals as environmental risk factors for CVDs: arsenic, lead, cadmium, mercury, chromium and iron. The pathological contribution of these heavy metals to the alternation of two molecular mechanisms: the renin angiotensin aldosterone system (RAAS) and oxidative stress has been discussed. The etiology of heavy metal-induced CVDs is viewed from the perspective of RAAS and oxidative stress. The significance of environmental improvement for better health will also be considered.

Keywords
Cardiovascular diseases, Environmental risk factors, Heavy metals, Oxidative stress, Renin angiotensin aldosterone system, Sustainable Development Goals

1. Introduction

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels (Mendis et al., 2011). An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths (Riley et al., 2017). Despite considerable advances in diagnosis, prevention and treatment, CVDs remain the leading causes of death globally (Cosselman et al., 2015). Of all deaths related to CVDs, 85% are due to heart attack and stroke (Riley et al., 2017). These two types of CVDs are caused by atherosclerosis, where fatty deposits (plaques) are formed on the inner walls of the blood vessels that supply blood to the heart or brain (Mendis et al., 2011; Riley et al., 2017). To prevent CVDs, researchers need to understand not only the mechanism underlying CVDs but also the contribution of risk factors to the development of CVDs.

The cardiovascular system is highly vulnerable to various environmental risk factors, including air pollution, tobacco smoke, chemicals and heavy metals (Cosselman et al., 2015). The risks from exposure to environmental agents are increasingly recognized (Solenkova et al., 2014; Cosselman et al., 2015; Riley et al., 2017). A recently published systematic review and meta-analysis by Chowdhury et al. (2018) revealed the importance of environmental toxic heavy metals in cardiovascular risk.

In this review, we focus on heavy metals, namely- arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg), chromium (Cr) and iron (Fe) - as environmental risk factors involved in CVDs. Their pathological contribution to the alternation of two molecular mechanisms, the renin angiotensin aldosterone system (RAAS) and oxidative stress, is discussed here. RAAS plays an important role in maintaining blood pressure and body fluid (Oparil et al., 2018). Inappropriate activation of RAAS will increase blood pressure (i.e. hypertension) (Oparil et al., 2018), which may lead to CVDs (Mendis et al., 2011; Cosselman et al., 2015; Riley et al., 2017). Oxidative stress produces molecular damage, causes formation of atherosclerotic plaques (Cervantes Gracia et al., 2017), and has been implicated in the pathology of atherosclerosis (Alissa and Ferns, 2011; Cosselman et al., 2015). The etiology of CVDs induced by heavy metals is viewed from the perspective of RAAS and oxidative stress.
2. CVDs and their risk factors

CVDs include diseases of the heart, the brain, and blood vessels (Mendis et al., 2011). The different types of CVD are listed below (Mendis et al., 2011; Riley et al., 2017):

I. CVDs due to atherosclerosis

(a) coronary artery disease (e.g. heart attack) – caused by the narrow and hardened arteries that supply blood to the heart muscle;
(b) cerebrovascular disease (e.g. stroke) – caused by impaired blood flow to the brain due to narrowed cerebral arteries;
(c) peripheral vascular disease – disease of the blood vessels supplying blood outside the heart and brain (e.g. to the arms and legs);

II. Other CVDs

(a) rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever caused by streptococcal bacteria;
(b) congenital heart disease – malformation of heart structure existing at birth;
(c) cardiomyopathy – disorder of the heart muscle;
(d) cardiac arrhythmias – disorder of the electrical conduction system of the heart;

Heart attack and stroke are two major causes of CVD deaths (Riley et al., 2017). The underlying process that results in coronary artery disease (heart attack), cerebrovascular disease (stroke) and peripheral vascular disease is atherosclerosis (Mendis et al., 2011).

In this process, fatty substances and cholesterol are deposited inside the lumen of medium- and large-sized blood vessels (arteries). As the deposits (plaques) build up, the inner surface of the blood vessels becomes irregular and the lumen becomes narrow, thereby blocking the blood flow. Eventually, the plaques can rupture, triggering the formation of a blood clot (thrombosis). When a blood clot develops in a coronary artery or a cerebral blood vessel, it causes heart attack and stroke, respectively (Mendis et al., 2011; Riley et al., 2017).

The behavioral risk factors for atherosclerosis are unhealthy diet (rich in salt, fat and energy intake), physical inactivity, tobacco use, and harmful use of alcohol (Mendis et al., 2011). The effects of behavioral risk factors are raised blood pressure (hypertension), raised blood sugar (diabetes), raised blood lipids, and obesity (Mendis et al., 2011). These risk factors can be attributed to the modifiable behaviors of individuals (Cosselman et al., 2015).

On the other hand, exposure to environmental pollutants or agents, which cannot be controlled by individuals, can also contribute to the development of CVDs. Environmental risk factors need to be recognized (Solenkova et al., 2014; Cosselman et al., 2015; Riley et al., 2017). These environmental agents enter the body through dermal absorption, inhalation, or ingestion; and may elicit cardiovascular dysfunction via augmentation or perturbation of CVD pathways (Cosselman et al., 2015).

Globally, about one third of CVD is attributable to ambient and household air pollution (13% and 17% respectively), second-hand tobacco smoke (3%), and exposure to lead (2%) (Prüss-Üstün et al., 2006; Riley et al., 2017). Various other environmental and workplace exposures increase the risk of CVDs, including arsenic (As) in drinking-water and high noise levels (Riley et al., 2017). Therefore, the contributions of both behavioral and environmental risk factors should be understood in order to cope with and reduce the risks for CVDs (Cosselman et al., 2015; Chowdhury et al., 2018).

3. Heavy metals as risk factors for CVDs

Heavy metals are commonly defined as naturally occurring elements with high atomic weight and a specific density of greater than 5 g/cm$^3$ (Alissa and Ferns, 2011; Planchart et al., 2018). Heavy metals are widely distributed in the earth’s crust (Alissa and Ferns, 2011). Some heavy metals such as copper (Cu), Fe, manganese and zinc are essential in trace amounts to maintain human metabolism (Martinez-Finley et al., 2012).

The toxicity of heavy metals at high levels of exposure is well known (Alissa and Ferns, 2011). Contamination caused by such metals is still a global concern. For example, Cd causes skeletal damage and its effect is manifested in the itai-itai (ouch-ouch) disease, which was reported in the 1950s in Japan and is caused by Cd-containing industrial waste water (Alissa and Ferns, 2011). Skin lesions and cancers in the lung, bladder and skin are caused by As (Oberoi et al., 2014). Drinking water contamination caused by As is a public health problem in several countries such as Bangladesh, Vietnam and Chile (Smith et al., 2000; Nordstrom, 2002). Recent investigations reported the presence of As in rice grains grown in As prone areas (Sandhi et al., 2017; Maher et al., 2018), heavy metal contamination in fruits and vegetables (Shaheen et al., 2016; Massadeh and Al-Masaedh, 2018) and in soils near an electronics manufacturing facility (Wu et al., 2018).

Heavy metals can enter the human body by various routes: food intake, cosmetics, environmental contamination, and occupational exposure (Alissa and Ferns, 2011; Solenkova et al., 2014). The concentration of heavy metals in human blood is summarized in Table-1. Chronic exposure to high levels of heavy metals has been associated with harmful effects, but it is suggested that continual
exposure to relatively low levels of heavy metals may also lead to adverse health effects (Alissa and Ferns, 2011). Recently, Chowdhury et al. (2018) conducted a systematic review and meta-analysis of epidemiological studies that investigated the association of five metals (As, Pb, Cd, Hg and Cu) with the risk of CVDs. The authors identified 37 unique studies comprising 348,259 non-overlapping participants, with 13,033 cases of coronary heart disease (heart attack), 4,205 cases of stroke, and 15,274 cases of composite CVDs (comprising heart attack and stroke). This study indicates that exposure to As, Pb, Cd and Cu is associated with an increased risk of coronary heart disease (heart attack) and overall CVDs, but Hg is not associated with cardiovascular risk. In addition, the authors carried out a dose-response meta-analysis and observed a linear association (a) between As level in well water and the risk for overall CVDs, (b) between blood Pb level and the risk of heart attack, (c) between urine Cd level and the risk for overall CVDs, and (d) between urine Cd level and the risk of heart attack. This analysis indicates that there is a link between exposure to these metals and risk of CVDs even at low concentrations highlighting the importance of environmental toxic metals in enhancing cardiovascular risks.

Table 1. Concentrations of heavy metals in human blood found in different studies.

| Heavy metal | Permissible limit (µg/L) | Concentration (µg/L) | Study location (city, country) | No. of samples | Measurement method | Study |
|-------------|--------------------------|----------------------|-------------------------------|----------------|-------------------|-------|
| As          | < 1 (ATSDR, 2007)        | 10.8*                | Araihazar, Bangladesh        | 849*           | Inductively coupled plasma mass spectrometry | Hall et al., 2006 |
|             |                          | 1.0–80.2 (8.8*)      | Araihazar, Bangladesh        | 317*           | Inductively coupled plasma mass spectrometry | Howe et al., 2016 |
| Pb          | < 100 (Alli, 2015)       | 43.39* ± 52.65‡      | Granada, Spain               | 162*           | Atomic absorption spectrophotometry | Gil et al., 2011 |
|             |                          | 35.59* ± 17.72‡      | Central Anatolia, Turkey     | 486*           | Atomic absorption spectrophotometry | Kayaaltı et al., 2015 |
|             |                          | 26–443               |                               |                |                   | Chowdhury et al., 2018 |
| Cd          | 0.3–1.2 (WHO, 1996)      | 0.49* ± 0.61‡        | Granada, Spain               | 162*           | Atomic absorption spectrophotometry | Gil et al., 2011 |
|             |                          | 1.25* ± 0.87‡        | Central Anatolia, Turkey     | 486*           | Atomic absorption spectrophotometry | Kayaaltı et al., 2015 |
|             |                          | 0.44–1.3             |                               |                |                   | Chowdhury et al., 2018 |
| Hg          | 5.8 (Riaz et al., 2016)  | 4.90*                | Augusta Bay, Italy           | 224*           | Atomic absorption spectrophotometry | Bonsignore et al., 2016 |
|             |                          | 0.004–3.5            |                               |                |                   | Chowdhury et al., 2018 |
| Cr          | 0.10–0.16 (ATSDR, 2012) | 1.31* ± 3.01‡        | Granada, Spain               | 178*           | Atomic absorption spectrophotometry | Gil et al., 2011 |
|             |                          | 12.45* ± 20.28‡      | Jinan, China                 | 115*           | Inductively coupled plasma mass spectrometry | Wang et al., 2012 |
| Fe          | 500–1500 (Yuen and Gossman, 2018) | 473.00* ± 88.00* × 10³ | Taiwan                      | 50*            | Atomic absorption spectrophotometry | Chin-Thin et al., 2002 |
|             |                          | 446.01* ± 81.87* × 10³ | Central Anatolia, Turkey     | 486*           | Atomic absorption spectrophotometry | Kayaaltı et al., 2015 |

Abbreviations: *, individuals exposed to heavy metal; ‡, healthy individuals; *, mean; ‡, standard deviation; #, refer to the study for details

4. Renin angiotensin aldosterone system (RAAS)

The RAAS is a key component of blood pressure homeostasis and plays a central role in regulating cardiovascular and renal function (Nabi et al., 2013). Renin specifically cleaves angiotensinogen to produce the decapeptide angiotensin-I (Ang-I), which is the rate-limiting step of the RAAS cascade (Skott and Jensen, 1993). Next, the dipeptidyl-carboxyl peptidase, angiotensin-converting enzyme (ACE), cleaves decapetide Ang-I into an octapeptide angiotensin-II (Ang-II) (Nafitlan et al., 1991; Rogerson et al., 1992; Schunkert et al., 1992; Ye et al., 2006) (Fig. 1A). The principal effector molecule, Ang-II, initiates various intracellular signal transduction cascades after binding to its receptors: the angiotensin II type 1 receptor (AT1R) and the angiotensin II type 2 receptor (AT2R) (Forrester et al., 2018).

Interaction with AT1R results in an increase of blood pressure by facilitating vascular constriction and by increasing sodium reabsorption in the kidney (Murphy et al., 1991; Goodfriend et al., 1996; Romero et al., 2015). On the other hand, binding of Ang-II
The binding of Ang-II to the AT1R causes ROS formation via NADPH oxidase dependent pathway involving phosphorylation of the phospholipase A2 (PLA2), phospholipase D (PLD) and protein kinase C (PKC). Among the ROS, hydroxyl radical (·OH) directly causes impairments of biomolecules (i.e. lipid oxidation, DNA damage) to bring about cellular oxidative stress. SOD: superoxide dismutase.

to the AT2R causes vasodilation and excretion of sodium in the urine by the kidney, and protects against hypertensive target-organ damage (Summers et al., 2015). Ang-II also stimulates the production of the steroid hormone, aldosterone, which is the final product of the RAAS cascade (Takeda et al., 1995; 1996). Aldosterone binds to the mineralocorticoid receptor and regulates the transcription of target genes, resulting in the upregulation of electrolyte flux pathways in the kidney (Silva et al., 1977). Disruption in the orchestration process of RAAS can lead to adverse effects on fluid homeostasis, which in turn may lead to organ damage followed by CVDs.
5. Oxidative stress

Oxidative stress has been defined as an imbalance between the production of free radicals or reactive oxygen species (ROS) and antioxidant defenses (Sies, 1997). Free radicals such as the hydroxyl radical (·OH), superoxide anion (O₂⁻), nitric oxide (NO⁻), and peroxynitrite (ONOÖ) are molecules with increased chemical reactivity that contain unpaired electrons (Yoshikawa and Naito, 2002). Free radicals can be generated endogenously as the by-products of many biochemical processes within the body including reduction of molecular oxygen during aerobic respiration (Betteridge, 2000) and/or through exogenous factors e.g. food agents, xenobiotics, smoking, gamma rays, heavy metals etc. (Betteridge, 2000; Frassetto et al., 2001; Kelly, 2003). Excess production of ROS disrupts cell membranes, alters protein expression and damages DNA (Halliwell, 2011). ROS molecules also interact with polyunsaturated fatty acids and induce lipid peroxidation (Barrera, 2012). Thiobarbituric acid reactive substances (TBARS) are the most studied biomarkers of lipid peroxidation, of which malondialdehyde is the best known. Serum TBARS level is a major predictor of cardiovascular events (Walter et al., 2004), and elevated TBARS levels also predict carotid atherosclerotic plaque progression (Salonen et al., 1997).

There are non-enzymatic and enzymatic antioxidant defense mechanisms. Some of the non-enzymatic antioxidants are ascorbic acid, vitamin E, glutathione, lipoic acid, carotenoids and iron chelators (Halliwell, 2011). The enzymatic group includes catalase, the enzymes of the glutathione thioredoxin system and superoxide dismutases (Nordberg and Arner, 2001). Catalase decomposes harmful hydrogen peroxide (H₂O₂) into molecular oxygen and water in both plants and animals (Nicholls, 2012). The glutathione system comprises three enzymes- glutathione reductase, glutathione peroxidase and glutathione-S-transferase, (GST) that protect cells against oxidative damage (Brigelius-Flohe, 1999; Meister and Anderson, 1983). The thioredoxin system comprises thioredoxin protein and thioredoxin reductase which act as scavenging factors for ROS (Arner and Holmgren, 2000). Superoxide dismutases are also antioxidant enzymes that catalyze the dismutation of free radical O₂⁻ by converting it to peroxide that can in turn be removed by catalase or glutathione peroxidases (Marrocco et al., 2017).

6. Alteration of RAAS by heavy metals

According to the WHO and International Agency for Research on Cancer (IARC), As and Cd have been recognized as group I human carcinogens (IARC, 1989; WHO, 1981). Previous studies demonstrated that As contamination in drinking water modulates biochemical (Nabi et al., 2005) as well as immunological and nutritional parameters (Islam et al., 2004; 2007; 2012) in the Bangladeshi population. Hossain et al. (2013) reported that As upregulates AT1R expression through ROS-mediated activation of the c-Jun N-terminal kinase signaling pathway in mouse aortic vascular endothelial cells (Table-2). Studies have documented the involvement of AT1R-mediated signaling in endothelial dysfunction, leading to hypertension (Hunyady and Catt, 2006). Chronic low-level exposure to Pb results in increased activity of ACE in rats and elevated levels of plasma renin, Ang-II, and aldosterone in both animals and humans (Table-2) (Vaziri and Sica, 2004; Simões et al., 2011). It has been reported that exposure to Cd results in cardiovascular diseases in humans (Navas-Acien et al., 2004; Tellez-Plaza et al., 2007). Acute Cd exposure probably induces endothelial dysfunction by a mechanism involving the increased local production of Ang-II by stimulating ACE activity, which could contribute to the establishment of hypertension (Table-2) (Puri, 1992; Angeli et al., 2013). High levels of Hg present in hair and blood were found to increase the risk of hypertension (Bautista et al., 2009). Wildemann et al. (2016) reported that only methyl Hg(I) has an effect on the RAAS. A much longer oral exposure to Hg(II) in male Wistar rats was shown to produce a significant increase in plasma renin and ACE levels (Table-2) (Carmignani et al., 1999). Cr has been reported to lessen the activity of the RAAS (Talpur et al., 2003; Perricone, et al., 2008). ACE activity was significantly lower or tended to be lower in male and female Sprague-Dawley rats consuming greater concentrations of niacin-bound Cr, resulting in reduced circulating Ang-II levels (Table-2) (Perricone et al., 2010). Chaudhary et al. (2018) reported that Fe overload significantly increased retinal renin expression in mice.

| Heavy metal | Effect on RAAS | References |
|-------------|---------------|------------|
| As          | Increases expression of AT1R (in mouse) | Hussain et al., 2013 |
| Pb          | Chronic exposure increases ACE activity (in rat), plasma renin activity, renin and aldosterone concentration (in both human and animals) | Vaziri and Sica, 2004; Simões et al., 2011 |
| Cd          | Increases local production of Ang-II via stimulation of ACE (in rat) | Angeli et al., 2013 |
| Hg          | Increases plasma renin and ACE levels (in rat) | Carmignani et al., 1999; Wildemann et al., 2016 |
| Cr          | Decreases ACE activity and Ang-II concentration (in rat) | Perricone et al., 2010 |
| Fe          | Increases renin expression (in mouse) | Chaudhary et al., 2018 |
through succinate receptor signaling, which caused neurodegeneration and vascular abnormalities (Table-2).

7. Modulation of oxidative stress by heavy metals

Toxicity of As causes increased production of ROS such as H$_2$O$_2$ as well as reactive nitrogen species, the dimethylarsenic radical, blood nonprotein sulphydryl and/or oxidant-induced DNA damage in humans and animals (Table-3) (Shi et al., 2004; Flora et al., 2007). Pb is reported to inhibit functional sulphydryl groups in several oxidative stress scavenging enzymes, thus altering their antioxidant activities (Table-3) (Chiba et al., 1996). Pb exposure also causes an imbalance between generation and removal of ROS in tissues and cellular components, and increased ·OH activity in rats resulting in oxidative stress (Table-3) (Vaziri and Sica, 2004; Patra et al., 2011). Kasprczyk et al. (2014) showed that occupational exposure to Pb induces oxidative stress in erythrocytes leading to elevated blood viscosity. Cd replaces iron and Cu in a number of cytoplasmic and membrane proteins and induces oxidative stress via the Fenton reactions (Casalino et al., 1997). Lipid peroxidation and intracellular glutathione levels are altered in Cd toxicity, which causes oxidative stress (Table-3) (Liu et al., 2009). In addition, Cd exposure suppresses the ROS scavenging activity of antioxidant enzymes (Table-3) (Pizzino et al., 2014). Colacino et al. (2014) found elevated oxidative stress markers after Cd exposure. An acute rise in concentration (0.3 mg/L) of Hg has been linked to inhibition of antioxidant enzyme activity and regulation of a series of gene expressions resulting in the accumulation of oxidative stress (Li et al., 2014). Teixeira et al. (2018) demonstrated that chronic exposure to low doses of inorganic Hg in adult rats led to Hg deposition in the brain parenchyma associated with oxidative stress and deterioration of motor function (Table-3). Toxicity caused by hexavalent Cr was found to be associated with oxidative stress (Velma and Tchounwou, 2013). Reduced Cr reacts with H$_2$O$_2$ to produce ·OH (Table-3) (Setyaningsih et al., 2012). Previously, Shi et al. (1999) also proved that Cr exposure significantly reduces cellular glutathione and NADPH levels (Table-3). Both in vitro and in vivo studies showed that Fe overload causes formation of free radicals that damage cell components (Table-3) (Valko et al., 2016). Sengsuk et al. (2014) found a significant correlation between Fe overload and oxidative stress markers. The O$_2^\cdot$ molecule facilitates Fe release from ferritin which later reacts with more O$_2^\cdot$ and H$_2$O$_2$, forming highly toxic free radicals such as ·OH (Fig. 1B) (McCord, 2004).

Table-3. Heavy metals causing oxidative stress.

| Heavy metal | Effect on oxidative stress | References |
|------------|-----------------------------|------------|
| As         | Increases formation of ROS and blood non-protein sulphydryl (in human and animals) | Shi et al., 2004; Flora et al., 2007 |
| Pb         | Catalyzes the production of ROS, increases ·OH activity and also weakens the antioxidant defense system (in human and animals) | Chiba et al., 1996; Vaziri and Sica, 2004 |
| Cd         | Alters lipid peroxidation, intracellular glutathione levels and antioxidant enzyme activity (in cell culture systems, intact animals and human) | Liu et al., 2009; Pizzino et al., 2014 |
| Hg         | Increases lipid peroxidation and nitrite concentration and decreases total antioxidant capacity (in rat) | Teixeira et al., 2018 |
| Cr         | Produces reactive ·OH, reduces cellular glutathione and NADPH level (in vitro and in human) | Shi et al., 1999; Setyaningsih et al., 2015 |
| Fe         | Augments free radical formation and lipid peroxidation (both in vitro and in vivo) | Valko et al., 2016 |

8. RAAS induces oxidative stress

In addition to the regulation of blood pressure and electrolyte balance, RAAS has been found to be involved in ROS generation (Fig. 1A and 1B) (Cooper et al., 2007; Hitomi et al., 2007; Wen, 2012; Forrester et al., 2018). It has been reported that specific binding of Ang-II to AT$_1$R is a possible free radical production initiating process in vascular smooth muscle cells, endothelial cells and cardiomyocytes via NADPH oxidase (Fig. 1B) (Rajagopalan et al., 1996; Mulrow, 1999; Griendling and Ushio-Fukai, 2000; Hitomi et al., 2007). In general, binding of Ang II to AT$_1$R activates the phospholipase A$_2$, phospholipase D and protein kinase C phosphorylation pathways followed by the generation of O$_2^\cdot$ by NADPH oxidase (Fig. 1B) (Hitomi et al., 2007). O$_2^\cdot$ is then converted into H$_2$O$_2$ by the action of superoxide dismutase (Fig. 1B) (Fridovich, 1997). Ferrous iron catalyzes formation of the hydroxyl free radical from H$_2$O$_2$ (Floyd and Lewis, 1983), which causes DNA damage and lipid oxidation resulting in oxidative stress (Fig. 1B) (Pizzino et al., 2017). In addition, Ang-II can inhibit anti-oxidant enzymes such as, peroxiredoxin-3, superoxide dismutase and catalase, which are involved in the breakdown of ROS (Murtaza et al., 2008; Lijnen et al., 2010; 2012).
Oxidative stress can be one of the primary or secondary causes for many CVDs (Pacher et al., 2007; Panth et al., 2016; Cervantes Gracia et al., 2017). Oxidative stress can initiate atherosclerosis, the main leading cause of CVDs. After endothelial inflammation, circulating low-density lipoprotein cholesterol is oxidized by cellular ROS (Mehta et al., 1998). The oxidized low-density lipoproteins, cellular waste, and surrounding materials accumulate in the innermost layer of the arteries, leading to the formation of atherosclerotic plaque (Zwaka et al., 2001). Additionally, involvement of ROS was reported in the progression of other types of CVD such as rheumatic heart disease, congenital heart disease, cardiomyopathy and cardiac arrhythmias (Mahajan and Tandon, 2004; Jeong et al., 2012; Forrester et al., 2018).

9. Status of oxidative stress and oxidative stress reducing enzyme in Bangladeshi tannery workers

The wastewater of tanneries contains heavy metals such as Cr and Pb which are disposed untreated into rivers or other places near the tannery factories, polluting the environment and affecting the health of both tannery workers and neighborhoods (Rastogi et al., 2008; Biswas and Rahman, 2013). Tannery workers are thus potentially exposed to harmful agents, especially Cr, rendering them...
vulnerable to several health problems along with DNA damage (Rastogi et al., 2008; Ambreen et al., 2014; Ali et al., 2015). We reported that individuals who are exposed to occupational health hazards are under oxidative stress. Their plasma level of TBARS was significantly increased compared with that in healthy individuals (Akther et al., 2016). The activity of GST, an oxidative stress scavenging enzyme, was also measured in the plasma of study participants. Using the raw data of that study (Akther et al., 2016), Pearson bivariate correlation analysis demonstrated a tendency of positive relationship between the duration of work of the tannery workers and their plasma TBARS levels (Fig. 2A) but the relationship was weak as it was not statistically significant. Similarly, a statistically insignificant trend of positive correlation was observed between the work period and GST activity (Fig. 2B).

These results suggest that the more the tannery workers spend time in their working environment, the more they are at risk of oxidative stress and the more their scavenging enzymes try to maintain homeostasis. In addition, GST activity among healthy individuals was found to be positively correlated with the generation of TBARS (Fig. 3A). On the other hand, in the case of tannery workers, no such correlation was observed (Fig. 3B). These findings lead us to hypothesize that GST activity was not able to cope with the production rate of TBARS in the tannery workers i.e. because of excess oxidative damage caused by the working environment, their GST became exhausted. However, in healthy individuals, such exhaustion was not observed; as increasing GST activity was found with increasing levels of TBARS (Fig. 3A).
10. Heavy metal-induced synergistic effect on RAAS and oxidative stress

It is clear from the above discussions that heavy metals and RAAS components lead to oxidative stress. Over production of ROS has been observed in a wide variety of experimental and clinical conditions related to CVDs (Panth et al., 2016; Cervantes Gracia et al., 2017). Moreover, antioxidant therapy has been shown to improve disease conditions in hypertension, atherosclerosis, ischemic heart disease, cardiomyopathies and congestive heart failure (Dhalla et al., 2000). Oxidative stress damages the endothelium leading to apoptosis, death of living cells or tissues and formation of thrombosis resulting in atherosclerosis which is the leading cause of CVDs (Scribano et al., 2014; Cervantes Gracia et al., 2017). Our experimental data showed decreasing GST activity leading to an increased level of TBARS in plasma (Fig. 3B). Studies have demonstrated an association between increased prevalence of CVDs and elevated levels of TBARS in humans (Schisterman et al., 2001; Lee et al., 2012). Thus, individuals exposed to heavy metals have increased oxidative stress and decreased activity of scavenging enzymes. As a result, oxidative stress induced by heavy metals through activation of RAAS and independent generation of ROS through Ang-II may have a synergistically deleterious effect on the cardiovascular system which may precipitate CVDs (Fig. 4).

Fig.4. Heavy metal-induced synergistic effect on RAAS and oxidative stress, leading to CVDs in humans. Heavy metals modulate RAAS and induce oxidative stress through excess generation of reactive oxygen species. Additionally, these metals and RAAS can also directly cause oxidative stress independently. As a result, these incidents all together may exaggerate the oxidative stress condition leading to increased prevalence of morbidity and mortality rates caused by CVDs.

Angiotensin receptor blockers are known to decrease cardiac damage and lessen the risk of nephropathy (Mavrakanas and Lipman, 2018). These blockers can competitively bind with AT1R, which is responsible for vasoconstriction (Fig. 1A) and generation of ROS (Fig. 1B). Controlled treatment with angiotensin receptor blockers may reduce the heavy metal-induced activation of RAAS.
11. Conclusion

In this review paper, we propose that heavy metal-induced synergistic effects on RAAS and oxidative stress lead to CVDs (Fig. 4). If environmental risk factors synergistically increase damage to the cardiovascular system and contribute to the development of CVDs, there should be proper medical attention and guidelines for people working in such an environment. Hence, special attention should be paid to the management of environmental risk factors including heavy metals.

The United Nation’s Agenda for Sustainable Development Goals (SDGs), which includes a comprehensive health goal, was adopted in 2015 (Nunes et al., 2016). The health goal (SDG3) is to ensure healthy lives and promote well-being at all ages. Health target 3.4, related to SDG3, aims to reduce premature mortality from noncommunicable diseases, through prevention and treatment, by one third by 2030. CVDs are noncommunicable. To accomplish health goal SDG3, people should further improve the environment by understanding what environmental factors contribute to the development of CVDs.

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