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REVIEW

Heavy metal-induced lipogenic gene aberration, lipid dysregulation and obesogenic effect: a review

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Abstract

Lipids are high energy, complex biomolecular compounds essential for cellular and organellar membrane formation. Accumulation of circulatory lipids is however associated with pathophysiological conditions including cardiometabolic disorders, diabetic dyslipidemia and obesity. Epidemiological studies have correlated heavy-metal exposure with dyslipidemias and metabolic syndrome. Here, we review the role of cadmium, lead, mercury and arsenic on inducing dyslipidemias through lipid metabolism dysregulation, with focus on metal effects on lipogenic genes, gut microbiome and endocrine secretion. The main gene transcription factors impaired by heavy metals are CCAAT-enhancer binding protein, peroxisome proliferative-activated receptor, sterol regulatory element binding protein, carbohydrate responsive element binding protein and liver × receptor. These factors regulate genes responsible for β-oxidation, *de novo* lipogenesis, and the synthesis and transport of fatty acids, cholesterol, phospholipids and triglycerides. Dysregulated lipid profiles in organisms exposed to metals show higher cholesterol and triglycerides, very low-density lipoprotein and non-high density lipoprotein cholesterol levels, with a corresponding low high-density lipoprotein cholesterol. Hormones and gut microbiome are also impaired by heavy-metal exposure.

Keywords Lipid metabolism · Heavy-metals · Dyslipidemia · Lipogenic genes · Diabetes · Obesity

Introduction

Lipids are hydrophobic molecules that form critical components in organisms, with a functional role of providing both structural and biological support. Lipids are essential for initiating organellar biogenesis and the proliferation of each distinct membrane-bound structures, vesicles and liposomes in the aqueous environment of cells, thus providing a barrier for regulating intracellular exchange of materials among cytoplasmic organelles (Airaodion et al. 2019; Stefan et al. 2017). Aside membrane formation, lipids also insulate neurons, facilitate cell signaling and impulse transmission (Amira et al. 2018), exhibit antioxidant and anti-inflammation properties (Brites et al. 2017) and may demonstrate cardioprotective functions (Nagao et al. 2018). Some forms of lipids are known to act as sensors of cellular stress and thus form important components of signal transduction molecules (Rangholia et al. 2021). Despite their many functional roles in cells, an excess accumulation of lipids in blood plasma and tissues, as a result of lipid-metabolism dysregulation, has striking effects on the health of an organism and has

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been found to contribute to the initiation and progression of pathophysiological conditions such cancers, cardiovascular deterioration, high blood pressure, kidney damage, hyperlipidemia, obesity and diabetes (Deprince et al. 2020; Gai et al. 2019; Nickels 2018). Although lipid redistribution does not necessarily pose a negative health risk to an individual, the location of its accumulation, however influences the overall health of a person. Example, accumulation of fat in visceral adipose tissues and organs relative to its accumulation in subcutaneous layers is reported to be associated with an increased risk of metabolic syndromes (Frank et al. 2019; Małodobra-Mazur et al. 2020). The concerted convergence of excess fat and sugar accumulation, hormonal imbalance, alterations in lipid and sugar metabolism genes, gut microbiome perturbation and de novo lipogenesis, resulting from heavy metal exposure, are among the many factors that may contribute to higher risk of lipid-related metabolic syndromes. Multiple reports, as reviewed in this study (Afolabi et al. 2015; Chi et al. 2019b; Skoczyńska et al. 1993; Zhou et al. 2016), reveal that acute or chronic exposure to heavy metals in humans or other organisms result in serum lipid profile dysregulation with a significant increase in total cholesterol, triglyceride, low-density lipoprotein cholesterol and non-high density lipoprotein cholesterol levels while contemporaneously leading to a decline in high-density lipoprotein cholesterol levels. The disproportionate increase in triglyceride, low-density lipoprotein cholesterol and total cholesterol or a combination thereof, and the corresponding decline in high-density lipoprotein cholesterol in bloodserum defines the condition of dyslipidemias (Li et al. 2021). This comprehensive review therefore explores how heavy metals alter the parameters of serum lipid profiles in model organisms (mice, rats, zebrafish) and in humans, and how these changes affect the quality of life.

Exposure and toxicokinetics of heavy metals

Sources and heavy metal toxicokinetics

The ubiquitous nature of heavy metals and their widespread toxicities in plants, animals and humans have been of major concern over the past several decades. Though heavy metals are released into the environment through natural processes such as erosion, spring waters and volcanic eruptions, the increased rate of anthropogenic activities such as fossil fuel combustion, agricultural activities and industrialization have accounted for the recent surge in heavy metal pollution and their overaccumulation on viable agricultural lands, water bodies and air, thus making human exposure inevitable (Briffa et al. 2020; Ferrante et al. 2019; Tchounwou et al. 2012). Cadmium (Cd^{2+}), lead (Pb^{2+}) and mercury (Hg^{2+}) are among the most bio-persistent toxic metals with a high ability to bioaccumulate in cells and tissues, but difficult to excrete once in cells, especially when the victim suffers from iron, calcium or zinc deficiency (Moiseenko and Gashkina 2020; Schaefer et al. 2020) whereas approximately 70 to 80% of arsenic (As^{3+}), a metalloid, can be largely excreted through urine, with hair, nail sweat and feces also contributing to As^{3+} removal (Chen et al. 2013; Roy et al. 2020). These heavy metals are ranked highest among the list of priority metals considered to be of great public health concern. Whereas cadmium occupies the seventh position, arsenic, lead and mercury are first, second and third, respectively, on the basis of their frequency of occurrence, toxicity and potential for human exposure (ATSDR 2020). These heavy metals were selected for this review based on experimental studies demonstrating their toxicities in tissues and cells after exposure (Cartularo et al. 2015; Elmorsy et al. 2021; Rosales-Cruz et al. 2018) and in cross-sectional studies involving human population with chronic or acute exposure (Ayoub et al. 2021; Kang et al. 2021), and for the fact that their primary medium of exposure is through inhalation [of polluted air], ingestion [of contaminated food and water], and to some extent, dermal contact, which all constitutes daily human routine (Ferrante et al. 2019; Kumari et al. 2021; Rivas-Santiago et al. 2019). With drinking water as the major source of human and animal exposure, the maximum permissible limit has been restricted to 10 µg/L (As^{3+}) (Kumar et al. 2020), 2 µg/L (Hg^{2+}) (Rana et al. 2017), 15 µg/L (Pb^{2+}) (Sui et al. 2020) and 5 µg/L (Cd^{2+}) (Kubier et al. 2019). In spite of these restrictions, most countries are reported to have metal concentrations in drinking water exceeding this stipulated permissible limit (Alidadi et al. 2019; Cobbina et al. 2015; Shaji et al. 2021; Tanvir et al. 2021). Moreover, blood, as transport medium for metals, is often used as reliable indicator for recent exposure to quantify toxicity level. The maximum tolerable blood-metal limit is indicated as Cd^{2+} (10 µg/dL) and Pb^{2+} (5 µg/dL) (Xu et al. 2021), As (1 µg/L) (Kumar et al. 2020) and Hg^{2+} (< 20 µg/L) (Ye et al. 2016) but these concentrations only reflect recent exposures and not necessarily long time exposure since they rapidly disappear from blood and are distributed to tissue storage sites. Due to the high level of toxicity associated with lead (Pb^{2+}), a net zero permissible limit in drinking water is recommended since even low-levels represent a risk factor for lipid metabolism dysregulation (Xu et al. 2021). Achieving this target however remains a challenge, even in effluent communities, due to the pervasive nature of this metal, with reports indicating that even certified lead-free plumbing products could leach Pb at a concentration greater than 1 µg/L as shown in a laboratory study (Parks et al. 2018).

Cadmium, mercury, lead and arsenic are all potent hepatotoxic heavy metals/metalloid which are easily incorporated into the food chain through absorption by plants and

animals, and subsequent biotransformation especially in aquatic organisms (Zhang et al. 2019). These metals are mostly present in their divalent forms and thus compete with essential metal ions for binding sites to be transported into cells and tissues. Once transported into cells, they bind strongly to proteins and nucleic acids, induce oxidative stress through reactive oxygen species generation which destroys macromolecular structures and disrupt their cellular function (Briffa et al. 2020; Engwa et al. 2019), alter lipid metabolism profile in the liver and induce epigenetic changes in the expression and function of lipid metabolism genes (Cartularo et al. 2015; Cheng et al. 2011; Lacerda Leocádio et al. 2020). Mercury, often converted to its toxic methylmercury form by bacteria in soil or water, enters the food chain and bioaccumulates in plants and fishes (Chang et al. 2020; Donadt et al. 2021; Vieira et al. 2021), has been associated with decreasing the antioxidant status of glutathione, increases oxidative stress and inflammation, alters lipid profile and influence the development of dyslipidemias, cardiovascular diseases, obesity and hypertension (Park and Seo 2017). Similarly, though arsenic (a metalloid) is toxic in all its oxidation states and forms, the inorganic trivalent arsenic (arsenite, As^{3+}) is known to be highly toxic compared to its oxidized pentavalent arsenic (arsenate, As^{5+}) (Kumari et al. 2021), and these modifications into different states are facilitated through bacterial metabolism and by the environment where As is exposed (Ferrante et al. 2019; Kumari et al. 2017; Rivas-Santiago et al. 2019).

Reports from in vivo, in vitro and epidemiological studies show a close association between chronic or acute heavy metal exposure and dyslipidemias as manifested by the upregulation in triglyceride, low-density lipoprotein cholesterol and total cholesterol levels with a corresponding decrease in high-density lipoprotein cholesterol levels (Cheng et al. 2011; Cho et al. 2020; Go et al. 2015; Olisekodiaka et al. 2012; Park and Seo 2017). The changes in these lipid profile markers are clinically used to determine one's susceptibility to developing metabolic syndromes such as diabetes, hypertension, obesity, stroke and heart diseases. Therefore, the ability for heavy metals to alter serum lipid profile through DNA damage, epigenetic modification via DNA methylation, lipid peroxidation induction and the dysregulation of several metabolic pathways, pose a significant health risk to individuals and could serve as a precursor for the initiation and progression of clinical conditions (Rivas-Santiago et al. 2019).

Heavy metal toxicology and metabolism dysregulation

Experimental and epidemiologic evidence indicate that acute and chronic exposure to heavy metals is associated with the development of clinical and metabolic symptoms relating to immunotoxicity, hepatotoxicity, cardiovascular disorders, cognitive deficiencies, nephrotoxicity, hypertensions, dyslipidemia and diabetes mellitus (He et al. 2015; Lamas et al. 2016; Nie et al. 2016). These toxicities elicited by heavy metals have been studied, and the mechanisms and pathways involved illustrated to some extent to aid the development and discovery of therapeutic agents. By altering the cellular and biochemical pathways of glucose, lipids and proteins metabolism and facilitating the induction of membrane phospholipid abnormalities through oxidative damage, toxic metals evoke lethal effect to cells by inducing apoptosis and a subsequent cell death in the process (Rivas-Santiago et al. 2019; Tinkov et al. 2021). Studies in recent years have tightly linked glucose and lipid metabolism dysregulation to the presence and accumulation of heavy metals within tissues and organs (Bambino et al. 2018; Wang et al. 2018a). It is widely reported that these toxic metals directly disrupts lipid and glucose metabolism by altering both glucose and lipogenic gene expressions (Adebayo et al. 2015; Sun et al. 2017; Zhang et al. 2018), disrupting endocrinal cell function and the release of hormones (Rana 2014; Sabir et al. 2019), altering the functioning of cell surface receptors and the uptake of glucose and lipids (Ficková et al. 2003), and influencing de novo lipogenesis (Adebayo et al. 2015), thus inducing lipid dysregulation and redistribution resulting in fat accumulation, weight gain and obesity (Fig. 1).

Heavy metals are also known to inhibit insulin signaling and have been suggested to be responsible for indirectly promoting de novo lipogenesis as a result of surge in circulating glucose among hyperglycemic patients (Leff et al. 2018). Cd^{2+}, Pb^{2+}, As^{3+} and Hg^{2+} are reported to influence the redistribution of cholesterol, fatty acids and triglycerides into various tissues and cells. Whereas multiple studies indict these heavy metals for their association with lipid metabolism disorders (Cheng et al. 2011; Feng et al. 2015; Go et al. 2015; Lacerda Leocádio et al. 2020), an assessment study by Rotter et al. (2015) and Padilla et al. (2010) showed a negative correlation to that effect which prompts the need for further investigation to confirm their specific role in lipid metabolism. It should however be noted that in contrast to these two reports, a substantial amount of experimental evidence associates heavy metals with lipid metabolism disorders and obesity (Attia et al. 2021) but a review on how they affect lipid metabolism genes and lipid regulatory factors is yet to be examined, hence this study seeks to partially fill this knowledge gap by evaluating available data through the years.

Lipoprotein and heavy metal interaction

Lipid transport and lipoprotein formation

The liver is the central organ for regulating systemic glucose and lipid metabolic fluxes (Mu et al. 2019). The principal

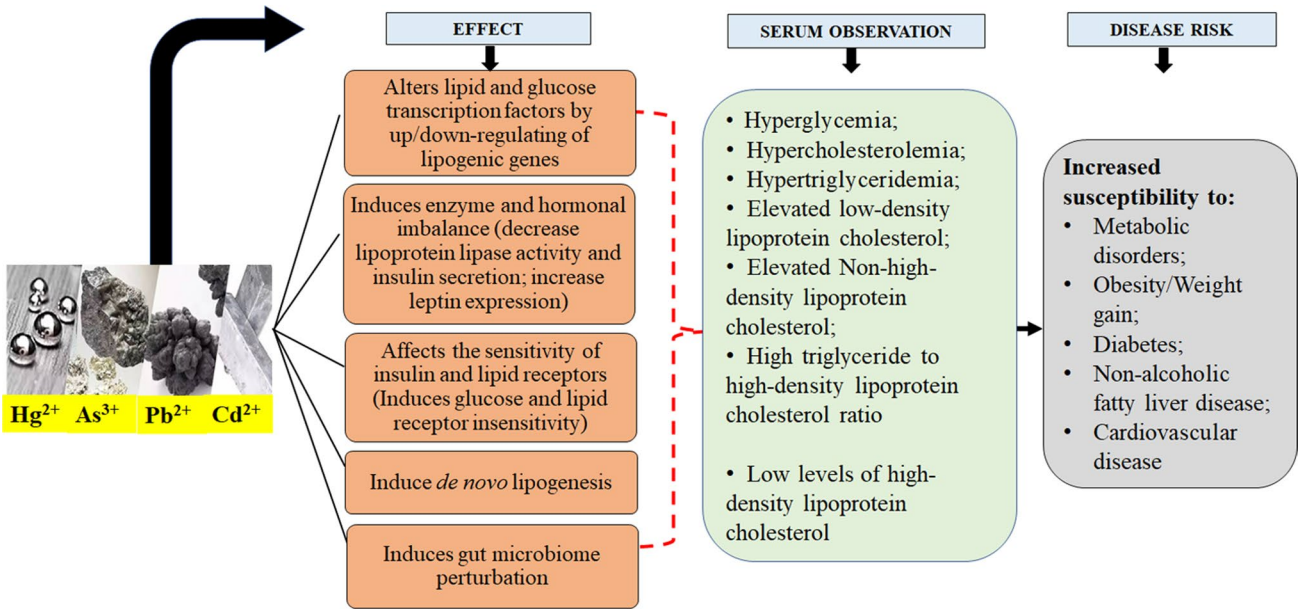


Fig. 1 Exposure of heavy metals to cells and tissues induces serum lipid profile dysregulation which results in the initiation and progression of several metabolic syndromes

sources of these systemic lipids are from dietary absorption and de novo lipogenesis. Absorbed lipid molecules from digestion, modified by the endoplasmic reticulum, are transported to the liver in association with hydrophilic protein molecules by forming a lipid-protein complex known as lipoprotein, due to the water insoluble nature of the absorbed lipid products (Wang et al. 2013).

Lipoproteins are macromolecular complexes consisting of a mixture of proteins and lipids with a cholesterol esters and triglyceride central core, surrounded by free cholesterol, phospholipids, and apolipoproteins which facilitates the formation and function of the lipoprotein. Apolipoproteins which binds to the surface of the lipoprotein structure are essential for lipoprotein stabilization, activation of lipophilic enzymes and facilitates the binding of low density lipoproteins to lipoprotein receptors on cell surface to aid their uptake (Gursky 2015). Plasma lipoproteins are classified into six groups based on size variations, lipid composition and apolipoproteins, and these include chylomicrons, chylomicron remnants, very low-density lipoprotein, intermediate density lipoprotein, low-density lipoprotein and high-density lipoprotein.

Lipoprotein metabolism and the effect of heavy metals

Lipoprotein metabolism occurs via two main pathways, exogenous and endogenous, depending on whether its origin is of dietary or hepatic source (Fig. 2). In exogenous pathway, dietary lipids are incorporated into chylomicrons in the intestines and absorbed into blood. During circulation, lipoprotein lipase found on the surface of endothelial cells cleaves the triglycerides from the chylomicrons which further hydrolyzes the triglycerides into fatty acids, diglycerides and monoglycerides (Zhyvotovska et al. 2019). These lipid components then diffuse into cells to be oxidized for the release of energy or become incorporated into adipose tissues to be re-synthesized into triglycerides and stored as fat (Ory 2007; Tao et al. 2020). In endogenous lipoprotein pathway, triglycerides synthesized in the liver are packaged into very low-density lipoprotein. The triglycerides carried in very low-density lipoprotein are stripped and hydrolyzed by the action of lipoprotein lipase, which then diffuses into muscle and adipose tissues to be metabolized or re-synthesized into storage fat. Very low-density lipoprotein after releasing its triglyceride is converted into intermediate density lipoprotein which is further metabolized to low-density lipoprotein (Behl et al. 2020; Feingold and Grunfeld 2018).

Heavy metals are a major disruptor to the homeostatic regulation of circulating lipids and the expression of lipid receptors. Afolabi et al. and Liu et al. observed an increase in total plasma cholesterol levels in rats after exposure to Cd^{2+} and reported that the reduced efflux of very low-density lipoprotein cholesterol was as a result of low-density lipoprotein activity loss or a decrease in low-density lipoprotein receptor function, leading to a decrease in low-density lipoprotein catabolism (Afolabi et al. 2012; Liu et al. 2020). Jolibois et al. (1999) also observed a decrease in the mRNA expression of low-density lipoprotein receptor (*LDLR*) in human placental cells after exposure to Cd^{2+}. Similarly, Chi et al.

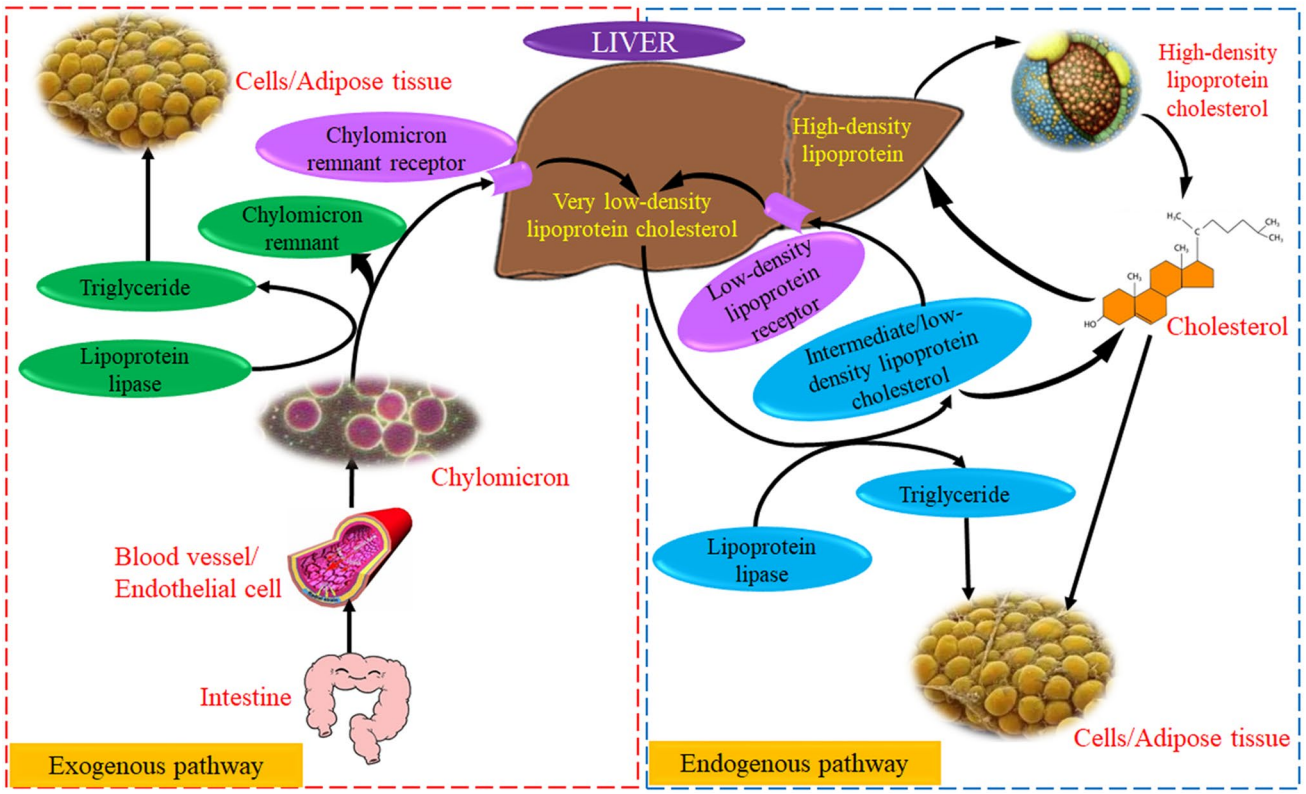


Fig. 2 Exogenous lipoprotein pathway is characterized by dietary lipid absorption, metabolism and transport to liver, cells and adipose tissue. Endogenous lipoprotein pathway involves the formation of very low-density lipoprotein from triglyceride and cholesterol esters, its efflux from the liver, metabolism, distribution to cells and recycling

(2019a) observed that expression of the cholesterol transporter genes low-density lipoprotein receptors (*LDLR*) and scavenger receptor class B type 1 (*SCARB1*) were significantly lower in mice exposed to arsenic compared to the control, suggesting that this effect might have been responsible for the high serum cholesterol levels. These findings together indicate that exposure to toxic metals can influence the levels of plasma cholesterol and low-density lipoprotein lipids by downregulating the expression and function of *LDLR*, lipoprotein lipase (*LpL*) and other lipid transporters, receptors and metabolism genes. Moreover, a decrease in the activity of lipoprotein lipase, as a result of metal inhibition, could also account for the reduced catabolism of very low-density lipoprotein and may explain the elevation of circulating proatherogenic lipid (Afolabi et al. 2012).

De novo lipogenesis and lipid accumulation

De novo lipogenesis is a complex and highly regulated biosynthetic pathway by which fatty acids are synthesized from acetyl CoA subunits produced within cells from various sources, especially from carbohydrate catabolism (Song et al. 2018). This metabolic process often takes place in the liver when excess sugars, which are not metabolized or stored as glycogen under physiological conditions, are converted into fatty acids and then esterified into triglycerides (Yilmaz et al. 2016). The process begins with an ATP-dependent carboxylation of acetyl coenzyme A (CoA) subunits to malonyl-CoA, catalyzed by the enzyme acetyl CoA carboxylase. With an acetyl CoA serving as a primer, malonyl CoA's are attached through the action of the multifunctional enzyme complex, fatty acid synthase. The sequential addition of the two-carbon malonyl CoA generates an elongated fatty acid which is then esterified into triglyceride (Sanders and Griffin 2016).

Initiation of de novo lipogenesis occurs mostly by feeding on hypercaloric or high-carbohydrate diet which results in sugar overload. De novo lipogenesis from carbohydrate, however, is an energetically expensive process due to its ATP-dependent nature and does not significantly contribute to total body fat deposit in healthy individuals (Giles et al. 2016; Song et al. 2018). Nonetheless, dependence on highly refined carbohydrates, changes in lifestyle and exposure to endocrine disrupting chemicals both alters glucose regulation which influences de novo lipogenesis, causing a surge in the synthesis of fatty acids where its contribution to total body fat becomes significant (Maradonna and

Carnevali 2018). A study by Vineeth Daniel et al. (2019) indicated that exposure of mice to Pb^{2+} caused an upregulation and transactivation of the carbohydrate responsive element binding protein (*ChREBP*), a transcription factor that regulates the expression of genes responsible for glycolysis and hepatic de novo lipogenesis. Lipogenic markers such as fatty acid synthase (*FAS*) and acetyl CoA carboxylase (*ACC*) were also found to be upregulated and resulted in a dense lipid droplet accumulation in the liver of Pb^{2+} treated mice. Similarly, Zhang et al. (2018) observed that Cd exposure led to the upregulation of *FASN* and stearoyl-CoA desaturase-1 (*SCD1*), typically involved in de novo lipogenesis through fatty acid and monounsaturated fatty acid synthesis, but its direct effect on inducing de novo lipogenesis was not determined. Present studies on heavy metal-induced lipid dysregulation through de novo lipogenesis however remain sparse indicating that more studies are required to establish this phenomenon.

Heavy metals and plasma lipid dysregulation

In vivo studies in animal models

Maintenance of optimal plasma and cellular lipid homeostasis is pivotal to the normal functioning of an organism. As such, an abnormal deviation from a balanced equilibrium of lipid uptake, metabolism, storage and redistribution may have deleterious lipid-associated health effect on an organism (Małodobra-Mazur et al. 2020). However, as indicated earlier, heavy metals are well known to induce a disturbance in the homeostatic redistribution of dietary lipid by downregulating lipid metabolism and transport genes, thus limiting its uptake by cells and liver. This change in lipid profile results in accumulation of hepatic and serum lipids and cholesterol.

In a study by Samarghandian et al. (2015), it was shown that the administration of cadmium (2.0 mg/L) in the drinking water of mice for 3 months led to an increase in serum triglyceride, low-density lipoprotein cholesterol and total cholesterol with a decrease in the level of high-density lipoprotein cholesterol. In a similar study by Olisekodiaka et al. (2012), rats administered with Cd^{2+} at a dose of 1.0 mg/kg body weight for 4 weeks saw an increase in plasma triglyceride, total cholesterol and low-density lipoprotein cholesterol with a corresponding decrease in high-density lipoprotein cholesterol. In both studies, Cd caused an increase in the levels of malondialdehyde, a product of lipid peroxidation and a decrease in the total antioxidant status. In another study, Oluranti et al. (2021) reported that after exposure of rats to Cd (5.0 and 30.0 mg/kg), the levels of free fatty acid, total cholesterol and triglyceride in the heart increased significantly with respect to control, with a reduction in lipoprotein activity among rats exposed to 30.0 mg/kg Cd. Glucose metabolic pathway was also significantly impaired in Cd exposed groups with a significant decline in serum insulin level, and pyruvate and hexokinase activities (Oluranti et al. 2021). These reported fluctuations in lipid and glucose metabolic fluxes in the heart may be a prime contributing factor to the development of cardiac dysfunction and other cardio-metabolic syndromes.

To examine the effect of chronic As^{3+} exposure on lipid metabolism alterations and its subsequent effect on murine offspring in intergenerational study, Rivas-Santiago et al. (2019) exposed Wistar rats to 3 ppm sodium arsenate in drinking water through gestation and lactation until the offspring were 4-months-old. Although no significant change was observed in the level of serum adiponectin, an adipocyte-derived hormone that increases insulin sensitivity and regulates lipid metabolism, the serum lipid metabolomic profile of the rats however showed significant changes in the metabolism of glycerophospholipid and glycerolipid. A decrease in the levels of phosphatidylcholines and an increase in the levels lysophosphatidycholines were also observed in the animals exposed to As^{3+} compared with the control. An increase in lipid peroxidation induced by As^{3+}-mediated oxidative stress in treated rats was also reported as indicated by the high malondialdehyde levels (Rivas-Santiago et al. 2019). The findings from the above studies show that both Cd^{2+} and As^{3+} have the ability to induce dysregulation in lipid metabolism and promote oxidative stress through lipid peroxidation as determined by the increase in malondialdehyde levels, whereas decreasing the antioxidant status through the production and accumulation of reactive oxygen species within cells and tissues.

In mice and rats exposed to MeHg and Pb, though the serum lipids were perturbed, the reported findings (as shown in Table 1) deviate from the expected and established outcome. While Moreira et al. (2012), after exposing mice to 40 mg/L MeHg observed an increase in all serum lipid profiles, Uzunhisarcikli et al. (2015) after exposing rats to 1 mg/kg body weight of $HgCl_2$ reported a decrease in triglyceride, total cholesterol and low-density lipoprotein cholesterol. Likewise Wadaan (2009) after exposing rats to 20 ppm $HgCl_2$ similarly observed a decrease in triglyceride, total cholesterol and high-density lipoprotein cholesterol. These apparent difference in the research outcomes may be attributed to the different nature of metal (MeHg and $HgCl_2$) and exposure dosage. Allouche et al. (2011) after chronic exposure of rats to different concentrations (0.025, 0.5, 0.1 and 0.3%) of lead acetate in drinking water observed that though Pb^{2+} contributed to weight gain and increased obesity risk, no association was found to exist between Pb and serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol

Table 1 Effect of heavy metals on serum/plasma lipid profile in murine model. Low-density lipoprotein receptor knockout (LDLr–/–)

Organism	Metal	Medium of exposure	Dosage	Duration	Plasma/liver cholesterol observation			Refs
					Increased	Decreased	No significant effect	
Sprague–Dawley rats (Male)	Cadmium chloride	Drinking water	2.0 mg/L	3 months	Triglyceride, low-density lipoprotein cholesterol and total cholesterol	High-density lipoprotein cholesterol		Samarghandian et al. (2015)
Albino rats (Male)	Cadmium chloride	Intraperitoneal injection	1.0 mg/kg body weight/day	4 weeks	Triglyceride, low-density lipoprotein cholesterol and total cholesterol	High-density lipoprotein cholesterol		Olisekodiaka et al. (2012)
C57BL/6 male mice	Cadmium chloride	Drinking water	10 mg/L	10 weeks	Triglyceride, low-density lipoprotein cholesterol, total cholesterol and free fatty acid		High-density lipoprotein cholesterol	Zhang et al. (2015)
C57BL/6 mice	Cadmium chloride	Drinking water	10 mg/L	20 weeks	Triglyceride, diacylglyceride, low-density lipoprotein cholesterol and total cholesterol	High-density lipoprotein cholesterol		Go et al. (2015)
Male ICR mice	Cadmium chloride	Diet	10, 100, 1000 ppm	6 days	Plasma (triglyceride, Apolipoprotein A2, Apolipoprotein C3p, Apolipoprotein E); Liver (Apolipoprotein E)	Plasma (Apolipoprotein A1); Liver (ApolipoproteinA1, ApolipoproteinA2, ApolipoproteinC3p)		Liu et al. (2020)
Wistar rats	Sodium arsenate	Drinking water	3 ppm	From pregnancy till pups were 4-months-old	Lysophosphatidycholines; 3-deoxyvitamin D_3	Phosphatidylcholines		Rivas-Santiago et al. (2019)
Female Wistar albino rats	Sodium arsenite	Arsenic contaminated rice	46.33 mg/kg	150 days	Triglyceride, low-density lipoprotein cholesterol, total cholesterol	high-density lipoprotein cholesterol		Hosen et al. (2016)

Table 1 (continued)

Organism	Metal	Medium of exposure	Dosage	Duration	Plasma/liver cholesterol observation			Refs
					Increased	Decreased	No significant effect	
Wistar rats	Arsenic trioxide	Drinking water	133 µg/ml	30 weeks		high-density lipoprotein cholesterol to low-density lipoprotein cholesterol ratio	Triglyceride; total cholesterol	Cheng et al. (2011)
Wistar rats	Sodium arsenite	Drinking water	25, 50, 100 ppm	90 days	Triglyceride, low-density lipoprotein cholesterol, total cholesterol	high-density lipoprotein cholesterol; high-density lipoprotein cholesterol to low-density lipoprotein cholesterol ratio		Waghe et al. (2017)
Male Wistar albino rats	Sodium arsenite	Intragastric administration	5 mg/kg BW/d	4 weeks	Triglyceride, low-density lipoprotein cholesterol, total cholesterol phospholipids; Free fatty acid; very low-density lipoprotein	High-density lipoprotein cholesterol		Muthumani and Prabu (2014)
Male Swiss Albino mice; C57BL/6 wild-type mic; LDL receptor knockout (LDLr–/–) mice	Methylmercury chloride	Drinking water	40 mg/L	28; 21; 21 days	Triglyceride, total cholesterol; high-density lipoprotein cholesterol; non- high-density lipoprotein cholesterol			Moreira et al. (2012)
C57Bl/6 female mice	Methylmercury chloride	Drinking water	20 mg/L	15 days	high-density lipoprotein cholesterol; total cholesterol		Triglyceride	Lacerda Leocádio et al. (2020)
Male Wistar albino rats	Mercury chloride	Orally	1 mg/kg BW	4 weeks		Total cholesterol; very low-density lipoprotein; triglyceride;		Uzunhisarcikli et al. (2015)

Table 1 (continued)

Organism	Metal	Medium of exposure	Dosage	Duration	Plasma/liver cholesterol observation			Refs
					Increased	Decreased	No significant effect	
Male albino rats	Mercury chloride	Drinking water	20 ppm	8 weeks		Total cholesterol; triglyceride; high-density lipoprotein cholesterol		Wadaan (2009)
Male Wistar rats	Lead acetate	Diet	500 mg lead/kg diet	6 weeks	Triglyceride; very low-density lipoprotein	Low-density lipoprotein; total cholesterol	High-density lipoprotein	Heidarian and Rafieian-Kopaei (2013)
Male Wistar Albino rats	Lead acetate	Drinking water	0.025%; 0.05%; 0.1%; 0.3%	43 weeks			Triglyceride; total cholesterol; Low-density lipoprotein; high-density lipoprotein	Allouche et al. (2011)
Male Buffalo rats	Lead acetate	Intragastric	35 mg lead/kg body wt. once weekly; 70 mg Pb/kg twice weekly	7 weeks	Triglyceride	Total cholesterol; high-density lipoprotein cholesterol		Skoczyńska et al. (1993)
Male Albino rats	Lead acetate	Drinking water	200,300, 400 ppm	4, 8, 12 weeks	Total cholesterol; Triglyceride; high-density lipoprotein cholesterol	Low-density lipoprotein; Phospholipids		Okediran et al. (2018)

and triglyceride among lead exposed groups compared to the control group. On the contrary, Heidarian and Rafieian-Kopaei (2013) observed an increase in triglyceride and very low-density lipoprotein levels and a decrease in low-density lipoprotein and total cholesterol levels with no observable difference in high-density lipoprotein cholesterol after rat were exposed to 500 mg lead acetate/kg diet. Okediran et al. (2018) on the other hand reported that alteration in lipid profile in rats exposed to Pb^{2+} was both time and dosage dependent. They observed that increasing dosage and time increased the serum levels triglyceride, total cholesterol, high-density lipoprotein cholesterol with a corresponding decrease in the serum levels low-density lipoprotein and phospholipids. Though a dysregulation in the lipid profile as induced by heavy metals is indicated, the extent of dysregulation for each metal differs to some extent, and these differences may be due to factors such as dosage, duration of exposure and the type of model organism used for the study.

Heavy metals and plasma lipid dysregulation in humans

Heavy metals remain a major health risk factor in humans due to their ability to induce cardiometabolic syndromes and other life-threatening illnesses. Of this, Steinmaus et al. (2015) have reported the association between arsenic exposure and its relation to obesity, increased weight and the risk of cancer. In a study by Shin et al. (2018) among a population of 1,567 children and adolescents, and Park et al. (2017a) from a population size of 200 healthy subjects, a positive correlation between total blood mercury levels, fat deposition, overweight and obesity was observed. A cross-sectional study by Zhou et al. (2016) among Chinese workers with occupational exposure to Cd^{2+} showed a positive correlation between Cd^{2+} levels and dyslipidemia. The prevalence of dyslipidemia was found to increase dose-dependently among subjects. They further found a close association between blood Cd^{2+} levels and body mass index as subjects with a higher Cd^{2+} concentration had a correspondingly higher body mass index. The levels of triglyceride, low-density lipoprotein cholesterol and total cholesterol were also found to be higher when Cd^{2+} concentrations were high, with a corresponding lower high-density lipoprotein cholesterol levels. Similarly, a cross-sectional study by Tangvarasittichai et al. (2015) among 534 volunteered subjects from cadmium contaminated and non-contaminated communities showed similar results as observed by Zhou et al. (2016).

Due to the correlation between serum/tissue lipid content and diabetes, other researchers have sought to find the relationship between heavy metal exposure and diabetes. In a cross-sectional study conducted among 5,544 volunteers, Nie et al. (2016) found that subjects who showed higher blood Cd^{2+} level were more likely to be obese or overweight. A comparatively similar cross-sectional studies and evaluations among populations exposed to Hg^{2+} ($n = 3951$) (Cho 2017), As^{3+} (1160) (Mendez Michelle et al. 2016), and Pb^{2+} (5558) (Wang et al. 2015a) have also been investigated concluding with similar results as that found in individuals with elevated blood cadmium in relation to lipid dysregulation, overweight, obesity and diabetes risks. Among 569 adults with arsenic exposure, Sarker et al. (2021) also observed an apparent disparity in arsenic-induced metabolic syndrome between males and females recruited from high- and low-arsenic exposure areas. Females were found to be more susceptible to developing metabolic syndrome with hypo-high-density lipoprotein cholesterol, hyperglycemia, high abdominal obesity and insulin intolerance compared to males.

Though metal exposure in the above studies showed lipid profile dysregulation, the pattern of triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol dysregulation differed, with some parameter remaining unaffected in some cases. Example, whereas Cd^{2+} is reported to cause a significant increase in serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, with a corresponding decrease in high-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol levels, after As^{3+} and Hg^{2+} exposure, are reported to be higher in some studies (Mendez Michelle et al. 2016; Sohn et al. 2020). Nonetheless, findings from other studies indicate no statistically significant differences in serum lipid profile (Cho et al. 2020; Kasperczyk et al. 2005; Sohn et al. 2020), and as well identified no correlation between metal exposure and changes in lipid profile (Kim 2012) (See Table 2 for details). Moreover, in spite of the higher antiatherogenic high-density lipoprotein cholesterol levels observed by Mendez et al., individuals with exposure to arsenic were found to be potentially at risk of developing cardiometabolic syndromes (Mendez Michelle et al. 2016).

In vivo studies on lipid metabolism gene aberration by heavy metals

a) Heavy metals on lipogenic gene expression

Regulatory genes, enzymes and transcription factors involved in lipid synthesis are reported to be altered by toxic metals which effectively results in the dysregulation of lipid metabolism process and fat accumulation, a precursor for diabetes, insulin resistance and obesity (He et al. 2015). The influence of heavy metals on altering the expression of genes and proteins that modulates lipid and glucose metabolism, synthesis, uptake and storage have been investigated as

Table 2 Effect of heavy metal exposure on serum/plasma lipid dysregulation in human studies

Population size	Survey period	Territory	Metal	Mean blood/urine metal concentration	Serum/plasma lipid observation		Risk effects (obesity/diabetes/BMI)	References
					Increased	Decreased		
$N=1489$	2013	China	Cadmium	5.79 ± 1.16 µg/L	Triglyceride; total cholesterol; low-density lipoprotein cholesterol	High-density lipoprotein cholesterol	High prevalence of dyslipidemia (66.3%) positively correlating with a higher body mass index	Zhou et al. (2016)
$N=258$	2010 – 2011	Thailand	Cadmium	9.76 ± 5.58 µg/g Creat	Triglyceride; Triglyceride/High-density lipoprotein cholesterol ratio	High-density lipoprotein cholesterol	Exposure to cadmium was associated to risk of hypertriglyceridemia and higher body mass index	Tangvarasittichai et al. (2015)
$N=3903$[a]	2005; 2008; 2009	Korea	Cadmium	1.16 µg/L	Triglyceride	High-density lipoprotein cholesterol	Increased cadmium body burden increases the risk of dyslipidemia through low High-density lipoprotein cholesterol and high triglyceride	Kim (2012)
$N=114$ (57 – exposed; 57 – non-exposed)	2015—2016	Italy	Arsenic	13.4 ± 6.1; 4.4 ± 6.1 µg/g Creat	Lipoproteins	Apolipoprotein-A1	The influence of arsenic on lipoprotein(a) and apolipoproteins suggests a potential risk of cardiovascular diseases even at low levels	Ledda et al. (2018)
$N=1160$	2008—2013	Mexico	Arsenic	<55.8 µg/L	Triglyceride,; total cholesterol; high-density lipoprotein cholesterol		Associated with increased cardiometabolic risk (diabetes, triglyceridemia, and cholesterolemia), but exposure was also associated with higher rather than lower high-density lipoprotein cholesterol	Mendez Michelle et al. (2016)

Table 2 (continued)

Population size	Survey period	Territory	Metal	Mean blood/urine metal concentration	Serum/plasma lipid observation		Risk effects (obesity/diabetes/BMI)	References
					Increased	Decreased		
$N=237$	2000 – 2001	Taiwan	Arsenic	0.23 µg/L	Low-density lipoprotein cholesterol; triglyceride; total cholesterol; non-high-density lipoprotein cholesterol; high triglyceride/high-density lipoprotein cholesterol ratio		Early-life arsenic exposure renders individuals susceptible to accumulation of higher atherogenic low-density lipoprotein cholesterol and other non-high-density lipoprotein cholesterol and the risk of developing As-related cardiovascular disease	Kuo et al. (2018)
$N=3228$[b]	2015 and 2017	Korea	Mercury	2.71 µg/L	Total cholesterol; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol—high in males; triglyceride—high in female		Association between mercury exposure and the risk of dyslipidemia	Sohn et al. (2020)
$N=1890$[c]	2010 – 2013	Korea	Mercury	1.89 µg/L	Total cholesterol; low-density lipoprotein cholesterol—males		The potential association between mercury exposure and the risk of hyper- low-density lipoprotein cholesterolemia in male adolescents	Cho et al. (2020)
$N=501$		Korea	Mercury	0.47 µg/g for men; 0.34 µg/g for women (toenail Hg)	Low-density lipoprotein cholesterol, triglyceride and total cholesterol	Hypo high-density lipoprotein cholesterolemia	Participant with high toenail mercury and low selenium shown hypercholesterolemia, Hyper- low-density lipoprotein cholesterolemia and dyslipidemia	Park and Seo (2017)
$N=6454$ (Hyperlipidemia group – 3699; Non-hyperlipidemia group – 2755)	2012 – 2014	Korea	Mercury	Hyperlipidemia group (Male—4.03 µg/L, Female—2.83 µg/L); Non-hyperlipidemia group (Male—3.48 µg/L, Female—2.69 µg/L)	Low-density lipoprotein, total cholesterol and triglyceride	High-density lipoprotein cholesterol	High blood mercury levels were associated with an 11% higher risk of hyperlipidemia	Lee et al. (2020)

Table 2 (continued)

Population size	Survey period	Territory	Metal	Mean blood/urine metal concentration	Serum/plasma lipid observation		Risk effects (obesity/diabetes/BMI)	References
					Increased	Decreased		
$N=110$®[d]; $N=60$		Nigeria	Lead	48.90 ± 19.11 µg/dL	Total cholesterol, low-density lipoprotein cholesterol and triglyceride®		Lead exposure increased cholesterol synthesis and transport to peripheral tissues but dyslipidemia was not observed	Obi-Ezeani et al. (2019), Ademuyiwa et al. (2005)
$N=137$[e]		Poland	Lead				Lipid peroxidation significantly increased by about 71% and concentration of 7-ketocholesterol by about 122% in hypertensives when compared with normotensives in the high lead exposure group	Kasperczyk et al. (2005)
$N=5558$	2014	China	Lead	44.00 µg/L—men; 37.79 µg/L—women	Triglyceride, low-density lipoprotein cholesterol-In females		Blood lead level was positively associated with body mass index and obesity and may relate with diabetes, dyslipidemia and hypertension in Chinese women, but not in men	Wang et al. (2015a)

[a] No correlation was found to exist between the high low-density lipoprotein cholesterol, triglyceride and increasing cadmium concentration

[b]No statistically significant differences were observed in cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein levels between arsenic exposed and non-exposed groups

[c]High-density lipoprotein cholesterol and triglyceride levels did not show significant associations with total blood mercury levels

[d]High-density lipoprotein cholesterol and triglyceride® levels were not affected

[e]No significant changes in concentration of 7-ketocholesterol and blood lipids (cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides) were found

shown in Table 3. The mechanism by which heavy metals cause an increase in serum lipid levels is shown in Fig. 3.

Adebayo et al. (2015) observed that chronic exposure of mice to low dose of arsenic modulates the hepatic expression of genes involved in the regulation lipogenesis. The exposure led to a reduced *SREBP-1c* expression which conjointly resulted in a disturbance of *SREBP-1c* specific lipogenic genes expression. Arsenic thus downregulated the expression levels of *SREBP-1c*, *FAS*, diglyceride acyltransferase (*DGAT*) and *LDLR* Adebayo et al. (2015). Wauson et al. (2002) also observed that treatment of C3H 10T1/2 cells with 6 μM arsenic for 2 months significantly reduced the expression levels of the adipose modulating genes peroxisome proliferative-activated receptor γ (*PPARγ*), CCAAT-enhancer binding protein α (*C/EBPα*) and adipocyte fatty acid-binding protein (*aP2*), blocked the upregulation of cyclin dependent kinase inhibitor protein 21 ($p21^{Cip1/Waf1}$) and inhibited the differentiating effect of the adipogenesis drug, pioglitazone which is clinically used to induce adipogenesis through PPARγ activation. In another study aimed at establishing the role of arsenic on inducing atherosclerosis through altered lipid metabolism, rats exposed to arsenic contaminated water (133 μg/mL), and/or high cholesterol diet showed a transient increase in heat shock protein 70 (*Hsp70*) and high-sensitive C-reactive protein (*hs-CRP*) which are markers of cellular stress and myocardial infarctions. It was further observed that the arsenic significantly suppressed the activities of cholesteryl ester transfer protein-1 (*CETP-1*) and liver X receptor β (*LXRβ*) while decreasing the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol (Cheng et al. 2011). Similarly, in zebra fish, arsenic was found to alter the expression of carnitine O-octanoyltransferase (*CROT*), fatty acid binding protein 3 (*FABP3*), and 3-hydroxy-3-methylglutaryl-CoA synthase 1 (*HMGCS1*), genes required for lipid metabolism and transport (Carlson and Van Beneden 2014). Likewise, exposure of diabetic db/m mice to inorganic arsenic downregulated the expression of lipid metabolism-related genes such as cluster of differentiation 36 (*CD36*), 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*), fatty acid synthase (*FASN*), ATP-binding cassette transporter A1 (*ABCA1*) and Pparγ coactivator (*PGC*), but upregulated the expression of *PPARR-2*, phosphoenolpyruvate carboxykinase (*PCK1*), Cyclin D1 (*CCND1*) and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) genes in liver (Liu et al. 2014). In male Sprague Dawley rat liver however, arsenic exposure significantly elevated the expressions of carnitine palmitoyltransferase 2 (*CPT2*), ecithin–cholesterol acyltransferase (*LCAT*), mitochondrial carnitine/acylcarnitine carrier protein (*CACT*), *CROT* and 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*) in high dose groups (sodium arsenite) (Wang et al. 2015b). Chronic exposure of C57BL6J male mice to sodium arsenite (300 μg/L for 9 weeks) revealed a significant impairment in both glucose and lipid homeostasis which affected the body heat production ability of the mice in cold environments. Although food intake or body weigh was not affected, the arsenic exposed group had an increased total fat mass and subcutaneous inguinal white adipose tissue mass. Expression of genes involved in regulating lipolysis, fatty acid metabolism, adipogenesis, adaptive thermogenesis and inflammation were significantly decreased in As-exposed group. The study revealed that 6 gene involved in PPAR signaling including, solute carrier family 27 (fatty acid transporter) member 2 (*SLC27A2*), *FABP3*, uncoupling protein 1 (*UCP1*), ATP citrate lyase (*ACSL5*), carnitine palmitoyltransferase 1b (*CPT1B*) and malic enzyme 1 (*ME1*), and as well as 23 other genes responsible for regulating various glucose and lipid metabolic processes were significantly reduced by 31–50% indicating that arsenic could be a potent obesogen capable of disrupting normal lipid and glucose homeostasis, and energy balance (Castriota et al. 2020).

The lipogenic influence of Cd^{2+} on lipid synthesis and cholesterol redistribution examined by Wang et al. (2018a) indicated that Cd^{2+} effectively upregulated the lipid transporter ABCA1 which led to an increase in serum lipid levels of triglyceride, low-density lipoprotein cholesterol and total cholesterol while lowering high-density lipoprotein cholesterol levels in Cd treated HepG2 cells. Although Zhang et al. (2018) also indicated that exposure to Cd^{2+} upregulated the mRNA level of hepatic *FASN*, stearoyl-CoA desaturase-1 (*SCD-1*), hepatic fatty acid uptake genes (*FABP1*, *FABP4*) and hepatic *LpL* among adult female CD1 mice, insulin resistance, obesity and hepatic lipid accumulation were not significantly affected. Moreover, the gene profile of mice exposed to sub-chronic dose of Cd^{2+} (10 mg/L for 10 weeks) revealed an alteration in the expression of key genes involved in both glucose metabolism and de novo free fatty acid synthesis and transport pathways. The mRNA levels of glucose metabolism genes such as glucose transporter 2 (*GLUT2*), *ChREBP*, citrate synthase (*CS*) glucose kinase (*GK*) and pyruvate kinase (*PK*) were observed to increase significantly in the liver of mice exposed to 10 mg/L of Cd^{2+} in drinking water. Similarly, the expression of lipid metabolism genes including the hepatic lipogenesis transcription factors (*PPARγ*, *SREBP1-c*), fatty acid synthesis and transport genes (*FAS*, *FAT*, *FATP2*, *FABP1*), triglyceride synthesis genes (*DGAT1/2*, *GPAT*) were significantly increased in mice exposed to sub-chronic dose of Cd (10 mg/L) thus perturbing lipid and glucose homeostasis, and hepatic energy metabolism process (Zhang et al. 2015). In female CD1 mice administered with a combination of $CdCl_2$ and methylmercury (II) chloride (MeHgCl), Camsari et al. (2017) reported of an impaired glucose homeostasis, a higher body weight and an increase in abdominal adipose tissue weight in male offspring of treated females. Genes (*GLUT4*, *IRS1*, *FASN*,

Table 3 List of heavy metals and their effect on lipid regulatory genes in the modulation of lipid synthesis and or dysregulation in in vivo studies

Target tissue/cell	Metal	Ingestion medium	Dose	Duration	Gene name	Function	Gene expression observation	References
C57BL/6 J mice	Sodium arsenite;	Drinking water	100 ppb	5 weeks	*SREBP 1-c*; *LXR*	Transcriptional factor	Decreased expression levels of target genes	Adebayo et al. (2015)
Wistar rats (liver)	Arsenic trioxide	Drinking water	133 µg/ml	30 weeks	*CETP-1*; *LXRβ*	Lipid metabolism; Transcriptional factor	Suppressed	Cheng et al. (2011)
Zebrafish (AB strain) liver	Sodium arsenite	Water	10, 50, 500 ppb	7 and 21 days	*CROT*; *FABP3*; *HMGCS1*	Lipid metabolism and transport	Suppressed	Carlson and Van Beneden (2014)
C57/BL/6 mice	Sodium arsenite	Drinking water	0.25, 1 ppm arsenic	2 weeks	*SREBP 1c*; *HMGCR*; *CYP7a1*; *ABCG5/8*; *CD36*; *LDLR*; *SCARB1*	Transcription factor; Cholesterol synthesis and metabolism; Cholesterol efflux	Low expression levels	Chi et al. (2019a)
C57BKS/Lepr^{db} (db/db) mice (liver)	Sodium arsenite	Drinking water	3 mg/L	16 weeks	*CD36*; *HMGCR* ; *FASN*; *ABCA1*; *PGC*	Lipid metabolism	Downregulated	Liu et al. (2014)
C57BKS/Lepr^{db} (db/db) mice (liver)	Sodium arsenite	Drinking water	3 mg/L	16 weeks	*PPARr-2*; *PCK1*; *CCND1*; *GPIHBP1*	Lipid metabolism and gluconeogenesis	Upregulated	Liu et al. (2014)
Sprague Dawley rats (liver)	Sodium arsenite	Drinking water	0.5, 2 or 10 ppm	3 months	*CPT2*; *LCAT*; *CACT* ; *MTR*	Lipid and amino acid metabolism	Upregulated	Wang et al. (2015b)
ICR mice (liver)	Cadmium chloride	Diet	10, 100, 1000 ppm	7 days	*ABCA1*; *LDLR*	Cholesterol transporter; Binding and maintaining cholesterol homeostasis	Upregulated (*ABCA1*) Downregulated (*LDLR*)	Liu et al. (2020), Wang et al. (2018b)
C57/BL/6 mice	Cadmium chloride	Drinking water	10 mg/L	10 weeks	*PPARγ*; *SREBP1c*; *FAS*; *FAT*; *FATP2*; *FABP1*; *DGAT1/2*; *GPAT*	Transcription factor; Fatty acid synthesis and transport; Triglyceride synthesis	Upregulated	Zhang et al. (2015)
CD1 mice	Cadmium chloride	Drinking water	10, 100 mg/L	10 weeks	*FASN*; *SCD-1*; *FABP1*; *FABP4*; *LpL*	Hepatic fatty acid synthesis; Hepatic fatty acid uptake; lipoprotein lysis	Upregulated	Zhang et al. (2018)
C57BL/6 mice	Cadmium chloride	Drinking water	10 mg/L	20 weeks	*INSIG2*; *IL4*; *OSBP*; *PPARγC1A/PGC-1A*; *PLA2G2E*; *SLC2A13*	Fatty acid synthesis and lipid metabolism	Upregulated (*INSIG2*; *IL4*, *OSBP*; *PPARGC1A/PGC-1A*); Downregulated (*PLA2G2E*; *SLC2A13*)	Go et al. (2015)
Wistar rats	Lead (II) acetate trihydrate	Drinking water	0.05% Pb	21 weeks	*LDLR*; *FATP*; *GLYCTK*; *DGAT1*; *DGAT2*; *CPT-2*; *MCAD*; *CYP4a*; *ACO*	Fatty acid transport and synthesis; Fatty acid oxidation	Expression inhibited as a result of DNA methylation	Sun et al. (2017)
ICR male mice	Lead acetate trihydrate	Drinking water	0.1 mg/L	15 weeks	*GK*; *CHREBP*; *FABP1*; *MTTP*; *PK*; *ACOX*; *PPAR-A*; *MCAD*; *CPT1A*; *DGAT1*; *DGAT2*; *GPAT*; *ACL*; *ACC* ; *SREBP-1C*; *FAS*; *SREBP-2*	Lipogenic gene transcription factors, lipid-metabolism-related genes	Gene expression were significantly increased in the liver of mice	Xia et al. (2018)

Table 3 (continued)

Target tissue/cell	Metal	Ingestion medium	Dose	Duration	Gene name	Function	Gene expression observation	References
C57Bl/6 female mice (Liver)	Methylmercury chloride	Drinking water	20 mg/L	15 days	*ABCA1*; *APOAI*; *HMGCR*; *LCAT*; *PON1*	Cholesterol synthesis regulation, reverse transport of cholesterol, esterification of free cholesterol, protects low-density lipoprotein and high-density lipoprotein from oxidation, and the elimination of biologically active oxidized lipids in lipoproteins and arterial cells	*ABCA1* and *APOAI* expression were unaltered by Hg; *HMGCR* – downregulated; *LCAT*—upregulated	Lacerda Leocádio et al. (2020)
C57BL/6 J female	Methylmercury chloride	Drinking water	0.5 and 5 ppm	30 days	*PPARγ*; *ACACA*; *FASN*; *PNPLA2*; *LpL*; *CPT1A*; *CD36*	Regulation of lipid homeostasis and stimulation of lipogenesis, lipolysis	*PPARγ*; *FASN*; *PNPLA2* – Expression decreased only in males	Ferrer et al. (2018)

SREBP1c, sterol regulatory element binding protein-1c; *LXR*, liver X receptor; *PPARγ*, peroxisome proliferative-activated receptor γ; *CETP*, cholesteryl ester transfer protein; *LXRβ*, liver X receptor β; *CROT*, carnitine O-octanoyltransferase; *FABP3*, fatty acid binding protein 3; *HMGCS1*, 3-hydroxy-3-methylglutaryl-CoA synthase 1; *CD36*, cluster of differentiation 36; *HMGCR* , 3-hydroxy-3-methylglutaryl-CoA reductase; *FASN*, fatty acid synthase; *ABCA1*, ATP-binding cassette transporter A1; *ABCG5/8*, ATP-binding cassette subfamily G member 5/8; *SCARB1*, Scavenger receptor class B type 1; *PGC*, PPARγ coactivator; *PCK1*, phosphoenolpyruvate carboxykinase; *CCND1*, cyclin D1; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; *CPT*, carnitinepalmitoyltransferase; *LCAT*, ecithin–cholesterol acyltransferase; *CACT*, mitochondrial carnitine/acylcarnitine carrier protein; *MTR*, 5-methyltetrahydrofolate-homocysteine methyltransferase; *GPAT*, glycerol-3-phosphate acyltransferase; *SCD-1*, stearoyl-CoA desaturase-1; *FABP1*, fatty acid-binding protein 1; *LpL*, lipoprotein lipase; *LDLR*, low density lipoprotein receptor; *INSIG2*, Insulin induced gene 2; *OSBP*, Oxysterol binding protein; *PLA2G2E*, phospholipase A2 group IIE; *SLC2A13*, Solute carrier family 2 member 13; *IL4*, interleukin 4 *FATP*, fatty acid transport protein; *GLYCTK*, glycerate kinase; *DGAT*, diacylglycerol O-acyltransferase 1; *CPT-2*, carnitine palmitoyltransferase 2; *MCAD*, medium chain acyl-CoA dehydrogenase; *MTP*, *CYP4A*, cytochrome P450 4A; *ACO*, acyl CoA oxidase; *FADS2*, fatty acid desaturase 2; *FATP1*, fatty acid transport protein 1; *ELOVL5*, methylmercury downregulated fatty acid elongase 5; *PON1*, paraoxonase 1; *APOAI*, apolipoprotein A1; *ACACA*, Acetyl-CoA carboxylase alpha; *PNPLA2*, patatin-like phospholipase domain containing 2; *CPT1A*, carnitine palmitoyltransferase 1a; *GK*, Glucose kinase; *MTTP*, Microsomal triglyceride transfer protein; *ACL*, ATP citrate lyase; *ACC*, Acetyl-CoA carboxylase

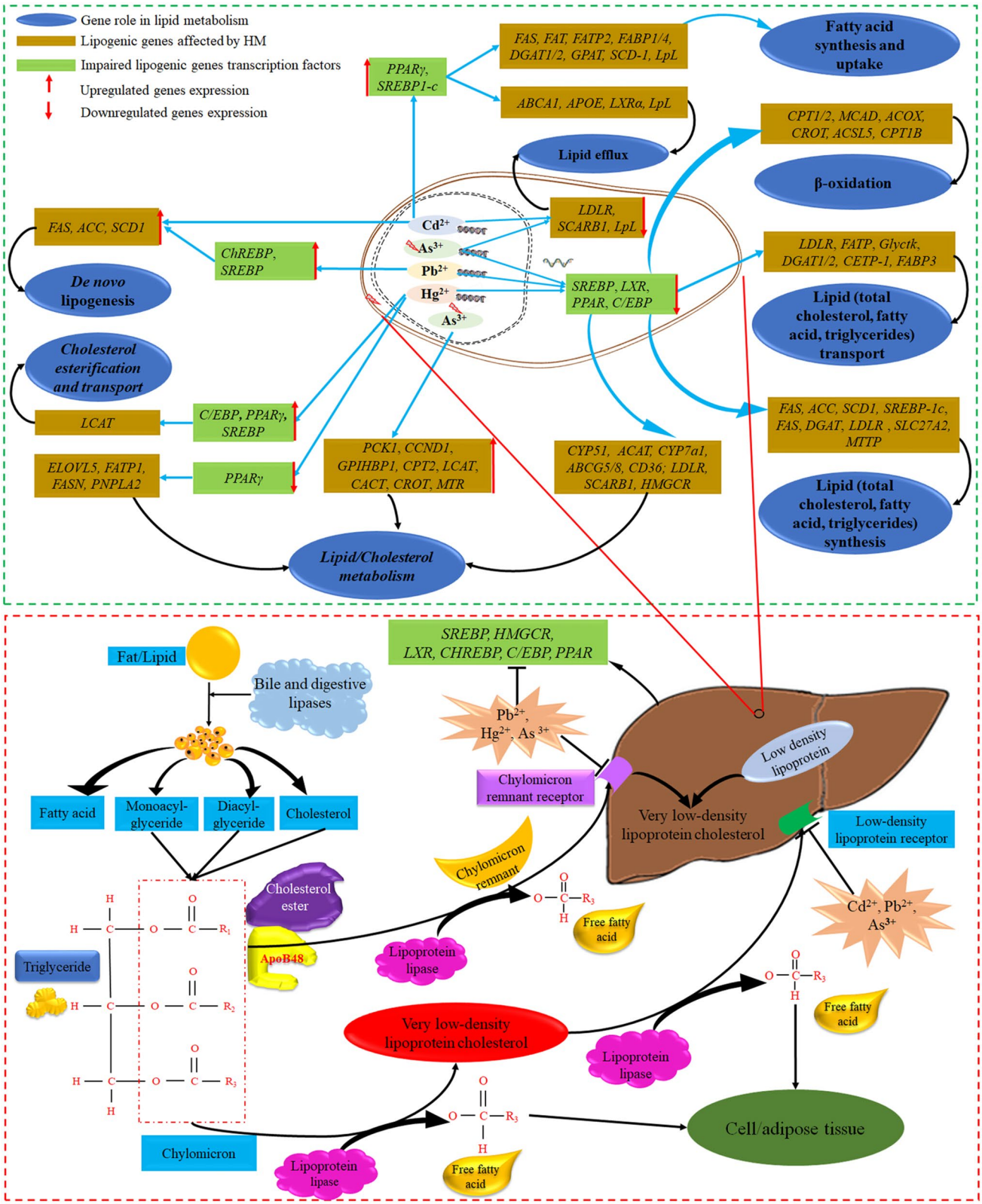
Acetyl-CoA carboxylase alpha (*ACACA*), *FATP2*, *CD36* and *G6PC*) associated with maintaining glucose and lipid homeostasis in the liver and abdominal adipose tissues were significantly altered indicating that the effect of heavy metal in females during gestation could persist through their offspring and may amplify the incidence of developing metabolic syndrome.

In lead related studies, Sun et al. (2017) observed that Pb^{2+}-induced obesity was as a result of DNA methylation of lipogenic and glucose metabolism genes. DNA methylation regulates gene expression by either inhibiting or suppressing the binding of transcription factors to target sequences and thereby downregulating their expression. Genes that were affected, according to their study, included those relating to fatty acid transport and synthesis (*LDLR*, fatty acid transport protein (*FATP*), glycerate kinase (*GLYCTK*), *DGAT1*, *DGAT2*), fatty acid oxidation (medium chain acyl-CoA dehydrogenase (*MCAD*), *CPT-2*, *CYP4a*, acyl CoA oxidase (*ACOX*)), very-low density lipoprotein-triglyceride assembling (microsomal triglyceride transfer protein (*MTTP*), apolipoprotein-CIII (*APO-CIII*), *APO-V*, *APO-IV*) and *LXR* and *SREBP-1c* transcription factors. The glucose metabolism related genes such as *PKA* and *AKT*, the gluconeogenesis genes phosphoenolpyruvate carboxykinase (*PEPCK*) and *G6pase*, as well as cholesterol metabolism genes such as *CYP51* and acetyl-CoA acetyltransferase (*ACAT*) were also affected. These genetic alterations were found to result in weight gain, glucose intolerance, insulin resistance, elevated serum triglyceride and the accumulation of hepatic lipids. To study the transgenerational effect of a 24 h Pb^{2+} exposure on zebrafish brain transcriptomics, Meyer et al. (2020) exposed zebrafish (*Danio rerio*) embryo to 10 µM after which they were allowed to mature and spawn producing first and second-generation offspring. Similar to Sun et al. (2017) observation, Meyer et al. (2020) noticed that Pb^{2+} induced epigenetic changes through DNA methylation across several systemic functions (nervous and endocrine systems) and metabolic pathways. A total of 323 genes associated with endocrine system and 80 genes relating to lipid metabolism pathways were found to be significantly altered, indicating that Pb exposure (even acute) could have long lasting generational effect.

In the adipose tissue of C57BL/6 J mice exposed to MeHg (0.5, 1.0, 5.0 µM), Ferrer et al. (2018) reported that mercury failed to significantly affect the adipogenic gene *PPARγ*, lipogenic genes (*ACACA*, *FASN*), lipolytic genes (patatin-like phospholipase domain containing 2 (*PNPLA2*) and *LpL*), and the genes that control β-oxidation (*CPT1a*) and transport (*CD36*). The mRNA expression for *PPARγ*, *FASN* and *PNPLA2* were however suppressed in a dose-dependent manner in the liver of male mice with MeHg exposure with a corresponding decrease in hepatic triglyceride. Irrespective of the observation made by Ferrer et al. (2018), studies on other model organisms subjected to mercury reports of significant changes in lipogenic genes. For example, Ferain et al. (2018) indicated that the phospholipid fatty acid profile in the liver of rainbow trout were affected by methylmercury exposure. The study showed that methylmercury significantly downregulated fatty acid elongase 5 (*ELOVL5*), *FATP1*, whereas *FASN*, carnitine palmitoyl transferase 1 (*CPT1*) and fatty acid desaturase 2 (*FADS2*) were upregulated. Similarly, in preadipocytes of rainbow trout cultured with MeHg supplementation, Tinant et al. (2021) observed an upregulation of the lipid metabolism genes, *FAS* and *FABP11a*, as well as several adipocyte-specific genes including perilipin 2 (*PLIN2*) and apolipoprotein Eb (*APOEB*) inducing an intracellular accumulation of the neutral lipid polyunsaturated fatty acid (PUFA) in MeHg dose dependent manner. Using *Caenorhabditis elegans* as a model organism for studying mammalian response to MeHg due to their shared conserved pathways in synthesizing and oxidizing fatty acids, and regulating lipid homeostasis, Caito et al. (2020) treated *C. elegans* with 10 or 20 µM MeHg for 30 min and examined its gene expression profile and triglyceride levels. Out of the 215 differentially regulated genes, 17 were involved in lipid metabolism and 12 involved in maintaining glucose homeostasis. Expression of the pro-adipogenic transcription factor *C/EBP-1* (a homolog of human *C/EBP*) known to play a role in the development of metabolic syndrome was upregulated. Other pro-adipogenic transcription factors upregulated by MeHg include *NHR-49* (homolog of *PPARγ*) and *SBP-1* (a homolog of human *SREBP*), the triglyceride synthesizing enzyme acyltransferase (a homolog of human glycerol-3-phosphate acyltransferase, *GPAT*), and the lipid transporter proteins vitellogenins (*VIT-2* and *VIT-6*). The above studies all demonstrate that Hg^{2+}/MeHg is an important environmental contaminant capable of inducing biochemical and metabolic changes in organisms especially, to the lipid profile and thereby leading to metabolic dysfunction. Heavy metals thus largely distort lipid metabolism by influencing the lipogenic gene expression patterns leading to lipid metabolism dysregulation and redistribution.

(b) In vitro and in vivo assessment of possible pathway of lipogenic gene aberration by heavy metals

Since hepatic cells regulate lipid metabolism and governs the whole-body energy metabolism process by serving as the major site for the storage and release of glucose and lipids, determining the expression pattern of lipid metabolism genes after exposure to heavy metals is important to understanding the mechanism and pathways by which metals induce dyslipidemia. The expression of lipid metabolism genes is regulated at the transcriptional level in a coordinated fashion among several transcriptional factors with poly- and mono-unsaturated fatty acids serving as natural


Gene role in lipid metabolism
Lipogenic genes affected by HM
Impaired lipogenic genes transcription factors
Upregulated genes expression
Downregulated genes expression
PPARγ, SREBP1-c
FAS, FAT, FATP2, FABP1/4, DGAT1/2, GPAT, SCD-1, LpL
ABCA1, APOE, LXRα, LpL
Fatty acid synthesis and uptake
Lipid efflux
CPT1/2, MCAD, ACOX, CROT, ACSL5, CPT1B
β-oxidation
LDLR, SCARB1, LpL
FAS, ACC, SCD1
ChREBP, SREBP
De novo lipogenesis
Cd2+
As3+
Pb2+
Hg2+
As3+
SREBP, LXR, PPAR, C/EBP
LDLR, FATP, Glyctk, DGAT1/2, CETP-1, FABP3
Lipid (total cholesterol, fatty acid, triglycerides) transport
Cholesterol esterification and transport
LCAT
C/EBP, PPARγ, SREBP
FAS, ACC, SCD1, SREBP-1c, FAS, DGAT, LDLR , SLC27A2, MTTP
Lipid (total cholesterol, fatty acid, triglycerides) synthesis
ELOVL5, FATP1, FASN, PNPLA2
PPARγ
PCK1, CCND1, GPIHBP1, CPT2, LCAT, CACT, CROT, MTR
CYP51, ACAT, CYP7a1, ABCG5/8, CD36; LDLR, SCARB1, HMGCR
Lipid/Cholesterol metabolism
SREBP, HMGCR, LXR, CHREBP, C/EBP, PPAR
Fat/Lipid
Bile and digestive lipases
Pb2+, Hg2+, As 3+
Chylomicron remnant receptor
Low density lipoprotein
Fatty acid
Monoacyl-glyceride
Diacyl-glyceride
Cholesterol
Very low-density lipoprotein cholesterol
Low-density lipoprotein receptor
Chylomicron remnant
Cholesterol ester
Free fatty acid
Cd2+, Pb2+, As3+
Triglyceride
ApoB48
Lipoprotein lipase
Very low-density lipoprotein cholesterol
Free fatty acid
Lipoprotein lipase
Cell/adipose tissue
Chylomicron
Lipoprotein lipase
Free fatty acid

◂**Fig. 3** Lipid metabolism pathway in the liver and the role of heavy metals on inducing lipid profile dysregulation through lipogenic gene aberrations. Alteration in lipid metabolism transcription factor expression significantly impairs serum lipid profile. SREBP1c, sterol regulatory element binding protein-1c; LXR, liver X receptor; PPARγ, peroxisome proliferative-activated receptor γ; CETP, cholesteryl ester transfer protein; LXRβ, liver X receptor β; ABCA1, ATP-binding cassette transporter A1; FAS(N), fatty acid synthase; CROT, carnitine O-octanoyltransferase; FABP, fatty acid binding protein 3; CPT, carnitinepalmitoyltransferase; SCD-1, stearoyl-CoA desaturase-1; LpL, lipoprotein lipase; LDLR, low density lipoprotein receptor; CYP, cytochrome P450; ACC, Acetyl-CoA carboxylase; MTTP, Microsomal triglyceride transfer protein; FATP, fatty acid transport protein; ELOVL5, elongase 5; GLYCTK, glycerate kinase; DGAT, diacylglycerol O-acyltransferase 1; CD36, cluster of differentiation 36; SLC27A2, Solute carrier family 2 member 13; SCARB1, Scavenger receptor class B type 1; PGC, PPARγ coactivator; PNPLA2, patatin-like phospholipase domain containing 2; GPAT, glycerol-3-phosphate acyltransferase; LCAT, lecithin–cholesterol acyltransferase; MCAD, medium chain acyl-CoA dehydrogenase; ACO, acyl CoA oxidase; APOE, Apolipoprotein E; PCK1, phosphoenolpyruvate carboxykinase; CCND1, cyclin D1; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; CACT, mitochondrial carnitine/acylcarnitine carrier protein; MTR, 5-methyltetrahydrofolate-homocysteine methyltransferase; ACAT, Acyl-coenzyme A: cholesterol acyltransferases; ABCG5/8, ATP-binding cassette subfamily G member 5/8; ACSL5, ATP citrate lyase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase

ligands that activate most of these transcription factors (Ayisi et al. 2018; Jump et al. 2006).

Studies have indicated that Cd^{2+} (Newairy et al. 2007; Olszowski et al. 2018) and arsenic (Chi et al. 2019b) can significantly decrease the levels of PUFA due to their high susceptibility to peroxidation (Gaschler and Stockwell 2017). Decline in poly- and mono-unsaturated fatty acids levels could therefore negatively affect the activation of transcription factors and may account for the down-regulation of most lipogenic gene expressions. Several lipogenic gene transcription factors have been identified among which *SREBPs*, *LXR(α/β)*, *ChREBP* and *PPAR(α/γ)* are most prominent (Cheng et al. 2016; Jump et al. 2006; Vineeth Daniel et al. 2019; Xia et al. 2018). *LXR* transcription factors are nuclear receptors with pivotal role in the transcriptional control of lipid metabolism. The transcriptional activity of *LXR* is induced in response to elevated cellular cholesterol levels. *LXRs* thus binds to and regulates the expression of genes that encode proteins involved in cholesterol absorption, transport, efflux, excretion and conversion to bile acids (Wang and Tontonoz 2018). Similarly, *SREBPs* are transcription factors that regulates fatty acid and cholesterol biosynthesis by directly activating the transcription of genes needed for the uptake and synthesis of cholesterol, fatty acid, triglycerides and phospholipids. Though heavy metals have been shown the affect the expression and activity of these transcription factors, differences in their expression pattern have been reported. The expression of *LXR* and *SREBPs* have been shown to be down-regulated by As and Pb in both in vivo and in vitro studies (Adebayo et al. 2015; Sun et al. 2017). Cheng et al. (2016) showed that As^{3+} inhibited the expression of *LXR* at both the mRNA and protein level and subsequently decreased the protein level *SREBP-1c*. The inhibition of *LXR* by As^{3+} resulted in a reduced efflux of cholesterol from HepG2 cell to the extracellular space. Moreover, As also elevated the expression of *C/ETP* involved in reverse cholesterol transport, where cholesterol is transferred from high-density lipoprotein to apolipoprotein B-containing lipoproteins to become low-density lipoprotein and delivering the cholesterol to the hepatocytes to be secreted into bile or bile acid.

Suppression of *SREBP-1c* expression by arsenic was found to inhibit the expression of *FAS*, *LDLR*, *SCD-1* and *DGAT-2* genes but this effect was time dependent as the inhibition observed at 6 h. waned, after which there was an upregulation in the expression levels of *SREBP-1c* and its target genes at 16 h. (Adebayo et al. 2015). It has been previously observed that DNA hypermethylation of *SREBP1-c* and *LXR* by Pb^{2+} could have been responsible for the gene repression and downregulation of genes involved in fatty acid transport (*LDLR*, *FATP*, *Glyctk*, *DGAT1* and *DGAT2*) and fatty acid oxidation (*CPT-2*, *MCAD*, *ACO*) and may have thus been responsible for the elevated lipid synthesis in the liver and serum (Sun et al. 2017). Taken together, an inhibition of lipid metabolism transcription factors is a major precursor for the downregulation of most lipogenic genes and may account for the dysregulation in the processes that ensures the maintenance of lipid homeostasis in both hepatic tissue and serum.

The downregulation of lipogenic genes is also closely associated with excess accumulation of cellular and serum lipids, and this could be due to limited protein and enzymes for biosynthesis, absorption, trafficking and cholesterol efflux. In contrast to the findings by Cheng et al. (2016) who reported that As down-regulates lipid transcription factors (*SREBPs* and *LXR*), a study by Xia et al. (2018) however indicated that chronic exposure to low doses of Pb^{2+} resulted in an upregulation of the transcription factors *SREBP-1c*, *SREBP2*, *PPARα* and *PPARγ* which activate key genes involved in fatty acid transport, β-oxidation, glycolysis, triglyceride synthesis and de novo lipogenesis. Although both authors observed a dysregulation in the lipid profile, Cheng et al. (2016) attributed the lipid and cholesterol accumulation to the reduced expression level of proteins and enzymes needed for the cholesterol metabolism, transport and efflux of cellular and serum cholesterol, whereas Xia et al. (2018) on the other indicated that the upregulation of *SREBP* may have induced the genes (*FAS*, *SCD1* and *ACC*) required for de novo lipogenesis, and thus, the accumulated lipids may have been as result of enhanced de novo lipogenesis.

Association of multiple heavy metals on serum lipid dysregulation

Whereas the positive association of each single heavy metal with serum lipid dysregulation is well documented, the correlation between exposure to multiple heavy metals and dyslipidemia show some apparent variations in reported studies. Poursafa et al. (2014) observed that a positive correlation between increasing serum Hg^{2+} and Pb^{2+} concentrations with higher triglyceride and total cholesterol in a cross-section of adolescents was linked to a higher risk of developing cardiometabolic syndrome. Xu et al. (2021) in a retrospective cross-sectional study on humans exposed to low-levels of Cd^{2+} and Pb^{2+} observed no apparent association between the two metals and dyslipidemia. They however reported that, whereas blood Pb was positively correlated with atherogenic serum lipid profiles, cadmium did not show any association with serum lipid profiles. In a study involving a group of elderly population with or without coronary artery disease, a positive correlation was found to exist between serum metal level and risk of developing coronary artery disease. Patients with coronary artery disease were found to have a significantly higher serum Pb^{2+}, Cd^{2+} and Hg^{2+} when compared with the control population. Moreover, although elevated serum metal level was positively associated with coronary artery disease patients, no significant association with triglyceride, high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol was established (Asgary et al. 2017).

Like all other cardiometabolic risks, ischemic stroke is a common disease associated with dyslipidemia, diabetes, pressure, obesity and other metabolic syndromes of which heavy metals are implicated as major contributors. Lin et al. (2018) thus examined the relationship between heavy metals and acute ischemic stroke but found no significant association between serum metal level and stroke risk factors such as body mass index, triglyceride and total cholesterol, fasting blood sugar and pressure among both stroke patients and control. After examining the association of 24 metals on blood lipid levels among 1201 participants with history of metal exposure, Li et al. (2021) observed that the relationship between different metal exposure and lipid markers are not identical, and that whereas essential metals showed a positive association with lipid markers (except high-density lipoprotein cholesterol), non-essential metals showed a negative association for lipid markers except for high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. Though in human studies different metabolic risk effects are observed after multiple metal exposure, hypolipidemia mediated by oxidative stress and metal interaction was reported for rats exposed to a combination of Pb^{2+} (1.4 mg/kg), Cd^{2+} (0.01 mg/kg) and Mn^{2+} (0.14 mg/kg) for 15 weeks (Oladipo et al. 2017). These finding together suggest that, even though toxic metals in combination can induce dyslipidemia and other metabolic and cardiometabolic syndromes, the mechanisms and pathways of inducing these metabolic risks may be different among different host.

Heavy metal, gut microbiome and lipid metabolism dysregulation

The gastrointestinal tract of humans serves as a home to a large community of microbiome known to engage in several metabolic activities which are profoundly intertwined with human health (Gao et al. 2017; Lu et al. 2014). Accumulating evidence in recent years have demonstrated that ingestion of exogenous toxicant such as heavy metals through food or water can disproportionately shape the nature of the gut microbiome and may increase one's susceptibility to contracting infectious diseases and may also be an underlying cause of metabolic syndromes such as lipid and lipoprotein metabolism dysregulations (See Table 4 and Fig. 4) (Dabke et al. 2019; Wang et al. 2020; Wu et al. 2016). This is because the gut microbiome has the capacity to perform many complex biochemical and metabolic processes that cannot be performed by the host, including the degradation of undigested carbohydrates through fermentation for the release of microbial metabolites that may function as energy substrates, inflammation modulators and signaling molecules (Lu et al. 2014; Oliphant and Allen-Vercoe 2019). It is commonly observed that among obese individuals, there is a dramatic change in the gut microbiome in relation to the ratio of Firmicutes to Bacteroidetes when compared with healthy lean individuals. Meaning, obese individuals are more likely to have a smaller proportion of Bacteroidetes than Firmicutes (Wu et al. 2016). Moreover, like heavy metals, it is reported that high-fat diet promotes an increase in Firmicutes while decreasing Bacteroidetes population in the gut (Wu et al. 2016).

In mice exposed to cadmium, He et al. (2020) observed that cadmium resulted in marked perturbation in gut microbiota which was characterized by a significant decrease in gut microbial richness and a lowered abundance in short chain fatty acid-producing bacteria leading to a reduced short chain fatty acid production in the gut. This change in the gut microbiome, as induced by Cd, resulted in substantial changes in the metabolic function of the mice and significantly inhibited gene pathways associated with amino acid, carbohydrate, lipid and energy metabolism (He et al. 2020). Short chain fatty acid generated from dietary fibers by gut bacteria play an essential role in modulating the hosts immune response, tumorigenesis and energy metabolism and as such a perturbation in microbial richness renders a person immune compromised (Xue et al. 2019).

Table 4 Relationship between heavy metals, gut microbiome perturbation and lipid profile dysregulation

Organism	Metal	Dosage	Medium of exposure	Duration	Effect on gut microbiome	Effect on lipid metabolism	References
C57BL/6 male mice	Cadmium chloride	10 mg/L	Drinking water	10 weeks	Decrease in Firmicutes and γ -proteobacteria	Increased serum lipopolysaccharide; Induced hepatic inflammation; Dysregulation in energy metabolism	Zhang et al. (2015)
Balb/c male mice	Cadmium telluride QD	0.2, 2, 20 200 µm	Oral-twice per week	4 weeks	A decrease in Firmicutes/Bacteroidetes ratio of gut microbiota	Negatively correlated with low-density lipoprotein, triglyceride and total cholesterol levels in serum	Li et al. (2020)
C57BL/6 male mice	Cadmium chloride	10, 50 ppm	Drinking water	20 weeks	Chronic Cd exposure decreased gut microbial richness	Altered the metabolic pathways of amino acid, carbohydrate, energy and lipid	He et al. (2020)
C57BL/6 mice	Cadmium chloride	50 ppm	Drinking water	2 weeks	Cd caused a significant change in mice gut microbiome resulting in lower microbial diversity	Cd effect on lipid profile was not reported	Li et al. (2019)
C57BL/6 mice	Sodium arsenite	50 ppm	Drinking water	2 weeks	Arsenic caused a non-significant decrease in the gut microbiome population. The abundance of 2 phyla and 24 genera were altered	As^{3+} effect on lipid profile was not reported	Li et al. (2019)
C57BL/6 female mice	Sodium arsenite	0.25, 1 ppm		2 weeks	Arsenic differentially perturbed microbiota	Liver lipid patterns were differentially perturbed in a microbiota-dependent manner	Chi et al. (2019a)
C57BL/6 female mice	Sodium arsenite	1 ppm	Drinking water	3 months	Arsenic exposure perturbed the gut microbiome community and differentially influenced the metabolism of omega-3 and omega-6 polyunsaturated fatty acid	Arsenic exposure perturbed the levels of several key polyunsaturated fatty acids; In mouse sera, metabolic features were significantly up- or down-regulated	Chi et al. (2019b)

Table 4 (continued)

Organism	Metal	Dosage	Medium of exposure	Duration	Effect on gut microbiome	Effect on lipid metabolism	References
C57BL/6 mice	Sodium arsenite	10 ppm	Drinking water	4 weeks	Gut microbiota was significantly perturbed by the combined exposure of infectious bacteria (*Helicobacter trogontum*) and arsenic	Changes of numerous metabolite pathways, including fatty acid metabolism, phospholipids, sphingolipids, cholesterols, and tryptophan metabolism	Xue et al. (2019)
CD-1 mice; Teleost fish	MeHg chloride	0.43, 4.39, 0.87, 5.50 µg/g	Diet	30 days	Mercury induced a xenobiotic-mediated dysbiosis of gut microbiome	Lipid metabolism was affected. MeHg downregulated the expression of fatty acid synthase and acyl CoA oxidase 1 genes which are responsible for the synthesis of fatty acids	Bridges et al. (2018)
Male SD rats	MeHg chloride	0.4 µg/mL	Oral	24 h	A significant decrease in the relative abundance of Bacteroidetes and proteobacteria while Firmicutes increased significantly	Prolife of lipid metabolism was altered	Lin et al. (2020)
ICR mice (male)	Lead acetate trihydrate	0.1 mg/L	Drinking water	15 weeks	The abundance of Firmicutes significantly decreased, whereas that of Bacteroidetes and Proteobacteria increased compared with the control group	Triglyceride and total cholesterol significantly	Xia et al. (2018)
C57BL/6 female mice	Lead chloride	10 ppm	Drinking water	13 weeks	Gut bacteria genera involved in regulating homeostasis in cholesterol and its derivatives were significantly altered by lead	Presence of key energy metabolites from glucose and lipid were altered; Vitamin E, bile acids, and cholesterol and its derivative were significantly reduced	Gao et al. (2017)

Table 4 (continued)

Organism	Metal	Dosage	Medium of exposure	Duration	Effect on gut microbiome	Effect on lipid metabolism	References
Viable yellow agouti (A^{vy}) mice	Lead acetate trihydrate	32 ppm	Drinking water	30–33 weeks	Lead significantly altered gut microbiota. Bacteroidetes population were significantly reduced whereas that of Firmicutes were significantly increased Bacteria from the genus *Pseudomonas*, *Enterobacter*, and *Desulfovibrio* were also increased	Pb exposure resulted in a high Firmicutes/Bacteroidetes ratio associated with altered lipid metabolism, weight gain and obesity	Wu et al. (2016)

Xia et al. (2018) also observed that chronic exposure of mice to Pb (0.1 mg/L for 15 weeks) decreased the relative abundance of both Firmicutes and Bacteroides but did not affect the relative abundance of Proteobacteria or Actinobacteria in the cecum. However, whereas the population of Firmicutes decreased significantly in the gut, there was a relative increase in the abundance of Bacteroidetes. Since the relative population of Firmicutes/Bacteroides is directly related to serum or hepatic lipid contents, it was observed that Pb significantly increased the expression level of key genes related to lipid metabolism in the liver, thus accounting for the elevation of the hepatic triglyceride and total cholesterol levels. This observation indicated that Pb was a potent agent for the disruption of hepatic and serum lipid homeostasis, and this was achieved through gut microbiome dysbiosis (Xia et al. 2018).

To understand the risk factors associated with perturbed gut microbiome, Xue et al. (2019) examine the serum metabolic profile of mice after exposure to 10 ppm arsenic for 4 weeks. They reported that whereas As^{3+} altered the gut microbiome, it also induced drastic changes in the metabolic pathways of fatty acid metabolism, phospholipids, sphingolipids and cholesterols metabolism when compared to the control, suggesting that As-induced gut microbiome perturbation can exacerbate metabolic disorders. It was further noted that when the population of gut microbiome was altered with microbial infection (*Helicobacter trogontum*), arsenic exacerbated the health risk of the host mice through elevated of lipid flux and a disruption of its metabolic function (Xue et al. 2019).

Bridges et al. (2018) examining how methylmercury induces alteration in intestinal microbiome and metabolome of teleost and mice observed that, the MeHg-altered gut microbiome led to significant changes in metabolic precursors related to neuronal function and lipid metabolism. The relative abundance of several long chain fatty acids, including stearic, palmitic, and oleic acids, were observed to have decreased significantly. Moreover, MeHg also significantly altered the availability of serine and phosphocholine precursors required for the generation of bioactive lipids. The MeHg-altered gut microbiome also resulted in changes in the expression of the lipid metabolism genes, *FAS* and *ACOX1*, and the metabolome, indicating that MeHg can influence the lipid profile of both teleost and mice by altering the microbiome and inducing epigenetic changes in its lipid metabolism genes (Bridges et al. 2018).

In view of the concept of developmental plasticity and a growing body of evidence that suggests that early-life exposure to an environmental toxicant could influence the establishment of a later-in-life gene dependent health defects through epigenetic dysregulation (Kuo et al. 2018), Wu et al. sought to find the underlying biological mechanism that regulates this event by exposing parental mice to 32 ppm Pb^{2+}

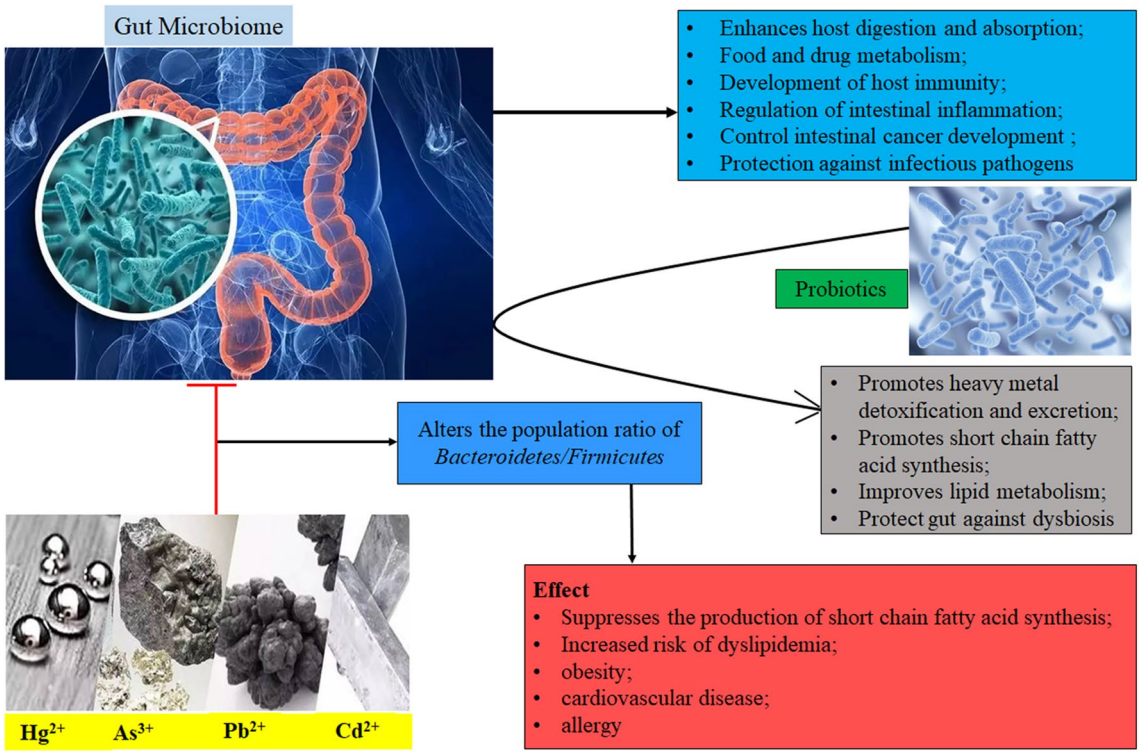


Fig. 4 Physiological interaction between gut microbiome and lipid produce beneficial health effect to host organism. This effect is however impaired by heavy metal (by ingestion) which perturbs gut microbiome population, their function in relation to lipid metabolism and may subsequently lead to metabolic syndrome

through gestation to lactation till offspring were 3-weeks-old (Wu et al. 2016). At 40 weeks of age, it was revealed that Pb^{2+} shifted the gut microbiota in the mice offspring though exposure to Pb^{2+} was ceased when the offspring were 3-weeks-old. A significant inverse change in the ratio of Bacteroides/Firmicutes was also observed among obese mice having a higher gut population of Firmicutes than Bacteroidetes. Wu et al. (2016) therefore underscored that early-life exposure to Pb^{2+} could induced gut microbiome alteration, suggesting that this may be a contributing factor to the increased adult body weight even when Pb^{2+} exposure is removed at a later point in time. Although the study did not examine the effect of Pb^{2+} on lipid metabolism or serum lipid profile, it was reported that mice exposed to Pb^{2+} showed an increase in body weight but that this observation was sex dependent as weight gain in male mice was more pronounced than in females (Wu et al. 2016).

Though toxic metals significantly influence dysbiosis, the gut microbiome responds to the effect of the metal toxicity differently (Wu et al. 2016). Whereas some bacteria are more susceptible to the toxicity of certain metals, others have developed metal-specific resistance and are been exploited for metal detoxification in food processing and in clinical trials (Duan et al. 2020; Ibrahim et al. 2006). In an attempt to subvert the effect of metal-gut microbiome perturbation and lipid dysregulation, it has been reported in several studies that oral administration of probiotics can inhibit heavy metals absorption, protects the intestinal barrier and limit its effect on negatively affecting lipid metabolism (Zhai et al. 2016). Probiotic bacteria belonging to the *Lactobacillus* genus have been commonly exploited to detoxify cadmium (Afraz et al. 2020; Bhattacharya 2020; Gerbino et al. 2014; Ibrahim et al. 2006), lead (Afraz et al. 2020; Ibrahim et al. 2006), arsenic (de Matuoka e Chiocchetti et al. 2020) and mercury (Majlesi et al. 2017) and several other heavy metals from the gut of animal models, in in vitro studies and in water and also to improve the population of the established microbiome. The detoxification ability of these probiotics are pH and dosage (metal concentration) dependent. Gut microbiome and inoculation of probiotics may thus play an important role in the biotransformation of toxic metals through which their toxicity effects are suppressed (Chi et al. 2019a).

Whereas metals perturb lipid profile and gut microbiome, different metals at different doses have been reported to illicit different forms of toxicity, dysbiosis and dyslipidemic effects in mice. Example Richardson et al. (2018) reports of significant changes in microbiota composition when mice were exposed to high doses of chromium and cobalt whereas significant changes in the microbiota composition

after exposure to arsenic, cadmium and nickel were dose-dependent and were also found to induce a large number of iron-importing gene suggesting the possibility of shared response pattern Richardson et al. (2018). As reported by (Li et al. 2020), different doses of cadmium in the form of telluride quantum dots similarly had different effect on gut microbiome. While low dose (0.2 and 2 μM) was reported to significantly increase gut microbiota diversity without affect the lipid profile, medium dose (20 μM) was found to have caused the biggest decrease in Firmicutes/Bacteroides ratio with a corresponding increase in triglyceride, low-density lipoprotein cholesterol and total cholesterol. Though changes in serum lipid profile was not detected, high dose (200 μM) caused toxicities in the liver and intestine and also affected intestinal immunity (Li et al. 2020). Particularly lacking is studies on the influence of mercury on gut microbiome dysbiosis and its relation to lipid metabolism dysregulation of which we recommend more studies.

Heavy metals, hormonal regulation and metabolic syndrome

Heavy metal induced insulin resistance and dyslipidemia

Insulin is a regulatory endocrine hormone that modulates circulating blood glucose. The role of insulin in regulating DNA synthesis and gene transcription of proteins involved in metabolic activities has also been observed (Batista et al. 2021; Sears and Perry 2015). One principal function of insulin is to suppress lipolysis of stored fat in adipocytes and gluconeogenesis in the liver. By inhibiting lipolysis, it promotes triglyceride storage and reduces the volume of circulating free fatty acids, and thus regulating very low-density lipoprotein production (Chakrabarti et al. 2013; Sears and Perry 2015).

Diabetes and dyslipidemia, common conditions of metabolic syndrome, are among the major disorders that emanate from insulin resistance as a result of accumulation of blood glucose and lipid metabolites. The levels of lipid metabolites in circulation are commonly used as biomarkers for insulin resistance and dyslipidemia and are also used as determinants for cardiovascular related diseases. The ratio of triglyceride to high-density lipoprotein cholesterol and total cholesterol to high-density lipoprotein cholesterol are the generally accepted best marker for insulin resistance (Artha et al. 2019). Studies over the years have linked heavy metal exposure to insulin and insulin receptor malfunction. Exposure to arsenic, for example, has been found to induce insulin insensitivity in humans and animals and is implicated as a factor for the onset of diabetes and the progression of obesity (Lin et al. 2014; Park et al. 2016). Chronic exposure of rats to cadmium has also been reported to impair pancreatic function, and induce insulin resistance in liver, muscle adipose tissue and cardiovascular tissue, thereby resulting in an increase in serum triglyceride, cholesterol, low-density lipoprotein cholesterol and very low-density lipoprotein, and a decrease in high-density lipoprotein cholesterol (Treviño et al. 2015). Findings from studies with arsenic (Afolabi et al. 2015; Padmaja Divya et al. 2015), mercury (Jung et al. 2016; Kim et al. 2015) and lead (Leff et al. 2018; Shyam et al. 2012) indicate similar observations suggesting that these heavy metals have specific effect on insulin signaling and the metabolism of fat or lipid and glucose and could lead to lipid accumulation, obesity and diabetes.

Role of heavy metals in diabetes

As an environmental and industrial toxicant, heavy metals have no known important biological roles except for their ability to alter the normal physiological function of the body by interfering with hormonal action, for which reason they are classified as endocrine disrupting chemicals (Lauretta et al. 2019; Leff et al. 2018). Studies on metal toxicology over the years have explored the hazardous effects heavy metals have on the initiation and progression of type 2 diabetes.

Although current understanding of the direct mechanism by which endocrine disrupting chemicals impair systemic function to promote diabetes initiation remains incomplete, evidence of their inhibitory roles on some endocrine glands and hormones that regulates sugar levels have been reported (Howard 2018; Sabir et al. 2019). Cadmium accumulation, for example, is reported to induce diabetes by competing with zinc, an essential metal required for insulin formation in pancreatic β-cells, thus impairing the function of the insulin producing pancreatic β-cells (El Muayed et al. 2012; Hong et al. 2021). Cadmium has also been found to reduce the number of insulin receptors and further renders the remaining unresponsive to insulin (Ficková et al. 2003). This negative dual effect of cadmium on insulin producing pancreatic β-cells and on insulin receptors may eventually account for the accumulation of blood glucose due to their inability to enter cells and may be a major contributing factor to the initiation and progression of type 2 diabetes. Like Cd^{2+}, the pro-diabetic nature of arsenic (Islam et al. 2012; Kirkley et al. 2017; Liu et al. 2014), Pb^{2+} (Leff et al. 2018) and Hg^{2+} (He et al. 2013; Rizzetti et al. 2019) have likewise been investigated in both human and animal models, with a pronounced effect on pancreatic β-cells dysfunction, insulin resistance and an increased gluconeogenesis in the case of arsenic. The pro-diabetic nature of these heavy metals is largely due to their adverse effect on insulin transduction signaling and the inhibition of some genes responsible for glucose metabolism (Islam et al. 2012). The initiation of

inflammation and oxidative stress provoked by heavy metals suppress insulin gene promoter mRNA expression and its activity in pancreatic islet cells thereby evoking an increase in systemic glucose levels and a downregulation in serum insulin levels, thus leading to hyperglycemia and diabetic progression (Khan and Awan 2014; Pizzino et al. 2017). Even though treatment of diabetes remains complicated, heavy metal chelators such as ethylenediaminetetraacetic acid (EDTA) (Diaz et al. 2018; Lamas et al. 2016) and lipoic acid (Ibrahimpasic 2013) have been found to suppress the progression of metal-induced diabetes and diabetes-associated cardiovascular events.

Heavy metals and the endocrine system

The endocrine system comprises of a network of glands that produce and secrete hormones responsible for regulating cellular and metabolic processes. Several environmental toxicants have been characterized as endocrine disruptors due to their ability to alter hormonal secretion by the glands, as well as their normal functioning and regulatory roles (Mahapatra et al. 2021; Szkudelska et al. 2021). Heavy metals have gained notoriety as endocrine disrupting chemicals due to their hazardous effect on the physiological functioning of both endocrine glands and the body in general. Stahr et al. (2021) observed a positive and dose-dependent correlation between postmenopausal women with arsenic exposure and obesity, hinting that high arsenic levels not only suppresses estrogen secretion but may also mimic or abrogate estrogen signaling pathway thereby altering all associated metabolic signaling processes including lipid metabolism. Nadal et al. (2017) observed that metabolic disrupting chemicals could regulate nutrient absorption and metabolism by altering intestinal transport and peptides that control food intake. Glucose uptake, for example, is reported to be altered significantly after the administration of metabolic disrupting chemicals such as polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin by either increasing the intestinal expression of sodium/glucose co-transporter 1 and glucose transporter type 2 genes, or by reducing insulin stimulated glucose uptake. These alterations together were associated with elevated plasma glucose levels suggesting an increase in intestinal glucose uptake and transport but a decrease in cellular glucose uptake and metabolism (Nadal et al. 2017).

In relation to heavy metals, Bell et al. (1990) reported of an elevated glucose levels in rats exposed to Cd^{2+} (0.84 mg/kg), whereas Sabir et al. (2019) describes Cd^{2+} and arsenic as hazardous endocrine disrupting chemicals that exhibits deleterious effect on carbohydrate metabolism pathways through modification and impairment of relevant key enzyme activity thus contributing to a considerably increase in blood glucose levels. These metals were also found to disrupt hormonal balance by damaging or altering the function of pancreatic islet and adrenal glands. These findings together indicate that heavy metals together with other endocrine and metabolic disrupting chemicals could influence the expression and secretion of gastrointestinal peptides and hormones responsible for dietary nutrient absorption of which glucose and lipid processes may be significantly affected.

In addition, the hypothalamus is an important region of the brain particularly responsive to hunger and satiety regulating signals and maintaining the overall energy balance by modulating food intake and energy expenditure (Austin and Marks 2009). An alteration in the expression and secretion of any hypothalamic peptide associated with glucose or lipid metabolism and appetite regulation may result in a compulsive eating behavior which could potentially lead to the development of hyperglycemia, hyperlipidemia and an accumulation of total visceral adipose fat (Nadal et al. 2017). Heavy metals, acting as endocrine disrupting chemicals, may thus induce obesity by influencing the hypothalamus and by distorting the expression of peptides that regulates appetite and satiety (Park et al. 2017b). The two major hormones, leptin and ghrelin, produced by adipose tissues and stomach but acts primarily on the hypothalamus to regulates food intake and body weight (Klok et al. 2007), have been observed to be influenced by toxic metals. Whereas Stasenko et al. (2010), Ferrer et al. (2018) and Kawakami et al. (2012) reports that Cd^{2+} and Hg^{2+} suppresses the mRNA expression of leptin, other studies have indicate that these two metals induced an elevation of leptin in plasma (Ashley-Martin et al. 2015; Ba et al. 2017; Rizzetti et al. 2019). Similar investigations on Pb^{2+} (Beier et al. 2015) and arsenic (Penta 2016) found that these metals induce an elevation of leptin hormone and implicating it as a factor for weight gain and obesity. Both elevation and suppression of leptin, above or below its optimal threshold, could trigger lipid and glucose dysregulation and potentially lead to the development of metabolic syndrome. This is because elevated leptin levels is directly associated with increased adipose tissue mass and insulin resistance which are factors for inducing obesity (Ashley-Martin et al. 2015), whereas persistently low leptin levels could trigger an incessant craving for food and subsequently lead to hyperglycemia, hyperlipidemia and cardiovascular diseases (Poetsch et al. 2020). Heavy metals may thus affect the production, release and function of these hormones in the hypothalamus, and may result hyperphagia leading to excessive food intake, abnormal lipid synthesis, accumulation and obesity.

Conclusion

The pervasive nature of heavy metals is a matter of public health concern due to the multiple cardiometabolic and pathophysiologic effect they induce after exposure, and the high

likelihood of increased mortality. Though lipids and lipoproteins are required for carrying out physiological functions such as impulse transmission, formation of cellular or organellar membrane, for energy reserve and for maintaining systemic homeostasis, evidence show that exposure to toxic doses could induce lipid and glucose metabolism dysregulation thus influencing redistribution and accumulation, which are precursors for developing metabolic syndrome and other life-threatening clinical conditions. Evidence show that heavy metals distort serum lipid profile through lipogenic gene aberration, receptor inhibition, hormonal imbalance and gut microbiome perturbation resulting in high pro-atherogenic lipid levels while significantly decreasing anti-atherogenic lipid levels.

The deleterious influence of heavy metals on altering significant lipogenic genes essential for maintaining lipid homeostasis through inhibition of function or causing an increase in pro-atherogenic lipids in serum is illustrated. The transcription factors *C/EBP*, *PPAR*, *SREBP*, *CHREBP* and *LXR* which regulates the expression of a large set of lipid and glucose metabolism processes including β-oxidation, de novo lipogenesis, and the synthesis and transport of fatty acids, cholesterol, phospholipids and triglycerides are the most largely impaired or downregulated genes.

Given that heavy metals perturb gut microflora population, it is found that perturbation in the ratio of *Firmicutes*/*Bacteroidetes* accounts for increased risk of obesity due to the notable decline in glycolysis and lipid metabolism genes. In addition, decline in insulin production, insulin receptor insensitivity, and the decline in ghrelin and leptin secretion are among the many hormonal factors affected by heavy metal exposure, which together contributes to lipid dysregulation. In spite of the availability of several reports on heavy metal induced lipid dysregulation, studies are limited when it comes to de novo lipogenesis, and also Hg^{2+} induced lipogenic gene alteration in model animals. Further studies may therefore be required to accelerate current understanding and insight into their role in dysregulating serum lipid profile.

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Declarations

Conflict of interest The authors declare that they do not have any conflict of interest.

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