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Research Article

Assessments of the Safety of Arsenicals on Dyslipidaemia and Reproductive Organ Morphology of Albino Rats

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ABSTRACT

Epidemiological studies have implicated Arsenic (As) an environmental toxicant in the etiology of many diseases which have been associated with dyslipidaemia and cardiovascular abnormalities. This study investigated the comparative effect of sub-chronic exposure to two arsenicals on the lipid profiles and morphology of the reproductive organs. Fifty albino rats were divided into five groups of 10 animals each (5 male and 5 female) were exposed to different doses of arsenic (As) either as sodium arsenite or sodium arsenate for 5 weeks. Lipids [triacylglycerol (TAG), cholesterol (CHOL) and phospholipids (PHOS)] concentrations were determined in the plasma, lipoprotein fractions, hepatic, renal, cardiac and brain tissues. In the male rats' tissues, both arsenicals generally elicited a hormetic response, while in the tissues of female rats; both arsenicals increased the CHOL concentration. Furthermore, the perturbations in TAG concentration in female animals did not follow any regular pattern; although, depletion of TAG characterized these arsenic-induced perturbations in male rats except in the kidney, where TAG was accumulated. The arsenicals generally increased PHOS concentration in exposed animals irrespective of the sex. While HDL-TAG and HDL-CHOL concentrations were significantly reduced in As-exposed groups, changes observed in VLDL+LDL-TAG and VLDL+LDL-CHOL varied with no regular pattern. Histopathology of the sex organs revealed altered morphology in arsenite-exposed rats. Results from this study further associated these arsenicals as potential agents that can cause dyslipidaemia in tissues and also possess the ability to alter the architecture of sex organs in albino rats.

Keywords: *Arsenic, Lipid profile, Sub-chronic exposure, Histology, Lipoproteins*

INTRODUCTION

Arsenic (As) is one of the most abundant metalloids in the earth crust, persisting as a toxicant with serious adverse epidemiological and environmental consequences (Wang *et al.,* 2007; Masuda, 2018). The Environmental Protection Agency (USA) has affirmed all forms of As as serious threats to human health (Sarkar and Rupali, 2007); however, As^{III} (arsenite) and As^{V} (arsenate) are the most prevalent forms of As to which humans can be exposed because these arsenicals leach from the soil and enter into drinking water (Ellen and Costa, 2010). Furthermore, As is more noxious to human health than most other toxicants, and while the list of its toxic effects continues to increase, evidence posits exposure is widespread throughout the world (Smith and Steinmaus, 2011). Several studies have implicated arsenicosis in a plethora of subclinical and clinical outcomes such as carotid atherosclerosis, peripheral vascular disease (PVD), ischemic heart disease (IHD), and cerebrovascular disease (CVD) such that interaction between nutritional, environmental, and genetic factors

play a role in the development of the observed outcome (Wang *et al.*, 2007). Furthermore, dyslipidemia with its accompanying disruptions in the metabolism of lipids and lipoproteins, including the changes these moieties undergo can ultimately lead to macrophage activation, foam cell formation, and other downstream cardiovascular changes common in arsenic-associated cardiovascular aftermaths (Wengrofsky *et al.,* 2019). From the other side, significant sex-related differences in the metabolism of drugs have been reported by Mennecozzi *et al.* (2015); furthermore, another study linked observed differences partly to hormonal influence (Nicolson *et al.*, 2010). Similarly, gender differences in As metabolizing enzymes have been shown to affect arsenic biotransformation which ultimately produced significant changes observed in different sexes (Muhetaer *et al.*, 2022). Although earlier reports on sex studies have shown gender differences in the metabolism of As (Jansen *et al.,* 2016; Muhetaer *et al.,* 2022); to the best of our knowledge no literature has reported the effects of these arsenicals on lipids at these doses (20 and 40 ppm) simultaneously on male and female albino rats; hence this study investigated the sub-chronic effects of two arsenicals (arsenite and arsenate) on lipid profile and sex organ morphology in both male and female albino rats.

MATERIALS AND METHODS

Chemicals

The arsenicals (sodium arsenite and sodium arsenate) used were products of Sigma-Aldrich, Missouri, USA. All other chemicals used in this study were of analytical grades.

Animals and treatment

All experimental procedures followed the guidelines of the Institutional Animal Care and Use Committee and received ethical approval (Ref No. FUNAAB/CBS/BCH/PG/11-0200-1) from the Animal Ethical Committee of the Department of Biochemistry, College of Biosciences, Federal University of Agriculture, Abeokuta, Nigeria.

Fifty albino rats (twenty-five male and twenty-five female), having weight ranging between 120-150 g, purchased from the breeding unit of the Animal Physiology Department, University of Ibadan, Ibadan were used for this research work. They were housed under ambient conditions at room temperature and maintained on a standard pellet diet. After two weeks of acclimatization, the male rats were divided into five groups of five each; the first group served as control and was given distilled water; Groups 2 and 3 received 20 and 40 ppm of sodium arsenite respectively, while groups 4 and 5 received 20 and 40 ppm sodium arsenate correspondingly. The female rats were similarly grouped as described earlier for their male counterparts. Exposure to the arsenicals was *via* their drinking water *ad libitum*. After five weeks (35 days) of administration, the animals were anaesthetized using 50 mg/kgbwt ketamine i.p and then sacrificed by abdominal dissection. Blood sample was collected from the animals through the abdominal artery into heparinized tubes. The blood obtained was centrifuged to obtain plasma from which the lipoproteins fractions were isolated. The liver, kidney, heart, and brain tissues were excised and homogenized, then centrifuge to get supernatants which were used for lipid analyses. Sections of the testes and ovaries of experimental rats were also fixed in 10 % buffered formalin for histological examination.

Isolation of lipoproteins from plasma

High-density lipoprotein (HDL) and very low density + low-density lipoproteins (VLDL+LDL) fractions were isolated from the plasma as reported by Ugbaja *et al.* (2016). Briefly, to obtain HDL fraction, 10 µL of heparin-$MnCl_2$ solution was added to 100 µL of plasma (1:10), vortexed, allowed to stand for 10 min and centrifuged at 4000 rpm for 10 min. The supernatant (HDL fraction) was removed using a micropipette into an Eppendorf tube. The pellet (VLDL+LDL) was re-suspended by adding 100 µL of distilled water.

Plasma and lipoprotein lipid profiles

The concentrations of the total cholesterol (CHOL) and triacylglycerol (TAG) in the plasma and lipoprotein fractions were determined using commercially available kits from Randox Laboratories Ltd (Crumlin, England). Cholesterol concentration was determined after enzymatic hydrolysis and oxidation of cholesteryl esters. Briefly, 10 µL of sample was mixed with 1 mL of the working reagent and allowed to react for 10 min at room temperature. The concentration of CHOL in the sample which correlated with the intensity of the indicator (quinoneimine) was measured spectrophotometrically at 500 nm. Triacylglycerol (TAG) concentration was estimated based on the enzymatic hydrolysis of TAG to glycerol and free fatty acids by lipoprotein lipase. In the procedure, 10 µL of sample was pipetted into an Eppendorf tube after which 1 mL of the working reagent was added, mixed and allowed to incubate for 10 min at room temperature. The absorbance of quinoneimine (chromogen) produced which correlated with the concentration of TAG was measured spectrophotometrically at 500 nm against a reagent blank. Phospholipids concentration in the plasma was also determined according to the method of Stewart (1980). Briefly, 33 µL of plasma was transferred into labelled tubes and evaporated to dryness over a water bath at 60°C. Afterwards, chloroform (667 µL) and 667 µL of ammonium ferrothiocyanate was added to the extract and shaken for 10 min, then the two phases were allowed to separate. The chloroform (lower) layer was carefully removed and absorbance read at 488 nm against a blank.

Extraction of lipids from organs

Extraction of lipids from the liver, kidney, heart, and brain tissues was done as described by Folch *et al.* (1957). Lipids extraction was carried out by using chloroform-methanol (2:1, v/v) mixture, in that 0.1 g of each tissue was homogenized in 0.9 mL of chloroform-methanol mixture. The homogenate was centrifuged at 4000 rpm for 10 min

and the supernatant collected. To remove other non-polar part from the mixture, 0.2 mL of 0.05 M of KCl was added to the supernatant which was vortexed at room temperature for 5 min. The mixture was then centrifuged again and the chloroform layer (lower layer) was taken and analyzed for lipids.

Organ lipid profile

Determination of CHOL and TAG concentrations in the organs harvested followed the methods described in the commercial kits (Randox diagnostic kits) used with slight modifications. Briefly, 0.1 mL of the lipid extract for each respective lipid was pipetted into a tube and evaporated to dryness at 60 ^{o}C using a water bath, followed by addition of 20 µL of Triton X-100/chloroform mixture (1:1 v/v) for resolution. The mixture was then evaporated and the respective working reagents (1 mL) for each lipid (CHOL and TAG) was added, mixed, and incubated before the absorbance was read using the spectrophotometer according to the procedure in the manufacturer's manual available in each kit package. Phospholipids concentration was however determined in the lipid extracts of the different organs as described earlier for plasma PHOS by the method of Stewart (1980).

Histological analysis

Histopathological examination was carried out as reported by Adeyi *et al.* (2021). Briefly, sections of testes and ovaries were fixed in 10 % buffered formalin for 48 h. The sections were further dehydrated in increasing concentrations of alcohol, cleared and subsequently fixed in paraffin with a tissue embedder (Leica EG1150H). From the embedded tissue, 5 µm was sectioned and stained with hematoxylin and eosin (H and E). Microanatomy of tissues was examined under a light microscope and images were captured with an attached digital camera. Histological assessment was done in a blinded fashion to avoid bias and finally observed at × 100 magnification under a Nikon light microscope.

Statistical analysis

Values presented are mean ± standard error of means (S.E.M) of five rats. The results of groups were analyzed using one-way Analysis of Variance (ANOVA), followed by Duncan Multiple Range Test (DMRT), with $p<0.05$ considered significant. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 20.0.

RESULTS AND DISCUSSION

Results

Table 1 shows the effect of As on CHOL concentration in the plasma and tissues of male and female albino rats. Significant increases ($p<0.05$) in plasma CHOL ensued on exposure to all doses of arsenicals except 20 ppm arsenite male group, which showed no significant difference ($p>0.05$) compared to the control group. In the brain tissue, CHOL was lowered by 11% and 20% in male and female animals exposed to 20 ppm arsenate and 40 ppm arsenate respectively. In the cardiac and renal tissues of the male rats, the arsenicals altered CHOL concentrations in a different manner. While the lower doses decreased cardiac CHOL concentration by 34 and 48%; the higher doses increased it by 45 and 48% with arsenite and arsenate respectively. In the liver of male rats, CHOL concentration increased only in the 40 ppm arsenite group. Similarly, female renal and hepatic CHOL also increased on exposure to As except in female exposed to 20 ppm arsenite.

Table 1. Effects of Arsenite and Arsenate on Total Cholesterol Concentration in Plasma and Organs of Male and Female Albino Rats

	Groups	Plasma (mmol/L)	Brain (mg/g tissue)	Heart (mg/g tissue)	Kidney (mg/g tissue)	Liver (mg/g tissue)
Male	Control	5.27 ± 0.16^{a}	18.98 ± 0.28^{b}	12.87 ± 0.27^{b}	12.83 ± 0.16^{b}	17.38 ± 0.28^{c}
	20 ppm arsenite	5.16 ± 0.35^{a}	19.77 ± 0.28^{b}	8.47 ± 0.41^{a}	9.69 ± 0.37^{a}	9.17 ± 0.04^{a}
	40 ppm arsenite	17.27 ± 0.47^{d}	19.13 ± 0.26^{b}	18.64 ± 0.44^{d}	18.87 ± 0.19^{d}	21.20 ± 0.20^{d}
	20 ppm arsenate	19.06 ± 0.30^{d}	16.83 ± 0.84^{a}	6.68 ± 0.71^{a}	7.89 ± 0.39^{a}	14.71 ± 0.12^{b}
	40 ppm arsenate	11.43 ± 0.31^{b}	19.54 ± 0.33^{b}	18.99 ± 0.90^{d}	17.44 ± 0.32^{c}	7.87 ± 0.61^{a}
Female	Control	10.24 ± 0.78^{b}	19.01 ± 0.60^{b}	10.99 ± 0.44^{b}	9.61 ± 0.15^{a}	10.75 ± 0.43^{a}
	20 ppm arsenite	15.30 ± 0.76^{c}	20.77 ± 0.32^{bc}	13.67 ± 0.24^{b}	13.09 ± 0.43^{b}	8.80 ± 0.20^{a}
	40 ppm arsenite	17.64 ± 0.50^{d}	20.15 ± 0.51^{bc}	11.79 ± 0.35^{b}	20.42 ± 0.25^{d}	22.04 ± 0.49^{d}
	20 ppm arsenate	16.94 ± 0.93^{cd}	19.23 ± 0.49^{b}	16.07 ± 0.25^{c}	20.27 ± 0.09^{d}	16.79 ± 0.07^{bc}
	40 ppm arsenate	23.82 ± 0.64^{e}	15.23 ± 0.38^{a}	15.71 ± 0.37^{c}	15.53 ± 0.49^{c}	15.48 ± 0.24^{b}

Values are mean ± S.E.M (n=5). Values having different superscripts are significantly different at $p<0.05$

Table 2 indicates effect of arsenic on TAG concentration in plasma and tissues of male and female rats. In the plasma, exposure to arsenicals at different doses resulted in significant increases ($p<0.05$) in TAG concentrations. In the brain of male rats, 40 ppm As doses lowered TAG while increased brain TAG characterized arsenite-exposed female animals. While decreased TAG characterized male cardiac tissue, there was variation with the females'. Exposure to As in both sexes increased renal TAG except in female exposed to 40 ppm arsenate (Table 2). In the hepatic tissue, exposure to As resulted in decreased TAG in both sexes except in female animals exposed to 40 ppm arsenite such that a slight insignificant increase (8%) ensued (Table 2).

Table 3 indicates effect of As on PHOS concentration in exposed animals. There was significant elevation ($p<0.05$) of PHOS concentrations in the plasma, cardiac and renal

phospholipids in exposed male rats. Conversely, in the hepatic tissue significant decrease ($p<0.05$) was observed when compared with the control animals. In the female rats, significantly ($p<0.05$) increased PHOS concentration characterized the cardiac, renal and hepatic tissues on exposure to both arsenicals.

Table 2. Effects of Arsenic on Triacylglycerol Concentration in Plasma and Organs of Male and Female Albino Rats

	Group	Plasma (mmol/L)	Brain (mg/g tissue)	Heart (mg/g tissue)	Kidney (mg/g tissue)	Liver (mg/g tissue)
Male	Control	102.35±5.34^{a}	17.14±0.24^{d}	17.72±0.20^{e}	13.92±0.12^{a}	18.65±0.23^{c}
	20 ppm arsenite	273.23±2.67^{f}	16.71±0.22^{d}	15.07±0.34^{c}	18.01±0.22^{d}	16.18±0.20^{b}
	40 ppm arsenite	336.42±6.23^{g}	11.31±0.35^{a}	15.59±0.12^{c}	18.58±0.28^{d}	17.85±0.16^{c}
	20 ppm arsenate	269.67±5.34^{f}	16.74±0.19^{d}	15.23±0.16^{c}	16.41±0.11^{c}	17.13±0.26^{c}
	40 ppm arsenate	276.79±3.56^{f}	12.90±0.25^{b}	13.02±0.35^{b}	16.81±0.24^{c}	14.82±0.39^{a}
Female	Control	124.73±2.56^{b}	14.87±0.18^{c}	13.65±0.16^{b}	14.83±0.09^{b}	18.13±0.34^{c}
	20 ppm arsenite	150.03±2.16^{c}	17.51±0.18^{d}	12.13±0.45^{a}	18.10±0.18^{d}	17.20±0.25^{b}
	40 ppm arsenite	139.25±1.33^{c}	19.69±0.58^{e}	16.22±0.31^{d}	18.35±0.14^{d}	19.54±0.41^{d}
	20 ppm arsenate	192.96±5.34^{e}	15.67±0.10^{c}	14.43±0.04^{b}	14.74±0.06^{b}	17.06±0.25^{b}
	40 ppm arsenate	164.57±5.66^{d}	14.90±0.14^{c}	16.06±0.42^{d}	17.61±0.36^{cd}	14.65±0.22^{a}

Values are mean ± S.E.M (n=5). Values having different superscript are significantly different at $p<0.05$

Table 3. Effects of Arsenic on Phospholipids Concentration in Plasma and Organs of Male and Female Albino Rats

	Groups	Plasma (mg/dl)	Brain (mg/g tissue)	Heart (mg/g tissue)	Kidney (mg/g tissue)	Liver (mg/g tissue)
Male	Control	205.69±0.45^{a}	56.35±0.36^{c}	44.83±0.45^{c}	41.75±0.26^{c}	48.25±0.40^{f}
	20 ppm arsenite	217.69±0.71^{c}	56.16±0.15^{c}	78.08±0.49^{g}	50.46±0.37^{f}	32.88±0.29^{b}
	40 ppm arsenite	224.36±0.31^{d}	59.84±0.33^{d}	53.41±0.28^{d}	50.51±0.18^{f}	32.24±0.13^{b}
	20 ppm arsenate	215.93±0.05^{c}	53.79±0.20^{b}	54.70±0.56^{d}	44.80±0.18^{d}	40.28±0.08^{d}
	40 ppm arsenate	212.56±0.92^{b}	64.47±0.30^{e}	61.81±0.47^{e}	49.70±0.18^{e}	38.48±0.38^{c}
Female	Control	237.25±4.55^{e}	56.16±1.58^{b}	25.78 ±1.05^{a}	26.38 ± 1.55^{a}	26.40 ± 0.73^{a}
	20 ppm arsenite	231.43±3.32^{e}	65.37±0.76^{e}	83.60±1.48^{h}	32.67±0.88^{b}	52.17±0.90^{g}
	40 ppm arsenite	294.21±2.22^{f}	45.39±1.51^{a}	32.64±1.59^{b}	33.27±1.34^{b}	33.04±1.12^{b}
	20 ppm arsenate	228.86±5.36^{de}	74.19±0.93^{f}	31.72±0.75^{b}	43.45±1 .06^{cd}	44.63±2.24^{e}
	40 ppm arsenate	232.40±4.18^{e}	75.06±1.16^{f}	71.03±2.24^{f}	67.52±1.10^{g}	59.38±2.07^{h}

Values are mean ± S.E.M (n=5). Values having different superscript are significantly different at $p<0.05$.

Depicted in Figure 1 is the effect of As on levels of HDL-TAG and HDL-CHOL in both male and female rats. In both sexes, As lowered HDL-TAG concentration except in male animals group exposed to 20 ppm arsenite such that difference was not statistically significant ($p<0.05$) when compared with control (Figure 1). Significant ($p<0.05$) depletion also characterized HDL-CHOL level in both male and female rats.

Figure 2 illustrates effect of As on VLDL+ LDL-TAG and VLDL+LDL-CHOL levels. In male rats, effect on VLDL+ LDL-TAG was not significant except in 40 ppm arsenate in which a significant decrease of 15.7% was observed. However, the concentration of this lipoprotein fraction increased in exposed female animals except in animals exposed to 20 ppm arsenite. Significant elevations hallmarked VLDL+LDL-CHOL concentrations in the male sex following exposure to all arsenicals while in the female, only the 20 ppm As doses increased the concentration (Figure 2).

Figures 3 A-E represent photomicrographs of the testicular tissues of animals exposed to As. Mild congestion of the testicular interstitium was observed in animals exposed to 40 ppm arsenite (group C- arrowed red). However, no visible testicular lesion was seen in other exposed groups.

Figures 4 A-E show photomicrographs of ovaries in exposed female rats. Large developing follicles (blue arrow) seen in control group (A). In groups exposed to arsenite, the medulla was seen to be severely congested (arrowed red). Similarly, few Graafian follicles featured in ovaries of animals exposed to 40 ppm arsenite (arrowed yellow). However, no visible lesion was observed in groups exposed to arsenate (D and E)

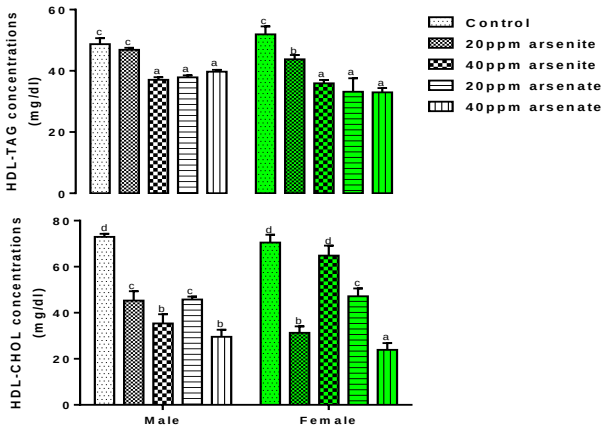

Figure 1. Effect of As on HDL-TAG and HDL-CHOL Concentration of Male and Female Rats.
Bars are mean ± S.E.M (n=5). Bars having different superscript are significantly different at $p<0.05$.

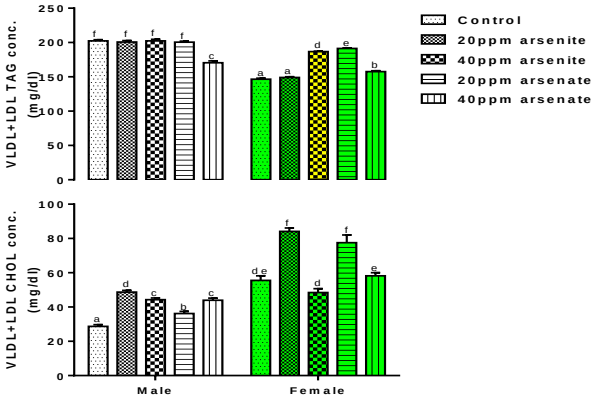

Figure 2. Effect of As on VLDL+LDL--TAG and VLDL+LDL--CHOL Concentrations of Male and Female Rats.
Bars are mean ± S.E.M (n=5). Bars having different superscript are significantly different at p<0.05.

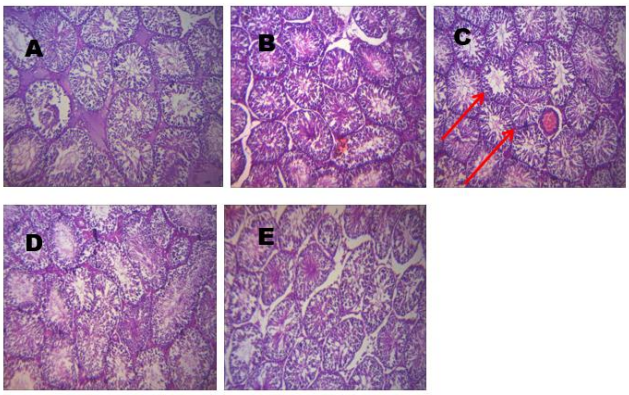

Figure 3. Photomicrographs of the Testicular Tissues of Albino Rats on Exposure to As (x100 H&E).
A= Control; B= 20 ppm arsenite; C= 40 ppm arsenite; D= 20 ppm arsenate; E= 40 ppm arsenate

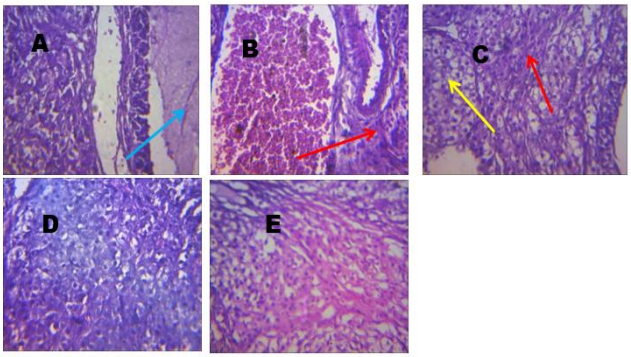

Figure 4. Photomicrographs of Ovaries of Albino Rats Exposed to Arsenite and Arsenate (x400 H&E).
A = Control group; B = 20 ppm sodium arsenite; C = 40 ppm sodium arsenite; D = 20 ppm sodium arsenate; E = 40 ppm sodium arsenate.

Discussion

Around the globe, chronic arsenicosis has been associated with long periods of ingestion of arsenic-contaminated water thereby reportedly contributing to the pathogenesis of many problems associated with the cardiovascular system (Singh *et al.,* 2018). In the same vein, epidemiological researchers have opined alterations in lipids and lipoproteins levels as risk factors in the aetiology and progression of cardiovascular diseases (CVDs) (Afolabi *et al.,* 2015; Singh *et al.,* 2018). Based on the aforementioned evidence, one can suppose a link between arsenic exposure, dyslipidaemia, and the accompanying cardiovascular issues. In addition to exploring this hypothesis, this study investigated and compared the effects of two arsenicals on the lipid profile in both sexes of albino rats.

Cholesterol being a requisite for all animal life can be synthesized by almost all animal cells and is a vital membrane lipid, involved in bio-signalling, and also a precursor molecule for bile acids and steroid hormones (Hanukoglu, 1992). Despite these beneficial functions, increased blood cholesterol concentration has been implicated in the incidence of cardiovascular irregularities (Steinberg, 2006; Ugbaja *et al.,* 2016). In this work, hypercholesterolemia ensued in both sexes exposed to As (Table I). Earlier studies on As by Afolabi *et al.* (2016) and Singh *et al.* (2018) on male rats and mice respectively reported a similar result indicating the hypercholesterolemic potential of As, this study further supports the fact and also indicated that female albino rats can also be similarly affected on exposure to As. In the cardiac and renal tissues of male rats, both arsenicals elicited a hormetic response; such that the lower dose (20 ppm) decreased cholesterol concentrations, while the higher dose (40 ppm) increased it. However, in the females', As increased CHOL in a non-dose dependent manner. Literatures have shown hormonal influence on the level of cholesterol (Hanukoglu, 1992; Qamar & Bhatt, 2015; Mao *et al.*, 2018). The effect of As observed in the female animals might have also been influenced by these hormones common in the female gender owing to the fact that some research work by Cypriani *et al.* (1998) and Mao *et al.* (2018) showed that estrogen levels rose during a woman's menstrual cycle which in turn affect the cholesterol levels; another possible cause for the non-dose dependent increase observed in this study. However, for brain CHOL concentration, a different pattern was observed in As-exposed animals such that the effect was minimal when compared to other tissues.

The brain has been reported to have a barrier called blood brain barrier (BBB) which selectively permits substances into the brain tissue (Rai *et al.,* 2010). Evidence by Hui *et al.* (2017) and Adeyi (2021) indicated that although As crosses the BBB, it is not readily bio-accumulated and this could be a reason for the mild effect of As on brain CHOL as observed in exposed animals in spite of sex differences. Furthermore, several studies have provided proofs that exposure to As influences cholesterol homeostasis; these studies posit that As stimulates cholesterol biosynthesis either by (i) up-regulating HMG CoA reductase activity; (ii) altering its metabolism to favour its efflux into the blood by down-regulating key lipid-metabolizing genes such as *Cyp7a1, Hmgcr* and *Srebp1c*; these effects possibly explain the observed hypercholesterolemia (Afolabi *et al.,* 2015; 2016; Singh *et al.,* 2018; Chi *et al.,* 2019).

The arsenicals also altered TAG metabolism in exposed animals as shown in Table 2. From this study,

hypertriacylglycerolemia was a common feature observed as an As-induced perturbation in line with the reports of Afolabi *et al.* (2016) and Singh *et al.* (2018). Alteration in the TAG concentration ensued in tissues of exposed animals; in the female tissues, the perturbations in TAG concentration did not follow any regular pattern; however, depletion of TAG characterized the male tissues except in the kidney, where TAG accumulated. Early reports by Afolabi *et al.* (2016) mentioned that this alteration that caused a reduction in TAG could be as a result of TAG hydrolysis, possibly due to increased adrenergic stress following arsenic exposure and/or increased lipid secretion due to increased expression of apolipoprotein B. On the other hand, studies have shown that renal failure can cause decrease in fatty acid oxidation (Kang *et al.,* 2015) which in turn leads to TAG accumulation as observed in the renal tissue of As-exposed animals in this study. Similarly, Scerbo *et al.* (2017) who worked on diabetic mice with kidney disease reported accumulation of TAG even when there was decreased expression of CD36 (a protein marker that mediates active transport of free fatty acids into cells) suggesting the kidney may have other regulatory mechanisms that is quite different from other organs.

Comparable to other lipid moieties monitored in this study, the phospholipids concentration was altered such that increased plasma phospholipid ensued in exposed male animals which are in consonance with the findings of Singh *et al.* (2018). Phospholipids being the major component of cellular membranes can also be affected by arsenic resulting in lipid peroxidation (Afolabi *et al.,* 2016) and efflux of cellular lipids (Chi *et al.,* 2019). The former effect arises from arsenic-mediated oxidative damage of membranes, which can lead to spillage of the phospholipids into the bloodstream. Similarly, increased phospholipids level was observed in most tissues which could be due to possible augmentation of their biosynthesis by the system in response to the arsenic-related stress so as to maintain homeostasis.

The liver is the major site of synthesis of lipids which are subsequently exported to other tissues; in the process, the hydrophobic lipid molecules have to pass through a hydrophilic medium (plasma), hence, they are packaged into a hydrophilic external shield called a lipoprotein for transport to other cells and tissues (Nelson and Cox, 2009). Of special interests are the LDL (which transport lipids from the liver to other tissues) and HDL (which does the reverse). In this study, both HDL-TAG and HDL-CHOL concentrations were markedly reduced (Fig. 1), whereas the reverse was the case for VLDL+LDL-TAG and VLDL+LDL-CHOL. These results indicate reverse cholesterol transport was favoured during arsenic exposure thus further affirming the atherogenic and cardiovascular threat that arsenic poses, which is consistent with previous reports by Afolabi *et al.* (2015), (2016) and Singh *et al.* (2018). Also, the male animals appeared to be more susceptible to these arsenic-induced perturbations in lipoprotein homeostasis. Physiological, sexual and hormonal differences may be a plausible explanation for the observed differences caused by the arsenicals in the male rats when compared with the female counterparts which was also reported by De Marinis *et al.* (2008).

Histopathological examination of the sex tissues (Figs. 3 and 4) showed alterations of the tissue architecture particularly in animals exposed to 40 ppm arsenite. There were marked changes in the tissues. Reports by Cohen *et al.* (2006) indicated that at physiological pH, trivalent As compounds such as arsenite are neutrally charged while pentavalent arsenicals such as arsenate are negatively charged; such that, the former As species readily transverse cell membranes than do the latter ones. This could be the basis for the effect of arsenite in the exposed groups. Furthermore, gender studies have established that females are more shielded from hypercholesterolemia-linked diseases up to menopause, indicating the influence of hormones on lipid homeostasis and estrogens which have been indicted as the principal mediator (Maxwell 1998; De Marinis *et al.,* 2008).

CONCLUSION

The results from this work demonstrated that exposure to both arsenicals (arsenite and arsenate) at doses (20 and 40) ppm interfered with lipid homeostasis, resulting in dyslipidemia, however in a manner independent of the doses used. Furthermore, these arsenicals possess the ability to alter the architecture of sex organs in albino rats.

Limitation and strength

A limitation in this work was the inability to study the effect of these arsenicals on the sperm characteristics and morphology.

AUTHORS' CONTRIBUTIONS

Author OEA: Conceptualization; Supervision; Investigation; Methodology; Writing- review and editing. OTS: Methodology; Formal analysis. EIU- Investigation; Writing-original draft. HOO: Investigation; Supervision. OAO-Investigation; Writing- original draft. AOA-Conceptualization; Writing- review and editing.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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