REVIEW ARTICLE

Arsenic: A Cause of Cardiometabolic Syndromes

Aimen Umer Khan[1] and Khawaja Zafar Ahmed[2]

ABSTRACT

Objective: The objective of the study is to identify major pathological biomarkers and their possible mechanisms in arsenic-induced cardiometabolic syndrome.
Methodology: The present review summarizes the data and literature taken from previously done studies from Research Gate, Science Direct, PubMed, PubMed Central, Medline, and some other scientific databases emphasizing the role of arsenic in cardiometabolic syndrome. The results obtained through this database were assembled, composed, critically elucidated and presented in explanatory and tabular form.
Results: The major pathological target of arsenic is antioxidant defense system and increase in Reactive Oxygen Species reduces the Nitric oxide production, reduction in vascular permeability, increases adhesion and production of inflammatory mediators (IL-6, TNF-á,), TCs, TGs, LDL-C, lipid peroxidation, â-cells dysfunction. The persistent accumulation and generation of these pathological biomarkers in blood vessels can induce hyperlipidemias, dyslipidemias, atherosclerosis, hypertension and diabetes.
Conclusion: There is a need to propose natural antioxidant with minimum side effects in the treatment of CMTs.

Key words: Arsenic, endothelial dysfunction, NO production**,** hypertension, atherosclerosis, hyperlipidemia, dyslipidemia

How to cite this article: Khan AU, Ahmed KZ. Arsenic: a cause of cardiometabolic syndromes (CMTs). Ann Jinnah Sindh Med Uni 2020; 6(2):66-71

DOI: https://doi.org/10.46663/ajsmu.v6i2.66-71

INTRODUCTION

Arsenic is the most abundant toxic metal on earth and is considered as a major health concern for 200 million people worldwide and major source of this contamination is through drinking water. The aim of present review is to figure out the various pathological and possible mechanisms in arsenic-mediated cardiometabolic syndromes. For this purpose, previously published 45 articles from Science of the Total Environment, African Journal of Microbiology Research, Environmental Science and Technology, International Journal of Environmental Research and Public Health, Current Environmental Health Reports, and American Journal of Epidemiology were assembled, composed, critically elucidated and presented in explanatory form. The data expedites the previously done pre-clinical, clinical, and in vitro studies mainly describing the pathological biomarkers and possible mechanisms involved in the development of arsenic-mediated cardiometabolic syndrome. Natural substances can be introduced to combat the pathological biomarkers involved in the development of CMTs.

Arsenic is considered as a major health concern for 200 million people worldwide[1].The International Agency for Research on Cancer ranked arsenic as Group 1 carcinogenic agent. Arsenic is also on top of the list of toxic substances according to The Agency for Toxic Substances and Disease Registry. The World Health Organization (WHO) described arsenic as the largest poisoning agent in human history. The exposure of arsenic to human population occurs through various ways e.g., industrial wastes, contaminated food, and, air[2]. However, the major source of toxicity is drinking water.

Arsenic exists in two forms (trivalent and pentavalent). The pentavalent form of arsenic in the body is converted to trivalent form via methylation in the liver in the presence of glutathione (GHs) and S-adenosylmethionine produces metabolites (monomethylarsonous (MMA) and Dimethylarsinous (DMA)[3]. This methylated trivalent form of arsenic is known to be responsible for toxicity. Reported 0.01 mg/L of arsenic is consumable range for humans[4]. Countries that are exposed to arsenic-intoxicated drinking water (above 0.01 mg/L) include Bangladesh[5], India[6], Pakistan[7],

1 Government College University Kotwali Road, Gurunanakpura, Faisalabad, Pakistan

2 Professor of Pharmacology Principal, Jinnah College of Pharmacy Street 6, Sector 7-A, Korangi industrial Area, Karachi, Pakistan

Correspondence: Aimen Umer Khan, Government College University Kotwali Road, Gurunanakpura, Faisalabad, Pakistan

Email: aimenumerkhan17@gmail.com

China[8], Taiwan[9], Mongolia, Mexico, Argentina, Chile[10], and some areas of the United States[11,12]. These countries are suffering from serious health related issues due to arsenic toxicity. Recently, arsenic concentration in ground water of various regions of Pakistan was found to be more abundant than expected[13,14]. Another report stated that, more than 50 million people in Pakistan are at risk of arsenic contaminated water[15]. The 95% of population of Pakistan is dependent on the ground water, which most probably exceeds the stated WHO safe limit of arsenic in drinking water[16].

In view of above introduction, there is a need to summarize the literature on this subject for further research and understanding. Therefore, the present review is organized to identify major pathological biomarkers and their possible mechanisms in arsenic-induced cardiometabolic syndrome.

METHODOLOGY

The present review summarizes the data and literature taken from previously done studies from Research Gate, Science Direct, PubMed, PubMed Central, Medline, and some other scientific databases emphasizing the role of arsenic in cardiometabolic syndrome. The results obtained through this database were assembled, composed, critically elucidated and presented in explanatory and tabular form.

The systematic survey of ground water in a study revealed that arsenic-contaminated water and drinking water resources in 2000, 2001, and 2003. Studies in the provinces of Punjab and Sindh revealed that 3% of community was exposed to arsenic above 50 ug/L in drinking water, while 20% of the community was exposed to arsenic above 10 ug/L[15]. The data of the province of Sindh showed even worse statistics of arsenic-exposed water. The 16% of community was exposed to above 50 ug/L and 36% of the community was exposed to 10 ug/L of Arsenic contaminated water[7].

Multiple epidemiological studies have disclosed the chronic arsenic exposure has been subjected to numerous cardiometabolic syndromes (CMTs) including, atherosclerosis[17,18], hyperlipidemias, dyslipidemia[19], endothelial dysfunctions[20], coronary artery disease (CAD), stroke, and Diabetes Mellitus (DM). Neurodegenerative disorders (NDDs)[21], dermatological disorders (DTD), and cancer (mainly of liver, kidney, lungs, and bladder)[22] have also been reported. Chronic arsenic consumption is associated with serious cardiometabolic syndromes[23,24]. The present review expedites the possible mechanism and pathophysiological biomarkers in the development of CVDs.

The entire human vascular system is covered with the endothelium. Endothelial cell structure integrity is an important factor in maintaining the circulatory functions. It exerts autocrine, paracrine and endocrine actions[25]. Endothelium is responsible for maintaining balance between the vasodilatory and contracting factors to regulate the vascular homeostasis[26]. Release of various mediators are regulated by endothelium. The most important and major vasodilatory substance is Nitric Oxide (NO). NO is generated in endothelium during the conversion of L-arginine to L- citrulline in the presence of eNOS (nitric oxide synthetase). eNOS is activated in the presence of ca^{2+}-calmodulin, flavin adenine nucleotide (FAD), flavin mononucleotide (FMN), tetrahydrobiopterin (BH4)[27].

Endothelium dysfunction can happen when an imbalance occurs in the vasoconstriction and vasodilation, which can further reduce NO production, eNOS expression, antioxidant status and increase oxidative stress, deposition of Low-Density Lipoprotein, very Low-Density Lipoprotein, Total Cholesterol, Triglycerides (LDL-c, LDL-c, TC, TGs). It further propagates the release of inflammatory mediators, cell adhesion molecules, and acute phase serum protein. VED is involve in pathogenesis atherosclerosis[28], heart failure[29], diabetic neuropathy[30], and hypertension[31].

Arsenic-Mediated Vascular Deterioration

In a preclinical study, Arsenic (1.5mg/kg, i.p, for a period of two weeks) was found to be associated with significant increase in the aortic superoxide anion generation and in the serum level of thiobarbituric acid reactive substance (TBARS: a biomarker of lipid peroxidation). The nitrile production and superoxide dismutase (SOD) was found to be reduced significantly. Tumour necrotic factor-á (TNF-á: biomarker of inflammation) was also found elevated. Histopathological studies also revealed loss of integrity of vascular endothelium cells.

Vascular reactivity study revealed the arsenic significantly reduced Ach-mediated endothelium dependent relaxation, but sodium nitroprusside-induced (SNP) endothelium independent relaxation was not affected by arsenic. The possible mechanism of arsenic-induced endothelial dysfunction can be concluded as increase in ROS in aorta by activation of NADPH oxidases and produces oxidative stress. The excessive ROS can further react with NO to reduce its production and upregulate the inflammatory mediators in the aorta, one of them is as mention above TNF-á. The damaging effects were visible in the aorta of rat by histopathological lesions[32].

In another study in which arsenic (2, 10, 20, and 50 mg /L) was given to rats for sub-chronic duration of three months, the level of arsenic in urine and water was found to be elevated. Dose-dependent damage was seen. The body weight of Arsenic treated group showed no significant difference compared to control group. The histopathological study of aortic arch showed structural variations of endothelial nuclei in arsenic-exposed (50mg/l) rat group, cytoplasm was loose, and swelling was very evident, erythrocytes were agglutinated in this area. vWF was elevated in all groups exposed to arsenic but, dose-dependent reduction was seen in NO production. The TNOS activity was also lower in same trends of NO production. The concentration of apoptotic cells was also found to be elevated in aortic arch. The rate of apoptosis was more in high exposure 50 mg/L group compared to 5, 10 mg. The serum level of pigment epithelial-derived growth factor was found to be significantly decreased in arsenic group compared to control.

The immunohistochemical analysis done on aortic Fas, FasL, P-53, P-p38 revealed higher level in high dose arsenic group (10 and 50 mg) compared to control group but not significantly higher in the low dose group (5 mg). The MDA level was much elevated and SOD level was lower in all arsenic exposed group. The possible mechanism of arsenic-induced endothelial dysfunction revealed major role of PEDF in arsenic-exposed endothelial dysfunction, optimal level of PEDF may act as antioxidant in VED. Lower level of it may cause higher ROS, that can initiate oxidative stress and lipid peroxidation as evident from the higher level of MDA and lower level of SOD.

Other possible mechanism could be the apoptosis of aortic arch by P-p38. PEDF protect P-53, P-p38 induced apoptosis. So, lower level of PEDF is involve in the apoptosis of aortic arch[33]. Arsenic was given to rats (25, 50, and 100 ppm in drinking water) for sub-chronic duration of 90 days. A dose-dependent damage was seen. The food intake, body weight, and water consumption were found to be reduced. The physical appearance was not changed significantly except the rough coating of hair of rat (exposed to 100 ppm). The relative and absolute weight of kidney and liver were not changed in (25, 50 ppm) compared to (100 ppm) group where weight of kidney and liver was found to be elevated.

Other vital organs (brain, heart, lungs, spleen, testis) weights were not significantly different as compared to control group. The biomarker of lipoprotein oxidation MDA and ROS was significantly higher in dose dependent manner compared to control. Antioxidant enzymes SOD and catalase activity was significantly lower in arsenic exposed rat compared to control. The dose-dependent reduction was also seen in Glutathione Reductase (GR), Glutathione Peroxidase (GPx), and GHS compared to control. The possible mechanism attributes to arsenic- induced deterioration of vascular redox homeostasis and physical health was due to oxidative stress (excessive ROS generation) and decrease in antioxidant enzymes (GSH, GPx, GR) which leads to oxidative damage to DNA, proteins, lipids. The cascade of lipoprotein oxidation begins here[34].

Sub-chronic study on arsenic (100 ppm in drinking water) was done and different parameters were evaluated. Vascular reactivity experiment revealed Ach-induced endothelial-dependent relaxation was found to be reduced but, the SNP-induced relaxation and Phenylephrine- induced contraction was not affected by arsenic exposure. Furthermore, the pro-inflammatory cytokines (IL-1â and IL-16), chemokines (MCP-1), Cell adhesion molecule (sICAMP-1, VCAMP-1), acute phase protein (CRP) were also found to be elevated by arsenic exposure. Arsenic-exposure reduced the concentration of eNOS protein, Phosphorylated eNOS concentration and, down-regulate the eNOS gene expression which in turn reduced the nitrite production in the tissues.

On the other hand, the iNOS mRNA expression and iNOS-mediated Nitrile production was found to be enhanced. The possible mechanism of arsenic-induced endothelial dysfunction is majorly associated with inhibiting NO production and suppressing eNOS, up-regulating the iNOS expression, as a result the vascular homeostasis is lost. The lining of endothelium becomes adhesive for the circulatory mediators of inflammation cytokines, cell adhesion molecules, acute phase serum protein[35].

Arsenic-Mediated Hypertension

Chronic arsenic consumption is a threat to the cardiovascular system and has strong association in the development of hypertension. Oxidative stress is the major factor in development of arsenic-mediated hypertension. A pre-clinical study assessed the arsenic (100 ppm via drinking water for 90 days). Weekly blood pressure was determined. The systolic, diastolic and mean arterial blood pressure was significantly elevated in rats on week 6 and 7 respectively. The aortic antioxidants enzymes superoxide dismutase, catalase, reduced glutathione, glutathione peroxidase was found to be significantly elevated on 91st day. The serum LDL-C, total cholesterol and triglycerides were found to be significantly elevated. The iNOS

expression was up-regulated and down-regulated the eNOS expression. Reactive oxygen species and lipid peroxidation was found to be significantly elevated. HDL-C was reduced. Several gene expressions aortic Nox-4 and p22Phox mRNA was prominently elevated. The possible mechanism of elevated blood pressure could be an increase in the reactive oxygen species and shutting down the antioxidant defense system. These ROS react, target the endothelium, and reduce the production of Nitric Oxide.

The possible mechanism of arsenic-mediated hypertension could be through alterations in the redox signaling and over production of ROS and this further propagates the accumulation of total cholesterol, triglycerides and low-density lipoprotein cholesterol and reduction in the high-density lipoprotein cholesterol and thus enhance the blood pressure[36]. In another study, the relationship between the arsenic mediated hypertension and role of antioxidant defense and CYP system was evaluated. Arsenic salt (arsenate and arsenite 50 ppm for 200 days) was administered in rats through drinking water. The systolic blood pressure was evaluated each 20th day at the same time. The blood sample sand tissues were also collected for the determination of antioxidant status, CYP4 and angiotensin converting enzyme activity. The weight gain and organ weights were also determined and compared with rats. The systolic blood pressure was significantly raised, antioxidant defense system showed time-dependent variations. The systolic blood pressure remained high until 200th day. The arsenic-exposed rats showed slight variations in body weight gain but, these were significant until day 200. The most common biomarker ACE was not affected significantly by arsenite. However, the CYP4A was expressed in higher concentration in arsenic-administered group which might have been more crucial in the development of hypertension.

The possible mechanism of arsenic-induced hypertension could be the overexpression of CYP4A and antioxidant system shut down thus elevate the systolic blood pressure[37]. Previously done studies have reported that arsenic via drinking water is associated with hypertension. Several mechanisms of arsenic-induced hypertension have been reported. It is suggested that arsenic may induce hypertension by enhancement of calcium sensitization in the blood vessels, myosin light chain phosphorylation-mediated vasoconstriction, disruption of antioxidating defense mechanism, increased â-receptor adrenoreceptor stimulation, potentiate peripheral vascular resistance, vasoactive agent stimulation, enhanced pressor response to preganglionic stimulation and increased expression of ET-1(endothelin-1)[38].

Arsenic-Mediated Diabetes

Previously done studies show that prevalence of type-2 diabetes mellitus is linked with high level of inorganic arsenic in drinking water. The pathophysiology of arsenic induced diabetes is similar to type 2 diabetes. Preclinical studies report that 50 ppm of arsenic intake through drinking water for eight weeks produce glucose intolerance. Studies have shown that rats and mice are less susceptible than humans to the diabetes induced by chronic arsenic intake. The reason may be the effective clearance of arsenic and its metabolites from tissues[39]. Several mechanisms of arsenic-mediated diabetes have been purposed previously[42].

Some of those mechanistic studies are purposed here for the understanding of pathological biomarkers and mechanism involved in the pathology of arsenic-induced diabetes. The pathophysiology of arsenic induced diabetes is similar to type 2 diabetes. A study disclosed the mechanism of arsenic-mediated diabetes. According to this study, the possible mechanism by which arsenic induces diabetes is through improper metabolism which in turn causes oxidative stress and affects the signal transduction pathway, impairs the metabolism of glucose, the transport of glucose is inhibited and gene expression is modified or altered[40]. Another study purposed the mechanism and the role of intermates in the pathogenesis of diabetes. Study claims that arsenic generates multiple intermediates which have potential to induce toxicity. Arsenic inhibits glucose metabolism, the secretion of insulin from â- cells is impaired. On the other hand, in signal transduction, the cells which were exposed to arsenic cause the inhibition activation of PKB/AKT. It is a necessary component of insulin induced signal transduction pathway. Thus, insulin-dependent signal transduction at the PKB/AKT level is inhibited and leads towards hyperglycemia. Furthermore, the uptake of glucose in skeletal muscles and adipocytes are inhibited. The chronic exposure of arsenic causes the upregulation of two cytokines, oxidative stress is increased and the expression of tumor necrosis factor alpha (TNF alpha) and interleukin-6 (IL-6) is upregulated. Both have their well-studied role in insulin resistance[44].

Another study reported the molecular mechanism of arsenic-mediated diabetes. It states that arsenic forms covenant in disulfide bridges present in the molecule of insulin and enzyme like pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase which are involved in glucose metabolism thus normal function of these is interrupted[43]. One more mechanistic study has reported that relates the pancreatic â cells dysfunction in the pathology of diabetes. Arsenic

mediates the pancreatic â cells damage by increased gluconeogenesis oxidative damage in liver; this oxidative stress can cause amyloid formation in the pancreas which may destroy insulin stimulating â cells. The impairment to beta cell function and resistance towards insulin by activating the nuclear factor-kappaB (NF-kappaB) has been reported to be linked with oxidative stress)[45].

CONCLUSION

The major pathological target of Arsenic is antioxidant defense system, and increase in Reactive Oxygen Species, reduce the Nitric oxide production, reduction in vascular permeability, increase in adhesion and production of inflammatory mediators (IL-6, TNF-á,), TCs, TGs, LDL-C, lipid peroxidation, â-cells dysfunction. The persistent accumulation and generation of these pathological biomarkers in the blood vessels can induce hyperlipidemias, dyslipidemias, atherosclerosis, hypertension and diabetes. There is a need to propose natural antioxidant with minimum side effects in the treatment of Cardio Metabolic Syndromes (CMTs).

Authors' contribution: AU conceived, searched for literature and wrote the manuscript. KZ reviewed the methodology, data and manuscript.

References

1. Naujokas MF, Anderson B, Ahsan H, Aposhian HV, Graziano JH, Thompson C. et al. The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. Environ Health Perspect. 2013; 121(3):295-302. doi: 10.1289/ehp.1205875.
2. Kumar M, Rahman MM, Ramanathan AL, Naidu R. Arsenic and other elements in drinking water and dietary components from the middle Gangetic plain of Bihar, India: health risk index. Sci Total Environ. 2016;539:125-134. doi: 10. 1016/j.scitotenv.2015.08.039.
3. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol.2014;7(2): 60-72. doi: 10.2478/intox-2014-0009.
4. Rocha-Melogno L, Yoo R, Broesicke O, Kallergis A, Garcia J, Herbas E.et.al. Rapid drinking water safety estimation in cities: Piloting a globally scalable method in Cochabamba, Bolivia. Sci Total Environ. 2014;654:1132-1145. doi: 10.1016/j.scitotenv.2018.11.119
5. Aziz Z, Bostick B, Zheng Y, Huq M, Rahman M, Ahmed K, et.al. Evidence of decoupling between arsenic and phosphate in shallow groundwater of Bangladesh and potential implications. Appl Geochem. 2017; 77: 167-177. doi: 10. 1016/j.apgeochem.2016.03.001.
6. Iyer S, Sengupta C, Velumani A. Blood arsenic: pan-India prevalence. Clin Chim Acta.2016;455:99-101. doi: 10. 1016/j.cca.2016.02.001.
7. Sanjrani M, Mek T, Sanjrani N, Leghari S, Moryani H, Shabnam A. Current situation of aqueous arsenic contamination in Pakistan, focused on Sindh and Punjab Province, Pakistan: A review. J Pollut Eff Cont. 2017; 5: 207. DOI: 10.4176/2375-4397.1000207.
8. Zhang L, Qin X, Tang J, Liu W, Yang H. Review of arsenic geochemical characteristics and its significance on arsenic pollution studies in karst groundwater, Southwest China. App geochem. 2017; 77: 80-88.
9. Tantry BA, Taher I, Shrivastava D, Nabi M. Arsenite-oxidizing bacteria isolated from arsenic contaminated surface and ground water of Uttar Pradesh, India. Afr J Microbiol Res. 2015: 9(48):2320-2327. DOI:10.5897/AJMR2015.7572
10. Smedley P, Nicolli H, Macdonald D, Barros A, Tullio J. Hydrogeochemistry of arsenic and other inorganic constituents in groundwaters from La Pampa, Argentina. App Geochem. 2002; 17(3):259-284.
11. Ayotte JD, Medalie L, Qi SL, Backer LC, Nolan BT. Estimating the high-arsenic domestic-well population in the conterminous United States. Environ Sci Technol. 2017: 51(21):12443-12454.
12. Welch AH, Westjohn D, Helsel DR, Wanty RB. Arsenic in ground water of the United States: occurrence and geochemistry. Groundwater.2000;38(4):589-604.
13. Ullah R, Malik RN, Qadir A. Assessment of groundwater contamination in an industrial city, Sialkot, Pakistan. Afr J Environ Sci Technol.2009; 3(12): 429-446.
14. Waseem A, Arshad J, Iqbal F, Sajjad A, Mehmood Z, Murtaza G. Pollution status of Pakistan: a retrospective review on heavy metal contamination of water, soil, and vegetables. BioMed Research Intern. 2014. https:// doi.org/ 10.1155/2014/813206.
15. Podgorski JE, Eqani SAMAS, Khanam T, Ullah R, Shen H, Berg M. Extensive arsenic contamination in high-pH unconfined aquifers in the Indus Valley. Sci Adv. 2017; 3(8): 1700935. DOI: 10.1126/sciadv.1700935
16. Tariq J, Ashraf M, Jaffar M, Afzal M. Pollution status of the Indus River, Pakistan, through heavy metal and macronutrient contents of fish, sediment and water. Water Res. 1996; 30(6):1337-1344.doi.org/10.1016/0043-1354(95)00300-2.
17. Balakrishnan P, Jones M, Vaidya D, Tellez-Plaza M, Post W, Kaufman J, et.al. Ethnic, geographic, and genetic differences in arsenic metabolism at low arsenic exposure: A reliminary analysis in the multi-ethnic study of atherosclerosis (mesa). Int J Environ Res Public Health. 2018; 15(6): 1179. doi: 10. 3390/ijerph15061179.
18. Lemaire M, Silva LFN, Lemarié CA, Bolt AM, Molina MF, Krohn RM, et.al. Arsenic exposure increases monocyte adhesion to the vascular endothelium, a pro-atherogenic mechanism. PloS One. 2015;10(9):0136592. doi: 10. 1371/journal.pone.0136592.
19. Yang H, Mao G, Zhang H, Zhang C, Qiu W, Guo X. Association between dyslipidemia and 8-OHdG/Cr among a population exposed to chronic arsenic. Zhonghua Liu Xing Bing Xue Za Zhi. 2014;35(7): 802-805.
20. Lee MY, Jung BI, Chung SM, Bae ON, Lee JY, Park JD,et.al. Arsenic-induced dysfunction in relaxation of blood vessels. Environ Health Perspect.2003; 111(4), 513-517. doi: 10. 1289/ehp.5916.

21. Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr Eenviron Health Rep.2014;1(2):132-147. doi: 10.1007/s40572-014-0012-1.

22. Abdul KSM, Jayasinghe SS, Chandana EP, Jayasumana C, De Silva PMC. Arsenic and human health effects: A review. Environ Toxicol Pharmacol. 2015; 40(3): 828-846. doi: 10. 1016/j.etap.2015.09.016.

23. Chen Y, Graziano JH, Parvez F, Liu M, Slavkovich V, Kalra T. et.al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. The BMJ. 2011:342. d2431.

24. Navas-Acien A, Sharrett AR, Silbergeld EK, Schwartz BS, Nachman KE, Burke TA,et.al. Arsenic exposure and cardiovascular disease: a systematic review of the epidemiologic evidence. Am J Epidemiol. 2005;162(11):1037-1049. doi: 10.1093/aje/kwi330.

25. Physiology of the endothelium H. F. Galley and N. R. Webster* Academic Unit of Anesthesia & Intensive Care, School of Medicine, University of Aberdeen AB25 2ZD, Scotland UK

26. Behringer EJJ. Calcium and electrical signaling in arterial endothelial tubes: New insights into cellular physiology and cardiovascular function. Microcirculation.2017;24(3):e12328. doi: 10.1111/micc.12328.

27. Costa ED, Rezende BA, Cortes SF, Lemos VS. Neuronal nitric oxide synthase in vascular physiology and diseases. Front Physiol.2016;7:206. doi: 10.3389/fphys.2016.00206

28. Gimbrone Jr MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res.2016.118(4).620-636. doi: 10.1161/ CIRCRESAHA. 115.306301.

29. Zhao Y, Vanhoutte PM, Leung SW. Vascular nitric oxide: Beyond eNOS. J Pharmacol Sci.2015;129(2):83-94. doi: 10.1016/j.jphs.2015.09.002.

30. Stirban A. Microvascular dysfunction in the context of diabetic neuropathy. Curr Diab Rep. 2014;14(11): 54. doi: 10. 1007/ s11892-014-0541-x.

31. Konukoglu D, Uzun H. Endothelial dysfunction and hypertension. In Hypertension: from basic research to clinical practice. Adv Exp Med Biol. 2017;956:511-540.doi: 10. 1007/ 5584_2016_90.

32. Jyoti U, Kansal S. K, Kumar P, Goyal S. Possible vasculoprotective role of linagliptin against sodium arsenite-induced vascular endothelial dysfunction. Naunyn-Schmiedeberg's archives of pharmacology.2016;389(2):167-175. doi: 10.1007/s00210-015-1184-4.

33. Guo X, Fu X, Liu X, Wang J, Li Z, Gao L,et.al. Role of Pigment Epithelium-Derived Factor in Arsenic-Induced Vascular Endothelial Dysfunction in a Rat Model. Biol Trace Elem Resarch. 2019;190(2): 405-413. doi: 10.1007/s12011-018-1559-8.

34. Waghe P, Sarath TS, Gupta P, Kutty HS, Kandasamy K, Mishra SK, et.al. Subchronic arsenic exposure through drinking water alters vascular redox homeostasis and affects physical health in rats. Biol Trace Elem Res.2014;162(1-3): 234-41. doi: 10.1007/s12011-014-0116-3.

35. Kesavan M, Sarath TS, Kannan K, Suresh S, Gupta P, Vijayakaran K, et.al. Atorvastatin restores arsenic-induced vascular dysfunction in rats: modulation of nitric oxide signaling and inflammatory mediators. Toxicol Appl Pharmacol. 2014;280(1):107-116. doi: 10.1016/j. taap. 2014. 07.008.

36. Sarath TS, Waghe P, Gupta P, Choudhury S, Kannan K, Pillai AH, et.al. Atorvastatin ameliorates arsenic-induced hypertension and enhancement of vascular redox signaling in rats. Toxicol Appl Pharmacol. 2014;280(3): 443-454. doi: 10.1016/j.taap.2014.08.032.

37. Yang HT, Chou HJ, Han BC, Huang SY. Lifelong inorganic arsenic compounds consumption affected blood pressure in rats. Food Chem Toxicol.2007;45(12): 2479-2487. doi: 10. 1016/j.fct.2007.05.024.

38. Balakumar P, Kaur J. Arsenic exposure and cardiovascular disorders: an overview. Cardiovasc Toxicol. 2009;9(4):169-176. doi: 10.1007/s12012-009-9050-6.

39. Paul DS, Hernández-Zavala A, Walton FS, Adair BM, Dìdina J, Matoušek T, et.al. Examination of the effects of arsenic on glucose homeostasis in cell culture and animal studies: development of a mouse model for arsenic-induced diabetes. Toxicol Appl Pharmacol.2007: 222(3): 305-314. doi: 10.1016/j.taap.2007.01.010.

40. Díaz-Villaseñor A, Burns AL, Hiriart M, Cebrián ME, Ostrosky-Wegman P. Arsenic-induced alteration in the expression of genes related to type 2 diabetes mellitus. Toxicol App Pharmacol. 2007; 225(2): 123-133. doi: 10. 1016/ j. taap. 2007.08.019.

41. Lu TH, Su CC, Chen YW, Yang CY, Wu CC, Hung DZ, et.al. Arsenic induces pancreatic â-cell apoptosis via the oxidative stress-regulated mitochondria-dependent and endoplasmic reticulum stress-triggered signaling pathways. Toxicol Lett. 2011; 201(1): 15-26. doi: 10.1016/j.toxlet.2010.11.019.

42. Maull EA, Ahsan H, Edwards J, Longnecker MP, Navas-Acien A, Pi J,et.al. Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review. Environ Health Perspect.2012;120(12): 1658-1670. doi: 10.1289/ehp.1104579.

43. Kulshrestha A, Jarouliya U, Prasad GBKS, Flora SJS, Bisen PS. Arsenic-induced abnormalities in glucose metabolism: Biochemical basis and potential therapeutic and nutritional interventions. World J Transl Med.2014;3(2): 96-111. doi: 10.5528/wjtm.v3.i2.96

44. Tseng CH. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol Applied Pharmacol. 2004; 197(2): 67-83. doi: 10.1016/j.taap.2004.02.009

45. Liu S, Guo X , Wu B, Yu H, Zhang X, Li, M. Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice. Sci Rep.2014; 4: 6894 doi: 10. 1038/srep06894