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ENVIRONMENTAL TOXICITY CAUSED BY HEAVY METALS WITH SPECIAL POSITIONTO ARSENIC, HOW IT INTERFERE WITH PHARMACO-KINETICS OF OTHER ESSENTIAL IONS AND OUTBREAK MAY LEAD TO THOUGHTFUL MODIFICATIONS IN CARDIOVASCULAR SYSTEM AND MALICIOUS ROLE IN DEVELOPMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Arsenic supposed to be dangerous heavy metal present widely in nature; It has the properties to replaces other ions present in human body after its successful absorption from small intestine. Excessive amount may lead to development of oxidative stress; Arsenic induced ROS production and depressed anti-oxidant defense system is the main cause of development of oxidative stress. Elevated MLCK and increased calcium sensitization results in cardiac dysfunctions. While impaired glucose metabolism and increased level of JNK, SPAS and NFkB cause insulin inactivation, resistance and subsequent Diabetes mellitus Type II.

1 INTRODUCTION

Heavy metals had been defined under different thinking but most important is based on its toxicological activity as compared to reference under atomic weight and properties. Heavy metals may also be defined as inorganic moieties having specific gravity five times to water. They naturally

exist as fragment of earth coating and the most familiar toxins for human from very initial time. The sources are ground water, metal ores, smelting mining, industrial processes, vehicle exhaust, contaminated food, pesticides, canned food, smoking, plumbing, venial paints, folk remedies and herbal products, the most important heavy metals are Arsenic (As), Cadmium (Cd), Lead (Pb) and Mercury Hg) among the category of toxins **1**. Heavy metals can produce damage to central nervous system, Hematopoietic system, gastro intestinal tract, and cardiovascular system **2, 5**. The induced oxidative trauma considered as main mechanism behind toxicity or altered pathways by heavy metals **3**, which could upshots in development of various diseases **2. 4.**

Arsenic

Metallic grey colored heavy metal symbol as As, having atomic number 33 is naturally occurring heavy metal as part of earth crust. It may found in combination with sulphar or other metals and may in pure crystalline form widely distributed in environment i.e. air water and land, extremely toxic when in mineral form, people may exposed to elevated levels of As. Via drinking water, use of filthy water in food preparation, irrigation of crops, industrial drain and smoking tobacco. As. may produce acute as well as chronic effects on human population; acute symptoms may include vomiting, diarrhea abdominal pain **18** and excess of salivation **19** leading to tingling of extremities and death in some cases. Chronic effects occurs after a minimum exposure of 5 years, usually starts from skin and include pigmentation, lesions and hard patches especially in palms and soles which may lead to skin cancer, bladder cancer and lungs cancer. The international agency of research also classified As. as carcinogenic. As. has deleterious effect on pregnant uterus resulting in adverse outcome on infant mortality and may cause child death **6**; exposure in early childhood may link to lungs diseases, heart attack and kidney failure **7**. Recent Studies proves that it may exert negative effects on intelligence and memory **8.** It has been recognized that about 140 million people in 50 countries use drinking water having arsenic level beyond the limit prescribed by WHO 10ug/L **9.**

1.1 Kinetics

The site of absorption for As. is small intestine **10** and the optimal pH is 5.0 **11.** The absorbed As. Produces mono methyl arsonic acid and dimethylarsinic acid by hepatic biotransformation **12, 13.** 50 % of the absorbed dose eliminated in the urine in 3 to

5 days, Dimethyl arsenic acid is about 65% of the excreted metabolites **14.** Recent studies show the higher concentration is in kidney, liver, heart and lungs while smaller in muscles, nervous system, spleen and GIT. **15.** The lethal dose in acute As. poisoning is 100 to 300mg **16**. The risk assessment information system database states that the acute lethal dose is about 0.6mg/kg/day. 23 years adult after ingestion of 8g of As. survive for 8 days **17.** Hematological issues include heamaglobinuria and normocytic normochromic anemia **20 21**.

1.2 Chemistry and toxicity

As. occurs in two oxidation sates first one is (As203 As III) and (As2O5 As V) the trivalent formula is about 60 times more toxic as compared to penta-valent form. Organic form is harmless while inorganic form is lethal, inorganic As. toxicity deactivate about 200 enzymes, particularly those, which involve in cellular energy pathways and DNA replication and repair, Unbound As. also responsible for production of uncontrolled ROS, results in lipid peroxidation and DNA damage **22.**

1.3 Organ system effects

1.3.1 Skin

Several skin alterationsarise with long term contact **23**. Dermatological alterations are a communal feature and the first clinical diagnosis is frequently based on hyperpigmentation palmar and solar keratosis.The keratosis may seem as even stiffening or as separate lumps **24**. **26**Itishighlightedthat both palmar and solar keratosis are a significant diagnostic standard. Hyperpigmentation occurs as diffuse dark brown spots, or less separate diffuse darkening of the skin, or has a typical "rain drop" look.**25** Arsenic linked skin cancer, Bowen's disease, is an unusualsign in Asians and may be due to the great skin melanin content and augmentedrevelation to ultraviolet radiation. Arsenic may cause a basal cell carcinoma in a non-melanin pigmented skin.**27** The latent period after exposure may be as long as 23 years and has been reported in patients treated with Fowler's solution, in sheep dip workers, in vineyard workers using arsenical pesticides, and from drinking contaminated wine.**28** Another demonstration due to arsenic deposition in keratin rich areas are prominent sloping white lines in the fingernails and toenails called Mee's lines.**2329**

1.3.2 Gastrointestinal system

Nonetheless diarrhea is a major and early onset indication in acute arsenic poisoning; in chronic toxicity diarrhea occurs in recurrent attacks and may be associated with vomiting. Notion of arsenic ingestion should

be produced if other manifestations such as skin changes and a neuropathy are alsopresent **30.** In248patientswithevidenceofchronicarsenic toxicity from West Bengal, India who consumed arseniccontaminated drinking water for one to 15 years, hepatomegaly occurred in 76.6%, and of the 69 who were biopsied, 63 (91.3%) showed non-cirrhotic portal fibrosis **31.** In another study, arsenic was considered the etiological agent in five of 42 patients with incomplete septal cirrhosis, an inactive form of macronodular cirrhosis, characterized by slender, incomplete septa that demarcate inconspicuous nodules, and an unusually high incidence of bleeding. **32.**

1.3.3 Cardiovascular system

Smelter employees are testifies at higher risk of cardiovascular disease due to arsenic exposure **33, 34, 35**. In a study in Millard County, USA, based on a ground for cumulative arsenic exposure, a significant growth in death in both males and females from hypertensive heart disease occurred.**42**Rahman et al from Bangaldesh in 1999described an increased rate of hypertension in a large study of 1481 subjects exposed to arsenic in well water.**36** Seventy four Taiwanese patients with ischaemic heart disease in "arseniasis-hyperendemic villages" were studied and a relation between ischaemic heart disease and long term arsenic revelation was suggested **37, 38**. Arsenic roots direct myocardial injury **38**, cardiac arrhythmias, and cardio-myopathy **39**.

Blackfoot disease is a unique peripheral vascular disease, causing gangrene of the foot unique to Taiwan, due to long term exposure to high arsenic in well water **38**. Peripheral vascular disease is also stated from Chile **40**.

1.3.4 Neurological system

The neurological system is the major target for the toxic effects of arsenic. The neurological effects are many and varied. The most frequent finding is a peripheral neuropathy mimicking Guillain-Barré syndrome with similar electromyographic findings **43**. The neuropathy is initially physical with a glove and stocking anesthesia. The effects of toxicity also comprise changes in behavior, confusion, and memory loss **44**. Cognitive impairment was testified in two workers from 14–18 months of exposure and mental function resumed to normal after removal from the source of arsenic **45**. There was increase in prevalence of cerebrovascular disease **46**.

1.3.5 Respiratory system

Respiratory disease was more common in patients with the characteristic skin lesions of chronic arsenic toxicity **47**. Similar findings of an association between skin manifestation sand lung diseases was reported in Chilean children **41**. The possibility of increased deposition of arsenic in the lung, although the reason is not known, is supported by necropsy studies in a limited number of patients **48 49**. An increased incidence of bronchitis occurs in a study on patients with black foot disease in Taiwan **43**.

1.3.6 Endocrine and hematological systems

Exposure to high concentrations of arsenic is associated with an increased risk of diabetes mellitus **43, 50,** in chronic arsenic toxicity neutropenia occurs **54**.

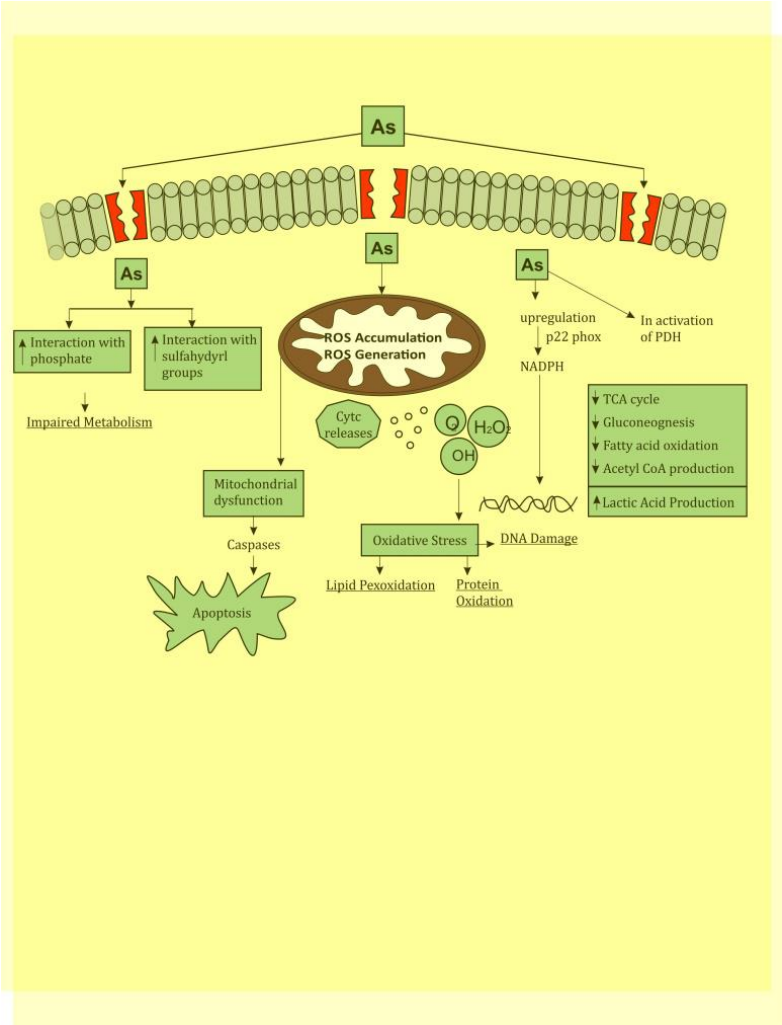
1.3.7 Malignant disease

The relationship between arsenic and malignancy is of growing concern as many millions of people are potential victims. In Bangladesh and India arsenic is associated with skin,lung, liver, kidney, and bladder cancers **51**. There is evidence from other countries that arsenic exposure causes malignancies of the skin, **53** lung, **34, 52** liver, **38** kidney, **42, 52** and bladder **55**.

1.4 Arsenic Induced oxidative stress

The mitochondrial electron transport chain is the main spring of ATP generation in the mammalian cell. During energy transduction, a small number of electrons escape to oxygen prematurely, forming superoxide, which has been implicated in the pathophysiology of oxidative stress [**56, 57**]. Complexes I and III, the main sources of superoxide generation, release superoxide into the matrix and the extra mitochondrial, space respectively [**58**]. Mitochondria are the prime targets for arsenic intoxication, either indirectly via ROS accumulation or directly through condensing mitochondrial matrix and opening of permeability transition pores by virtue of its thiol-oxidizing property. In either case, arsenic-induced mitochondrial insult initiates apoptosis [**59**]. Because decreased MMP further generates ROS, it may be difficult to conclude whether arsenic-induced ROS are the cause of mitochondrial damage or a consequence of it. Scientist reported that arsenicinduced mitochondrial damage in guinea pig liver leads to leakage of superoxide ions into the cytosol [**60**]. Arsenic induces significant ROS generation mainly through complex I and complex II of the electron transport chain (ETC). Superoxide radical generated through the ETC reacts with various other radicals present in the cell to form stable and long-lived reactive species, damaging

macromolecules and inducing apoptosis via various pathways **59, 60**.



1.4.1 Alterations in Enzyme Activity

Arsenic intensively affects the ROS metabolizing enzymes called antioxidant enzymes, such as SOD, CAT, glutathione peroxidase (GPx), GST, and glutathione reductase (GR). Generally, short-term exposure to low arsenic concentrations results in an increase in the activity of these enzymes, whereas chronic exposure usually results in their reduction. Arsenic is also known to regulate the activity of thioredoxin reductase, heme oxygenase reductase, and NADPH oxidase in vitro [**61, 62**]. Arsenic is also known to alter activities of cytochrome P450s.. Arsenic is also shown to inhibit pyruvate dehydrogenase (PDH) activity either via oxidative damage or through binding to vicinal dithiols in both pure enzyme and tissue extract. However, the arsenic concentration required to deactivate

the enzyme is much lower than what is required for direct binding to thiol groups, suggesting an alternative mechanism [**63**]. NADPH oxidase is another important target for arsenic toxicity. Arsenic has been shown to induce up-regulation, phosphorylation, and membrane translocation of key subunits of NADPH oxidase [**64,65,66**]. Whereas up-regulation of NADPH oxidase via p22phox has been linked to DNA damage in vascular smooth muscles and actin filament reorganization, resulting in lamellipodia and filopodia [84], Further mutations in these subunits may result in reduced immunity and lead to immuno-compromised congenital diseases such as chronic granulomatous disease **67**. Further, activation of NADPH oxidase leads to generation of superoxide anion as part of the oxidative burst of phagocytosis **68**.

1.4.2 Effects of Arsenic on the Cellular Defense Mechanism

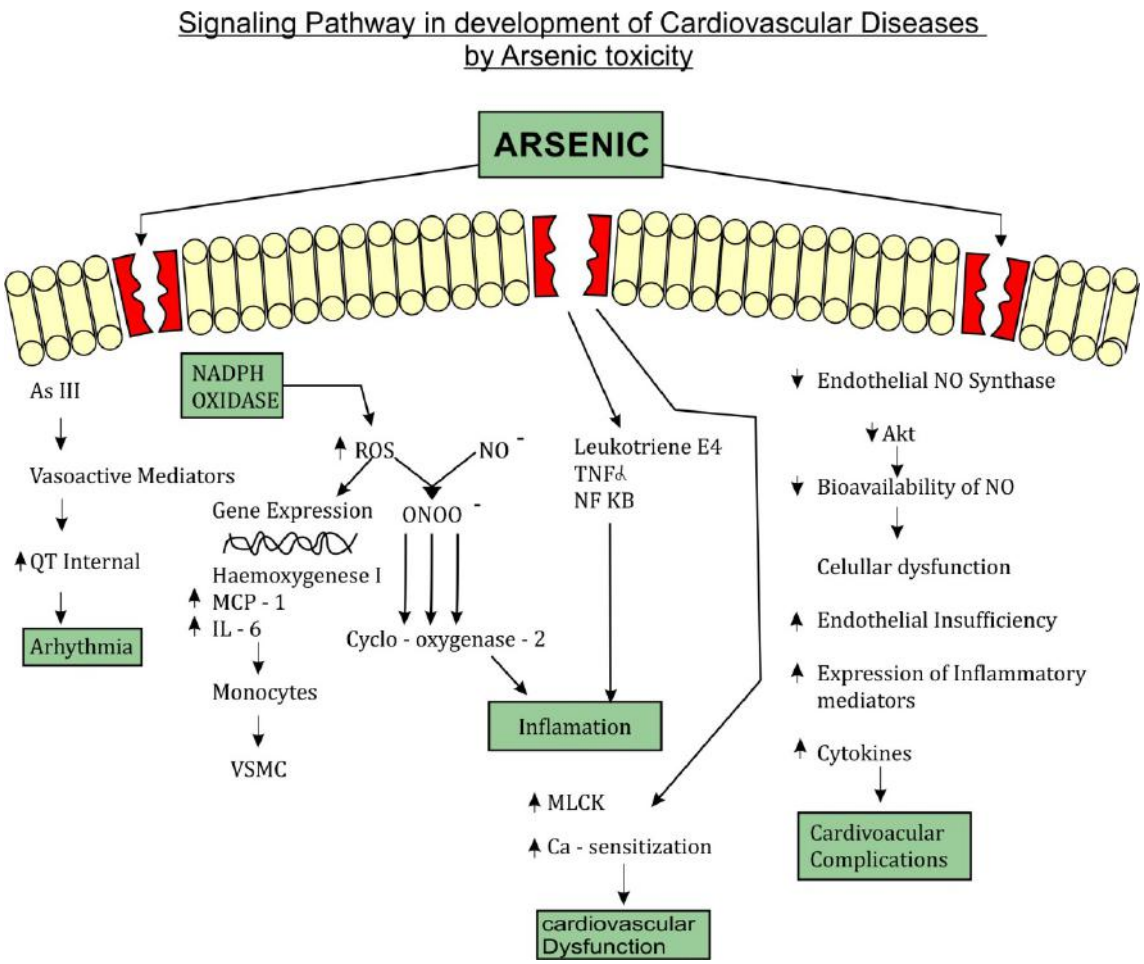
Antioxidant response is the major cellular defense mechanism that a cell has against arsenic insult. Arsenic-induced antioxidant imbalance has been reported in numerous studies [**69, 70, 71, 72**]. These studies have demonstrated that various enzymatic and nonenzymatic factors help in protecting cells by scavenging and clearing ROS [**73**]. The ability of glutathione, the most abundant nonproteinthiol in cells, to react with electrophiles directly or as a cofactor (for enzymes GPx and GST) may play an important role in arsenic detoxification and against arsenic-induced oxidative stress [**74,75,76**]. Chronic arsenic exposure (4–6 months; 25 ppm in drinking water), or very high dose, acute exposure (15.86 mg/kg, ip) causes GSH depletion in mice and rats, respectively **[60, 77,78,79**]. This could be due to the utilization of GSH as electron donor for arsenic metabolism or direct binding due to thiol preference. For example, mice exposed to a lower arsenic dose of 3.2 ppm in drinking water for 2 months showed increased hepatic GSH level, whereas long-term exposure (4 months) decreased GSH in the same study [100]. Increase in GSH level thus indicates an adaptive mechanism of the cell to counter arsenic attack. Arsenic may induce GSH increase by facilitating GSH biosynthesis via up-regulated gene expression of glutamate–cysteine ligase subunits, as evident by an in vitro study in a murine hepatocyte cell line. This effect was inhibited by N-acetylcysteine (NAC), indicating a role for ROS [**76**]. GSH also modulates the redox status of specific thiol residues of arsenic targeted proteins such as transcriptional factors, caspases, and stress kinases [**74, 75, 76–80**]. Arsenic-induced

depletion of other antioxidant defense enzymes, such as SOD, CAT, and GPx, also demonstrates dose-, time-, and organ-dependent variability [**60, 78, 81**]. Again, where chronic exposure invariably results in decreased enzyme activity, such as that of hepatic CAT, GST, and GR after 9, 12, and 15 months of arsenic exposure, respectively, low concentrations (0.1–10 μM) and acute exposure are generally reported to enhance enzyme activity of SOD, CAT, and GPx **[61**].

2 SIGNALING PATHWAY IN DEVELOPMENT OF CARDIOVASCULAR DISEASES BY ARSENIC TOXICITY

Mineral form of As. is the basisof cardiovascular pathologies such as, atherosclerosis, hypertension, arrhythmia and ischemic heart diseases **82, 83, 84, 85**, As. excite NADPH-oxidase in vascular smooth muscle cells (VSMC) and cause upturn in ROS**86,87**. Freshly molded ROS joined with nitic oxide (NO) to form peroxynitrite, which grab opportunity to discharge of inflammatory mediators such as cyclooxygenase-2**88**. Freshly models ROS cause increase the expression of those genes involves in atherosclerosis i.e. heam oxygenase –I, mococyte chemo attachment protein (MCP-I) and IL-6, all this promote the attachment and movement of monocytes in VSMC **89**. As. also endorses multiplying of adhesion proteins **90**. In addition with this As. enhance thefabrication of inflammatory mediator such as leukotriene E4, TNF α and NFkβ to prompt pathogenic progression in atherosclerosis **91, 92**.

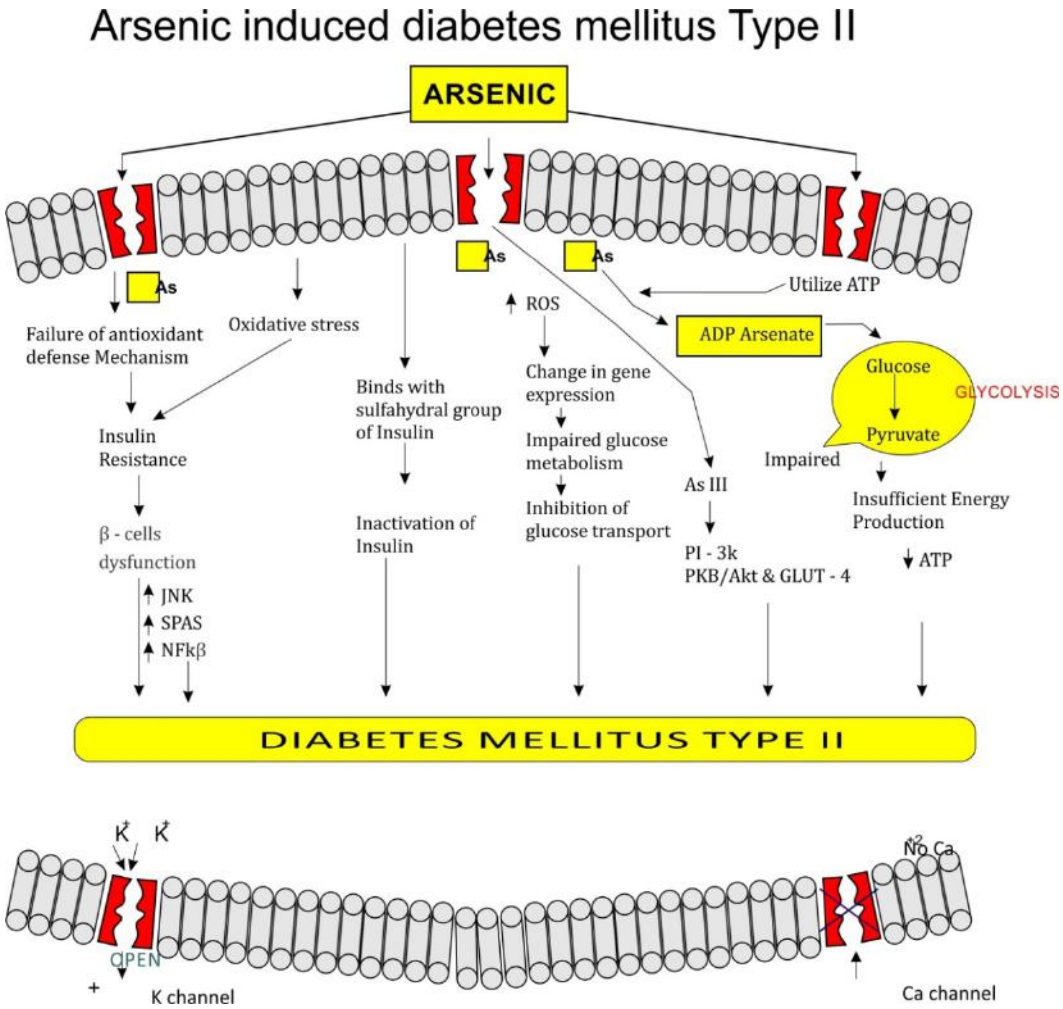
As. also causes inflammation of blood vessels by increasing release of substance P **93**. And also promote protein kinase-C, which cause phosphorylation of beta catenin and inverse the bonding between beta catenin and vascular endothelial cadherin, beside with formation of actin stress fiber result in rise in intracellular gap formation **94**, As. also has been reported asfacilitator, which cause decrease in endothelial nitric oxide synthase and Akt, which afterward decrease the bioavailability of NO which may cause cellular dysfunction and cardiovascular complications **95, 96**. As also contribute in development of hypertension by increase in myosin light chain kinase (MLCK) and calcium sensitization **97**. Long term exposure may cause hypertension by the way of ROS production **98**. Trivalent arsenic release vasoactive mediators which caused enhance Q-T interval leading to arrhythmia **85, 99**.



3 SIGNALING PATHWAY IN DEVELOPMENT OF DIABETES MELLITUS TYPE-II

Sustained contact to As. diminishes the sensitivity of insulin which is liable for type II diabetes mellitus **100**. As. replaces phosphate group present in trivalent of adenosine, result in formation of ADP-arsenate, which downcast the glucose breakdown, interpose the energy cycle (Glycolysis), result in compromised production of energy. All this contribute to depressed release of insulin which was dependent on ATP production, as due to less production of ATP, the voltage gated K+ channels doesn't close and no opening of ca++ channels due to lack of repolarization **101**. Furthermore, As. has strong affinity toward sulfhydryl group of insulin and become covalently bound to it, outcomes is inactivation of insulin36. A thought-provoking biphasic answer in glucose breakdownowing to arsenic exposure was initiate through glucocorticoid receptor-

mediated transcription with hyperglycemic result at low concentration (<120 ppb) besides hypoglycemia at high absorption (>120 ppb) **102.** Long term exposure may cause hypoglycemia due to decrease production of glucose 6-Phosphate dehydrogenase (an enzyme of oxidative phase of pentose phosphate shunt) in both liver and kidney **38**. Inorganic arsenic causes insulin resistance and beta cells dysfunction by production of oxidative stress and failure of anti-oxidant defense system. Both these effects results in overexpression of stress mediators such as c-Jun-N-terminal kinase/stress-activated protein kinase (JNK/SPAS) and NFkβ **103**. The trivalent As. i.e. AS (III) depress the phosphorylation by inhibiting the activity of its key enzyme (PDK-I), which effect in reserve of insulin dependent glucose uptake leading to hyperglycemia **104, 105**.



4 CONCLUSION

Arsenic exposure may cause change in pharmaco kinetics variables after successful absorption. It may interfere with a variety of signaling pathways leading to serious disorders and also cause compromised cure during the treatment of diseases, early detection may be helpful in prognosis and diagnosis of diseases.

5 CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interests

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