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Review

Nutritional management can assist a significant role in alleviation of arsenicosis

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ABSTRACT

Consumption of arsenic contaminated water causes serious skin disease and cancer in a significant number of exposed people. Chelating agents, consider an expensive therapy, are employed in the treatment of arsenic intoxication. There are reports which suggest that the poorest suffer the most from arsenicosis. This may be due to improper diet intake, consist of low protein and micronutrients which increase the vulnerability to arsenic-related disorders.

Several human studies demonstrated the associations between malnourishment and the development of arsenic-caused skin lesions, skin cancer and cardiovascular effects. Thus, there is an urgent need of implementation of mitigation strategies for improving the health of exposed populations. Nutrition enhances the detoxification process so food rich in vitamins, protein, antioxidants help in its detoxification process. Methylation is the detoxification process which takes place via S-adenosylmethionine (SAM). It is a methyl group donor and it derived its methyl group from diet. Nutritional intervention thus may appear as a practical and inexpensive approach. Nutrition provides protection from toxic effect of arsenic by two ways (i) methylation of As (ii) antioxidants which provides protection against free radical species.

The governments and NGOs may run awareness programmes in arsenic affected area regarding prevention and alternate therapy which can decrease the susceptibility of the exposed population. They could also help in distributing cheaper, high protein diets particularly to the masses who cannot afford such foods. Thus, to prevent arsenicosis alternate therapy and proper nutrition could be the important strategy for alleviating its toxic effects. This mini review provides an insight on the importance of nutrition in preventing adverse effect cause by arsenic to suffer population.

1. Introduction

Arsenic is a 20th most abundant element, metalloid, highly toxic element and known as class (I) human carcinogen. In the environment, Arsenic is present in both inorganic (arsenite and arsenate) and organic forms (monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), arsenobetaine). Natural as well as anthropogenic sources contribute to the presence of arsenic in soil and groundwater [1]. Around 105 countries particularly Southeast Asia has been affected by arsenic contaminated groundwater with more than 200 million people are exposed. It has affected more than 100 million people in Bengal Basin [2]. The arsenic contamination of ground water above the permissible limit (10 μg/l) set by WHO is reported in Indian states like West Bengal, Jharkhand, Bihar, Uttar Pradesh, Assam, Manipur and Chhattisgarh. In India, in absence of an alternative source of water, the permissible limit of arsenic is 50 μg/l. Low socioeconomic status and malnourishment increase adverse health effects because such population have no option other than drink arsenic contaminated water [3,4]. Host response towards the environmental toxicants is depended on its nutritional intake. Numerous diseases have been documented to be associated with chronic arsenic poisoning from drinking water like hyperpigmentation, depigmentation, hyperkeratosis, Bowen disease, increase risk for cardiovascular conditions, pregnancy complications, effect on neurobehavioral development, and various types of cancers such as skin, lung, urinary bladder, kidney, and liver [5,6].

Diet as nutrition for health is the indispensable necessity for the survival of human so influence of diet on arsenic toxicity is a very important factor for its risk assessment. It is also reported that better nutrition status can resist arsenic toxicity and major population living in arsenic affected areas are suffering from malnutrition with poor literacy rate [2,7]. Several human studies demonstrated the associations between malnourishment and the development of arsenic-caused skin lesions, skin cancer and cardiovascular effects [8–11]. Deficiency of beta-carotene, methionine, zinc and selenium or excess amounts of

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copper, nickel and manganese in the diets may be playing some role in the toxicity of arsenic [12–15]. Nutrition enhances the detoxification process so food rich in vitamins, protein, antioxidants help in its detoxification process. Methylation is the detoxification process which takes place via S-adenosylmethionine (SAM). It is a methyl group donor and it derived its methyl group from diet. There are reports which suggest that arsenic toxicity can be alleviated by the administration of certain vitamins, minerals and antioxidants. For instance, deficiency of beneficial elements such as selenium (Se) and zinc (Zn) may increase arsenic toxicity [16]. Jaggery can reduce the oxidative, DNA damage and clastogenic effects [17,18]. Maiti et. al., investigated the neuroprotective and antioxidative potential of green tea (*Camellia sinensis*) against arsenic-induced oxidative stress [19]. Epidemiologic survey indicated that high obesity related dietary pattern is connected with lower arsenic levels in toe nail [20]. A number of epidemiological studies have reported that enhanced methylation capacity could decrease the risk of arsenical skin lesions [21,22]. Nutrition affects the methylation of arsenic. Ingested inorganic arsenic is methylated to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) through folate-dependent one-carbon metabolism so folate nutritional status may affect arsenic methylation consequently its toxicity. People with low plasma folate provided folic acid supplementation, an increased in arsenic methylation was found. Persons will be at greater risk of skin, bladder cancers and peripheral vascular disease whose urine profiling demonstrate less DMA and high MMA and inorganic arsenic. Analysis of plasma folate concentration of 200 adults in a rural region of Bangladesh was shown low folate concentration. This group of peoples were kept on folic acid supplement trial at a dose of 400 μg/d. The increased in the DMA and decreased in MMA and inorganic arsenic after folic acid treatment was significant gave evidence that folic acid supplements enhanced arsenic methylation [23]. Thus nutritional supplementation approaches to this problem might be a helpful option.

2. Mechanism of arsenic toxicity

The toxicity of arsenic in various cellular systems is because of generation of reactive oxygen species (ROS) as shown by many studies. To inhibits ROS, antioxidants such as glutathione, vitamin E and enzymes catalase, superoxide dismutase or glutathione peroxidase help in decrease in arsenic toxic effects [24–26]. The effect of arsenic on redox signaling pathway such as Keap1/Nrf2 system has been investigated [27]. Nrf2 is a transcription factor that is activated in response of a cellular defence mechanism against toxicants. It works differently in unstressed and stress conditions. The low level of Nrf2 is maintained by a negative regulator (Keap1) under unstressed condition. It forms an E3 ubiquitin ligase complex with Culin 3 and ring −box 1 that help the ubiquitination of Nrf2 [28,29]. Then Nrf2 directed to degrade 26S proteasome. Under stressed condition, the cysteine residues in Keap1 are S-alkylated causing a conformational change in the Keap1-Cul3-Rbx1 E3 ubiquitin ligase complex thus obstructing Nrf2 ubiquitination due to this Nrf2 accumulates and translocates to the nucleus where it combines with a small Maf protein then binds to cytoprotective genes that are accountable for the detoxification and elimination process of toxicants [30,31]. Few research groups have demonstrated that a selective substrate adaptor protein, p62 and autophagy may play an important function in arsenic mediated Nrf2 activation [27,32,33]. Activation of Nrf2 can protect cell at acute exposure of arsenic but at chronic exposure Nrf2 activation may result in detrimental cellular effects [34]. The arsenic may be interfere with signal transduction pathway to show genotoxicity and carcinogenicity effect [35–37]. Transcription factors such as nuclear factor kappa B (NF- kappa B) and activating protein-1 (AP-1) are involved in cellular antioxidant defence mechanism [38]. The effect of acute and chronic arsenic exposure may alter AP-1 and Nf kappa activity by up regulating thioredoxin and Redox activating factor-1 [39].

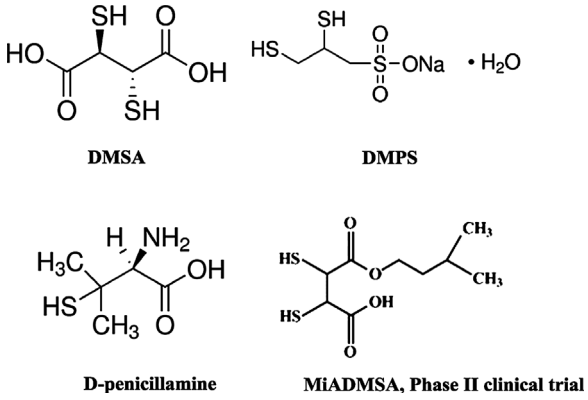

Fig. 1. Structures of chelators.

3. Treatment of arsenic intoxication

Chelating agent, specifically thiol chelators such as meso-2,3-dimercaptosuccinic acid (DMSA), sodium 2,3-dimercaptopropane 1-sulfonate (DMPS) and D-penicillamine are used for the treatment of chronic arsenic toxicity. Chelators reduce arsenic from the body thus reducing risk of various types of cancer caused by it and giving relief from systemic clinical symptoms. However there is a need of more effective drug for arsenicosis patients because currently used drugs have serious side effects. Monoisoamyl dimercaptosuccinic acid (MiADMSA) is a DMSA analogue, highly efficient and potent in removing arsenic from target organs through scavenging reactive oxygen species. It is currently under phase II clinical trial [40] (Fig. 1).

The use of two structurally different chelators for the treatment of arsenicosis would be more effective in elimination of arsenic from the body. This concept is known as combination therapy which lies on the fact that two different chelating agents will act through different mechanism which lead to additional effect or behaves synergistically. The two chemically different chelators possessing different affinity for cell membranes i.e., one is lipophilic which is suitable for intracellular arsenic elimination and other is lipophobic which is for extracellular arsenic elimination. The co-administration of DMSA and MiADMSA in experimental animals not only reduce arsenic-induced oxidative stress and but also minimize many serious side-effects [41].

Arsenic induces the generation of reactive oxygen species and also there is a fall of antioxidants in the body that can result in disruption of antioxidants balance in mammalian tissues. Thus therapeutic strategies which could lead to increase the antioxidant capacity of cells may strengthen the long term effective treatment of arsenic poisoning. This may be accomplished by supporting the cells antioxidant defenses through exogenous supplementation of antioxidant molecules. Nutritional antioxidants scavenge free radicals species therefore remove active oxygen and repair the oxidized cell membranes. These supplements are polyphenols, flavonoids, amino acids, protein, and functional food such as jaggery and honey that can be helpful in combating arsenic toxicity. Therefore, combination therapy proves more beneficial than conventional chelation monotherapy in the management of chronic arsenic toxicity. A comprehensive clinical study is required to be performed for the precise determination of dose of nutraceuticals and functional foods against arsenic toxicity [42].

4. Is arsenic toxicity is affected by food consumption?

Nutrition plays a crucial role in the prevention or the onset of arsenic related disorders. Low dietary intake of protein and micronutrients increases susceptibility to arsenic-related diseases. This could be due to the fact that nutrition deficiency results in slow removal of arsenic from the body. Malnutrition is highly prevalent in developing countries and a high proportion of individuals are likely to be deficient