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Chronic arsenic poisoning and Hepatotoxicity

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Abstract:

Arsenic (As) is a toxic and carcinogenic metalloid. Arsenic toxicity is a global health problem affecting many millions of people. Contamination is caused by arsenic from natural geological sources leaching into aquifers, contaminating drinking water and may also occur from mining and other industrial processes. Chronic arsenic poisoning, or arsenicosis, is typically defined by the classical skin manifestations, together with involvement of internal organs, such as liver injury, in the presence of known arsenic exposure. Probably, the most important concern with arsenic exposure is its carcinogenic potential. Epidemiologic studies have demonstrated an association between chronic arsenic exposure and cancer of the skin, lung, urinary bladder, and possibly liver, kidney, and prostate in humans. The epidemiological data for the skin, lung and urinary bladder are widely accepted as showing an etiological role for arsenic exposure, whereas other sites, such as liver, are considered more controversial. This article reevaluates epidemiology studies, rodent studies together with in vitro models, and

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focuses on the liver as a target organ of arsenic toxicity and carcinogenesis. Hepatocellular carcinoma and hepatic angiosarcoma, have been frequently associated with environmental or medicinal exposure to arsenicals. Hepatomegaly, hepatoportal sclerosis, fibrosis, and cirrhosis often occur after chronic arsenic exposure. There are a variety of potential mechanisms for arsenical-induced hepatocarcinogenesis, such as oxidative DNA damage, impaired DNA damage repair, acquired apoptotic tolerance, hyperproliferation, altered DNA methylation, and aberrant estrogen signaling. Some of these mechanisms may be liver specific/selective. Overall, accumulating evidence clearly indicates that the liver could be an important target of arsenic carcinogenesis.

Keywords: arsenic, hepatotoxicity, carcinogenesis, epidemiology,

Introduction:

Arsenic toxicity is a global health problem affecting many millions of people. Many aquifers in various regions of the world are contaminated with arsenic (As) at concentration above 50 µg/l. Of these, the most noteworthy occurrences are in West Bengal (India), Bangladesh, Taiwan, Northern China, Hungary, Mexico, many parts of the USA, Chile and Argentina. It is a major environmental health hazard throughout the world including India. It is suspected that about 5 million people drink arsenic contaminated water in West Bengal. Chronic Arsenic Poisoning can result from chronic exposure to high levels of Arsenic (As) in the air, food or water. However most cases result from consuming water with toxic levels of Arsenic. Arsenic toxicity impacts on the entire body but some clinical features are pathognomic e.g skin hyper pigmentation and classical hyperkeratosis of palms and soles. Prolonged ingestion of arsenic-contaminate water is reported to produce not only pigmentation and keratosis, but also many systemic features like weakness, anaemia, chronic lung disease, conjunctival congestion, hepatomegaly and non cirrhotic portal fibrosis, polyneuropathy, chronic diarrhoea, dyspepsia, solid oedema of limbs, gangrene of toes, skin cancer and other malignant neoplasms. Skin characteristics change and pigmentation and keratosis have long been known to be hallmark signs of chronic arsenic exposure. These lesions are the most common health effect found in populations exposed to arsenic-contaminated drinking water in Chile, Argentina, Mexico and various countries of Asia[1].

Arsenic (As) is a toxic and carcinogenic metalloid. The inorganic forms of arsenic exhibit the highest toxicity level, while

organoarsenicals are usually less toxic than the inorganic arsenic species. Chronic arsenic poisoning, or arsenicosis, is typically defined by the classical skin manifestations, together with internal disorders, such as liver injury, in the presence of known arsenic exposure. Probably, the most important concern with arsenic exposure is its carcinogenic potential. Epidemiologic studies have demonstrated an association between chronic arsenic exposure and cancer of the skin, lung, urinary bladder, and possibly liver, kidney, and prostate in humans. The epidemiological data for the skin, lung and urinary bladder are widely accepted as showing an etiological role for arsenic exposure, whereas other sites, such as liver, are considered more controversial.[2, 3, 4]

Arsenic is well absorbed from the gastrointestinal tract, and first reaches the liver. Arsenate is reduced to arsenite in the liver. Because the liver is rich in glutathione, it is a major site of arsenic detoxication, either from glutathione acting as an antioxidant, or by glutathione-arsenic conjugation for cellular efflux and biliary excretion. The liver is also the major site of arsenic methylation, which is catalyzed by arsenic methyltransferase or AS3MT using S-adenosylmethionine (SAM) as the substrate. Arsenic methylation capacity is often compromised in patients with liver diseases including cirrhosis. The role of compromised arsenic methylation in hepatic pathology or carcinogenesis is not well defined.[5]

The hepatotoxic action of arsenic, when used as a therapeutic agent, has long been recognized. The association of chronic liver disease with long-standing arsenic ingestion is well documented, although the spectrum and incidence of liver disease due to arsenic remain uncertain. There were reports that patients with chronic liver disease and arsenical skin changes that followed previous chronic arsenic ingestion developed macronodular cirrhosis and the other non-cirrhotic portal hypertension with perisinusoidal fibrosis. Primary liver cell cancer was also reported along with reported case of malignant hepatoma in a non-cirrhotic liver complicating chronic arsenicism.[4]

Material and Methods:

An extensive systemic review of various studies was done to study the effect of Chronic arsenic poisoning on liver. This systematic review was conducted using electronic databases to report on long term effect of chronic arsenic toxicity. To find relevant studies various databases was used including PubMed, and the Cochrane Library. All types of relevant studies were included like journal articles, reports and book chapters, because of limited information regarding the topic of interest. Moreover, the research

question could be answered by any type of study. All titles and abstracts were screened first, followed by a full-text review of relevant review articles, including meta-analyses, and published studies based on original data and then all the suitable references were added to the list of articles

Result and discussion:

Data on liver involvement following chronic exposure to arsenic-contaminated water are scanty. The nature and degree of liver involvement are reported on the basis of hospital based studies in patients who consumed arsenic contaminated drinking water for one to 15 years. Two hundred forty-eight patients with evidence of chronic arsenic toxicity underwent clinical and laboratory examination including liver function tests and hepatitis B surface antigen (HBsAg) status. Liver biopsy was done in 69 cases; in 29 patients, liver arsenic content was estimated by neutron activation analysis. Hepatomegaly was present in 190 of 248 patients (76.6%). Non-cirrhotic portal fibrosis was the predominant lesion (91.3%) in liver histology. The maximum arsenic content in liver was 6 mg/kg (mean 1.46 [0.42], control value 0.16 [0.04]; p <0.001); it was undetected in 6 of 29 samples studied. The largest number of patients with liver disease due to chronic arsenicosis from drinking arsenic contaminated water are reported. Non-cirrhotic portal fibrosis is the predominant lesion in this population. Hepatic fibrosis has also been demonstrated due to long term arsenic toxicity in an animal model. Initial biochemical evidence of hepatic membrane damage, probably due to reduction of glutathione and antioxidant enzymes, may be seen by 6 months. Continued arsenic feeding resulted in fatty liver with serum aminotransferases elevated at 12 months and hepatic fibrosis at 15 months.[6,7]

Besides noncirrhotic portal fibrosis which has been reported to occur in humans due to prolonged intake of arsenic contaminated water, oxystress and hepatic fibrosis have been demonstrated in chronic arsenic induced hepatic damage in murine model. Cytokines like tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) are suspected to play a role in hepatic collagenesis. In an experiment on mice it was found that increasing dose and duration of arsenic exposure in mice cause progressive increase of oxystress and elevation of cytokines associated with increasing level of collagen in the liver. [8]

Hepatocarcinogenicity of arsenic is well documented. Evaluation of epidemiology studies, rodent studies together with in vitro models was done with focus on the liver as a target organ of arsenic toxicity and carcinogenesis. Hepatocellular carcinoma and

hepatic angiosarcoma, have been frequently associated with environmental or medicinal exposure to arsenicals. Hepatomegaly, hepatoportal sclerosis, fibrosis, and cirrhosis often occur after chronic arsenic exposure. Recent work in mice clearly shows that exposure to inorganic arsenic during gestation induces tumors, including hepatocellular adenoma and carcinoma, in offspring when they reach adulthood. Chronic exposure of rat liver epithelial cells to low concentrations of inorganic arsenic induces malignant transformation, producing aggressive, undifferentiated epithelial tumors when inoculated into the Nude mice. There are a variety of potential mechanisms for arsenical-induced hepatocarcinogenesis, such as oxidative DNA damage, impaired DNA damage repair, acquired apoptotic tolerance, hyperproliferation, altered DNA methylation, and aberrant estrogen signaling. Perturbation of methylation of promoter region of p53 and p16 genes, and genomic methylation alteration may be involved in arsenic-induced disease manifestation in humans. Some of these mechanisms may be liver specific/selective. Overall, accumulating evidence clearly indicates that the liver could be an important target of arsenic carcinogenesis.[5]

Abnormal liver function, manifested by gastrointestinal symptoms such as abdominal pain, indigestion, loss of appetite and by elevations of serum bilirubin and enzymes like ALT, AST and ALP, frequently occurs from exposure to arsenic in the drinking water, 9 or from environmental exposure to arsenic through burning high-arsenic coal in interior stoves.[10, 11]

In hospitalized arsenicosis patients from West Bengal, India, the rate of hepatomegaly exceeds 75% and is positively correlated with the level of drinking water arsenic and hepatic arsenic content.6In a large scale epidemiology survey in this region, the prevalence of hepatomegaly (10%) was significantly higher. 9 In Southwest Guizhou, China, where arsenic exposure occurs from burning arsenic-containing coal in indoor stoves, the occurrence of hepatomegaly was 21%,10 a rate much higher than other areas with elevated drinking water arsenic in China [12]

Hepatoportal sclerosis is a rare but relatively specific condition that may occur after chronic arsenic exposure. [12] Hospitalized Indian arsenicosis patients have very high rates of hepatoportal sclerosis developed from drinking water highly contaminated with arsenic.[7,9] Chronic oral arsenic intoxication (from drinking water, traditional medicines, etc.) is thought to be an etiology factor for hepatoportal sclerosis in India populations.[13] Hepatoportal sclerosis is often a result of damage to the local vasculature. [14,15] Chronic arsenic exposure in animals can also produce liver endothelial cell damage, which subsequently damages parenchymal cells.[16]

High hepatic arsenic levels can be associated with cirrhosis.[17] This can be especially true in cirrhotic patients who consume “home-made brew” made with water highly contaminated with arsenic. Liver fibrosis is also common in arsenicosis patients from West Bengal, India. [7,9] or in patients consuming high-arsenic contaminated food from burning arsenic coal in Guizhou, China. 10, 19 Liver cirrhosis appears to be a primary cause of arsenic-related mortality in Guizhou, China, and is potentially associated with hepatocellular carcinoma (HCC).[10,12, 18]

The association between increased liver cancer mortality and elevated drinking water arsenic was first reported in a population from Southwest Taiwan. In the initial study, the standardized mortality ratio (SMR) was 1.7 for arsenic intoxicated men and 2.3 for similarly exposed women.[19] Further studies in this area showed a significant association between duration of consumption of high-arsenic containing water and liver cancers, with an age- and sex-adjusted odds ratio of 2.67. [19, 20] A dose-response relationship between arsenic levels in drinking water and age-adjusted liver cancer mortality was also observed. [21, 22, 23] Arsenic-exposed men had higher liver cancer mortality than women in almost all age groups. [24] Further analysis using EPA-adjusted arsenic concentrations in the drinking water (170, 470, and 800 ppb) demonstrated increased liver cancer mortality with increasing arsenic concentration with corresponding SMR's of 1.2, 1.5, and 2.5 for men ($p < 0.001$ for trend) and 1.6, 2.1, and 3.6 for women ($p < 0.001$ for trend). 25 Risk assessments using different models showed a dose-response trend for liver cancer.[26]

To investigate the dose-response relationship between arsenic exposure and the activities of major serum enzymes used for LFTs in the individuals living in arsenic-endemic areas in Bangladesh. A total of 200 residents living in arsenic-endemic areas in Bangladesh were selected as study subjects. Arsenic concentrations in the drinking water, hair and nails were measured. The serum hepatic enzyme activities of alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) were then assayed. Serum hepatic enzymes (ALP, AST and ALT) used for the LFTs were found to be elevated in the higher exposure groups as compared to the group with the lowest exposure to arsenic in the drinking water. Similarly, levels of serum hepatic enzyme activity were also increased in the higher exposure groups of arsenic in the hair and nails. Thus, the results of this study provided new insights into arsenic-induced liver toxicity.[27]Similar study conducted in Murshidabad district of West Bengal showed elevated levels of serum bilirubin and hepatic enzymes. The injured hepatic cells may induce increased secretion of the inflammatory cytokines (IL6, IL8, TNFα) in the arsenic

exposed individuals which in turn contributes to cardiovascular risk. [28]

Mitigation option available for dealing with the health problem of ground water arsenic contamination rests mainly on supply of arsenic safe water in arsenic-endemic region of Indo-Bangladesh subcontinent. It is, therefore, an urgent need to make arrangement for availability of safe water source among the arsenic-affected people in the district. Many of the people in the affected villages are not aware of contamination of their home tube wells with arsenic. Awareness generation and motivation of the people for testing their drinking water sources for arsenic and environmental interventions like rain water harvesting, ground water recharge, and restricting excessive use of ground water for domestic and agricultural purposes are also important to prevent further exposure of arsenic to these people.[29]

Conclusion :

Epidemiologic data, fortified by data from case reports and data from rodent and cell model systems, clearly indicate that the liver is a potential target of arsenic carcinogenesis. It is probable that multiple mechanisms are involved in arsenic-induced hepatocarcinogenesis, some of which may be specific to the liver.

Environmental exposure to arsenic is unavoidable and medicinal use of arsenicals in the treatment of certain cancers is increasing. Attention should be paid to arsenic-induced liver dysfunction, hepatomegaly and liver fibrosis, as these preneoplastic changes could advance to malignancy. Special caution should be paid to early life arsenic exposure, as gestation and early life appear highly sensitive to arsenic carcinogenesis occurring much later in life. A better understanding of these mechanisms will be critical in the prevention and treatment of liver cancers associated with arsenic exposure.

Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease; patients once affected may not recover. Only cessation of exposure to drinking water or items of elevated concentration of arsenic was believed to provide effective remedy. So, primary prevention by rising levels of awareness among primary care providers of the local region about signs and symptoms of arsenicosis and available intervention will definitely help to mitigate this important public health problem.

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