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Health Effects of Chronic Arsenic Exposure

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Arsenic is a unique element with distinct physical characteristics and toxicity whose importance in public health is well recognized. The toxicity of arsenic varies across its different forms. While the carcinogenicity of arsenic has been confirmed, the mechanisms behind the diseases occurring after acute or chronic exposure to arsenic are not well understood. Inorganic arsenic has been confirmed as a human carcinogen that can induce skin, lung, and bladder cancer. There are also reports of its significant association to liver, prostate, and bladder cancer. Recent studies have also suggested a relationship with diabetes, neurological effects, cardiac disorders, and reproductive organs, but further studies are required to confirm these associations. The majority of research to date has examined cancer incidence after a high exposure to high concentrations of arsenic. However, numerous studies have reported various health effects caused by chronic exposure to low concentrations of arsenic. An assessment of the health effects to arsenic exposure has never been performed in the South Korean population; thus, objective estimates of exposure levels are needed. Data should be collected on the biological exposure level for the total arsenic concentration, and individual arsenic concentration by species. In South Korea, we believe that biological exposure assessment should be the first step, followed by regular health effect assessments.

Key words: Arsenic, Health effects, Carcinogenicity

INTRODUCTION

Given its well-established toxicity and know hazards, knowledge about arsenic is of great importance in the field of environmental health. Arsenic is a metalloid, which possesses characteristics of both a metal and a non-metal, and is widely distributed in the soil, water, air, and rocks. Among the types of naturally occurring arsenic , inorganic arsenic is most prevalent. While naturally occurring arsenic cannot be destroyed, it can react with oxygen or other molecules in the air, water, or soil to form various compounds [1]. Examples of inorganic arsenic compounds include trivalent arsenite and pentavalent arsenate. Examples of organoarsenic compounds, or organoarsenicals, include monomethylarsonic acid (MMA), dimethylarsonic acid (DMA), trimethylarsonic acid and arsenobetaine. Arsenic is used in the semiconductors, glassware, alloys, and wood preservatives. In addition, arsenic was commonly found in pesticides, but has since been removed. Furthermore, arsenic has been utilized in medicine; historically, to treat syphilis, yaws, and amoebic dysentery [2], and recently, to treat leukemia [3].

Human exposure to arsenic occurs through the oral, respiratory, or dermal routes. In ordinary individuals who are not exposed to arsenic through their work environment, the main source of arsenic exposure is likely to be through oral exposure from water, soil, and contaminated agricultural and fish products. Exposure to trivalent or pentavalent inorganic arsenic

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compounds occurs through contaminated water, air, or soil; however, exposure to organoarsenicals occurs through the consumption of marine animals and plants. Toxicity to the human body varies across the different forms of arsenic. Inorganic arsenic compounds are more toxic than organoarsenicals are, and trivalent arsenite is more toxic than pentavalent arsenate is [4]. The major arsenical in most species is arsenobetaine, which human cannot metabolize and is considered to have negligible toxicity. However, arsenic was confirmed as a carcinogenic agent in humans associated with skin and lung cancers [5]. The US Environmental Protection Agency has lowered its permitted arsenic concentration in drinking water from 50 to 10 ppb, and this permitted concentration is likely to be decreased further [6,7].

Urinary arsenic is regarded as the most useful general indicator of arsenic exposure, because it reflects digestive and respiratory exposures. Arsenic absorbed into the body is metabolized and expelled mainly through the urine, The separation and quantification of trivalent and pentavalent inorganic arsenic, as well as that of MMA and DMA, is believed to be the most accurate indicator of a recent arsenic exposure [7]. However, methodology able to assess the level of arsenic exposure in humans has not been well established, and representative data on arsenic exposures by species in the Korean population are still lacking. Nevertheless, recent advances in research methodologies may allow for the collection of this type of data; thus, studies on arsenic exposure and its health effects in the South Korean population are still needed.

In South Korea, there are numerous abandoned metal mines with high arsenic contamination levels in the soil, and these mines pose a risk of environmental arsenic contamination [8]. Moreover, a large proportion of the average South Korean diet includes fish, shellfish, and marine plants such as seaweed and kelp, which often contain arsenic; therefore, an objective assessment of the level of arsenic exposure and risk is required. In this report, we review the latest knowledge regarding the effects of arsenic on human health and emphasize the role of arsenic exposure as an environmental health issue in South Korea.

PHARMACOKINETICS

Arsenic is absorbed primarily through inhalation or oral consumption and is rarely absorbed through the skin. During oral consumption, the absorption rate of arsenic in the gastrointestinal tract is 90%, which is greater than that of other heavy metals. Absorbed arsenic binds to red blood cells, and deposits in the liver, kidneys, muscle, bone, hair, skin, and nails, but is expelled mainly through the urine. Inorganic arsenic compounds suppress the activities of various enzymes involved in cellular respiration, glutathione metabolism, and DNA synthesis, and may pass through the placenta affecting the development of the fetal nervous system [9]. Arsenic metabolism is a complex process that involves more than five metabolites, and begins with the methylation of inorganic arsenic compounds. In the body, the inorganic arsenic compound pentavalent arsenate is converted into trivalent arsenite. The majority of trivalent arsenite is metabolized into MMA, and then into DMA, before being excreted in the urine.

The major metabolic pathway of arsenic is methylation. Trivalent arsenite is methylated to the major metabolites MMA and DMA before it is expelled through the urine. Methylation was once thought to detoxify arsenic; however, recent studies have reported increased toxicity because of methylation in some metabolites containing trivalent arsenite [10]. MMA and DMA are primarily excreted and not metabolized. However, in humans, MMA is converted into a small amount of DMA [11].

MECHANISMS

The carcinogenicity of arsenic has been confirmed; however, the precise mechanisms that acute or chronic exposure to arsenic performs to induce cancer are not yet understood. The toxic mechanism of arsenic is complex, because arsenic toxicity is affected by its oxidation state and solubility, in addition to numerous other internal and external factors [12]. Recent studies have shown that the toxicity of arsenic is dependent on the exposure amount, length, and frequency; the biological species; age; sex; individual sensitivity; genetics; and nutritional factors [13]. A well-described toxic mechanism of arsenic is the impairment of cellular respiration through interference with oxidative phosphorylation caused by the inhibition of various mitochondrial enzymes. The majority of arsenic toxicity in humans is associated with inorganic arsenic. Trivalent arsenite is 2 to 10 times more toxic than pentavalent arsenate is. Trivalent arsenite suppresses the activity of more than 200 enzymes after bonding with thiol or sulfhydryl groups, thus affecting numerous organs [14]. Pentavalent arsenate can be replaced with phosphorus, after which it affects numerous biochemical pathways [14,15].

TOXICITY

Carcinogenicity

Arsenic is the only carcinogen known to cause cancer through respiratory exposure and gastrointestinal exposure [16]. In the 1980s, arsenic was officially recognized as a carcinogenic substance and registered with the International Agency for Research on Cancer (IARC) [17]. After the association between arsenic exposure and carcinogenicity was revealed, studies were conducted in the United States, Taiwan, Bangladesh, India, Argentina, and Chile to further examine this association, and these results supported those of previous reports [18]. Results from animal and epidemiological studies have shown that inorganic arsenic compounds can be categorized as clear carcinogens (group 1) or potential carcinogens (group 2B) such as DMA and MMA, while arsenobetaine and other organoarsenicals have not been categorized as carcinogens (group 3). Several hypotheses regarding the carcinogenicity of inorganic arsenic compounds have been suggested; nevertheless, the biomolecular mechanisms are poorly understood. Nine different hypotheses regarding the toxic mechanism behind arsenic have been suggested, including induced chromosome abnormalities, oxidative stress, altered DNA repair, altered DNA methylation patterns, altered growth factors, enhanced cell proliferation, promotion/progression, suppression of p53, and gene amplification. To date, the IARC has confirmed the association of arsenic exposure with cancers of the skin, lungs, and bladder, while reports on the relationship with the liver, kidney, and prostate cancer remain limited. Key epidemiological evidence regarding the carcinogenicity of arsenic stems from studies from those in Taiwan [19], Bangladesh [20], Chile [21], and Argentina [22], who consume drinking water containing high concentrations of arsenic (150 μg/L). However, despite the well-established toxicity of arsenic, studies regarding the association between chronic exposure to low concentrations of arsenic and the development of cancer are lacking; further study is needed to support effective public health management.

Skin cancer

Several studies have reported an association between arsenic exposure and skin cancer. Specifically, exposure to trivalent arsenite was found to be associated with the occurrence of UV-induced skin cancers [23]. In multiple regions, skin cancers associated with arsenic are often basal cell carcinomas or squamous cell carcinomas caused by keratinization. For example, a cohort study on 654 Taiwanese residents showed that the observed incidence rate of skin cancer was 14.7 per 1000 person-years [24]. In addition, skin cancer incidence increased significantly with the length of stay in a black foot disease-infected region, length of drinking water usage, arsenic concentration in the drinking water, and accumulated exposure to arsenic [24]. Moreover, a recent study has reported an association between skin cancer and vascular diseases [25]. In a recent epidemiological study conducted on residents of Hungary, Romania, and Slovakia that assessed the carcinogenic risk of long-term low concentrations of arsenic in drinking water (the Arsenic Health Risk Assessment and Molecular Epidemiology Study), low concentrations of arsenic (≤100 μg/L inorganic arsenic) were significantly associated with the risk for developing basal cell carcinoma [26].

Lung cancer

Hopenhayn-Rich et al. [22] observed a significant increase in lung cancer-related deaths with arsenic intake. Moreover, numerous studies have investigated the dose-dependent relationship between arsenic intake and lung cancer incidence, making lung cancer the most well-known cancer associated with arsenic exposure [27,28]. Epidemiological studies have shown that the incidence of lung cancer is consistently higher in groups exposed to arsenic than it is among the general population or a control group [29]. In a recent study conducted in Taiwan, a high mortality rate and standardized mortality ratio of lung cancer was observed among patients who consumed high-arsenic concentrated drinking water for the past 50 years [30]. Moreover, reductions in the arsenic concentration of tap water also decreased lung cancer mortality rates [30]. In the majority of epidemiological studies, the relative risk of lung cancer is between 2 to 3. However, tobacco smoking combined with and arsenic exposure increases the risk of lung cancer, and decreasing arsenic exposure was also found to decrease lung cancer risk in smokers [31].

Until now, research has focused on the association between lung cancer and exposure to high levels of arsenic studies of the association between lung cancer and low-level arsenic exposure are lacking. A cohort study on 3932 Native Americans aged between 45 to 74 years investigated the association between cancer mortality and low to medium arsenic concentrations was conducted (average inorganic and methylated arsenic in the urine was 9.7 μg/g creatinine) [32]. They reported a hazard ratio was 1.56 (95% confidence interval [CI], 1.02 to 2.39),

indicating a significant, but relatively minor risk level. Given the potential relevance of low level arsenic exposure, this paucity of data necessitates additional investigation.

Bladder cancer

Incident bladder cancer and arsenic exposure through drinking water has been verified by studies in Taiwan and Bangladesh [33]. However, these studies have only verified the association after exposure to high concentrations of arsenic; however, there is thought to be no association with low exposures to arsenic (100 to 200 μg/L). Recent studies have debated whether, exposure to low concentrations of arsenic is related to bladder cancer because of potentially insufficient statistical power and errors in the classification of exposure status in the previous studies. Thus, studies accurately address these issues are needed. Under exposure to high concentrations of arsenic, smoking interacts synergistically with arsenic to increase the risk of bladder cancer. During this process, there is also a high possibility that the arsenic detoxification process is inhibited because of DNA repair inhibition and reduced levels of essential nutrients [34,35]. In 2010, Meliker et al. [36] reported no association with bladder cancer incidence after low concentrations of arsenic exposure and smoking, but further confirmation is needed. One major limitation of these previous studies might be an inability to a accurately measure of smoking and arsenic exposure levels, which are needed future studies.

Liver cancer

Although previous studies conducted in Argentina, Chile, Denmark, and other regions have reported a relationship with liver cancer, no consensus has been made on this relationship mostly because of a limited availability to representative data [37,38]. Recently, the results of a 20-year retrospective cohort study on liver cancer patients (802 male and 301 female) from 138 communities in Taiwan found a significant increase in liver cancer incidence in both genders at a arsenic concentration above 0.64 mg/L, but no association was found at exposure levels lower than lower 0.64 mg/L [39].

Prostate cancer

The association between exposure to high concentrations of arsenic and prostate cancer was reported in Taiwan [5]. However, the association between exposure to low concentrations of arsenic and prostate cancer is unclear, and epidemiological research is lacking. In a recent study investigating low to medium inorganic arsenic exposure (via urine collection) and cancer mortality in 3932 Native Americans (45 to 74 years of age), a high prostate cancer mortality hazard ratio was observed (3.30; 95% CI, 1.28 to 8.48), which was even higher than that for liver cancer (1.56; 95% CI, 1.02 to 2.39) [32].

Leukemia

Very few studies have investigated the association between arsenic exposure and leukemia. One report observed that the number of leukemia patients (n=28) in Woburn, Massachusetts between 1966 and 1986 was more than 4 times greater than the average incidence rate of the US, and the drinking water in this region was found to be contaminated with heavy metals such as arsenic (70 μg/L) and chromium (240 μg/L) at levels greater than the limit permitted by the state government [40]. Furthermore, in a recent population-based case-control study on 69 pediatric leukemia patients in California, a significant association between arsenic exposure and leukemia was reported in most pregnant mothers (OR, 1.33; 95% CI, 1.02 to 1.73) [41].

Non-carcinogenic Effects

Neurological effects, memory, and intellectual function

Arsenic accumulated in the body during childhood may induce neurobehavioral abnormalities during puberty, and neurobehavioral changes as an adult [42]. In addition, increased effects may result after lead exposure; thus, caution is required. Neuritis caused by arsenic is a recognized complication of arsenic toxicity, and is known to affect the sensory functions of the peripheral nerves. Research on Mexican children has indicated an association between arsenic exposure and deficits in verbal intelligence quotient and long-term memory. Furthermore, the effect was proportional to the dose; therefore, a child exposed to 50 μg/L of arsenic performed significantly lower than a child exposed to 5.5 μg/L of arsenic did [43]. However, the effects of toxicity may vary with the length of arsenic exposure, dose, and other nutritional factors.

Diabetes

Recently, the possibility of arsenic exposure affecting the incidence of diabetes has been suggested. In particular, an association has been reported between type 2 diabetes occurring in obese individuals aged 40 years or older and inorganic arsenic exposure. Studies conducted in Taiwan reported that the incidence rate of diabetes for residents in a region with a high

arsenic drinking water level was 2 to 5 times higher than it was in unexposed subjects, which suggests arsenic may influence diabetes incidence [44,45]. However, another study reported no association [46]. It has been predicted that inorganic arsenic may be diabetogenic in humans, but additional research is needed to elucidate the potential mechanism.

Effects on the skin

Several studies have examined the incidence of various skin disorders because of arsenic exposure. According to a study conducted in Bangladesh, melanosis and keratosis occurred in 36 of 167 residents (13.9%) exposed to drinking water with low concentrations of 10 μg/L or less arsenic [47]. Another recent study on 11 746 residents of Bangladesh exposed to arsenic in the drinking water at concentrations of 8.1 to 40.0, 40.1 to 91.0, 91.1 to 175.0, and 175.1 to 864.0 μg/L reported ORs of 1.91, 3.03, 3.71, and 5.39, respectively [48]. These results suggest that exposure to various concentrations of arsenic might affect skin cancer risk, and is related to disorders in the prodromal phases of skin cancer.

Effects on cardiovascular disorders

Lee et al. [49] reported that arsenic might affect thrombocytes, which play an important role in cardiovascular diseases. In the presence of thrombin, trivalent arsenite increases the agglutination of thrombocytes. In animal studies, arsenic in drinking water was observed to increase arterial thrombus formation. The study by Lee et al. [49] also reported that long-term intake of drinking water with arsenic can increase thrombocyte agglutination and induce cardiovascular diseases. However, additional studies are required to determine the relevance of these results in humans [18].

Effects on the reproductive system

Pregnancy complications because of arsenic exposure from drinking water have been reported [50]. In particular, fetal mortality and preterm birth increased as exposure to arsenic increased. It was also found that exposure to arsenic during pregnancy affects urine excretion and the distribution of metabolites, it affect the development of the fetus. Moreover these effects are thought to manifest in various ways depending on the stage of pregnancy [51]. Animal studies have suggest that these effects may be caused by necrosis, apoptosis, and loss of the fertilized egg due to arsenic exposure [52]. While Hopenhayn et al. [53] suggested the possibility that chronic exposure to low concentrations of arsenic (<50 μg/L) may cause low birth weight and impair the growth of the placenta in the uterus [53], additional research in this area is needed.

EXPOSURE ASSESSMENT

Identification of arsenic exposure is crucial in the diagnosis of arsenic toxicity and arsenic-related clinical disorders. While environmental exposure assessment data are typically needed to verify an exposure, biological monitoring data is also highly valued as an objective measurement. Arsenic absorbed through the respiratory system or the digestive system is converted within a few hours into more than five different metabolites, which are then expelled through the urine. Blood, urine, nails, and hair are all possible indicators of bodily exposure to arsenic, but each has advantages and disadvantages as an indicator [7]. Arsenic measured in the blood is the most accurate reflection of a recent exposure to high concentrations of arsenic, but blood measurements are more difficult to analyze than those from urine are, because of characteristics of the blood matrix. Arsenic in urine can reflect arsenic exposure over the previous 2 to 3 days, and because most arsenic species are expelled in the urine and can be measured in the urine, it is known the ideal biomaterial for measuring arsenic exposure [7]. However, various confounding factors such as sex, age, individual variation, smoking, and dietary factors make analysis of arsenic values in the urine difficult [54,55]. For an accurate exposure assessment of inorganic arsenic, consumption of seafood must be prohibited for 2 to 3 days prior to urine sampling. Analysis of arsenic in the hair has been suggested as a new method of measuring arsenic exposure; nevertheless, there are limitations in its application in epidemiological studies owing to difficulties in its analysis. Therefore, arsenic measured via urine sample is currently the most appropriate method for use in epidemiological studies.

LEVEL OF HUMAN EXPOSURE TO ARSENIC

In the general population, measurement of arsenic in the urine has been accepted as the most suitable method. In South Korea, several studies have measured the total arsenic concentration (trivalent, pentavalent, MMA, and DMA) in the urine. In a study by Bae et al. [56] that enrolled 580 Korean adults (242 males and 338 females) 20 years or older, the average the urinary arsenic concentration was 7.10 μg/L (males, 7.63 μg/L; females, 6.75 μg/L). Another study by Eom et al. [57] reported an

average concentration of 8.47 μg/L using the same methods. In a high-risk area for arsenic exposure in Bangladesh, the total urine arsenic concentration was 20.77 μg/L on average [58], which is lower than that in China (28.30 μg/L) [59] and Taiwan (20.71 μg/L) [60], but higher than that in Spain (1.14 μg/L). However, these findings cannot be generalized to the South Korean population; thus, further studies regarding arsenic exposure level using representative data in South Korea are needed. When collection data on total arsenic concentration can be difficult to clearly determine the state of arsenic exposure. As such, analysis of the exposure level by separation and quantification of each type of arsenic is needed. In addition, subsequent assessments of arsenic exposure are needed to establish appropriate management policies.

CONCLUSION

Given its toxicity, arsenic exposure is an important issue in public health, and more research is warranted. Cancers of the skin, lungs, and bladder have been confirmed to be associated with arsenic exposure, while human data on liver cancer, kidney cancer, prostate cancer, and leukemia are limited. For diabetes and other disorders, further research regarding its non-carcinogenic toxicity is needed. Recent, previous studies have investigated the health effects of chronic exposures to low concentrations of arsenic, but additional studies are required. To determine the level of arsenic exposure and its associated health effects in the South Korean population, biological monitoring data that can objectively assess human exposure must be developed. However, data on the total arsenic exposure level and that by arsenic species are lacking in the Korean population; therefore, further research of this kind is needed to support effective public health management.

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CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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