

Prevalence of Skin Cancer in Chronic Arsenicosis in Chittagong Medical College Hospital, Bangladesh

Mansurul Alam^{1*}, Saroj Kanti Singh Hazari², A.S.M. Towhidul Alam³, Saima Alam⁴, Khohinur Nahar Chowdhury⁵, Tafikur Nahar⁶, Aymn Jahangir Selim⁷

¹Professor & Head (Ex), Department of Dermatology & Venereology, Chittagong Medical College, Chittagong, Bangladesh

²Professor, Department of Chemistry, University of Chittagong, Chittagong, Bangladesh

³Professor, Department of Medical Biochemistry, Chittagong Medical College, Chittagong, Bangladesh

⁴Medical Officer, MS Phase B Resident, Chittagong Medical College Hospital, Chittagong, Bangladesh

⁵Assistant Professor, Gynae & Obs, Chattogram International Medical College, Chattogram, Bangladesh

⁶Junior Consultant, Gynae & Obs, Chittagong Medical College, Chittagong, Bangladesh

⁷Assistant Professor, Cardiology, Chittagong Medical College, Chittagong, Bangladesh

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*Corresponding author: Mansurul Alam

Professor & Head (Ex), Department of Dermatology & Venereology, Chittagong Medical College, Chittagong, Bangladesh

Email: profdralam1984@gmail.com

Abstract

Original Research Article

A descriptive study was done in the Department of Dermatology and Venereology; Chittagong Medical College Hospital, Chittagong, during the period of July 2004 to June 2008, to find out the prevalence of skin cancer among various skin manifestations of chronic arsenicosis. All suspected patients of chronic arsenicosis coming from endemic zones of Bangladesh were the study population. A total number of 234 patients of chronic arsenicosis were included in this study. The patients were diagnosed by physical examination and by estimation of arsenic level of scalp hair. The majority of the patients came from Noakhali, Chitagon, Feni, Laxmipur, Comilla and Chandpur districts. The mean age of the patients was 27.80 years \pm 10.22 SD (Range: 12-70 years). About 70% patients were around 30 years of age. The male & female ratio was 1.9: 1. Most of them came from average socio-economic status. About 28.6 % patients were students, while about 25% patients were daily labour. 94 % patients used tube well as drinking water source. 12.80 patients had family history of chronic arsenicosis and about 19% patients took alternative medicines (homeopathic /kobirajee) for treatment of the same or other illness. The cent percent patients presented with hypo and hipermelanosis (rain drop pigmentation), while 90,6 % patients were with hyperkeratosis in palms and soles. The measurement of arsenic in scalp hair was done. The mean arsenic level of scalp hair was found to be 2.63 1.39 SD (range: 2.0 - 17.6 mg/kg). Skin biopsy for histopathology was done for suspected patients and skin lesions of 21.4% patients were detected as arsenical keratosis. Among the total patients, 6 (six) patients were found to develop skin cancers (2.6 %). Among them, 3 patients developed Squamous Cell Carcinoma (SCC), 1 patient developed Basal Cell Carcinoma (BCC), while Bowen's disease and Melanoma was found in 1 patient each. Regarding treatment response, about 48% patients showed good response with topical keratolytics- 6% to 12% salicylic acid and potent corticosteroid- clobetasol propionate .05% & systemic antioxidants (Vit. A, E& C). Arsenic is an emerging chemical carcinogen. In addition to the social problems, skin cancer along with other internal malignancies will be a serious health hazards in our country in near future. It is established that drinking tube-well water is the main source of chronic arsenic intoxication and different skin cancers are due to arsenic. So safe arsenic free drinking water may prevent chronic arsenicosis and its complications. It is necessary to take short and long term emergency intervention programme by government and NGO's for prevention of further endemicity of chronic arsenicosis in Bangladesh. So public awareness about chronic arsenicosis due to arsenic contaminated drinking water is essential.

Keywords: Prevalence, Skin Cancer, Chronic Arsenicosis.

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INTRODUCTION

Arsenic along with antimony and bismuth belong to group VA of the periodic table, was amongst the earliest elements to have been isolated and it was

known before either Nitrogen (1772) or Phosphorous (1669) had been obtained as the free elements. The properties of arsenic sulfide and related compounds have been known to physicians and professional poisoners

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since the fifth century BC though their use is no longer recommended by either group of practitioners. Isolation of the element is sometimes credited to Albertus Magnus (AD 1193 to 1280) who heated orpiment (As₂S₃) with soap, and its name reflects its ancient lineage. It seems clear that As, Sb, and Bi become increasingly recognized in its free form during the thirteenth to fifteenth centuries. They are therefore contemporary with Zn and Co and predate all other elements except the 7 metals and 2 nonmetallic elements known from ancient times (Au, Ag, Cu, Fe, Hg, Pb, Sn; C and S) arsenic and antimony are classed as metalloids or semi-metals. The other name of the water is life. So the water should be pure, not contaminated because none can live without pure water. Water contains some essential as well as toxic elements or metals which can be concerned with our proper living, such as Na, K, Ca, Mg, Fe, Cu, Mn, Cr, As etc. These are essential elements for human body as well as other living organisms too. Some of these elements are needed at high concentration and some are needed at low concentration for usual growth and development of human body. We ingest arsenic as small quantity in vegetable, fruits, fish, drinking water and in some medicine like Fowler's solution and Asiatic Pill. Arsenic absorption, excretion and retention are influenced by the amount and the chemical forms in which it is ingested. Arsenic in the forms that ordinarily present in drinking tubewell water, food and the organic compounds of arsenitic acid, 3-nitro 4-hydro phenylarsenic acid and arsenobenzene used as health and growth stimulants are well absorbed. After absorption arsenic is distributed rapidly and widely to all tissues of the human body such as liver, spleen, kidney, heart, lung, stomach, pancreas, muscles, thyroid, brain, spinal cord, skin, hair and nails.

MATERIALS & METHODS

Type of study

The type of study undertaken was based upon purposive sampling and this was observational study.

Study place and duration of study

The study was conducted in the Department of Dermatology of venereology, Chittagong Medical College Hospital, during the period of July 2004 to June 2008.

Study population

All suspected patients of chronic arsenicosis attending in the Department of Dermatology and Venereology, Chittagong Medical College Hospital.

Samples size: A total number of 234 patients of chronic arsenicosis.

Chronic arsenicosis case definition

Arsenicosis was defined in this study as the 'presence of characteristic arsenical skin with a history of drinking arsenic contaminated water for at least 6 months.' This definition was also validated by other

reports [1, 2]. The diagnosis of arsenical skin lesions were reported in earlier publications [3, 4].

Patients' selection

Patients who attended the arsenic clinic, Department of Dermatology & Venereology, Chittagong Medical College Hospital (CMCH) with typical clinical manifestations of chronic arsenicosis as per standard instruction and recommendation considering the endemicity of disease in the region, only clinical criteria were used for diagnosis.

Inclusion Criteria

1. Patients who had given verbal consent and were willing to comply with this study process.
2. Chronic arsenicosis patients of both sex groups of more than 5 years.
3. Patients having history of consumption of arsenic contaminated tube-well water more than 6 months with or without family history of chronic arsenicosis.
4. Patients coming from endemic zones presented with acquired palmo-plantar punctate hyperkeratosis.
5. Patients who had hyper pigmentation or leucomelanosis on the trunk and extremities and other typical signs and symptoms of chronic arsenicosis.

Exclusion Criteria

1. Patients who refused to be included in the study.
2. Patients with age below 5 years.
3. Mottled pigmentations since birth.
4. Drug induced hypo or hyper pigmentation.
5. Occupational or hereditary or other skin diseases associated with palmo-plantar hyperkeratosis.

Data collection procedure

A close ended pre-tested questionnaire was used to collect information on sociodemographics, water use and occupation. Skin lesions of chronic arsenicosis i.e. melanosis, leucomelanosis and keratosis was examined by dermatologists under daylight (Appendix-I). A total of 234 patients were enrolled. Different skin manifestations of chronic arsenicosis were analyzed. Skin biopsy from the lesion of hyperkeratosis for histopathology done to find out different types of skin cancers. A total of 234 scalp hair samples were collected and all these preserved hair samples were sent to Atomic Energy Centre, Dhaka where these were analyzed by flow-injection hydride generation atomic absorption spectrophotometer (FIHG-AAS). The minimum detection level for this method is 3 mg / kg.

Statistical analysis

All analysis were performed using SPSS software (Version 12). Baseline parameters of the study populations were calculated and comparison between different baseline variables was done using student t-test,

chi-square test and Pearson's correlation test (Appendix III & IV).

RESULTS

A total of 234 cases, 154 (65.8 %) males, 80 (34.2 %) females, fulfilling the inclusion criteria were enrolled during the study period. The mean age of the patients was 27.80 years \pm 10.22 SD (range: 12-70). About 70% patients were under 30 years of age. The male: female ratio was 1.9: 1. The median value for the age was 25 years. Most of the patients were students (28.6 %) and daily labours (24.8 %). About 74 % came from average socio-economic status. Noakhali was found most endemic area in southern part of Bangladesh. Maximum patients are tube-well water user (94 %). About 13% patients had family history of arsenicosis, and about 19 % had history of using homeopathic medications. Various types of skin manifestations were found. Among them, the most common was rain drop pigmentation (100 %). 90.6 % patients showed palmo-plantar punctate keratosis. Arsenic level of scalp hair was estimated. The mean arsenic level was detected to be as 2.63 mg/kg \pm 1.39 SD (range: 2.0- 17.6). 27.8 % among the total patients were detected as arsenicosis (\geq 3.0 mg/kg). Skin Biopsy for histopathology was done for suspected patients, and skin lesions of 21.4 % patients were detected as arsenical keratosis. Among the total patients, 6 (six) patients were found to develop skin cancer (2.6%). Among them, 4 patients developed squamous cell carcinoma, while Bowen's disease and Melanoma was found in 1 patient each. Clinical improvements after treatment of patients were observed. Hyperkeratosis was improved clinically and good

response was observed in about 48 % patients. About 33 % patients were found to be as non responders.

Table 1: Demographic characteristics of study population (n=234)

Sex	n	%
Male	154	65.8
Female	80	34.2
Total	234	100
SES		
Low	60	25.6
Average	174	74.4
Total	234	100
Sources		
Tube Well	220	94
Surface Water	8	3.4
WASA	6	2.6
Total	234	100
Age		
<20 yer	67	28.6
21-30 yer	97	41.5
31-40 yer	44	18.8
41-50 yer	21	9
>50 yer	5	2.1
study population		
Student	67	28.6
Daily Labour	58	24.8
House Wife	44	18.8
Farmer	34	14.5
Service Holder	21	9
Businessman	10	4.3

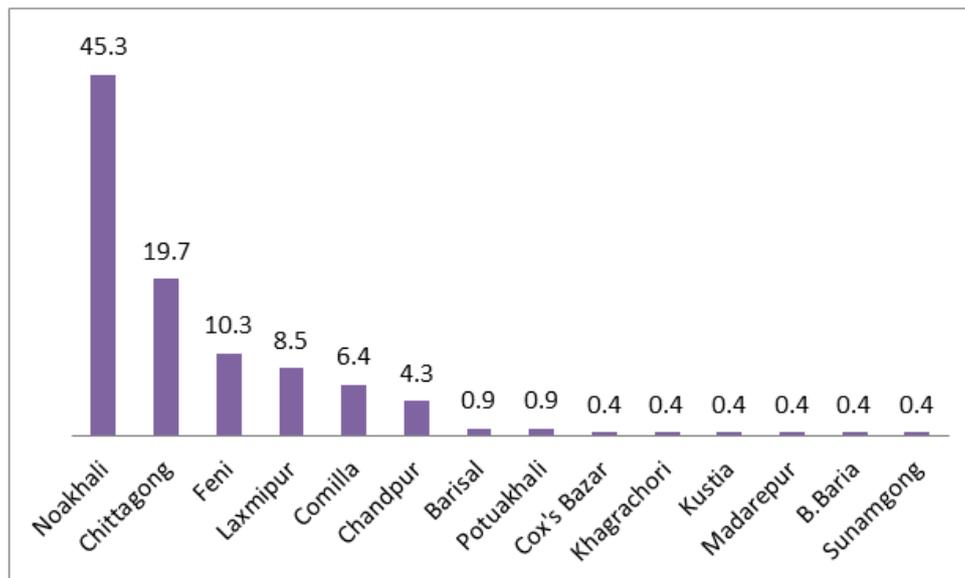


Figure 1: Distribution of inhabitation of study population (n=234)

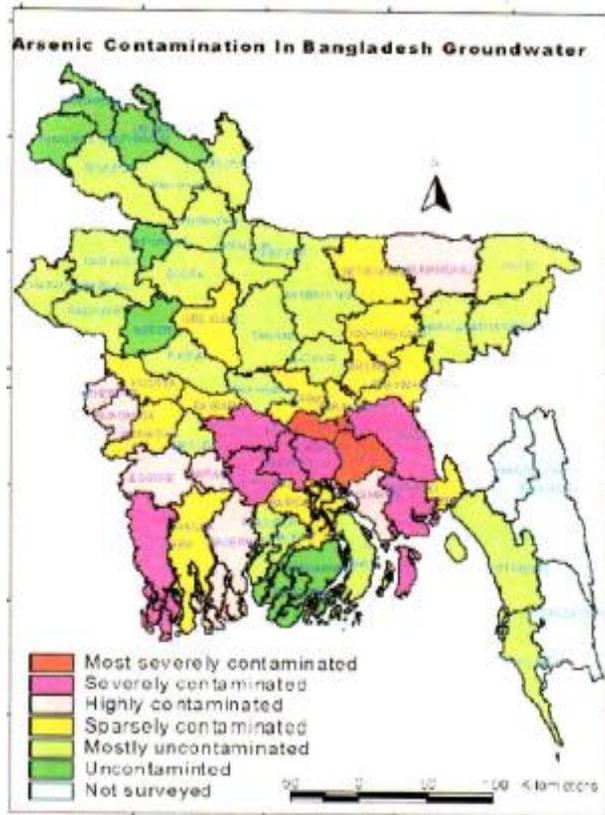


Figure 2: Severity of arsenic contamination in ground water in Bangladesh

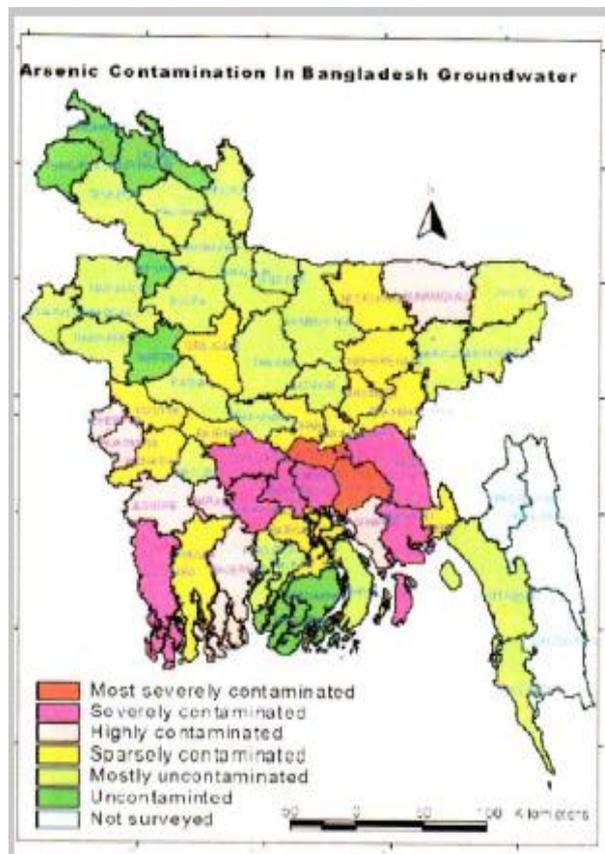


Figure 3: Intensity of arsenic contaminated (>50µg/L) tube-wells in Bangladesh

Table 2: Family history, Hyperkeratosis and Hyperhidrosis and hyperhidrosis of study population (n=234)

Family history	n	%
Present	30	13
Absent	204	87
Hyperkeratosis		
Present	21	9
Absent	213	91
Hyperhidrosis		
Present	82	35
Absent	152	65

Table 3: Arsenic Status, Skin biopsy, Treatment response and Skin cancer of study population (n=234)

Arsenic Status	n	%
Normal	169	72.2
Arsenicosis	65	27.8
Total	234	100
Skin biopsy		
Not done	184	78.6
Arsenical Keratosis	50	21.4
Total	234	100
Treatment response		
Good response	112	47.90
Non responder	78	33.30
Discontinued treatment	44	18.80
Total	234	100
Skin cancer		
Detected	6	2.6
Not detected	228	97.4
Total	234	100

Table 4: Association between skin cancer and arsenic status with x²

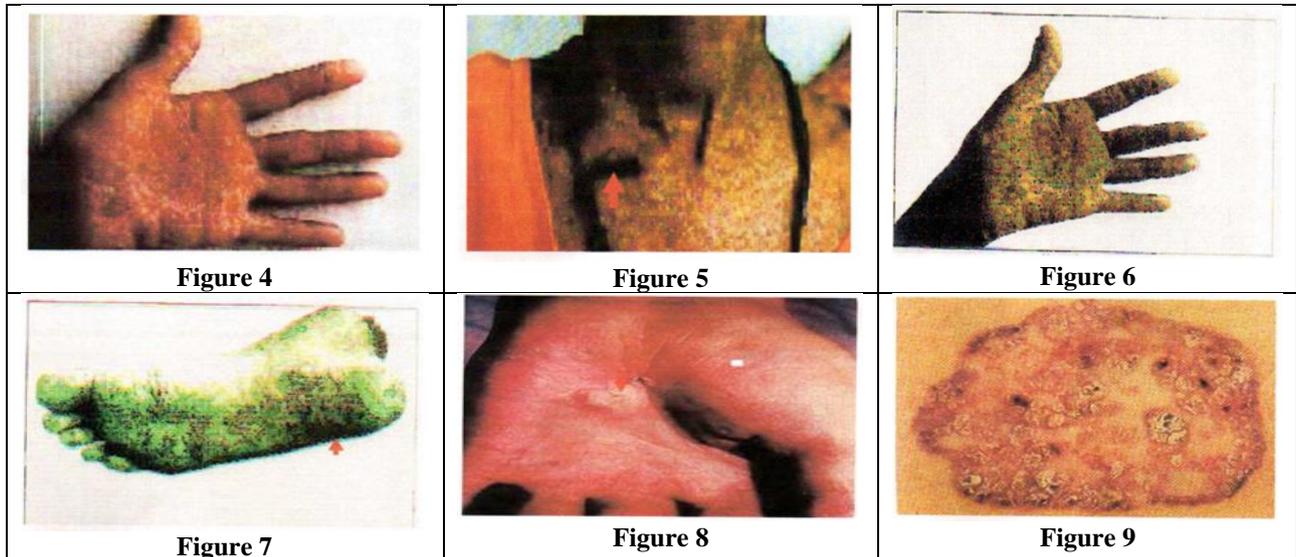
		Skin cancer detected by biopsy				X ²	p
		Not detected		Detected			
		n	%	n	%		
Arsenic status in scalp hair	Normal	167	98.8	2	1.2	4.642	0.031 (< 0.05)
	Arsenicosis	61	93.8	4	6.2		
Skin biopsy for histopathology	Not done	184	100.0	0	0.0	22.661	0.000 (< 0.001)
	Arsenical keratosis	44	88.0	6	12.0		
Hyperkeratosis	Absent	22	100.0	0	0.0	0.639	0.424 (> 0.05)
	Present	206	97.2	6	2.8		
Hyperhidrosis	Absent	81	98.8	1	1.2	0.914	0.339 (> 0.05)
	Present	147	96.7	5	3.3		

Table 5: Mean differences among arsenic status with t-test results

Continuous variables	Arsenic status in scalp hair	n	Mean	SD	t	p
Age (years)	Normal	169	24.64	8.58	8.791	0.000 (< 0.001)
	Arsenicosis	65	36.02	9.57		
Arsenic level in scalp hair (mg/kg)	Normal	169	2.00	0.00	10.095	0.000 (< 0.001)
	Arsenicosis	65	4.27	1.81		
Duration of illness (years)	Normal	163	2.21	0.99	5.655	0.000 (< 0.001)
	Arsenicosis	64	3.15	1.18		

Table 6: Relation between skin cancer and arsenic status of scalp hair

Type of skin cancer	Arsenic status of scalp hair (mg/kg)	Normal level of arsenic in scalp hair (mg/kg)	P value of t test result
Bowen's disease	3.5	<3.0	<0.001
Melanoma	4.8	<3.0	
SCC	10.4	<3.0	
BCC	5.3	<3.0	



DISCUSSION

The discovery of arsenic contamination of ground water in many nations, including Argentina, Chile, China, India, Mexico, Taiwan, Thailand, the United States and now, Bangladesh shows that this is a global problem. Bangladesh is facing with the largest mass poisoning of a population in history because ground water used for drinking has been contaminated with naturally occurring inorganic arsenic. It is estimated that about 77 million inhabitants of Bangladesh are at risk of drinking arsenic contaminated water [5]. The scale of this environmental disaster is greater than any seen before. In Bangladesh, arsenic contamination of water in tube-wells was confirmed at first in 1993 in the Nawabganj district [6]. Further testing was done in the following years by different agencies and institutions like the Bangladesh Atomic Energy Commission, the Dept. of Public Health Engineering Laboratories, the National Institute of Preventive and Social Medicine in Dhaka. For Bangladesh Arsenic Concentration in drinking water recommended by WHO is $\leq 50 \mu\text{g/L}$ [7]. Chronic arsenicosis appearing in rural population in an epidemic proportion at the 20th century in our country is an alarming health hazard at present. Arsenic is widely distributed in body tissues like blood, skin, hair, nails. It can be detected long times after it has disappeared from the urine & feces. Rare acute arsenic poisoning may occur in short time but chronic arsenicosis may take longer period. Mottled pigmentations or raindrop pigmentation occurs most commonly in the trunk and extremities. Palmo-plantar punctuate hyperkeratosis

occurs after a long period of chronic arsenic poisoning. Initially there may be dermatitis, hyperkeratosis, conjunctivitis, diarrhea & later on anemia, peripheral neuropathy & multorgan failure. In the last stage, patient may develop gangrene of limbs & skin cancers including SCC, BCC, melanoma, Bowen's disease & other internal malignancies like carcinoma of stomach, lung & liver.

Arsenic is widely distributed in body tissues like blood, skin, hair, nails. It can be detected long times after it has disappeared from the urine. Rare acute arsenic poisoning may occur in short time but chronic arsenicosis may take longer period. Mottled pigmentations or raindrop pigmentation occurs most commonly in the trunk and extremities. Palmo-plantar punctuate hyperkeratosis occurs after a long period of chronic arsenic poisoning. Initially there may be dermatitis, hyperkeratosis, conjunctivitis, diarrhea & later on anemia, peripheral neuropathy & multorgan failure. In the last stage, patient may develop gangrene of limbs & skin cancers including SCC, BCC, melanoma, Bowen's disease & other internal malignancies like carcinoma of bladder, stomach, lung & liver.

A study conducted in the Rajarampur village of the Nawabganj district, by the National Institute of Preventive and Social Medicine and the School of Environmental studies; found that 29% of the 294 tube-wells tested had arsenic concentrations greater than $50 \mu\text{g/l}$, [8] Between September 1996 and June 1997, a

survey was jointly conducted by Dhaka Community Hospital and the School of Environmental Studies. An examination of 265 tube-wells in Samta village in the Jessore district found that about 91% of the tube-wells had arsenic concentrations higher than 50µg/l [9].

In 1998 a British Geological Survey of 41 districts collected 2022 water samples, 35% were found to have arsenic concentrations above 50 µg/l. and 8,4% were above 300 µg /l (British Geological Survey and Mott MacDonald [10]. Based on population density measured in 1998 this group estimated that the number of people exposed to arsenic concentrations above 50µg/l. was about 21 million. This number would be approximately doubled or more if WHO's standard of 10 µg /l. were adopted. Further studies conducted by the School of Environment Studies and the Dhaka Community Hospital found that 59% of the 7800 ground water samples had arsenic concentrations greater than 50 µg/l [11].

From December 1996 to January 1997, a three week survey was conducted by the Dhaka Community Hospital and the School of Environmental Studies. The survey team visited 18 affected districts. Of the 1630 adults and children examined, 57.5% of them had skin lesions due to arsenic poisoning [12]. In another study approximately one-third of the 7364 patients examined had skin lesions due to arsenic [13].

In the 200 villages surveyed by the Rapid Action Programme, 1802 of 469424 people were found to have arsenic-induced skin lesions. During the same period a more detailed study of 4 villages with arsenic-contaminated tube-wells was conducted, and 1481 adults were interviewed and examined. Of these 430 were found to have skin lesions [14], The actual extent of the arsenic contaminations and the number of people with skin disease caused by arsenic might be many times higher than is currently estimated.

The latency for arsenic-caused skin lesions (I.e., the time from first exposure to manifestation of disease), in particular keratosis, is typically about 10 years [15]. In the 1997 consultancy, it was found that the youngest individuals with skin lesions caused by arsenic were about 10 years old [16], which was comparable with my study i.e. the youngest case of chronic arsenicosis was 12 years old in my study. Other studies have shown that skin lesions also occur in children younger than 10 years. However, latency that is shorter or longer than 10 years may occur, and the rapidity of the appearance of skin lesions appears to be dose dependent. The typical latency of skin cancer is more than 20 years after the beginning of exposure to arsenic. A study of large population in Taiwan found a clear dose-response relationship between arsenic concentrations in drinking water and the prevalence of skin cancer [17].

In their study, the average concentration of arsenic in water was about 500µg/l and by age 60 more than 1 in 10 had developed skin cancer (US Environmental Protection Agency, 1988). In my study the arsenic level of scalp hair 2.63 mg/kg ± 1.39 SD (range 2.0 - 17.6 mg/kg) (P<0.001) though large number of skin cancers have been reported in Taiwan, the future burden of arsenic caused skin cancer in Bangladesh is uncertain. Differences in susceptibility between the populations of Taiwan and Bangladesh may exist that only time and further study will identify. However, as yet there is no evidence to indicate that the long-term risks of skin cancer would be any lower in Bangladesh than in Taiwan.

In Argentina, a mortality study in the arsenic-exposed region of Cordoba found increased risks of bladder and lung cancer among men and women from 1986 to 1991, although arsenic concentrations were lower (average 178 µg/l) than in Taiwan [18]. Using the current US Environmental Protection Agency standard of 50 µg /l it has been estimated that the life time risk of dying from cancer of liver, lung, kidney, bladder and skin while drinking 1 liter a day of water containing arsenic at this concentration could be as high as 13 per 1000 persons exposed [19].

The latest document on arsenic in drinking water, the US National Research Council concluded that exposure to 50 µg could easily result in a combined (skin & internal) cancer risk of 1 in 100 [20].

In case of Bangladesh it can be inferred that since there are many people who currently have skin lesions caused by ingesting arsenic, many more cancers will occur if exposure to arsenic continues. It is established that mortality from cancers due to arsenic ingestions by any means will increase in future if sufficient latency for cancer formation has been allowed. The basic treatment is to supply the arsenic free drinking water which is the fast priority because providing arsenic free water reduces the risk of further complications and disease caused by arsenic. Though there are no well-designed studies to show whether cessation of exposure leads to improvement in skin keratosis or skin cancers. But it suggests that mild to moderate skin manifestations do improve with cessation of exposure to arsenic. Since evidence from Taiwan suggests that some nutritional factors may modify cancer risk associated with arsenic [21]. It has been proposed that providing vitamins and improving nutrition may be of benefit to patients particularly vitamin A, E & C are known to be beneficial particularly in those populations who may have inadequate levels of micronutrients. Veret *et al.*, [22] reported that supplementation with vitamin E and selenium either alone or in combination, slightly improved skin lesion conditions although the improvement was not statistically significant. Recently, success in the treatment of arsenicosis with indigenous medicine 'Spirulina' has been claimed. Several

investigators like Sikder MS and Islam AZMM *et al.*, Khan *et al.*, Chowdhury *et al.*, Huq *et al.*, [23-26] reported that spirulina, a natural microalgae is found to be effective in the treatment of chronic arsenicosis. Khandaker S and Islam AZM *et al.*, [27] should that combination of drinking arsenic safe water and use of antioxidants give good results in improvement of arsenicosis. Misbahuddin *et al.*, [28] reported that alcohol extracted spirulina in combination with zinc is effective for the management of chronic arsenicosis patients. In our study the treatment of chronic arsenicosis with antioxidant (Vitamin A, E and C) was good (47.9%), For these reasons it is recommended that all patients with skin lesions should be given multivitamin tablets particularly vitamin A, E and C with considering side effects of hyper vitaminosis A.

In our study, most of the patients came from endemic zone of greater Noakhali. Chowdhury MAI *et al.*, [29] showed that Chandpur, Comilla, Noakhali, Munshiganj, Faridpur, Madaripur, Gopalganj, Shariatpur and Satkhira are the most arsenic contaminated part of the country. It was found that about one-third of the total patients of our study had high level of arsenic in scalp hair, maximum patients were of middle age. About 13% patients has got positive family history of chronic arsenicosis. Almost all patients used tube-well water for drinking purpose and some patients took homeopathic & kabirajee medicine for different illness for variable times before the development of chronic arsenicosis.

6 (six) patients out of 234 cases developed skin cancers, like SCC, Bowen's disease & melanoma. The association between skin cancer and arsenic status of different body tissues was found to be statistically significant ($P < 0.001$). Rong chun Yu *et al.*, [30] showed that chronic ingestion of arsenic from drinking water is associated with the occurrence of skin cancer. They showed that skin lesion cases had had higher percents of inorganic arsenic, methylarsonic acid (MMA) and lower percent of dimethyl arsenic acid (DMA). It is established that individual with higher percentage of MMA (> 15.5%) had an odds ration of developing skin cancer 5.5 times (95% confidence interval) higher than those having a lower percentage of MMA. It is concluded that arsenic biotransformation including methylation capacity may have a role in the development of arsenic induced skin disorders.

None of the patients had manifestations or evidence of diabetes mellitus or other major endocrinopathy. Though some study reports show that arsenic is a probable contributor to causation of diabetes mellitus and hypertension [31]. Advanced keratoses on palms and soles are extremely vulnerable for superimposed infections such as fungal infections and cancer formation wish may cause serious problems. Providing topical keratolytics and antifungls and systemic antioxidants may be beneficial and should be

part of routine care in advanced cases. Urinary glucose should tasted in all patients with chronic arsenicosis and patient's blood pressure should be monitored routinely because arsenic exposure may induce hypertension [31].

The limitations of our study was that we were not able to do, arsenic estimation of tube well water during the time of examinations of patients of chronic arsenicosis. Serum arsenic level or urinary arsenic level was not estimated due to lack of facilities in our country. The possibility of continuing exposure to arsenic via drinking water or food or by other means should be tasted by screening of arsenic in blood or urine samples. At present there is no kit for blood or urine sample testing. So a reference laboratory should be equipped to measure arsenic in biological samples.

CONCLUSION

Public awareness about chronic arsenicosis due to arsenic contaminated drinking water is essential. It is the high time to classify arsenic in drinking water as a public health emergency in Bangladesh. It is necessary to take short and long term emergency intervention programme by government and NGO's for prevention of further endemicity of chronic arsenicosis in the country. Early case detection and early management with follow up treatment may prevent cancer formation and premature death. So a broad based study is necessary to find out the multiple sources of arsenic and different consequences of chronic arsenic poisoning, including cancers of different organs of the body. It is established that drinking tube-well water is the main source of chronic arsenic intoxication, and different skin cancers are due to arsenic. Save arsenic free drinking water may prevent chronic arsenicosis that leads to disfigurement, social problems, multi- organ failure, different cancer fomation, mortality and morbidity of the patients.

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