Arsenic ingestion and increased microvascular disease risk: observations from the southwestern arseniasis-endemic area in Taiwan

Jeng-Min Chiou,1 Shu-Li Wang,2* Chien-Jen Chen,3 Chia-Ru Deng,1 Wender Lin4 and Tong-Yuan Tai5

Accepted 28 April 2005

Background We established the association between arsenic ingestion and increased risk of vascular diseases associated with diabetes. However, the specific microvascular diseases in relation to arsenic exposure level have not been well reported.

Methods The study population was obtained through national health database linkage. A total of 28 499 subjects living in the study area were successfully linked with their medical records from the National Health Insurance database in 1999–2000. The arsenic concentrations of artesian well water in the villages of the study area were utilized as indices of previous ingestion level. Both stratified analysis and unconditional logistic regression were used to examine mainly neurological and renal disease in relation to the arsenic exposure taking into account diabetes status.

Results The age-adjusted and gender-adjusted prevalence of microvascular diseases was 7.51% [95% confidence interval (CI) 7.50–7.51] for arsenic level of <0.1 mg/litre, and then increased from 6.59% (6.59–6.60) for the arsenic concentrations of 0.1–0.29 mg/litre to 8.02% (8.02–8.03) and 11.82% (11.81–11.83) for those of 0.3–0.59 mg/litre and ≥0.6 mg/litre in non-diabetic subjects. For diabetic patients, the prevalence was 16.41% (95% CI 16.37–16.45), 15.85% (15.8–15.9), 21.69% (21.6–21.8), and 28.31% (28.2–28.4) for arsenic levels <0.1, 0.1–0.29, 0.3–0.59, and ≥0.6 mg/litre, respectively. The prevalence of microvascular diseases increased significantly with arsenic exposure, especially at higher levels, and the relationship is stronger in diabetics than in non-diabetic subjects. The results for neurological disease are very similar, and the patterns are the same for renal disease.

Conclusions The increased prevalence of microvascular diseases, including neurological and renal disorders, is associated with arsenic ingestion. This excess risk was further elevated in diabetic subjects. Further studies are necessary to verify the hypotheses of threshold or dose–response relationships.

Keywords Arsenic, health insurance, neurological disease, renal disease, environmental health, microvascular disease, non-insulin-dependent diabetes mellitus, water pollutants

1 Institute of Statistical Science, Academia Sinica, Taipei, Taiwan, R.O.C.
2 Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Graduate Institute of Occupational Safety and Health, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.
3 Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan, R.O.C.
4 Department of Health Care Administration, Chang Jung Christian University, Tainan, Taiwan, R.O.C.
5 Division of Gerontology Research, National Health Research Institutes, Taiwan, R.O.C.
6 Corresponding author, Shu-Li Wang, Division of Environmental Health and Occupational Medicine (DEHOM), National Health Research Institutes (NHRI), 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan, R.O.C. E-mail: slwang@nhri.org.tw
Across the world, it is common knowledge that the natural arsenic level in the groundwater is higher than the current maximum recommended level for human consumption. Also of relevance is the recent large increase in the world’s dependence upon groundwater resources owing to the ongoing increase in the world population and the progressive increase in per capita water requirements. For many years, there has been an ongoing vigorous debate regarding the setting up of maximum permissible arsenic levels for tap water, voicing concerns relating to the mounting evidence of the cancer-causing nature of arsenic and the high cost of the reduction of arsenic levels in water. Even though the water consumed is well within the arsenic-specifed limit, humans may still be exposed to high arsenic levels through the bioaccumulation of arsenic in aquaculture-bred fish species and/or agricultural products. In addition to arsenic-associated cancer risks, we suggest that certain vascular diseases may also be attributable to arsenic exposure, therefore, attention needs to be paid to the high prevalence of such diseases, the needs for long-term treatment of affected patients, and the high health care costs of such diseases.

We noted an increased prevalence of diabetes and related vascular diseases in the south-western arseniasis-endemic area of Taiwan using the National Health Insurance (NHI) database. Other previous studies revealed a dose-dependent relationship between long-term arsenic exposure and the prevalence of peripheral vascular disease, ischaemic heart disease, and cerebrovascular disease. However, the specific does–response relationship between the substantial prevalence of microvascular diseases and the related arsenic exposure of affected individuals has not yet been examined.

Microvascular diseases such as renal or neurological dysfunction generally need a period of development. In order to examine the risk factors associated with exposure to a toxin such as arsenic, a sufficient sample size and observation period is required. Residents of the south-western arseniasis-endemic area of Taiwan have been relying upon artesian well water as a potable source since well before the 1970s. Large and up-to-date databases of local medical records from the NHI database together with the previously conducted artesian well water arsenic concentrations have provided us with a unique opportunity to assess the relationship between arsenic exposure and the prevalence of microvascular disease.

Materials and methods

Study areas and subjects

The study population in the south-western arseniasis-endemic area of Taiwan included Yenshui, Beimen and Shuehchia of Tainan County, and Putai and Yichu of Chiayi County. More than 50% of the artesian wells in these five townships contained arsenic concentrations >0.35 mg/litre (p.p.m.), according to the national survey of wells in Taiwan. Residents in these areas started using artesian well water from the 1920s because the shallow well aquifers tended to contain high-salinity water. In addition to drinking water contamination by arsenic, it has been previously reported that some agricultural products and some locally produced fish were contaminated with high concentrations of arsenic in the study area. According to statistics provided by the Ministry of Internal Affairs, the population in the study area has decreased gradually during the past 40 years, while the population in urbanized counties such as Taipei, Hsin-Chu, and Taichung has increased. Thus, it appeared fair to conclude that immigrants from outside areas only constituted a very small proportion of the population contained within the study area. It was noted that >90% of the local residents who resided in the study area had lived there all their lives.

Residents of 47 villages from the five specified townships in the arseniasis-endemic areas of Taiwan participated in this study. The residential records of the subjects who lived in these villages were validated through the National Household Registration system. These records were linked to the township and village-specific information pertaining to artesian well water quality. Residents were considered eligible to participate in this study if they were >25 years of age in the year 2000. These residents represented a population that was more than likely to have relied upon arsenic-contaminated artesian water for their source of potable water, and thus had ingested arsenic through artesian well water prior to the introduction of tap water into the study area during the 1970s. A total number of 28,499 residents were successfully linked through the household registration and arsenic contamination of groundwater databases. The specific disease status of each subject was then ascertained according to the 1999–2000 NHI database.

Arsenic contamination levels of artesian wells

Arsenic levels in artesian well water of the study area have been reported to be stable based on the data from two national surveys. For the present study, we utilized arsenic concentrations of well water provided by the National Taiwan University (NTU) group with greater sampling density and validation by international laboratory comparisons. There were 60% of the villages having more than one well. The method used to determine arsenic concentration was according to the 1961 technique of Natelson with a slight modification. The number of wells per village ranges from 1 to 14, except one village with 47 wells. We used median water arsenic contamination levels as surrogates of arsenic exposures for villages that featured more than one artesian well as a source of potable water as recommended during the exposure assessment.

Disease ascertainment

Patient disease status was ascertained through specific diagnostic codes from the NHI database based on drug prescriptions. A team of researchers including the clinician, diabetologist, NHI data management researcher, and epidemiologist verified parts of the subjects’ codes for the data quality assurance. Thus we have achieved consensus for all diseases’ codes with some of them modified according to the conventional coding scheme among clinicians. Diabetic patients were defined as patients diagnosed with the ICD-9-CM (International Classification of Diseases, 9th version, Clinical Modification) codes of 250 or the A-code (abridged code) of A181. Type 1 diabetic patients, who were defined as registered for catastrophic illness in diabetes mellitus or commenced using insulin injections at < 25 years of age, were excluded in this study. Microvascular diseases included renal diseases (ICD-9 codes 250.4, 581.8, 582.8, 583.8, 585.0, 586.0), neurological disorders (250.6, 357.2, 358.1, 355), and retinopathy (codes 250.5, 362.0, 362.01, 362.02, 366.4). We refer to prevalence as...
the number of individuals ever having an entry with the disease codes in the insurance records divided by the total population in 1999–2000. The NHI in Taiwan is compulsory and universal, and provides comprehensive health benefits for its members. Since 1995, >96% of the total population of Taiwan has been covered for each year by the NHI System. Of all health care providers ~93% have been contracted to the Bureau of National Health Insurance, and those not contracted appear to provide only a minimal amount of health services. The co-payment rate for the patients is as low as from 8 to 20% of the total medical cost of a medical visit with a fixed charge of US $1.5 per visit. Therefore, it would appear likely that virtually all the residents in the study area, particularly those suffering from chronic diseases, used medical services from one or more of the contracted health providers. Of people covered by NHI >96% had used some form of health services through NHI-contracted health providers from 1999 to 2000.

Data analysis
The age-adjusted prevalence was calculated stratified by gender and diabetes status for each arsenic level group. The arsenic concentration levels were categorized into four groups with ranges <0.1, 0.1–0.29, 0.3–0.59, and >0.6 mg/litre, with distributions 25.5, 20.7, 22.9, and 20.9%, respectively. Statistical significance of the trend for each stratum was examined by the Cochran–Armitage test. A model-based multivariable logistic regression analysis was performed to adjust the association with arsenic for possible confounders. The response variable denoted the prevalence of individuals suffering from the disease while the candidate risk or confounding variables included the arsenic level, gender, age, and diabetes status. The patient’s age and water arsenic concentration were taken as continuous variables in the model, and possible transformations of these variables, such as quadratic and non-parametric spline functions, were also considered as the candidate predictors in the logistic regression models in order to find better fits. We performed a model selection procedure according to the Akaike information criteria (AIC) that measures deviations of the fitted model from the observed data.

Results
The prevalence of microvascular diseases according to arsenic levels by age, gender, and diabetes status are shown in Table 1. For the age-adjusted summarized prevalence, the increasing trends for all subgroups were significant ($P$ values<0.001), apart from the male diabetic patients. The prevalence of microvascular diseases was much higher among the diabetic patients than among the non-diabetic subjects. For the diabetic patients, the prevalence of microvascular diseases among female subjects was greater than for male subjects for all categories of the arsenic levels. This is also true for the non-diabetic subjects, but the prevalence difference between the genders was less obvious for the non-diabetic subjects. The ratios of microvascular disease prevalence among the diabetic patients relative to the non-diabetic subjects were quite similar across various arsenic levels, being 2 to 3. When analysing for each disease group, we found the same pattern for neurological and renal diseases which is not shown here.

Table 2 reveals the subgroup analysis for neurological and renal diseases. The group shown with top arsenic concentration experienced a significantly higher risk of neurological disease ($OR = 1.68$, 95% CI 1.49–1.89). There appeared stronger positive relationships for neurological and renal diseases for Type 2 diabetic patients than for non-diabetic subjects. The results for retinopathy disease were not presented because there were only 16 cases among non-diabetic subjects.

Explanatory variables including diabetes status and gender, and the continuous variables of the linear and quadratic ages and arsenic concentration had highly significant association with microvascular disease prevalence (Table 3, left panel). The prevalence odds ratio (OR) for male subjects to female subjects in the same age category, arsenic concentration level, and diabetes status was 0.78 (95% CI 0.72–0.84), indicating that women reflected a higher prevalence for microvascular diseases on average than men. Similarly, the prevalence OR for diabetic patients to non-diabetic subjects for the same gender, age, and water arsenic concentration category was 2.77 (95% CI 2.48–3.09), indicating that diabetic patients exhibited a much higher prevalence of microvascular diseases than non-diabetic subjects. The results for neurological disease were very similar to those for microvascular diseases. For renal disease, we chose the same variables as predictors for comparison purpose, which excluded patients with retinopathy and neurological disorders (Table 3, right panel). The prevalence OR for diabetic patients to non-diabetic subjects for the same gender, age, and arsenic concentration level category was 3.31 (95% CI 2.44–4.50) while the gender effect showed no differences.

The interaction effect between age and level of concentration was significant with a positive coefficient, indicating that the older the age, the higher the increasing rate. The perspective plots display the relationships clearly. The two upper panels of Figure 1 displayed prevalence probability of microvascular diseases for diabetic patients classified by gender (males on the left). The two lower panels were presented in a similar fashion for non-diabetic subjects. The increasing probability was more pronounced for diabetic patients than for non-diabetic subjects; this was also the case for female subjects. We noted that the slope of the increasing probability was steeper for individuals at an older age than for younger individuals. With a fixed water arsenic contamination level, the prevalence of microvascular diseases appeared to increase sharply at a younger age and then tended to plateau at an older age.

Discussion
To the best of our knowledge, this is the first occasion reporting the relationship between arsenic ingestion levels and the increased prevalence of microvascular diseases, particularly for renal disease and neurological disorders. Current results further illustrate the impact of the co-existence of diabetes and arsenic intoxication, with age-adjusted and gender-adjusted rates being 15.85% (95% CI 15.8–15.9), 21.69% (95% CI 21.6–21.8), and 28.31% (95% CI 28.2–28.4) for the water arsenic levels 0.1–0.29 mg/litre, 0.3–0.59 mg/litre, and >0.6 mg/litre, respectively. Previous studies have discussed the dose-dependent relationship between the long-term exposure to arsenic and the prevalence of peripheral vascular disease, ischaemic heart disease, cerebrovascular disease, and even carotid
### Table 1
Prevalence of microvascular diseases in percentage (no. in the study population) according to diabetes status and water arsenic concentrations (mg/litre) by age and gender for the south-western arseniasis-endemic area of Taiwan

<table>
<thead>
<tr>
<th>As level</th>
<th>Diabetic patients (n = 2399)</th>
<th>Non-diabetic subjects (n = 26100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender, age (years)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–34</td>
<td></td>
<td>9.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11)</td>
</tr>
<tr>
<td>35–44</td>
<td></td>
<td>14.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(55)</td>
</tr>
<tr>
<td>45–54</td>
<td></td>
<td>16.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(98)</td>
</tr>
<tr>
<td>55–64</td>
<td></td>
<td>25.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(127)</td>
</tr>
<tr>
<td>≥ 65</td>
<td></td>
<td>20.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(176)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td></td>
<td>15.58</td>
</tr>
</tbody>
</table>

### Table 2
Age and gender-adjusted prevalence (%) of neurological and renal disease by diabetes and water arsenic concentration (mg/litre) for the south-western arseniasis-endemic area of Taiwan

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type 2 diabetic subjects (n = 2399)</th>
<th>Non-diabetic subjects (n = 26100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (n) (95% CI) OR (95% CI)</td>
<td>Prevalence (n) (95% CI) OR (95% CI)</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>8.89 (1038) (8.86–8.92)</td>
<td>1.00</td>
</tr>
<tr>
<td>≤0.1</td>
<td>9.53 (404) (9.49–9.57)</td>
<td>1.08 (0.73–1.60)</td>
</tr>
<tr>
<td>0.1–0.29</td>
<td>14.94 (577) (14.89–14.99)</td>
<td>1.80 (1.32–2.46)</td>
</tr>
<tr>
<td>0.3–0.59</td>
<td>21.36 (380) (21.30–21.42)</td>
<td>2.78 (2.01–3.85)</td>
</tr>
<tr>
<td>≥0.6</td>
<td>1.92 (1038) (1.91–1.93)</td>
<td>1.00</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.34 (404) (1.33–1.35)</td>
<td>0.69 (0.27–1.81)</td>
</tr>
<tr>
<td>≤0.1</td>
<td>2.54 (577) (2.52–2.56)</td>
<td>1.33 (0.67–2.63)</td>
</tr>
<tr>
<td>0.1–0.29</td>
<td>3.91 (380) (3.88–3.94)</td>
<td>2.08 (1.04–4.11)</td>
</tr>
</tbody>
</table>
Table 3 Parameter estimates of the logistic regression models evaluating relative risk of the microvascular disease for the south-western arseniasis-endemic area of Taiwan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Microvascular diseases</th>
<th>Renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (OR)</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>-3.924</td>
<td>0.278</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Male (95% CI)</td>
<td>0.778</td>
<td></td>
</tr>
<tr>
<td>(0.717–0.843)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.603</td>
<td>0.111</td>
</tr>
<tr>
<td>Age²</td>
<td>-0.053</td>
<td>0.011</td>
</tr>
<tr>
<td>Cnct</td>
<td>-1.366</td>
<td>0.370</td>
</tr>
<tr>
<td>Cnct²</td>
<td>1.725</td>
<td>0.325</td>
</tr>
<tr>
<td>Age*Cnct</td>
<td>0.140</td>
<td>0.049</td>
</tr>
<tr>
<td>Type 2 DMᵇ</td>
<td>1.019</td>
<td>0.057</td>
</tr>
<tr>
<td>Non-DM (95% CI)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>2.769</td>
<td></td>
</tr>
<tr>
<td>(2.478–3.094)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Standard error.
ᵇ Diabetes mellitus.

Figure 1 Probability of microvascular disease by age and artesian well water arsenic concentration (mg/litre). The upper-left and upper-right panels correspond to Type 2 diabetic patients by gender. The lower-left and lower-right panels represent non-diabetic subjects by gender.
with diabetes included as an examined risk factor. Arsenic has previously been suggested to be associated with an increased risk of diabetes. Part of the mechanism might result from atherosclerosis associated with arsenic ingestion and hyperglycaemia status. Long-term hyperglycaemia may be one cause of microvascular diseases including nephropathy, neuropathy, and retinopathy. Thus, arsenic-associated diabetes may exaggerate the development of atherosclerosis and glomerulosclerosis leading to an increased risk of subsequent microvascular disease. Microcirculatory assessments have revealed that deficits in capillary blood flow and permeability exist within the clinically normal skin of subjects chronically exposed to arsenic as compared with control subjects. It has been further elucidated that the long-term atherosclerotic effects of exposure to arsenic may exist in both macrovascular and microvascular systems, particular for diabetic patients.

The specific mechanisms underlying the role of arsenic in the aetiology of atherosclerosis has been recently reviewed and it appears that such a mechanism is still not well understood. To this end, various mechanisms, both in vitro and/or in vivo, have been previously investigated with diverse target-cells and selecting different arsenic varieties, concentrations, and time points of exposure. Inorganic arsenic, with its trivalent form is reportedly more toxic than its pentavalent form and may increase oxidative stress, mainly through the depletion of glutathione, resulting in endothelial cell damage and/or apoptosis. Furthermore, such exposure may also suppress the activity of endothelial NO synthesis. Oxidative stress has also been shown to be the stimulus for apoptosis related to glomerulosclerosis for human renal mesangial cells. Such changes may be related to exposure-induced vasculature leakage, smooth-muscle cell proliferation, and decreased fibrinolytic activity. Arsenite, the trivalent inorganic form of elemental arsenic, has previously been shown to enhance platelet aggregation and thrombus formation in an animal model. Inorganic arsenic may cause DNA damage or alter gene expression related to vascular lesions. Mono-methylated trivalent arsenic, the organic form, has been reported to be even more cyto-toxic than arsenite although this compound may be rapidly converted to di-methyl arsenate or strongly bound to endogenous ligands thus reducing the relative toxicity. The reported effects of arsenic as well as other effects may arise as a result of the interaction of various arsenic species and other trace elements or nutrients.

The prevalence of neurological disorders among diabetic patients increased from 9% (7% for non-diabetic subjects) to 10% (6%), 15% (8%), and 21% (11%), respectively, for the following arsenic exposure levels: <0.1, 0.1–0.29, 0.3–0.59, and ≥0.6 mg/litre. There have been fewer reports on arsenic-related neuropathy than on cardiovascular diseases. A recent survey revealed arsenic-related prevalence of neuropathy of 37% and 87% for two areas of West Bengal, India, featuring groundwater that was highly contaminated by arsenic, although the underlying mechanism for such pathology needs further investigation. Arsenic may induce neural damage directly or indirectly via induced angiopathy. The investigation of the influence of these two options warrants future investigation.

We have used the arsenic concentration levels of artesian well water within the study area as the index of the exposure measure. We acknowledge that the precise level of arsenic exposure at the individual level, as a consequence of well-water consumption, is rather difficult to assess without individual lifetime histories. The consequences of exposure misclassification were discussed in many studies. Although the measure index of arsenic exposure used in this study may reveal limitations for studying relationships, the potential bias owing to exposure misclassification seemed unlikely to introduce artificially observed effects in this population-based dataset. Clinicians did not know individuals’ previous arsenic exposure levels during practice, and therefore this potential bias owing to diagnosis could only reduce the significance of a positive relationship, which generally biases the OR estimates towards the null.

In the current study we found the non-diabetic group with top arsenic concentration (≥0.6 mg/litre) experienced a significantly higher risk of neurological disease (OR 1.68, 95% CI 1.49–1.89); whereas the last two exposure level (0.3–0.59, 0.1–0.29 mg/litre) groups did not. A threshold for concentrations ≥0.6 for the increased risk might be suggested. The current observation implicated a lower threshold (0.3 mg/litre) for diabetic subjects, which is in agreement with biomedical knowledge. Alternatively there might be a dose–dependent association; or the dose–response might have occurred after a certain level of exposure. The testing of the hypotheses requires further investigation with individual exposure and vascular risk confounders taken into account. In conclusion, adverse effects from ingested arsenic existed not only on macrocirculatory but also on microcirculatory systems that may exhibit renal or neurological diseases. This excess risk was further elevated in diabetic subjects. Further studies are necessary to test the hypotheses of threshold or dose–response relationships.

Acknowledgements
This work was supported by the National Health Research Institutes, Taiwan (NHRI BS-092-PP-07 and EO-092-PP-01). We thank the Bureau of National Health Insurance—Southern Branch for providing the local insurance database. We also greatly appreciate the excellent documentation assistance by Ms Wei-Ling Chou from the DEHOM, NHRI.

Disclaimer statement
The Scientific contents of this manuscript have been reviewed and approved for publication by the Division of Environmental Health and Occupational Medicine of the National Health Research Institutes. Approval for publication does not necessarily signify that the contents reflect the views and policies of the DEHOM/NHRI, its condemnation, endorsement, or recommendation for use pertaining to the issue presented.
KEY MESSAGES

- Arsenic ingestion might be associated with increased risk for microvascular disease such as renal and neurological disorders.
- The association might have a threshold of >0.6 mg/litre for non-diabetic individuals and >0.3 mg/litre for diabetic patients.
- Dose–response pattern cannot be ruled out.
- The hypotheses require further study with complete individual risk confounders being adjusted.

References

11 Lo MC. The arsenic content of farm products and fishes in areas where high arsenic well water was used for agriculture and fish-culture. In: Report on blackfoot disease research. Taichung: Taiwan Provincial Department of Health 1980, vol 8, pp. 10–21.
14 Kuo TL. Arsenic content of artesian well water in endemic area of chronic arsenic poisoning. Reports, Institute of Pathology, National Taiwan University 1964;20:7–13.
35 Galle J, Heermeier K, Wanner C. Atherogenic lipoproteins, oxidative
36 Pi J, Kumagai Y, Sun G et al. Decreased serum concentrations of nitric
oxide metabolites among Chinese in an endemic area of chronic
28:1137–42.
37 Klahr S. Oxygen radicals and renal diseases. *Miner Electrolyte Metab*
1997;23:140–3.
38 Lijnen HR, Collen D. Endothelium in homeostasis and thrombosis.
39 Jiang SJ, Lin TM, Wu HL, Han HS, Shi GY. Decrease of fibrinolytic
activity in human endothelial cells by arsenite. *Thromb Res*
40 Lee MY, Bae ON, Chung SM, Kang KT, Lee JY, Chung JH. 
Enhancement of platelet aggregation and thrombus formation by
arsenic in drinking water: a contributing factor to cardiovascular
41 Lynn S, Gurr JR, Lai HT, Jan KY. NADH oxidase activation is involved
in arsenite-induced oxidative DNA damage in human vascular
42 Kapahi P, Takahashi T, Natoli G et al. Inhibition of NF-kappa B
activation by arsenite through reaction with a critical cysteine
275:36662–6.
43 Tai SH, Hsieh MS, Chen L, Liang YC, Lin JK, Lin SY. Suppression of
Fas ligand expression on endothelial cells by arsenite through reactive
44 Petrick JS, Ayala-Fierro F, Cullen WR, Carter DE, Vasken Aposhian H.
Monomethylarsonous acid (MMA(III)) is more toxic than arsenite in
Low serum carotene level and increased risk of ischemic heart disease
46 Houtman JP. Trace elements and cardiovascular diseases. *J Cardiovasc
47 Wu G, Meininguer CJ. Arginine nutrition and cardiovascular function.
48 Mukherjee SC, Rahman MM, Chowdhury UK et al. Neuropathy in
arsenic toxicity from groundwater arsenic contamination in West Bengal,
49 Brouwer OF, Onkenhout W, Edelbroek PM, de Kom JF, de Wolf FA,
Peters AC. Increased neurotoxicity of arsenic in methylene-
trahydrofolate reductase deficiency. *Clin Neurol Neurosurg* 1992;
50 Mahajan SK, Aggarwal HK, Wig N, Maitra S, Chugh SN. Arsenic
52 Wacholder S, Benichou J, Heineman EE, Hartge P, Hoover RN.
Attributable risk: advantages of a broad definition of exposure. *Am J
53 Kosinski AS, Flanders WD. Evaluating the exposure and disease
relationship with adjustment for different types of exposure