Research Article

Arsenic Methylation Patterns Before and After Changing from High to Lower Concentrations of Arsenic in Drinking Water

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Abstract

Inorganic arsenic (In-As), an occupational and environmental human carcinogen, undergoes biomethylation to monomethylarsonate (MMA) and dimethylarsinate (DMA). It has been proposed that saturation of methylation capacity at high exposure levels may lead to a threshold for the carcinogenicity of In-As. The relative distribution of urinary In-As, MMA, and DMA is used as a measure of human methylation capacity. The most common pathway for elevated environmental exposure to In-As worldwide is through drinking water. We conducted a biomarker study in northern Chile of a population chronically exposed to water naturally contaminated with high arsenic content (600 μg/l). In this paper we present the results of a prospective follow-up of 73 exposed individuals, who were provided with water of lower arsenic content (45 μg/l) for 2 months. The proportions of In-As, MMA, and DMA in urine were compared before and after intervention, and the effect of other factors on the distribution of arsenic metabolites was also analyzed. The findings of this study indicate that the decrease in arsenic exposure was associated with a small decrease in the percent In-As in urine (from 17.8% to 14.6%) and in the MMA/DMA ratio (from 0.23 to 0.18). Other factors such as smoking, gender, age, years of residence, and ethnicity were associated mainly with changes in the MMA/DMA ratio, with smoking having the strongest effect. Nevertheless, the factors investigated accounted for only about 20% of the large interindividual variability observed. Genetic polymorphisms in As-methylating enzymes and other co-factors are likely to contribute to some of the unexplained variation. The changes observed in the percent In-As and in the MMA/DMA ratio do not support an exposure-based threshold for arsenic methylation in humans.

Key words: arsenic, arsenic methylation, arsenic speciation, Chile, exposure change, intervention studies, water pollution. Environ Health Perspect 104:1200-1207 (1996)

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Introduction

Inorganic arsenic (In-As) is known to increase the risk of cancer at several target sites. Inhalation of arsenic, mainly from dust exposure in occupational settings such as metal smelters and pesticide production, increases the risk of lung cancer while ingestion of arsenic, mainly from contaminated drinking water sources, causes skin cancer (1). Epidemiological evidence also indicates that In-As ingestion is associated with increased risks of lung, bladder, kidney, and liver cancers (2-5). Based on data from studies conducted in Taiwan, we estimated that at the present EPA arsenic water standard of 50 μg/l, the risk of internal cancers could be of comparable magnitude to those from environmental tobacco smoke and radon in homes (6). Similar cancer risks from arsenic in drinking water were derived by Chen et al. (7) in another risk assessment based on the same data.

In-As can be ingested as either arsenite (AsIII) or arsenate (AsV). Although AsV is less toxic, it is reduced biologically to AsIII prior to undergoing methylation, which is considered a detoxification mechanism for In-As (8,9). Two methylation steps take place, the first producing monomethylarsionate (MMA), which is then further methylated to dimethylarsinate (DMA). Both MMA and DMA are considered less toxic and bind less to tissues than In-As (8).

It has been proposed that saturation of the methylation capacity may lead to a threshold for the carcinogenicity of ingested In-As (8,10). Under this hypothesis, as exposure increases, one would expect to see an increase in the proportion of In-As (the more toxic species), with a corresponding decrease in MMA and DMA.

Urinary arsenic is generally regarded as the most reliable indicator of recent exposure to In-As and is used as the main biomarker of exposure (11,12). In the case of ingestion, experimental studies show that around 60-75% of the dose is excreted in the urine within a few days (8,9,13). Blood arsenic is not considered a good indicator because it is cleared within a few hours (11,14). Although In-As accumulates in hair and nails, external surface arsenic contamination make these samples less accurate for assessing dose (15).

While total urinary arsenic has been used to assess In-As exposure, it is important to differentiate In-As and its metabolites from other organic forms. In particular, certain types of seafood contain arsenobetaine, a much less toxic organic form of arsenic that is excreted quickly in the urine. Using methods of speciation analysis, In-As, MMA, and DMA can be separated from other arsenic compounds. Currently, the sum of these species in urine constitute the preferred measure of exposure to In-As and, for convenience, we will refer to it as total arsenic (Tot-As). The relative proportions of urinary In-As, MMA, and DMA have been used as indicators of methylation capacity (6,16-19).

In a previous report, we examined the results of several studies reporting speciated urinary arsenic measures. Collectively, they showed that the published evidence of human studies did not support the methylation threshold hypothesis (17). The relative percentages of In-As, MMA, and DMA averaged approximately 15-20%, 10-15%, and 60-70%, respectively, across different populations studied, with no systematic increase in the percent In-As with increasing exposure. More recently, we conducted two studies of populations exposed to unusually high arsenic levels in drinking water. One study in Nevada compared individuals drinking well water containing arsenic levels over 500 μg/l (mean = 1300 μg/l) to an unexposed group drinking water with an average of 16 μg/l (18). In a larger investigation conducted in Chile, we compared methylation patterns of 122 people from a town with around 600 μg/l arsenic in water to 108 people from a neighboring town with 15 μg/l (20). Both studies found that
methylation patterns did not vary greatly by exposure levels while, in contrast, they noted large interindividual variability independent of exposure level. In addition, other factors such as gender, smoking, and ethnicity seemed to have a greater effect on species distributions than did urinary arsenic levels. The influence of these other factors applied mainly to the relative proportions of MMA and DMA (summarized as the MMA/DMA ratio), but not to the percent In-As.

All of the studies conducted so far have been cross-sectional in nature, either comparing individuals of similar arsenic exposure levels (background, occupational, or environmental) or of contrasting exposures (high versus low exposure groups). There have been no previous population studies reporting the effects of changing exposure on methylation patterns. In this study, a subgroup of highly exposed subjects from the previously reported study in northern Chile (20) were provided with water containing lower arsenic levels (45 µg/l) for a 2-month period. Urinary arsenic was collected before and at the end of the intervention phase. We investigated the effects of change in arsenic exposure on the patterns of urinary metabolites as a measure of methylation capacity in a longitudinal follow-up using each person as his/her own control.

**Methods**

**Study population.** Study subjects were residents of San Pedro de Atacama, a town of 1600 people in the Atacama Desert of northern Chile, previously found to have high arsenic levels in their water supply (21,22). The water sources derive from surface waters originating in the Andes mountains, and their arsenic content depends on the natural geological composition of their course (22). San Pedro has two sources of drinking water: water from the Vilama river, which is piped to most homes and contains around 600 µg As/l, and water from the San Pedro river, with about 170 µg As/l, which is used by some homes having no public water supply.

Participants for this study were a subset of those of a larger investigation, described in detail elsewhere (20,23,24). Briefly, prospective study subjects were recruited through public announcements, meetings, and door-to-door contact. They had to be at least 18 years old and to have lived in the town for the last 3 months. A cross-sectional study was conducted, comparing residents of San Pedro to those of a neighboring town having low arsenic water. All study subjects were interviewed by trained interviewers regarding general characteristics; smoking and drinking habits; and medical, occupational, and residential histories; first morning urine samples were obtained as described below.

For the intervention study reported here, we selected a subsample of participants from San Pedro, including only residents who drank from the higher arsenic water source (tap water). For a 2-month period, they were provided with water containing a lower arsenic concentration. The only available source of water for this purpose was from the town of Calama, located about 100 km from San Pedro, which has a water supply with about 45 µg As/l. Water was brought in twice a week by truck and delivered to participants’ homes in 60-liter containers, which were equipped with spigots. Participants agreed to use this water for all drinking and cooking purposes.

About 40 homes were enrolled in the intervention study, from which 78 persons participated (not counting other family members, primarily children, who lived in the same house and used the water but were not study subjects). During the 2 months of the study, there were two urine sample collection periods about 2–3 weeks apart to monitor compliance by study participants in using the provided water. At the end of the study period, all subjects were interviewed and sampled again while they were still receiving the lower arsenic water.
Laboratory analysis. First morning urine samples were obtained and kept frozen in the field laboratory at -20°C until they were transported in dry ice to the University of Washington in Seattle. They were analyzed for arsenic content by hydride generation atomic absorption spectroscopy (HGAA) based on Andreae's method (25) as described for our cross-sectional study (20). Briefly, In-As, MMA, and DMA were reduced to their corresponding arsines with sodium borohydride and were subsequently measured by atomic absorption spectroscopy. Detection limits for In-As, MMA, and DMA were 0.5 μg/l, 1.0 μg/l, and 2 μg/l, respectively.

Some samples were found to have an unusually low proportion of methylated species. Replicates of these samples were tested by spiking in the laboratory with a mixture of known amounts of In-As, MMA, and DMA, which revealed strikingly low recoveries (less than 25%) of MMA and especially DMA. It was concluded that, for those samples, the methylation assay suffered from interference from an unidentified substance. An alternate method was derived, which resulted in more complete recovery of the methylated species but yielded a slightly lower recovery for In-As. Due to differences in methodology and in recovery rates and given that it affected only a few samples from the intervention subgroup (n = 4), they were omitted from this analysis.

During the study, water samples were taken from the water supply and analyzed for arsenic content by HGAA according to a procedure similar to that used for urine specimens (26). Urine samples were also assayed for creatinine content to allow expression of Tot-As in relation to urine concentration.

Statistical analysis. Sociodemographic and lifestyle characteristics of study participants were compared to describe their distribution by age, gender, ethnicity, education, length of residence, smoking habits, and drinking of alcoholic beverages. Compliance with usage of the provided water was assessed by comparing the different Tot-As measurements of urine samples taken before, during, and at the end of the intervention phase.

Tot-As (In-As + MMA + DMA) was used as the measure of exposure. Our previous analysis of the creatinine-adjusted (micrograms As per gram of creatinine) and unadjusted values (micrograms As per liter of urine) led us to use the latter (20). In brief, creatinine excretion can vary considerably by a number of exogenous and endogenous factors (27). The results of our cross-sectional methylation study in this same population showed that the distribution of In-As metabolites did not vary by urinary creatinine concentrations nor were there any major differences in using creatinine-adjusted or unadjusted Tot-As values (20). In this study, the same comparisons were performed and showed no substantial differences; therefore, we decided to use unadjusted urinary arsenic concentrations in the current analysis as well.

For the analyses of the distribution of arsenic metabolites, Tot-As, the percentages of In-As, MMA, and DMA, and the MMA/DMA ratio were calculated for each of the two sampling periods: before the change in water supply and after the 2 months of lower arsenic water usage (referred to as before or initial and after or final measurements). The mean of each period was derived by first calculating each individual measurement and then averaging over the group. Since attention has recently focused on the MMA/DMA ratio (19,28), we also conducted analyses using this measure.

The distribution of arsenic species before and after intervention were compared for the group as a whole and then stratified by gender, age, years of residence, ethnicity, and smoking and alcohol drinking habits. These factors had been associated with methylation in the cross-sectional comparison of the low and high exposure towns (20). In order to quantify the magnitude of the change in percent In-As, percent MMA, percent DMA, and MMA/DMA between the two sampling periods, a measure of change was
derived, calculated by subtracting the second measure from the first (before - after). The associations between the magnitude of this difference or measure of change in the distribution of metabolites and that of the change in Tot-As (before - after) were evaluated.

Multiple regression analysis was used to examine the effect of various factors on the distribution of metabolites before and after intervention, including Tot-As, gender, age, smoking, and years of residence. The same type of analysis was performed using the measures of change in metabolite distribution between the two periods as the outcome variables to assess the potential contribution of other factors to the differences observed.

Results

The study group originally consisted of 78 participants, but 4 were excluded from the final analysis for irregularities in the urinary speciation assay as explained above. One additional subject was excluded because of evidence that he was clearly not complying with the intervention plan: three urine samples taken during that time were consistently very high and of the same general level as the initial preintervention sampling (first = 939 µg/l; subsequent three were 1162, 737, and 1344). Therefore, the final study sample included 73 participants.

The distribution of general characteristics is summarized in Table 1. A similar number of men (n = 39) and women (n = 34) participated, and most of them were long-time residents (92% had lived in San Pedro for at least 5 years) and were of Atacameño ethnicity (79%). About the same percentage of men and women were smokers, while almost twice as many men than women reported drinking alcohol (67% vs. 38%). Because we found it common for people to report smoking or drinking occasionally, we also compared smokers who smoked at least one cigarette per day (regular smokers) to nonsmokers and drinkers who consumed at least one drink per week (regular drinkers) to nondrinkers [one drink was defined as 355 ml beer, 118 ml wine, 30 ml liquor, 355 ml aloja (an alcoholic beverage made from fermented pods of the Algarrobo tree)]. The average number of cigarettes per day among regular smokers was around 6 for both men and women, while among regular drinkers men drank more than three times as much as women (9.4 vs. 2.2 average drinks per week).

The results of arsenic water analyses conducted during the study period for San Pedro tap water ranged from 615 to 670 µg/l, which is consistent with levels reported in previous investigations (21,22). The arsenic concentration of the water delivered to participants during the intervention period was 45 µg/l. All the As was in the inorganic form, but the assay we used for water measurements did not distinguish the oxidation state of In-As. However, a previous study in the same area, which used a different method, found that the As was practically all in the pentavalent form (AsV) (21).
Stratified comparisons of arsenic metabolite species before and after intervention are presented in Table 2. Although all four measures (percent In-As, percent MMA, percent DMA, and MMA/DMA) are shown, for the sake of brevity we will mainly limit our discussion below to percent In-As and the MMA/DMA ratio. The average urinary levels of Tot-As before and after intervention were 636 µg/l and 166 µg/l, respectively. The effect of intervention on species distribution for all participants combined showed a mean decrease of 3.2 (from 17.8 to 14.6) in the percent In-As and a decrease of 0.05 (from 0.23 to 0.18) in the MMA/DMA ratio. There were 28 people whose Tot-As decreased to levels below 100 µg/l (from 457 µg/l to 65 µg/l) and 9 who had final concentrations under 50 µg/l (from 431 µg/l to 38 µg/l). For these two groups, the final average percent In-As and MMA/DMA ratios were 14.2% and 14.7% and 0.17 and 0.14, respectively. A large variability between individuals was observed (overall group range in percent In-As change was -11.1 - +23.9 and in the MMA/DMA ratio was -0.31 - +0.27).

During the intervention phase, an attempt was made to collect urine on two different occasions, but not all subjects participated, mainly because they were not available at the time they were visited. As a result, two follow-up urine samples were collected from 44 study participants. For this subset of subjects, the average Tot-As before intervention was 696 µg/l, and the subsequent three measures, starting about 2-3 weeks after the change in water supply and ending at the final sample collection period 2 months later, were quite similar: 213 µg/l, 198 µg/l, and 185 µg/l. The same type

<table>
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<tr>
<th>Measurement</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tr>
<td>Tot-As</td>
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<tr>
<td>Before¹</td>
<td>666 ± 402</td>
<td>212-1803</td>
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<tr>
<td>1</td>
<td>173 ± 192</td>
<td>39-1162</td>
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<td>2</td>
<td>139 ± 173</td>
<td>39-737</td>
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<tr>
<td>4</td>
<td>105 ± 215</td>
<td>22-1264</td>
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<td>Percent In-As</td>
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<tr>
<td>Before</td>
<td>17.8 ± 7.9</td>
<td>7-38</td>
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<tr>
<td>1</td>
<td>13.0 ± 5.5</td>
<td>6-38</td>
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<tr>
<td>2</td>
<td>14.3 ± 7.1</td>
<td>6-35</td>
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<tr>
<td>4</td>
<td>13.3 ± 6.7</td>
<td>3-31</td>
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<td>MMA/DMA</td>
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| Before      | 0.23 ± 0.1 | 0.05-0.5 |}

¹Prior to change in water supply.
²During intervention period.
³End of the study period.
of pattern was seen for the percent In-As and the MMA/DMA ratio across the four samples obtained for this study subgroup (Table 3).

![Graph showing changes in percent In-As and MMA/DMA ratio relative to changes in Tot-As.](image)

The overall changes in percent In-As and the MMA/DMA ratio are plotted against the corresponding changes in Tot-As in Figure 1. The line going through zero on the y-axis denotes no change, while a negative value for the change means a decrease in percentage or ratio (value after intervention lower than before). The values on the x-axis correspond to the change in Tot-As from before to after intervention. These graphs indicate two main findings: most participants experienced some decrease in percent In-As and in MMA/DMA (67% and 78% of the group, respectively) and the magnitude of the decrease did not appear to be associated with the magnitude of the decrease in Tot-As.

Stratification on gender showed that initially men had a higher average percent In-As and a higher MMA/DMA ratio than women (18.8% vs. 16.8% and 0.27 vs. 0.19, respectively) and that, after intervention, they experienced the same mean decrease of 3.2 in percent In-As. However, men had over twice the decrease in MMA/DMA ratio than women (0.27–0.20 vs. 0.19–0.16). Stratification by age did not show a clear pattern, although the oldest group (>50 years old) seemed to have the greatest changes. Participants with less than 5 years duration of residence in the town showed a greater change both in percent In-As and in MMA/DMA ratio than longer duration residents (Table 2). The correlation between age and length of residence was not very high ($r = 0.35$) so that the two variables are likely to contribute independent effects.

In the comparison by ethnicity, because 80% were of Atacameño origin, we divided the group into Atacameños and all others combined (which included other indigenous groups as well as people of European and unknown origin). Both groups had about the same initial mean percent In-As, and similar decreases after the 2 months, but because Atacameños had a lower MMA/DMA ratio initially (0.22 vs. 0.27), a similar ratio following intervention resulted in a greater change for the non-Atacameño group. However, the small, heterogeneous nature of this group (three European, three Aymara/Mapuche, seven other, two unknown) made the comparison hard to interpret. When ethnicity was entered into the multiple regression analysis, dichotomized as Atacameño and non-Atacameño, the coefficient was not statistically significant (not shown). For these reasons, we chose not to
include ethnicity in the final regression models.

When categorized by smoking status, nonsmokers had a somewhat lower initial proportion of In-As than smokers (17.3% versus 19.0%), and both had the same mean decrease of 3.2 (Table 2). With respect to the changes in MMA/DMA ratio, smokers had higher initial values and experienced three times the decrease than nonsmokers (0.29-0.20 vs. 0.21-0.18). The differences were slightly greater when regular smokers (subcategory of smokers) were compared to nonsmokers (data not shown).

Since stratification by smoking status showed the largest differences, the changes in percent In-As and MMA/DMA relative to Tot-As change were examined separately for smokers and nonsmokers. Both groups had quite similar changes in percent In-As, with 64% and 67% showing a decrease, respectively. However, the difference between smokers and nonsmokers in MMA/DMA ratio was quite clear, since all but one of the smokers (21/22 or 95%) had a decrease in the ratio (Fig. 2A), while among nonsmokers, 70% (36/51) had a decrease (Fig. 2B).

In general, the results show that greater changes occurred in the MMA/DMA ratio than in percent In-As, and the subgroups with the highest mean MMA/DMA values before the intervention showed a sharper decrease in the MMA/DMA ratio at the end of the study. In particular, smokers and men showed the greatest changes with respect to nonsmokers and women, respectively.

Figure 2.
Change in monomethylarsonate/dimethylarsinate (MMA/DMA) relative to change in total urinary arsenic (Tot-As) for smokers (A) and nonsmokers (B) after reduction of arsenic concentrations in drinking water.
The results of the regression analysis using percent In-As and MMA/DMA as the dependent variables are presented in Table 4, showing three regression models for each outcome: one for before (A and D), one for after intervention (B and E), and one using the change in percent In-As or MMA/DMA over the intervention period (C and F). The distribution of arsenic species both before and after intervention did not reveal any clear association between Tot-As levels and the percent In-As (models A, B) or the MMA/DMA ratio (models D, E). In contrast, a wide range of interindividual variation was observed, with a range of 0.05-0.6 for the MMA/DMA ratio across all study subjects, for each of the two sampling periods (Table 2). Similarly, there was no association between the change in urinary Tot-As (from before to after intervention) and the change in percent In-As or MMA/DMA.

Smoking and being male were associated with somewhat smaller MMA/DMA ratios before and after intervention, while no associations were found with percent In-As. Age did not show any significant effect. Length of residence was associated with percent In-As and MMA/DMA before but not after intervention, but the small coefficients indicate a minor effect (a 1% decrease in percent In-As and less than 0.02 decrease in MMA/DMA for 10 years of residence in San Pedro). The only variable associated with the change in MMA/DMA (from before to after the water change) was length of duration in the town. In general, the magnitude of all coefficients indicate the variables analyzed did not contribute substantially to the observed variations in percent In-As and MMA/DMA.

Discussion

This is the first epidemiological study to investigate the effect of reducing exposure on arsenic methylation patterns in a population with chronic environmental exposure to In-As from drinking water. In addition, this research design has the advantage of having each person serve as his/her own control, thus reducing interindividual variability found when comparing two populations with contrasting exposures.

Following 2 months of receiving an alternate water supply with lower arsenic concentration, a substantial decrease in the mean urinary Tot-As was observed. However, the final urinary levels were higher than what would be expected from sole consumption of water with 40-50 μg As/l, indicating that some additional In-As was consumed. There may be several reasons for these higher levels: a) participants drank fluids or ate foods prepared outside their homes; b) they consumed food grown in the area and with the usual farming water source (San Pedro River, containing 170 μg As/l); and c) compliance was incomplete, although most study subjects reported using only the provided water at home at the time of the last interview. The
higher levels could also be partly attributed to arsenic stores in internal tissues from previous exposure. Studies of volunteers show that 50-70% of a single ingested dose of In-As is excreted within a few days (13,14,29,30). In one investigation, four subjects were given different arsenic doses for 5 days. Following 14 days of urinary monitoring (9 days after exposure stopped), levels went down to near background concentrations (31). However, the effect of reduction from high to lower arsenic exposure on urinary excretion has not been monitored constantly over time among chronically exposed persons, which could have a different pharmacokinetic profile from potentially higher stores in internal tissues. In our study, the follow-up samples taken during the intervention period at about 2-3 week intervals on 44 participants did not show any substantial pattern of decrease in Tot-As after the first follow-up sample, indicating that, after a couple of weeks, a new steady state had likely been reached. It is also noteworthy that the mean percent In-As and MMA/DMA remained quite constant after the initial small reduction following the change in water supply.

In this study, the overall distribution of In-As metabolites was similar before and after intervention, with wide interindividual variations observed for both sampling periods. The 2 months of intervention were accompanied by a general small decrease in the percent In-As and percent MMA, a correspondingly small increase in percent DMA, and a decrease in the MMA/DMA ratio. The differences observed between before and after the water supply change were within the ranges of those seen between San Pedro and the lower exposure town in our cross-sectional study in the same population (20), even though the contrast in mean Tot-As were somewhat higher between the two exposure towns (583 µg/l vs. 61 µg/l) than between the before/after intervention (636 µg/l vs. 166 µg/l).

Although there was a general decrease in percent In-As and in the MMA/DMA ratio, suggesting a slight improvement in methylation capacity, the magnitudes of the changes in metabolite distributions were small and were not related to the magnitude of the decrease in urinary Tot-As (Fig. 1). The change was greater for the MMA/DMA ratio than for the percent In-As, which is again in agreement with our cross-sectional study findings, comparing methylation patterns between the two exposure towns.

Our findings of an increase in MMA relative to DMA are supported by experimental studies in vitro with rat liver cytosol, which suggest that high In-As concentrations inhibit only the second methylation step (32). However, the large variability observed and the relatively small magnitude of the change in relation to interindividual variations in this human population implies that the role of In-As exposure is minor in determining methylation, as measured by the distribution of urinary metabolites. In fact, even before intervention, this group with average Tot-As urinary levels over 600 µg/l showed metabolite distributions well within the ranges described for other populations with much lower exposures (17,33,34).

The greatest changes in the MMA/ DMA ratio occurred among the subgroups that appeared to be less efficient methylators at the second methylation step (e.g., smokers and men), and the differences were similar to those reported for the cross-sectional study (20). However, the greater change in those subgroups resulted not from general decreases of greater magnitude (as shown in Fig. 2) but rather to a more consistent pattern of changing in the same direction. Particularly for smokers, practically all showed a decrease in their MMA/DMA ratio. As suggested previously (20), it is possible that chemicals in cigarette smoke compete for some of the same detoxification enzymes or co-factors as for In-As methylation, particularly in the second methylation step. Experimental studies have shown that the addition of mercuric ions to a culture media treated with In-As has an inhibitory effect on the production of DMA relative to MMA, but not on the first methylation reaction (35). This finding is consistent with the fact that detoxification of both In-As and Hg are thiol dependent (36). Because S-methyltransferases have a thiol (sulphydryl) group as the substrate, under high exposures or competitive substrates, the activity of the second
methyltransferase appears to be the rate-limiting step. Smoking involves the intake of such a myriad of chemicals that such a scenario is plausible with other thiol-dependent toxicants. Given the incomplete knowledge of the steps involved in arsenic detoxification, the nature or magnitude of substrate competition cannot be currently ascertained.

Genetic polymorphisms in the activity of enzymes or related co-factors in one or more of the steps of arsenic detoxification are likely to play an important role in what still remains as unexplained variations between individuals. Support for this comes from several sources, including the large genetic variability found for the activity of methyltransferases involved in drug metabolism and clinical pharmacology (37,38). Similarly, glutathione is known to play a role in several steps of In-As detoxification, and genotypical differences have been described for glutathione transferases, for example, in relation to ethnicity, with over twofold variations between groups (39).

The effects of factors such as gender and age on arsenic methylation capacity remain to be explained, although they do not seem to explain variability to a great extent. The level of arsenic exposure does not appear to have a significant impact on the percent In-As, but its effect is somewhat greater in relation to the MMA/DMA ratio. This finding was very similar in the comparison of high and low exposure towns in the same study area (20) and in the comparison of before and after intervention presented in this study.

In conclusion, several factors have impacted differently on the effect of decreasing arsenic exposure on the distribution of In-As metabolites. Most of the differences were found for the MMA/DMA ratio, but the significance of these findings to human health remains unclear. In addition, most of the variability was not explained by exposure levels or by the other variables investigated, and the role of genetic variability in factors related to the metabolism of In-As, as well as the effect of other concurrent exposures or lifestyle factors, need to be investigated. However, the data produced to date in population studies is quite definitive in concluding that substantial proportions of In-As, MMA, and DMA are found across wide ranges of exposure levels and that there is no evidence of an exposure-based threshold for arsenic methylation in humans.

References


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