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High serum arsenic and cardiovascular risk factors in patients undergoing continuous ambulatory peritoneal dialysis

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ABSTRACT

The present study aims to assess arsenic accumulation and explore its association with renal function and biomarkers of CVD risk in chronic kidney disease patients receiving continuous ambulatory peritoneal dialysis (CAPD). The serum was collected from 87 CAPD patients and 26 healthy subjects between 2015 and 2016. The arsenic concentration was measured by inductively coupled plasma mass spectrometer. Clinical variables related to CVD risk were determined with automatic biochemical analyzer. Serum arsenic was higher in CAPD patients as compared to healthy volunteers. Moreover, significant differences of BMI, serum phosphorus, eGFR and Ccr were observed among groups. Positive correlation between serum arsenic and serum phosphorus was found ($r = 0.453$, $p < 0.001$). While serum arsenic was negatively associated with Ccr ($r = -0.328$, $p = 0.002$) and eGFR ($r = -0.248$, $p = 0.020$). The logistic regression models revealed that high serum arsenic was related to hyperphosphatemia (ORs, 1.827; 95%CI, 1.145–2.913) after adjusted for the potential confounding factors. Overall, our findings inferred the accumulation of arsenic in CAPD patients. In addition, high serum arsenic was independently associated with the occurrence of hyperphosphatemia, which was a special and ubiquitous CVD risk factor in CAPD patients. This study provided a clue for the association between arsenic and CVD burden in CKD patients. At the same time, it suggested that prevention of arsenic accumulation should be taken into consideration clinically.

1. Introduction

Chronic kidney disease (CKD) has been a huge public health issue [1]. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with CKD [2]. CVD affects greater than 50% of CKD patients receiving dialysis [3]. An epidemiological study from China revealed that CVD accounts for nearly 44.2%–51.0% of overall mortality among these patients [4]. Many metabolic alterations commonly observed in these patients, like dyslipidemia, hypertension and hyperphosphatemia, may contribute to the increased risk of CVD in this population [5–8]. Some trace elements were reported to be associated with these CVD risk factors in general population [9,10]. However, the potential association between trace elements and CVD risk factors in CKD patients receiving dialysis has been less well defined.

Among all the trace elements, arsenic is referred to as a metalloid with nephrotoxicity [11]. Current cross-sectional evidences suggested urine arsenic was associated with biomarkers of renal function [12]. Moreover, some studies found that high arsenic exposure through drinking water contributes to rapid progression and higher mortality rates in CKD patients [13,14]. The results from animals noted arsenic might be related to podocyte and proximal tubular injury by inducing oxidative stress and endothelial dysfunction [15]. On the other hand, arsenic has also been recognized as a risk factor for CVD [16]. Clinical studies demonstrated that arsenic-induced cardiovascular effects, including atherosclerosis and coronary heart disease, were in a dose-dependent manner [17]. Besides, arsenic was related with some CVD

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traditional risk factors like hypertension and diabetes [18,19]. In addition, chronic arsenic poisoning increased the serum inorganic phosphate. This provided a clue for the association between arsenic and hyperphosphatemia, a special CVD risk factor in CKD patients [20].

As it is mainly eliminated through kidney, arsenic theoretically trends to accumulate in CKD population. However, available evidence is inconclusive. CKD patients and those on hemodialysis showed a higher level of arsenic in blood, serum, hair or plasma in some studies [21,22]. While other observed a lower blood or plasma level of arsenic than controls in hemodialysis patients [23]. Our previous study observed insufficient daily excretion of arsenic in CKD patients receiving continuous ambulatory peritoneal dialysis (CAPD), which inferred possible accumulation of arsenic [24]. However, few studies reported arsenic accumulation as well as the association of arsenic with CVD risk factors in CKD patients with CAPD. Therefore, the objective of this study was to assess the arsenic accumulation by serum level and explore its association with renal function and CVD related biomarkers in CAPD patients.

2. Methods

2.1. Study population

Eighty-seven CKD patients receiving CAPD were recruited between January 2013 to October 2015 in Tongji Hospital, Wuhan, China. The inclusion criteria were as follows: (1) aged more than 18 years; and (2) treated with CAPD for longer than three months. The following exclusion criteria were used during recruitment of patients: (1) diabetic nephropathy; (2) peritonitis or other infectious complications 30 days prior to the sample collection. Twenty-six healthy subjects were recruited as a reference. The inclusion criteria were as follows: (1) aged more than 18 years; (2) without renal disease. And the volunteers with infectious disease were excluded. The study protocol was approved by the Ethics Committee of Tongji Hospital (IRB ID: TJ-C20120501) and all the subjects signed the informed consent form.

2.2. Sample collection and the determination of arsenic

Venous blood was collected from both CAPD patients and healthy subjects following an overnight fast. Samples were centrifuged at 3000 rpm for 30 min to get serum. All samples were stored at −80 °C in the laboratory, sequentially and immediately.

Serum samples were stored at −80 °C, and thawed on ice. Serum arsenic was measured by inductively coupled plasma mass spectrometry with an octopole-based collision/reaction cell (Agilent 7700 Series, USA) following 1:5 dilutions of 100 μL of serum with diluent containing 0.5% (v/v) HNO3. Working standard solutions were prepared by dilution of 1000 mg/L calibration verification standard (Agilent P/N 5183-4682). For quality assurance, the CRM (certified reference material) ClinChek human serum controls (ClinChek® – Control, Recipe, Germany) were used. A concentration of 10.15 ± 2.40 μg/L was determined for No.8880 (certified: 9.71 ± 1.96 μg/L) and for No.8882, 20.13 ± 2.00 μg/L was measured (certified: 19.3 ± 3.85 μg/L). Quality control was performed per 20 samples, and the inter-assay and intra-assay coefficients of variation were < 5% and < 5%, respectively.

2.3. Demography information

Personal information on demography, including sex, age, ethnicity, education was collected by questionnaires, Medical history, including the causes of renal failure, edema and the starting date of dialysis were collected from the medical records Anthropometric data including height (m) and weight (kg) were determined by standardized techniques. BMI was calculated as weight divided by the square of height (kg/m^2). The duration of dialysis (month) was calculated from the interval between the date of initiation of dialysis and the date of the nutrition interview.

2.4. The determination of biomarkers for cardiovascular risk factors

The well-characterized CVD risk factors including hypertension, dyslipidemia, obesity/overweight and inflammation were determined [25,26]. Incident hypertension was defined based on the first discharge diagnosis or systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Dyslipidemia was defined low density lipoprotein (LDL) ≥ 2.56 mmol/L, total triglyceride (TG) ≥ 1.70 mmol/L or total cholesterol (TC) ≥ 5.72 mmol/L [27]. Overweight was defined as BMI ≥ 24 kg/m^2, which was modified from the recommendation by the Working Group on Obesity in China [28].

Abnormalities of serum phosphorus and corrected serum calcium (especially hyperphosphatemia) were special CVD risk factors in dialysis population [6]. Hyperphosphatemia was described as serum phosphorus ≥1.78 mmol/L [29]. Moreover, factors relating to hyperphosphatemia including residual renal function, dialysis adequacy, inflow of dialysate, serum intact parathyroid hormone and corrected serum calcium were also determined [30]. All biochemistry measurements were performed by BS-200 Automatic chemistry analyzer (Mindray, Shenzhen, China) at the central laboratory of Tongji Hospital.

2.5. The assessment of residual renal function and dialysis adequacy

Urine volume were measured using standard methods. The residual glomerular filtration rate (eGFR) was calculated as an average of the 24-h urinary urea and creatinine clearances. These two biomarkers were to evaluate the residual renal function. Weekly total urea clearance (Kt/V) and weekly total creatinine clearance (Ccr), parameters reflecting dialysis adequacy, were calculated from a 24-h collection of dialysate and urine with the use of standard methods [31]. Dialysis adequacy was diagnosed as Kt/V ≥ 1.7 and Ccr ≥ 50 L/1.73 m^2.

2.6. Statistical analysis

Data were presented as mean ± standard deviation, median and range as appropriate for continuous variables, or percentages (%) for categorical variables. EpiData 3.0 (The EpiData Association, Odense, Denmark) was used for the double-key data entry and the program control of the data entry. The statistical analysis was performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA) for WINDOWS. To identify differences between groups, data were analyzed using the Mann-Whitney test or Kruskal-Wallis test. We used Chi-square test for categorical variables. Multinomial logistic regression analysis was used to assess the associations of serum arsenic concentration with hyperphosphatemia. ORs were adjusted for known cofounding factors of hyperphosphatemia. Statistical significance was set at $p < 0.050$.

3. Results

3.1. Patient characteristics

The anthropometric and clinical characteristics of the study subjects were summarized in Table 1. Eighty-seven participants in the analyses included 36 males and 51 females. The mean age was 43.76 ± 11.78. They had undergone CAPD for 15.90 months (ranging from 3 to 119 months). The mean BMI of CAPD patients was 21.13 kg/m^2 and 13 patients (14.94%) were with BMI lower than 18.5 kg/m^2 while 7 patients (8.04%) were with BMI greater than 24 kg/m^2.

3.2. The serum arsenic concentration

Table 2 showed the comparison of anthropometric characteristics

Table 1
The anthropometric and clinical characteristics of CAPD patients.

Variables	Mean ± SD	Median	Minimum	Maximum
Age (years)	43.76 ± 11.78	44.52	20	72
Sex (Male/Female)	36/51	–	–	–
Body height (cm)	161.54 ± 7.95	160.00	143.00	176.00
Body weight (kg)	56.12 ± 9.26	55.00	36.00	82.00
BMI (kg/m^2)	21.13 ± 3.25	20.2	15.7	38.6
Duration of dialysis (months)	24.35 ± 23.57	15.90	3.00	119.00
Hypertension (yes/no)	67/20	–	–	–
Urine volume (mL/d)	585.75 ± 518.72	500	0	2150
Ccr (L/w/1.73 m^2)	61.69 ± 18.34	60.15	31.21	116.32
Kt/V	1.98 ± 0.38	1.98	1.17	2.87
Salb (g/L)	40.00 ± 3.82	40.10	31.90	49.00
Serum phosphorous (mmol/L)	1.71 ± 0.61	1.61	0.47	4.14
hs-CRP (mg/L)	2.99 ± 4.89	1.15	0.10	32.00
FBG (mmol/L)	5.43 ± 0.819	5.22	4.04	8.83
TC	5.49 ± 4.98	4.89	2.63	50.30
TG	1.85 ± 1.29	1.46	0.50	7.20
LDL	2.73 ± 0.87	2.70	0.88	5.23
HDL	1.25 ± 0.36	1.21	0.53	2.05
eGFR	4.63 ± 1.67	4.40	2.30	12.60
Upro (g/L)	0.54 ± 0.55	0.31	0.02	2.15

Ccr: weekly creatinine clearance; Kt/V: weekly total urea clearance; Salb: Serum albumin; hs-CRP: high-sensitivity C-reactive protein; FGB: fasting blood glucose; TC: total cholesterol; TG: total triglyceride; LDL: low density lipoprotein; eGFR: evaluated glomerular filtration; Upro: 24-h total urinary protein.

Table 2
The demographic characteristics and serum arsenic of patients and control.

Variables	patients (n = 87)	controls (n = 26)	*p* value
Age (years)	43.76 ± 11.78	29.82 ± 7.82	< 0.001
Sex (Male/Female)	36/51	10/16	0.654
BMI (kg/m^2)	21.13 ± 3.25	20.87 ± 1.97	0.640
Serum arsenic (μg/L)	3.79(1.53–8.98)	0.52(0.36–1.99)	0.002

and serum arsenic between patients and healthy controls. Compared to these healthy controls, patients showed a significantly higher serum arsenic. This suggested that arsenic accumulation may occur in this special population. As significant difference in age exists between CAPD patients and healthy controls ($p < 0.05$), We further compared the arsenic levels among different age groups (20–40 years, 40–60 years, and 60–80 years), and no significant differences were observed ($p = 0.399$).

3.3. Biomarkers of CVD risk factors in patient with different serum arsenic levels

Patients were divided into four groups according to the percentile of serum arsenic. Biomarkers related to CVD risk factors in CKD patients, including hypertension, hyperglycemia, serum lipid levels and hs-CRP were compared between groups (shown in Table 3). Significant difference in BMI ($p = 0.007$) was found among these groups. Fisher's exact test was further done to analysis the relationship between serum arsenic and overweight. No statistical significance was found. In addition, comparisons of residual renal function and special CVD risk factors were analyzed. Significant differences in serum phosphorus ($p = 0.024$), Ccr ($p = 0.009$) and eGFR ($p < 0.001$) were observed among groups. At the same time, the difference in cases of hyperphosphatemia seemed to be marginally significant ($p = 0.060$). However, no significant difference in cases of dialysis inadequacy was observed between two groups.

3.4. Correlation analysis of serum arsenic with clinical variants

The correlation of serum arsenic with clinical variants are shown in Table 4. Serum arsenic was negatively associated with Ccr ($r = -0.328$, $p = 0.002$), urine volume ($r = -0.228$, $p = 0.034$) and eGFR ($r = -0.248$, $p = 0.020$). And a positive correlation of serum arsenic was found with serum phosphorus ($r = 0.453$, $p < 0.001$). These results further implied an association of arsenic accumulation with renal function loss, declining Ccr and high phosphorus.

3.5. Association between serum arsenic and hyperphosphatemia

We used a multinomial logistic regression model to further assess the association of serum arsenic with hyperphosphatemia. Table 5 presents odds ratios (ORs) for hyperphosphatemia associated with the levels of serum arsenic concentrations as continuous variables. After adjusted for the cofounding factors, including age, sex, BMI, residual renal function, dialysis adequacy, inflow of dialysate, serum intact parathyroid hormone and corrected serum calcium, the adjusted OR for hyperphosphatemia across 1 μg/L was 1.827 (95% CI, 1.145–2.913). In other words, high arsenic was independently associated with hyperphosphatemia.

4. Discussion

The present study demonstrated that excessive serum arsenic levels were observed in CAPD patients. Similarly, a few cross-sectional studies have found the mean blood levels of arsenic was significantly higher in CKD patients receiving hemodialysis (HD) as compared to healthy volunteers [33]. Excessive plasma concentration of arsenic in HD patients were also observed in a recent prospective study [34]. One concern from this study is that the mean age of healthy controls was different from patients. Since no difference was seen in serum levels with age in our study and previous study from others [32], and one of our previous study has inferred that accumulation of arsenic as well by insufficient daily arsenic excretion in CAPD patients [24], higher serum arsenic in CAPD patients seems credible.

Interestingly, our results suggested that high serum arsenic was independently positively related to the occurrence of hyperphosphatemia in CAPD patients. An earlier study in a population of 40 million people showed that chronic arsenic poisoning could increase serum phosphorous [20]. Skalny et al. also found that children living in metal-polluted area showed high blood and hair arsenic, and higher blood phosphorous level [35]. The related mechanism might refer to that the arsenic can compete with phosphorus in the oxidative phosphorylation process by replacing phosphorus or utilized the phosphate transporters in the cells thereby causing an elevated serum phosphorus [36,37].

Hyperphosphatemia is clinically associated with cardiovascular mortality in CKD patients on dialysis [6,38]. And the hyperphosphatemia-induced endothelial dysfunction contributed to vascular calcification and atherosclerosis [30,39]. In addition to hyperphosphatemia, arsenic is also associated with vascular calcification. For example, long-term and low/medium exposure had been shown to cause damage to vascular system in an epidemiological report [40]. Wang et al. observed an increased incidence of disease in the blood vessels for population living in areas with arsenic-polluted wells [41]. At the same time, an ecological study conducted in the USA found a significant increase in the number of deaths from arteriosclerosis in the areas of high arsenic exposure [42]. Based on these, both hyperphosphatemia and high arsenic seem to be associated with CVDs like vascular calcification and atherosclerosis. Combining the current evidences, it appears that high arsenic could increase CVD outcomes in CAPD patients through inducing hyperphosphatemia considering the results in the present study. However, arsenic accumulation has not yet been attached enough importance in clinical practice. Therefore,

Table 3
The demographic characteristics and clinical biomarkers of patient according to serum arsenic levels.

Variables	Quatile of serum arsenic levels (μg/L)				*p* value
	1 (< 2.73)	2 (2.73–3.74)	3 (3.75–4.74)	4 (< 4.74)	
Age (years)	41.76 ± 11.75	42.94 ± 14.81	43.97 ± 9.50	45.17 ± 11.75	0.920
Sex (Male/Female)	9/13	9/13	10/12	8/13	0.940
BMI (kg/m^2)	20.40 (16.50–27.60)	19.85 (15.70–23.60)	21.20 (16.70–24.50)	22.60 (18.8–38.60)	0.007
overweight (yes/no)	5/17	7/15	8/14	7/14	0.787
Hypertension (yes/no)	10/12	11/11	10/12	9/12	0.836
TC (mmol/L)	4.80 ± 1.14	5.08 ± 1.13	4.67 ± 1.07	5.12 ± 0.90	0.525
TG (mmol/L)	1.40 (0.50–3.77)	1.54 (0.51–2.71)	1.56 (0.57–6.38)	1.66 (0.76–6.10)	0.371
LDL (mmol/L)	2.59 ± 0.81	2.83 ± 0.87	2.62 ± 0.84	2.80 ± 0.84	0.699
HDL (mmol/L)	1.36 ± 0.39	1.27 ± 0.38	1.23 ± 0.40	1.16 ± 0.29	0.467
Dyslipidemia (yes/no)	12/10	16/6	13/9	14/7	0.629
hs-CRP (mg/L)	0.60 (0.10 - 8.20)	0.90 (0.20 - 18.00)	2.40 (0.20 - 32.00)	2.10 (0.20 - 0.00)	0.143
Urine volume (L/d)	0.50 (0.00–2.15)	0.63 (0.00–1.25)	0.48 (0.00–1.50)	0.30 (0.00–1.50)	0.131
eGFR	3.40 (0.00 - 10.89)	1.67 (0.00 - 5.42)	1.20 (0.00 - 4.85)	0.78 (0.00 - 2.99)	< 0.001
Kt/V	2.01 ± 0.47	2.02 ± 0.36	2.06 ± 0.37	1.83 ± 0.32	0.176
Ccr (L/w/1.73 (m^2)	70.91 (31.21 - 116.32)	60.09 (42.39 - 97.15)	63.39 (39.99 - 94.99)	52.80 (37.44 - 75.23)	0.009
dialysis inadequacy (yes/no)	5/17	8/14	6/16	10/11	0.362
corrected serum calcium (mmol/L)	2.47 (2.25 - 2.79)	2.54 (2.24 - 3.32)	2.52 (1.70 - 3.06)	2.49 (2.24 - 2.76)	0.336
Serum phosphorus (mmol/L)	1.39 (0.47 - 4.14)	1.50 (0.65 - 2.98)	1.61 (1.01 - 2.69)	1.93 (0.90 - 3.47)	0.024
Hyperphosphatemia (yes/no)	4/18	7/15	8/14	12/9	0.060

Table 4
Spearman correlation of serum arsenic with related variables.

Variables	Coefficient	*p* value
BMI (kg/m^2)	0.134	0.215
TG (mmol/L)	0.194	0.073
Urine volume (mL/d)	−0.228	0.034
Kt/V	−0.160	0.141
Ccr (L/w/1.73 (m^2)	−0.328	0.003
eGFR	−0.248	0.020
Serum phosphorus (mmol/L)	0.453	< 0.001

Table 5
Associations of serum Arsenic concentration with hyperphosphatemia.

hyperphosphatemia	Per 1 μg/L of serum As	*p* value
Model 1	1.584 (1.134–2.213)	0.007
Model 2	1.764 (1.133–2.748)	0.012
Model 3	1.827 (1.145–2.913)	0.011

Model 1, adjusted for age, sex and BMI. Model 2, adjusted for Model 1, residual renal function, dialysis adequacy and inflow of dialysate. Model 3, adjusted for Model 2, serum intact parathyroid hormone and corrected serum calcium.

nephrologist should take it into account.

In addition, high arsenic was related to declining residual renal function and Ccr in this study. In accordance, arsenic exposure was associated with decreased kidney function as summarized in a meta-analysis of twenty-five articles [12]. And acute tubule interstitial nephritis was described as a clinical manifestation of acute arsenic poisoning [43]. Theoretically, arsenic accumulation also plays a role in aggravated renal function in CKD patients. Moreover, a decrease of Ccr was associated with an increased death and incidence of hospitalization as well as a decreased technique survival of dialysis [44,45]. As it is associated with decreased Ccr, high arsenic seems to bring these adverse outcomes as well. To our knowledge, this is the first report of such an association of high arsenic with Ccr, which should be verified in a larger numbers of patients.

This study has several limitations. First, the cross-sectional nature does not allow us to assess any causality of serum arsenic with hyperphosphatemia as well as declining renal function. Therefore, further prospective cohort studies should be conducted. Second, as a single-center study, it was hard to avoid the possibility of selection and survivor biases. At last, there exists the unbalanced age distribution between healthy volunteers and CAPD patients. Thus, two ways to exclude the potential effect of unbalanced age on the results of comparison: (1) No difference in arsenic levels was observed among different age group. (2) Compared to the other arsenic data of Chinese population, CAPD patients still exceed the values manifold [46]. Therefore, the comparison of arsenic between patients and control was credible.

5. Conclusion

In the present study, it was found that many CAPD patients had excessive serum level of arsenic, which suggested that arsenic accumulation did exist in this population. At the same time, high serum arsenic was associated with decreased residual renal function and low quality of dialysis. In addition, high arsenic was independently associated with hyperphosphatemia and both the former and the latter could lead to vascular calcification in general population. These provide the clues for further study on the association of arsenic with CVD outcomes in CKD patients and serum arsenic should be taken into monitoring in clinical practice.

Conflicts of interest

The authors declare no conflict of interest.

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