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Original Article

Biochemistry Section

Blood Arsenic and Cadmium Concentrations in End-Stage Renal Disease Patients who were on Maintenance Haemodialysis

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ABSTRACT

Background: In India, there is a rising burden of chronic diseases like hypertension and diabetes. It has been estimated that 25-40% of these patients are likely to develop chronic kidney disease (CKD), with a significant percentage requiring renal replacement therapy. Haemodialysis is the most common method which is used to treat advanced and permanent kidney failure. Derangements in the metabolism of several toxic and trace elements such as antimony, arsenic cadmium, molybdenum, nickel, and selenium have been reported for several decades in patients with chronically reduced renal functions. Overall, the available literature suggests that the blood levels of some elements such as cadmium, chromium, fluorine, iodine, lead, or vanadium are high in end-stage renal disease (ESRD).

Aim and Objectives: Our aim was to study the levels of blood arsenic and cadmium in ESRD patients who were on maintenance haemodialysis (MHD), and to study whether there was any relationship between their concentrations and the duration of the MHD.

Methods: The blood lead levels were determined in 50 healthy subjects with normal renal functions and in 50 patients with ESRD, who were on MHD. None of them had any history of smoking or any industrial exposure.

Results: The results of the study revealed that the blood arsenic and cadmium concentrations were higher in the ESRD patients who were on MHD than in the healthy adults. The blood arsenic and cadmium concentrations were found to increase with the duration of the MHD.

Conclusion: The mild increase in the blood arsenic and cadmium concentrations, with an increase in the duration of the MHD in the study population, may be viewed in the wider context, that a prolonged exposure to arsenic and cadmium, even at low levels, may result in renal damage and/or progression of an already existing CKD.

Key Words: Arsenic, Cadmium, End-stage renal disease, Maintenance haemodialysis

INTRODUCTION

End-stage renal disease (ESRD) represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function to a degree which was sufficient to render the patient permanently dependent on renal replacement therapy (RRT), which may be dialysis or kidney transplantation [1]. Haemodialysis (HD) can lead to the accumulation of certain toxic elements which may be deleterious and the depletion of certain trace elements, which will affect the normal functions of the body and have significant clinical implications, which include an increased risk for cancer, cardiovascular disease, immune deficiency, anaemia, renal function impairment and bone disease. Considering the magnitude of the problem of CKD/ESRD globally and the availability of RRT, it is essential that we further our knowledge about the effect of CKD and RRT/MHD on trace element homeostasis.

When the renal system is not functioning properly, the clearance of many trace elements is also affected. Several trace and toxic elements such as arsenic, cadmium, copper, germanium, lead and mercury have been implicated in the decline of the renal functions [2, 3]. The arsenic levels in the serum and blood cells correlate with a worsening kidney disease, which may be attributed to the arsenic-induced oxidative stress [4, 5]. Cadmium is a cumulative environmental toxin that accumulates in the human body after it is inhaled or absorbed in the gastrointestinal tract. A chronic exposure to cadmium can cause renal damage. The aim of this study was to assess and compare the levels of blood arsenic and cadmium in ESRD patients who were on MHD, with those of healthy adults with normal renal functions, and to check whether their concentrations changed with the duration of the MHD.

MATERIALS AND METHODS

This study was conducted on 50 normal subjects (control, group A) with normal renal functions and on 50 ESRD patients who underwent MHD (cases, group B). Both males and females who were in the age group of 40 to 60 years were included. This study was done in conformity with the Declaration of Helsinki, it was approved by the Sri Ramachandra University Institutional Ethics Committee and it was conducted at the Sri Ramachandra Medical Centre haemodialysis unit. The conventional technique of low-flux haemodialysis was employed. All the patients had been on regular bicarbonate haemodialysis for more than 6 months with the use of a polysulfone membrane dialyzer; 4 hours per session and three times per week. Those with a history of occupational exposure to heavy metals, metal intoxication and smoking and those patients who were on haemodialysis for <6 months and for causes other than ESRD, were excluded from the study. The group B subjects were further grouped, based on the duration of their MHD. Group C was ESRD patients who were on MHD for 6 to 12 months; Group D was ESRD patients who were on MHD for

12 to 24 months; and Group E was ESRD patients who were on MHD for more than 24 months. All the study subjects were interviewed regarding their full medical and occupational history, the duration on their MHD, the presence of any associated illness, their dietary and tobacco intake history, and their current medications. Blood samples were collected in sterile, royal blue topped vacutainers from the healthy individuals (Group A) and for Group B, blood was collected just before the start of the mid-week dialysis session for the estimation of serum creatinine, blood urea, arsenic and cadmium.

The blood samples were stored and analyzed in batches within one week of the sample collection. The sample analysis was done in batches by using an inductively coupled plasma-optical emission spectrophotometer. Calibration curves were plotted before running each batch. The wavelengths of the sample for the arsenic and cadmium analysis were 188.979 and 228.802. Blood urea and serum creatinine were estimated by using the automated ADVIA centaur.

RESULT

The SPSS, version 15, statistical software tool was used for the data processing. All the values were expressed as mean ± standard deviation unless it was otherwise indicated. The differences in the mean values between the Groups A and B were analyzed by using Student's t-test. The one-way analysis of variance (ANOVA) was used to compare the different groups of haemodialysis, based on the duration of the dialysis treatment (Groups C, D and E). A p-value of < 0.05 was considered as statistically significant. The clinical characteristics of the study group are shown in [Table/Fig-1]. The blood arsenic and cadmium concentrations of the groups A, B, C, D, and E are shown in [Table/Fig-2].

	GROUP A (control)	GROUP B (cases)
Age (years) (mean)	52.5	52.5
MHD duration (months)		6 to 24
Diabetes (yes/no)	Nil	50/0
Hypertension (yes/no)	Nil	45/5
Total n= (male/female)	50 (29/21))	50 (31/19)
Tobacco use	Nil	Nil
Medication % Erythropoietin Lipid lowering agents		 100 20

[Table/Fig-1]: Demographic profile.

		Urea	Creatinine	Arsenic		Cadmium	
Study Group	n	Mean ± SD (mg/dL)	Mean ± SD (mg/dL)	Mean ± SD (µg/L)	P value	Mean ± SD (µg/L)	P value
Group A	50	17.00±2.01	0.70 ± 0.15	2.30±0.00	0.00	2.025±0.45	0.000
Group B	50	78.62±5.12	8.13 ± 1.69	3.20±0.42		2.103±0.56	
Group C	14	69.06±4.01	7.08 ± 1.05	3.15±0.41	0.00	2.095±0.53	0.016
Group D	14	77.25±5.05	8.06 ± 1.72	3.20±0.32		2.104±0.55	
Group E	22	89.55±8.30	9.24 ± 2.30	3.26±0.45		2.112±0.50	

[Table/Fig-2]: Comparing the concentration of blood arsenic & cadmium level between groups A, B, C, D, E.

DISCUSSION

Deficiencies of the essential trace elements (such as zinc, copper and selenium) and excesses of the potentially harmful toxic elements (such as lead, arsenic, cadmium) are both known to cause adverse consequences in the general population [6-9]. The end-stage renal disease patients have a mortality risk which is several times higher than their counterparts who do not have any significant renal disease. This may mainly be due to their enhanced risk for cardiovascular (CV) disease and also due to their risk for infectious diseases and neoplasia [9]. Despite the spectacular improvements in RRT, the mortality remains particularly high in the dialysis patients as compared to that in the general population. Research has been focused on the impact of "mineral" (namely calcium and phosphate metabolism) abnormalities and iron store derangements on the morbidity and mortality in ESRD patients [9, 10]. The derangements in the metabolism of several toxic and trace elements such as antimony, arsenic cadmium, molybdenum, nickel, selenium and zinc have been reported for several decades, in patients with chronically reduced renal functions [9]. Overall, the available literature suggests that the blood levels of some elements such as cadmium, chromium, fluorine, iodine, lead, or vanadium are high in ESRD and that the levels of selenium, zinc or manganese are lower in HD patients, as compared to those in the controls. The magnitude of these differences was pronounced, suggesting that renal patients could have subsequent different but relevant (albeit being asymptomatic in many cases) clinical characteristics in this respect. The authors, Marcello Tonelli et al., concluded that, according to their review and meta-analysis, the average blood levels for several (potentially) biologically important trace elements were different in haemodialysis patients as compared to those in the healthy control subjects [10]. This is not necessarily surprising, as more familiar issues such as total cholesterol or blood pressure have a peculiar significance in ESRD patients as compared to that in the general population; this phenomenon is generally characterized as "inverse epidemiology" [6, 9, 11].

The blood concentrations of arsenic for Groups A, B, C, D and E are shown in [Table/Fig-2]. In the present study, the mean ± SD for normal subjects (Group A) was 2.30 ± 0.00µg/L and that for the end-stage renal disease patients who were on haemodialysis (Group B) was 3.20 ± 0.42 µg/L. The two Groups (A and B) were compared for any difference in the concentrations of arsenic by using the independent Student's t test. Thus, the arsenic concentration was observed to be higher in the haemodialysis patients than in the normal subjects, which was statistically significant with a p value of 0.000. The mean ± SD for the arsenic concentration among those who were on haemodialysis for 6 months (Group C) was 3.15 ± 0.41µg/L, for those who were on haemodialysis for 12 months (Group D) it was 3.20 ± 0.32 µg/L, and for those who were on haemodialysis for 24 months (Group E) it was 3.26 ± 0.45 µg/L. The arsenic concentrations were compared between the groups C, D and E by using ANOVA. The mean arsenic concentration was found to increase with an increase in the duration of the MHD, which was statistically significant with a p value of 0.000 [Table/Fig-2].

Arsenic exists in a number of toxic and nontoxic forms. The nontoxic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the two most common forms of organic arsenic that are found in food [12]. The foods that most commonly

contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain. The environmental sources of arsenic include groundwater, pesticides (which cause food contamination), seafood, folk or alternative remedies, and products which are used for wood preservation [13]. High drinking water arsenic levels have been associated with an increased mortality from CKD [14]. Arsenic is also a known carcinogen [15]. There is an evidence of an increased risk of bladder and skin cancers following the consumption of water with high arsenic contamination, and a risk of lung cancer following smoking [16, 17]. A causal association has been established between the exposure to environmental tobacco smoke and lung cancer, with a relative risk in the order of 1.2 [16, 18]. The arsenic levels in the serum and blood cells correlate with worsening kidney disease, with the development and progression of CKD, which are attributed to arsenic-induced oxidative stress [13]. A retrospective study which was done in Taiwan demonstrated a negative correlation between the urinary arsenic levels and it also estimated the glomerular filtration rate (eGFR), and a positive correlation between the plasma lycopene (antioxidant) level and eGFR in the same patients [19].

Van Renterghem et al., detected elevated arsenic levels in the serum of five patients with ESRD, who were undergoing treatment with haemodiafiltration [20]. De Kimpe J et al., observed more than a tenfold increase of arsenic in the serum and packed cells of chronic haemodialysis patients [21]. Mayer et al., found decreased arsenic levels in 85 patients who were suffering from renal failure and undergoing haemodialysis treatment [22]. Higher arsenic (As) concentrations have been reported in the blood and bone marrow of patients with renal failure [23, 24]. In healthy subjects, arsenic is usually excreted in urine and it is removed to a certain extent by haemodialysis; however, the removal of arsenic by haemodialysis may not be sufficient, thus leading to its accumulation in the body of haemodialysis patients [25-27]. The correlations between lower serum selenium and arsenic toxicity, i.e., skin lesions have been reported [28-30].

The magnitude of the arsenic accumulation may be related to the degree of chronic renal insufficiency. Zhang et al., determined the serum arsenic level to be 5.8±3.3 µg/L as compared to a normal value of 0.382 µg/L, for a mean serum creatinine of 4.4±3.3 mg/dL. In addition, higher arsenic concentrations were found in the serum and the packed cells of patients who had a greater degree of chronic renal insufficiency [30]. A recent study demonstrated that the arsenic level in hair was significantly higher in the haemodialysis patients, as compared to that in healthy subjects [31].

In the present study, the mean ± SD for serum cadmium in normal subjects (Group A) was 2.025 ± 0.45 µg/L and for the ESRD patients who were on MHD (group B), it was 2.103 ± 0.56 µg/L. The two Groups (A and B) were compared for any difference in the serum concentrations of cadmium. The serum cadmium was higher in hemodialysis patients than in the normal subjects, with a p value of 0.000, which was statistically significant. The mean ± SD for the serum concentration of cadmium among those who were on haemodialysis for 6 months (Group C) was 2.095 ±0.53 µg/L, for those who were on haemodialysis for 12 months (Group D) it was 2.104 ± 0.55 µg/L, and for those who were on haemodialysis for 24 months (Group E) it was 2.112 ± 0.50 µg/L. The cadmium concentration level was compared between the Groups C, D and E. The mean cadmium concentration was found to increase with an increase in the duration of the MHD, which was statistically significant with a p value of 0.000 [Table/Fig-2].

Michael Krachler et al., who determined toxic and trace elements in the plasma samples of 68 haemodialysis patients by inductively coupled plasma mass spectrometry, had demonstrated a higher concentration of cadmium than the high limits for healthy adults [32]. D Van Renterghem et al., had demonstrated elevated concentrations of cadmium in the sera of five patients who were on haemodiafiltration [31]. Bing Chen et al., who studied the whole blood and serum samples of stable Chinese chronic renal failure patients (n=81), haemodialysis patients (n=135), posttransplant patients (n=60) and subjects with normal renal functions (n=42), found a high prevalence of elevated cadmium levels in the haemodialysis patients [33]. The blood cadmium level in the haemodialysis patients was also significantly higher as compared to that in the subjects with stable chronic renal failure ($p<0.01$). As compared to those in the subjects with normal renal functions, the overall cadmium levels were higher in the post-transplant patients, irrespective of the degree of renal failure; $p<0.01$). Thus, Bing Chen et al., found a positive correlation between the blood cadmium levels and the time on dialysis. Such observations were also been reported by Skarupskiene et al., [33, 34]. Sharupskiene et al had also reported elevated blood cadmium levels in haemodialysis patients [34]. Su-Hui Lee et al., reported elevated cadmium levels in haemodialysis patients; 333 (73%) out of the 456 haemodialysis patients had high cadmium levels (>2.5 µg/L), and the mean concentration was 3.32 ± 1.49 µg/L [35].

A chronic exposure to cadmium can cause accumulated renal damage [36]. Navas-Acien et al., reported in the large 1999-2006 NHANES adult population, which was a representative sample of the general US adult population, the existence of an association between renal dysfunction and the blood cadmium levels [37]. Pietro Manuel Ferraro et al., also confirmed, in the subset of the same NHANES population, who had urinary cadmium data, that blood cadmium was associated with impaired renal functions and proteinuria [38]. It seems that the chronic accumulation of cadmium in the renal cortex is responsible for the nephrotoxicity [39]. A study on the subpopulation of the NHANES population (1999-2004) has been published, which discloses the association of blood cadmium, but not urinary cadmium, with a modest elevation in the blood pressure levels [40]. Besides industrial pollution, the other sources of cadmium exposure are cigarette smoke, ingestion of polluted vegetables and the ambient air in urban-industrialized areas [40, 41]. Kazi et al., reported that the concentrations of lead, cadmium, nickel and aluminium in the hair was higher in haemodialysis patients, who were all smokers [42]. Akinobu Ochi et al., found that the cadmium concentrations correlated significantly and positively with the durations of the haemodialysis [30]. The higher cadmium levels in the haemodialysis patients may be due to a decreased excretion of cadmium in the body burden as compared to those in the normal controls [34].

In conclusion, according to the present study, the blood arsenic and cadmium concentrations were increased in the maintenance haemodialysis patients. The increase in blood arsenic and cadmium with an increase in the duration of the MHD, might infer a causal relationship and this may be due to a decreased excretion as compared to those in the normal controls. However, further studies are recommended on a large number of ESRD patients who are on MHD, to elucidate this relationship.

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