Journal of Nephrology and Kidney Diseases
Volume 5 | Issue 1
ISSN: 2767-9225

Research Article Open Access

Maintenance Hemodialysis Exacerbate Aluminum and Arsenic Toxicity in Chronic Kidney Disease Patients

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Citation: Abdorrahim Absalan, Hamid Momeni, Ashraf Salehi, Mohsen Karimi (2024) Maintenance Hemodialysis Exacerbate Aluminum and Arsenic Toxicity in Chronic Kidney Disease Patients, J Nephrol Kidney Dis 5(1): 104

Received Date: April 10, 2024 **Accepted Date:** May 10, 2024 **Published Date:** May 14, 2024

Abstract

Background: Maintenance hemodialysis (MHD) is the most effective interventional therapy for patients with chronic kidney disease (CKD). Our aim was to investigate the serum levels of aluminum (Al) and arsenic (As) in CKD patients.

Methods: A total of 29 CKD patients receiving MHD were surveyed for selected biochemical, and dialysis quality indices. Serum Al and As levels were measured before and after MHD. Statistical analyses included independent samples t-test or Mann-Whitney, Pearson, or Spearman's rho correlations.

Results: All patients (n=29; 100%) had detectable levels of arsenicosis (cut-off=1µg/L) both before hemodialysis (BFH) (mean±SD=7.58±1.99µg/L) and after hemodialysis (AFH) (mean±SD=8.61±1.82µg/L). Al toxicity was detected (cut-off=10µg/L) in 24 (82.8%) individuals BFH (mean±SD=25.6±15.61µg/L) and in 28 (96.6%) patients AFH (mean±SD=30.08±15.18µg/L). The mean age of the patients was 60.41±15.30 years (11 females and 18 males). Al BFH was positively correlated with its AFH level (R=0.765; p=0.000), but this was not true for As (R=0.296; p=0.167). Serum phosphate was negatively correlated with Al BFH (R=-0.547; p=0.008). MHD was not efficient in eliminating Al and As from blood circulation when we compared their concentrations in inlet and outlet dialysis apparatus samples.

Conclusions: Our findings suggest that CKD patients undergoing MHD are at risk for overt Al and As toxicity, which highlights the importance of regularly monitoring toxic elements in these patients. Treatment with chelators and redefinition of cut-off points for Al and As blood levels in hemodialysis patients may be necessary.

Keywords: Chronic Kidney Disease; Trace Elements; Maintenance Hemodialysis; Dialysis Efficacy

Abbreviations: Adenosine triphosphate (ATP), Alkaline phosphatase (ALP), Arsenic (As), As. B: As before dialysis, As.A: As after dialysis, Aluminum (Al), Al.B: Al before dialysis, Al.A: Al after dialysis, blood urea nitrogen (BUN), body mass index (BMI), calcium (Ca), Chronic Kidney Disease (CKD), deoxyribonucleic acid (DNA), dialysis adequacy (Kt/V), en-

zyme-linked immunosorbent assay (ELISA), inductively coupled plasma-optical emission spectrometers (ICP-OES), iron (Fe), Liters (L), natural logarithm (Ln), parathormone hormone (PTH), phosphorus (Phos), post-dialysis BUN (Post BUN) (mg/dL), pre-dialysis BUN (Pre BUN), standard deviation (SD); standard error (se); total iron binding capacity (TIBC), volume of removed ultrafiltrate/ultrafiltration (UF)

Introduction

Maintenance hemodialysis (MHD) is an effective intervention for treating patients with CKD [1]. In CKD patients, the ability to excrete excess metabolites such as urea, creatinine, uric acid, toxic elements, and ions is lost, leading to serious consequences of the toxicity of these substances [2-4].

Aluminum (Al) enters the body through inhalation, ingestion, and drug consumption. It accumulates in various bodily fluids and tissues, including urine, bile, feces, sweat, hair, nails, semen, milk, and sebum [5, 6]. Al toxicity induces oxidative stress, lipid peroxidation, immunosuppression, and enzyme blockade or reactivation [7]. Al impairs metabolic pathways, such as glycolysis and the Krebs cycle, and reduces cell proliferation and differentiation through DNA damage and other genotoxic effects. By altering the absorption and uptake of minerals, Al disrupts the metabolism of essential ions, including iron, phosphate, calcium, zinc, and copper [8]. Al toxicity is also associated with hormonal disturbances, renal osteodystrophy, a common complication of CKD, which leads to bone demineralization and release of essential elements into circulation [9-11].

Acute arsenic (As) poisoning typically does not have specific acute symptoms. Chronic As poisoning can be associated with general or specific symptoms such as colitis, weakness, weight loss, hair loss, and anorexia. Organ-specific manifestations of As poisoning can affect the nervous, cardiovascular, circulatory, hepatic, and renal systems. High levels of As can damage DNA and cause genetic and epigenetic alterations, leading to inflammatory responses and tumorigenesis. As poisoning has been linked to skin, renal, hepatic, bladder, and lung cancers [12, 13]. Renal dysfunction and prolonged MHD treatment can lead to the retention of metabolites, end-products, and elements in various organs. Acute and chronic poisoning is a critical issue that requires evaluation in clinical settings and during medical visits [2, 14-19].

Patients undergoing MHD experience a chronic illness and a diminished state of well-being. The objective of our study was to investigate a potential underlying cause of this condition, specifically the accumulation of toxic metals such as Al and As in vital tissues. We believe that the toxicity of Al and as in patients with CKD who receive MHD treatment is a neglected health issue that affects various metabolic and physiological processes. We hypothesize that metabolic and physiological alterations can manifest as acute responses or insidious/chronic presentations, leading to permanent illness or morbidity. By emphasizing the significance of measuring Al and As levels in MHD patients, it is recommended that therapeutic guidelines include regular assessment of heavy metal concentrations in these individuals. Therefore, the aim of the present study is to measure Al and As serum levels in MHD patients referred to our hospital and to explore any potential association between these elements and selected routine laboratory and clinical indices.

Material and Methods

A total of 29 CKD participated (11 women and 18 men) who were undergoing MHD treatment at our university hospital in Khomein, located in the central part of Iran. We obtained consent from all patients whose data and samples were used in the study. In our hospital, patients underwent MHD two to three times a week. The only exclusion criterion was a patient's refusal to participate in the study, as no interventions were performed on MHD patients. Blood samples were collected from each patient within one day of admission, both before and after dialysis. Serum samples were separated and stored at -21°C until the measurement day. We only assessed trace elements in clinical samples routinely collected for blood chemistry tests. This study was reviewed and approved by the ethical committee of Khomein University of Medical Sciences (Registration code IR.KHOME-

IN.REC.1398.001).

In our hospital, routine monthly tests for MHD patients included measuring serum levels of ALP, Ca, Phos, Fe, TIBC, and PTH. In addition to the patients' BMI, we assessed blood chemistry tests using an automated biochemistry analyzer (BT 3500; Biotecnica Instruments S.p.A.; Roma RM, Italy) and Pars Azmun kits (Pars Azmun Co; Iran). Our immunoassay staff measured PTH blood levels using an ELISA kit (Monobind Inc; Lake Forest, CA, USA).

To assess the quality of MHD, we surveyed UF and MHD adequacy (Kt/V). To calculate Kt/V, we used an online calculator based on the Daugirdas formula, as follows: Kt/V = -ln((Post dialysis BUN/Pre dialysis BUN) - (0.008*Dialysis duration)) + (4-3.5*(Post dialysis BUN/Pre dialysis BUN)) *(UF/post dialysis Weight). The target value for Kt/V in MHD patients is ≥1.3, as recommended by the United States National Kidney Foundation. The delivered dose is at least 1.2, which we considered as the minimum value in our study. In the Daugirdas formula, the dialysis clearance of urea (K), dialysis time (t), and the volume of distribution of urea (V) are roughly equal to the total body water of the patient [20].

We determined the serum levels of Al (Wavelength: 396.152 nm) and As (Wavelength: 188.98 nm) using an inductively coupled plasma-optical emission spectrometer instrument (720/730-ES; ICP-OES; Varian Inc; SpectraLab Scientific Inc; Canada). To clarify excretion of Al and As through MHD, we compared the Al and As contents in three samples of inlet dialysis water and outlet samples from all patients 30 minutes after the beginning of MHD.

Statistical Analysis

Statistical analysis included descriptive statistics, independent samples t-tests, and Mann–Whitney U tests to compare mean±SD between two groups depending on the normal distribution status of the data. We also used Pearson or Spearman's rho correlations to determine association between the studied variables. P-values less than 0.05 (95% confidence interval) were considered significant.

Results

The mean age±SD for women (n= 11) and men (n= 18) was 61.91±15.82 and 59.50± 15.37 (p= 0.692), respectively. The mean±SD dialysis year was 3.52±2.65 (range: 1-12 years). Of the 29 participants, 24 (82.8%) had toxic levels of serum Al before MHD. Al blood levels under 10μg/L and As blood levels under 1μg/L were considered reference values in the non-CKD population.[21] However, 28 (96.6%) patients had toxic levels of serum Al after MHD. We defined arsenic toxicity in the studied patients when As serum levels exceeded 1μg/L. Thus, all studied patients (100%) had As toxicity before and after MHD. There were no significant differences between males and females before and after dialysis for Al and As serum levels (Table 1; Part A). Diabetes and hypertension were the most frequent comorbid conditions (15 out of 29 patients; 51.7%) for CKD outcomes in MHD patients (Table 1; Part B).

Of the 28 participants, seven patients had a smoking habit or a history of smoking, and there was no significant difference between smokers and non-smokers for serum levels of Al or As before and after dialysis. In non-smokers, Al mean±SD before dialysis was equal to 33.20±15.32 (μg/L) and in smokers was equal to 20.74±10.92 (μg/L) (p= 0.55). In non-smokers, Al mean±SD after dialysis was equal to 26.65±16.97 (μg/L) and in smokers was equal to 22.47±11.06 (μg/L) (p= 0.058). As mean±SD before dialysis in non-smokers= 7.38±2.07 (μg/L) and in smokers= 8.32±1.62 (μg/L) (p= 0.312). In non-smokers, As mean±SD after dialysis was equal to 8.65±1.95 (μg/L) and in smokers was equal to 8.51±1.42 (μg/L) (p= 0.878). One patient expired at the time of data gathering, and we had no information about his smoking history. After MHD, the serum concentration of Al significantly increased (p= 0.033; Figure 1; A). In both sessions, before and after dialysis, the mean serum Al was in the toxic range; 82.8% and 96.6% of individuals had toxic (>20μg/L) Al serum levels, respectively. Similarly, the serum level of As increased after MHD compared to before dialysis (p= 0.025; Figure 1; B). Serum levels of Al before MHD were positively correlated with Al after MHD (R= 0.765; p= 0.000) and

with ALP (R= 0.457; p= 0.037). After-MHD Al was positively correlated with TIBC (R= 0.483; p=0.027). The serum levels of As before MHD were not significantly correlated with its concentrations after MHD (R= 0.296; p= 0.167). The level of phosphorus was negatively correlated with Al before dialysis (R= -0.547; p= 0.008). The As serum level after MHD was significantly associated with UF (R= 0.577; p= 0.003). The other associations between before/after dialysis As serum levels with other studied variables were not significant (Figure 2).

Table 1: Part A: Comparison of mean±SD dialysis years, serum levels of Al and As, before and after dialysis among male and female patients; there was no significant difference between male and female patients considering serum level of Al and As. **Part B**: Frequency of comorbid conditions among studied CKD patients; the most frequent comorbid conditions were diabetes and hypertension.

A		**Mean±SD**	***p*-value**
	Years of dialysis	F= 3.55±3.3	0.965
		M= 3.50±2.28	
	Al before dialysis (µg/L)	F= 21.46±11.49	0.267
		M= 28.29±17.59	
	Al after dialysis (µg/L)	F= 25.68±11.01	0.223
		M= 32.94±17.07	
	As before dialysis (µg/L)	F= 8.01±2.01	0.375
		M= 7.31±1.99	
	As after dialysis (µg/L)	F= 8.66±2.11	0.917
		M= 8.588±1.68	
	Comorbid conditions		**n (%)**
B	**Diabetes Mellitus**		7 (24.1)
	Hypertension		9 (31.0)
	Diabetes + Hypertension		8 (27.6)
	Rectal caner		1 (3.4)
	Bardet-Biedl syndrome		1 (3.4)
	Gallbladder cancer		1 (3.4)
	Polycystic kidney disease		1 (3.4)
	Glomerulonephritis		1 (3.4)
	Total		29 (100)

Al: aluminum, As: Arsenic, F: female, M: Male, CKD: chronic kidney disease

Table 2 shows the mean±SD of age, dialysis years, BMI, selected biochemical and dialysis quality determinants (UF and KT/V). Routine laboratory tests belong to the before-dialysis session, but UF and KT/V were for the after-dialysis session. All normal ranges belong to the adult age group. Mean±SD of ALP, Phos, Fe, and PTH were higher than the normal limits. Nevertheless, UF volume was lower than the normal range. Dialysis adequacy was not good in our population (Kt/V mean±SD= 0.95±0.26; considered favorable when Kt/V≥ 1.2). Mean±SD of other studied variables were within normal ranges.

Table 2: Mean±SD of age, dialysis years, BMI, selected biochemical, and dialysis quality determinants (UF and KT/V) of studied patients. All measurements belong to the before MHD. The Al and As serum levels before and after MHD were reported for comparison with their reference ranges.

Variables	N	Minimum	Maximum	Mean±SD	Reference range*	than normal range
Age (years)	29	31	88	60.41±15.30	NA	NA
Dialysis years	29	1	12	3.52±2.65	NA	NA
BMI (Kg/m2)	29	16.23	36.48	25.64±4.43	18.5 to 24.9	↑
Al before MHD (µg/L)	28	2.80	69.7	25.6±15.61	<10	↑
Al after MHD (µg/L)	28	9.10	79.3	30.08±15.18	<10	↑
As before MHD (µg/L)	28	1.56	10.6	7.58±1.99	<1	↑
As after MHD (µg/L)	28	5.68	13.58	8.61±1.82	<1	↑
ALP (IU/L)	22	137.0	945	353.81±214.63	20 to 147	↑
Ca (mg/dL)	23	7.40	13.9	9.68±1.88	8.5 to 10.2	Nrm
Phosphorus (mg/dL)	23	2.40	7.2	5.28±1.36	2.8 to 4.5	↑
Fe (µg/dL)	22	30.0	748	285.36±219.18	60 to 170	↑
TIBC (µg/dL)	22	160.0	690	313.09±118.06	240 to 450	Nrm
Albumin (g/dL)	22	2.50	5.3	3.62±0.78	3.4 to 5.4	Nrm
Ferritin (µg/L)	21	27.80	545.6	231.89±171.89	11 to 336	Nrm
PTH (pg/mL)	23	4.70	900	181.72±200.36	10 to 55	↑↑
UF (mL)	25	583.33	4566.67	2459.35±953.14	--	Nrm
Kt/V (dialysis adequacy) (Ratio)	24	0 .55	1.57	0.95±0.26	≥ 1.2	↓

BMI: body mass index; MHD: maintenance hemodialysis; UF: Ultrafiltration volume, i.e. the liquid volume taken from the patient body during dialysis; NA: not applicable; Nrm: in normal range; ↓ lower than reference range; ↑higher than reference range

*Normal ranges are not restricted to patient's sex and adult age is of interest.

We estimated the correlation coefficients between all parametric variables in this study. As shown in Figure 3, most coefficients were insignificant except in some cases. ALP was correlated with dialysis years and PTH. Fe was significantly correlated with Albumin and ferritin. Ferritin was also correlated with dialysis years. The KT/V index was correlated with TIBC. UF was correlated with BMI and As serum levels after dialysis. Kt/V was only correlated with TIBC (Figure 2).

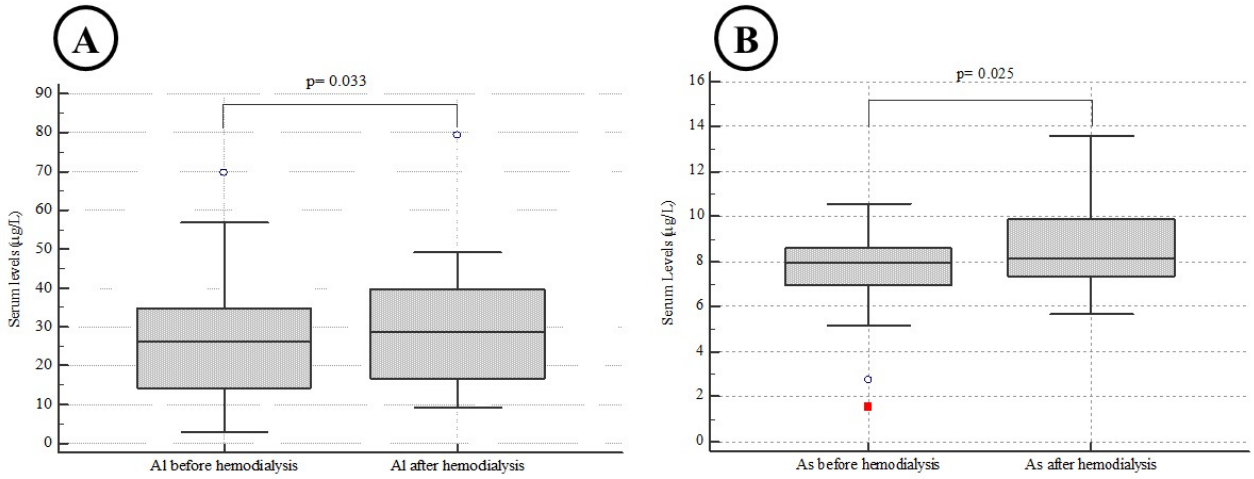

Figure 1: Comparison of serum levels of Al and As among dialysis patients. **Part A:** Al serum levels before dialysis (Mean±SD= 25.61±15.61µg/L; range= 2.8-69.7µg/L) were increased significantly after dialysis (Mean±SD= 30.1±15.19µg/L; range= 9.1-79.3µg/L) (p= 0.033). **Part B:** As serum levels before dialysis (Mean±SD= 7.58±1.99µg/L; range= 1.56-10.6µg/L) were increased significantly after dialysis (Mean±SD= 8.62±1.83µg/L; range= 5.68-13.58µg/L) (p= 0.025).

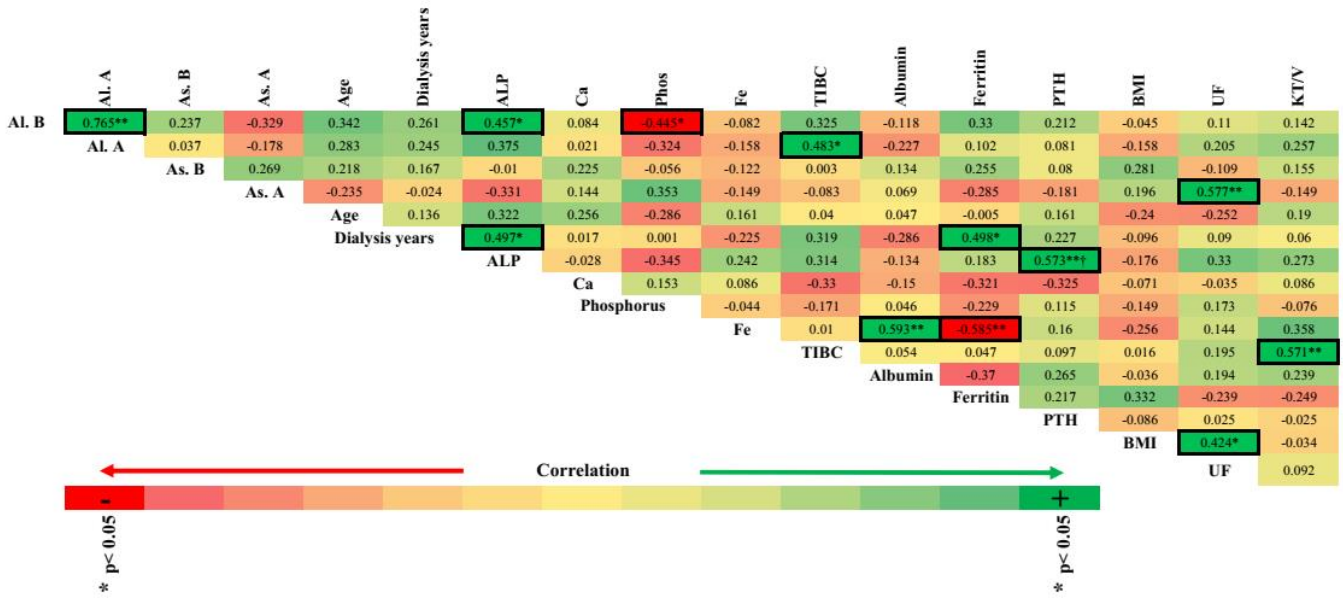

Figure 2: Heat map of correlation estimations (R-values) between study variables to evaluate the dependence of selected paraclinical indices; significant results are marked with the asterisks and thick borders.

Removal of Al and As From the Body by MHD Ultrafiltration

Nine patient samples had measurable concentrations of As in the MHD outlets. The mean±SD of As concentration in the three inlet samples was 0.7±1.21μg/L, and in the outlet samples was 2.67±1.17μg/L (p= 0.032; n=9). This finding shows that As is removed via MHD but not efficiently. These two numbers indicate that the concentration of As in the outlet water in the 30th minute of the MHD session is 1.97 units (3.8 times) higher than in the inlet water. Furthermore, the mean±SD of serum As levels were 7.58±1.99μg/L before MHD and 8.61±1.82μg/L after MHD and subsequent hemoconcentration. The mean±SD of Al serum levels before and after MHD (and hemoconcentration) were 25.6±15.61μg/L and 30.08±15.18μg/L, respectively. Al concentrations in three inlet water samples were unmeasurable, whereas the mean±SD of 13 outlet water samples had Al mean±SD= 4.7±3.92μg/L. This finding shows that Al is removed via MHD, but not efficiently (average 4.7μg/L in our study and minute 30 of MHD session).

Discussion

We evaluated Al and As serum levels in MHD patients referred to a university hospital as described in the materials and methods. Based on expected values, most MHD patients had Al toxicity and arsenicosis. Similar to our previous experiences,[22, 23] performing MHD increased serum concentrations of heavy metals (Al and As in the present study). We believe this finding is due to hemoconcentration and excess water elimination from the body during a dialysis session. Generally, water elimination results in an increase in the concentration of the most soluble analytes and metals.

Rahimzadeh et al. (2022) stated that Al levels are generally lower than 10μ/L in normal individuals and lower than 60μ/L in dialysis patients. They also noted that critical Al toxicity occurs when its levels exceed 100μ/L [21]. In our investigation, mean levels of Al were about 26μg/L before MHD and 31μg/L after dialysis. We should note that critical values are only for emergent situations, not monitoring or maintenance circumstances. Regardless, there is a fundamental question: do the metabolism, toxic effects, and regulatory pathways generally differ between individuals with normal kidney function and those with CKD? The answer is no. Both groups have similar circumstances against Al and As toxic levels. When the adverse effects of Al or As do not appear until critical value manifestation, this relates to the compensation mechanisms, compatibility, or tolerability of the tissues that result in morbidity or chronic sickness. We believe that the definition of cut-off points of Al and As toxicity in MHD patients remains a serious pitfall. As a result, new cut-off points for Al and As serum levels are necessary for MHD patients. These cut-off points should be determined based on the precise side effects of Al and As overloads in MHD patients compared to the non-CKD population, not on acute clinical outcomes. Carbonara et al. (2022) evaluated 260 CKD patients and reported that osteoporosis (77 patients) and Al accumulation (65 patients) are frequent findings in these patients. They detected osteitis fibrosa, mixed uremic osteodystrophy, a dynamic bone disease, and osteomalacia in 85, 43, 27, and 10 patients, respectively. Hospitalization and death rates were influenced by the type of renal osteodystrophy [10]. Carbonara et al.'s findings confirm our statement about the existence of not well-being status in CKD patients, which could be due to the chronic toxicity of the heavy metals.

The Gender of the Patient Does Not Affect the Serum Levels of Al and As

Some reports have emphasized that patient gender is a determinant of As metabolism, at least among chronically exposed subjects [24]. Using an animal model, researchers linked the effect of patient gender on As metabolism to different epigenetic regulations that are distinguishable between males and females [25]. In the present study, male and female patients did not have significant differences in Al and As serum levels, which means that gender does not cause significant changes in Al and As metabolism in MHD patients.

Hemodialysis is Not Efficient in Al and As Elimination from the Body

In most cases, Al and As serum levels remained in the toxic range after MHD. Before- and after-MHD Al (significant) and as (non-significant) levels were positively correlated. These findings suggest that MHD intervention raises Al and as blood concentra-

tions. We evaluated the presence of Al and As in MHD inlet and outlet waters but efficient removal of them was not demonstrable. Different types of Al toxicity manifest with specific features as addressed in Coburn J report [26]. In our clinical experience, MHD patients suffer from poor mood, ill-being, and morbidity. We believe that such illnesses and maladies are worsened by essential element insufficiency and toxic metal overload. Both events disturb cell metabolism, organ function, and health quality.

Although Cigarettes Contain High Levels of Al and As, Smokers Did Not Have Higher Serum Levels Than Non-Smokers

Al concentrations in a cigarette range from 699-1200μg/g. However, in non-Al-exposed individuals, the mean plasma level is reported to be 4.2μg/L. Age and smoking habits do not influence plasma levels of Al [27, 28]. Tobacco products consist of inorganic arsenic species ranging from 144 to 3914μg/kg [29]. Nearly 0.8 to 2.4μg of inorganic arsenic is present in 20 cigarettes, and 40% of these contents are deposited in the lungs during smoking [30]. There were only 7 smokers in our study, but they did not have significantly different Al and As serum levels than non-smokers, probably due to the prominent toxicity observed in all patients. We suggest that chronic MHD causes a prolonged accumulation of toxic elements such as As and Al in various tissues. Al and As are eliminated from the body through the urinary tract [21]. Therefore, we suggest that the rate of elimination process is reduced in CKD patients. Since our patients have Al and As overload or toxicity, and MHD has not been efficient in removing these elements from circulation, treatment with chelators such as deferoxamine is preferable.

Al and As Correlations with Laboratory Indices in the Studied Population

Reverse or direct correlations between Al or As and biochemical indices could be fortuitous or factual. Serum Al levels were negatively correlated with Phos before MHD; this could be due to metabolic interventions or the effect of excess Al on Phos cell membrane transporters and channels. We believe that the negative correlation between Al and Phos before MHD shows a direct effect of Al overload on Phos metabolism and contents.

Although As is a water-insoluble element, its compounds could be readily soluble [31]. We expected As serum levels to be low in MHD patients, at least after a MHD session. However, As levels remained toxic in most studied patients. Therefore, MHD is not a perfect intervention for removing excess As from blood circulation. As serum levels before MHD were also well correlated with UF volume. This effect belongs to the hemoconcentration event after decreasing the water volume from the body. Considering CKD patients could not efficiently excrete toxic substances in the urine, we expect As and Al to be the silent causes of morbidity or even mortality in MHD patients. However, this claim needs more evidence on heavy metal toxicity in CKD individuals. Metabolic disturbances may not be differentially diagnosed in clinical settings due to the complexity of the pathways or the covering of tiny effects by the compensating process. Nonetheless, we suggest that the toxic impact of heavy metals has a cumulating behavior in a timely and chronic manner in CKD patients; i.e., it is not acute in MHD patients.

Dialysis Adequacy

In this study, MHD intervention was not adequate in most cases. In addition, toxic metals were not adequately eliminated from the circulation during MHD, and their concentration even increased. Therefore, we suggest that inadequate dialysis can exacerbate Al and as retention and toxicity in the bodies of CKD patients. Al and as overloads can severely affect metabolic pathways in MHD patients; however, demonstrating these effects requires animal or ex vivo experiments. Igbokwe (2019) and colleagues have reviewed and described different aspects of Al toxicity in metabolic pathways [8]. Al accumulates in bone (60%), lung (25%), hair, nail, semen, liver, brain, milk, and sebum. The most toxic effects of Al include oxidative stress and lipid peroxidation, inhibition of cell proliferation, apoptosis induction, impairment of metabolic pathways, DNA damage, interference with essential element uptake or absorption, and disruption of endocrine function [8, 21]. Figure 3 briefs current study in a view, and implying that CKD patients whom undergoing maintenance dialysis need concurrent treatments and follow up. However, redefinition of cut-off values for serum levels of toxic metals in dialysis patients seems to be required for a more sensitive therapeutic decision.

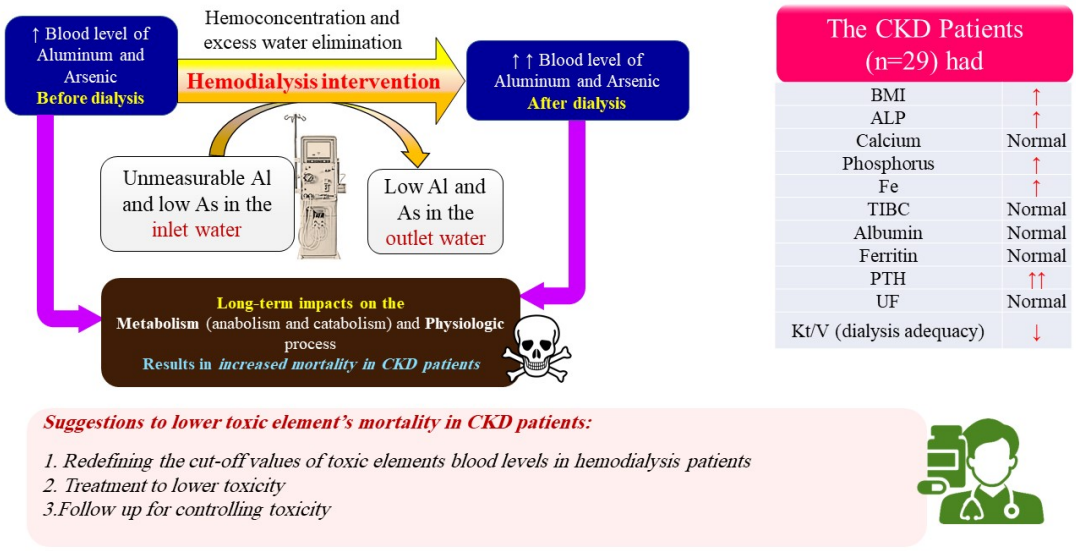

Figure 3: Graphical representation of the maintenance dialysis impact on the aluminum and arsenic blood levels in chronic kidney disease patients

Conclusion

We have reported overt Al and As toxicity among CKD patients exacerbated by the MHD intervention. Based on our results, we infer that CKD leads to kidney insufficiency in excreting excess toxic metabolites and Al or As. Therefore, clinicians should monitor and prevent toxicant overload in MHD patients instead of waiting for overt poisoning before requiring critical services or emergency interventions. We suggest that physicians pinpoint adjuvant and concomitant therapy in therapeutic guidelines for alleviating the adverse effects of toxic element overload in CKD patients. We think that toxic element overload is associated with the morbidity of CKD patients. As epigenetic regulation is a determinative factor in As metabolism, we suggest evaluating epigenetic changes in chronic MHD patients to identify any suspected unsatisfying changes. However, demonstrating such an association requires basic science studies.

Study limitations

We evaluated all available CKD patients in our town, including 29 CKD individuals referring to the hemodialysis department for maintenance dialysis. We hypothesize that repeating this study with a higher sample size in other centers may demonstrate a significant impact of toxic elements on the mortality of CKD patients.

The inclusion of a healthy control group and the comparison of Al and As serum levels between the control group and patients undergoing MHD proved to be a valuable design choice for our study. However, instead of employing a traditional case-control design, we opted for an interventional design to evaluate the overall impact of dialysis on the primary study variables. One potential source of confounding bias was the duration of dialysis. In order to mitigate this effect, we collected samples from all patients 30 minutes after the initiation of dialysis. Other confounding factors included the nutritional regimen and daily cigarette consumption. Furthermore, laboratory indices of patients could be influenced by the severity of inflammation, as well as the types of medications, additional therapeutic interventions, and complementary medicine utilized by each patient. However, controlling or matching these variables in a population with a limited sample size proved to be challenging. It is important to note that all dialysis patients in our city who consented to participate were included in this study. To address these confounding biases, we employed a robust strategy of comparing the levels of the primary study variables before and after dialysis, as implemented in our study.

Acknowledgment

We express our special thanks to the staff of the hemodialysis department of Emam-Khomeini University Hospital of Khomein City for their enthusiastic collaboration in gathering the samples and data.

Conflict Of Interest

The authors declare there is no conflict of interest in publishing this study.

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