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Internal Medicine Section

Trace Elements in Chronic Haemodialysis Patients and Healthy Individuals-A Comparative Study

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ABSTRACT

Introduction: End Stage Renal Disease (ESRD) patients despite receiving adequate Haemodialysis (HD) develop significant risk of Cardiovascular Disease (CVD). Abnormality in levels of trace elements may potentiate vascular injury by producing sustained inflammation and endothelial dysfunction. Hence, the present study was undertaken to evaluate the levels of trace elements in patients receiving HD.

Aim: To study the blood levels of arsenic, cadmium, mercury, lead, chromium, barium, cobalt, caesium and selenium among ESRD patients undergoing HD and compare it with healthy individuals.

Materials and Methods: It was a cross-sectional, comparative study done in a tertiary care center. About 40 established ESRD patients aged above 18 years, belonging to both sexes, undergoing chronic HD for more than six months were enrolled as Group A (Cases). Patients who had history of smoking and occupational exposure to heavy metals were excluded from the study. About 40 age and sex matched apparently healthy individuals attending health check-up were enrolled as Group B (Controls). Participants of this group had normal e-GFR by Modification of Diet in Renal Disease (MDRD) equation.

About 5ml of fasting venous blood sample was obtained from both groups and analyzed for trace elements. Chi-square/Fisher's-exact test was used for comparing ratios. A p-value of <0.05 was considered statistically significant.

Results: In the present study, the mean blood levels of arsenic, cadmium, chromium and cobalt was found to be significantly higher in Group A as compared to Group B with all these parameters attaining a p-value of <0.001. Similarly, the mean blood levels of lead and caesium was high in Group A with a p-value of 0.001 each. The blood levels of mercury and barium did not vary significantly between both the groups with p=0.656 and 0.096 respectively. The blood levels of anti-oxidant selenium was lower in Group A, but did not attain statistical significance (p=0.217).

Conclusion: The mean blood levels of toxic trace elements were significantly elevated with a simultaneous reduction in essential trace elements in patients receiving HD, which probably may contribute to an increase in CVD.

Keywords: Endothelial dysfunction, Inflammation, Toxic elements

INTRODUCTION

Haemodialysis (HD) remains an important form of Renal Replacement Therapy (RRT) in End Stage Renal Disease (ESRD) patients. Though, it is traditionally considered to be a bridging therapy for renal transplantation, in developing countries like India, it still remains a primary modality of treatment due to growing numbers of ESRD patients and lack of adequate donors and transplantation centers.

Though accelerated hypertension, atherosclerosis, lipid abnormality, inflammation and oxidative stress have been found to play a major role in progression of vascular events and potentially increase the cardiovascular risk, there are untouched trace element levels which may also play a vital role in their overall survival. A deficiency of essential trace elements or an excess of toxic trace elements can affect health [1]. ESRD is usually associated with a state of oxidative stress, antioxidant depletion and an imbalance of some trace elements such as copper, zinc and selenium concentrations in the body [2]. Hence, the present study was undertaken to delineate the blood levels of arsenic, cadmium, mercury, lead, chromium, barium, cobalt, caesium and selenium among ESRD patients undergoing hemodialysis. Even after an extensive literature search we could not find any previously published data from India that have evaluated all these elements in a single study.

On the same sample population, the serum lipid profile and cardiovascular risk biomarkers have been analysed and the results of which are under the process of publication. Also, platelet parameters were studied on the same sample size and the study is published elsewhere.

MATERIALS AND METHODS

This cross-sectional and comparative study was done in a tertiary care hospital between October 2014 and October 2015. The present study was done on 80 subjects, which included both male and female subjects in the age group of 30-60years.

Group A (Cases) included 40 patients with established ESRD undergoing intermittent HD for more than six months at Mahatma Gandhi Medical College and Research Institute (MGMCRI), Puducherry, India. All patients were undergoing three sessions of HD a week with each lasting for 4 hours using bicarbonate buffer with a blood flow of 250ml/min and dialysate flow of 500ml/min, with 1.6m^2 surface area hollow fiber polysulfone membrane dialyzer. Subjects with history of occupational exposure to heavy metals were excluded from the study. Analysis of Reverse Osmosis (RO) water was done for heavy metals and they were found to be normal.

Group B (Controls) included 40 apparently healthy adult age and sex matched male and female volunteers with normal renal function who were employees of MGMCRI Hospital, Puducherry, India, and individuals who attended health check-ups.

This study was done in conformity with the Declaration of Helsinki and it was approved by Institutional Human Ethics Committee of Mahatma Gandhi Medical College and Research Institute, Puducherry, India.

All the participants were interviewed and a full medical, substance abuse and occupational history (industrial exposure to any of the heavy metals) were taken. The duration of maintenance HD, presence of any co-morbidities, dietary history and current medication history was taken from participants of Group A.

About 5ml of blood was collected to assess arsenic, chromium, cobalt, lead, barium, caesium, cadmium, mercury and selenium levels using mass spectrometry in both the groups. The reference range was obtained after considering 95% population as cut-off.

STATISTICAL ANALYSIS

The SPSS, version 19 software tool was used for the data processing. All the values were expressed as mean ± standard deviation unless otherwise indicated. The differences in the mean values between the groups were analyzed by using the Student's t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

In the present study we had 80 participants. The gender distribution was predominantly male in both groups. There was a significant difference in Body Mass Index (BMI), Blood Urea Nitrogen (BUN), serum creatinine, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) among Group A and Group B [Table/Fig-1]. Subjects in Group A had higher mean levels of arsenic, chromium, cobalt, lead, barium, caesium and cadmium. Amongst these, levels of arsenic, chromium, cobalt, lead, caesium and cadmium attained statistical significance [Table/Fig-2].

Subjects in both Group A and B were found to have levels of mercury, chromium, barium and caesium within the normal limits [Table/Fig-3]. Subjects in Group A had abnormal levels of arsenic,cadmium and lead. Among these arsenic and cadmium achieved statistical significance [Table/Fig-3].

Parameters	Group A - Cases	Group B – Controls	p-value
Total Number (N)	40	40	
Sex:			
Male	33	32	0.775
Female	07	08	
Age	48.30±10.95 Years	48.18±9.73 Years	0.957
BMI	20.76±4.24	24.33±4.46	<0.001
Addictions	Nil	Nil	
Occupational Exposure	Nil	Nil	
Systolic Blood Pressure (SBP)	156.25±22.15 mm Hg	121.38±7.97 mmHg	<0.001
Diastolic Blood Pressure (DBP)	93.75±13.90 mmHg	75.06±5.768 mmHg	<0.001
Blood Urea Nitrogen (BUN0	53.75±17.75 mg/dl	12.12±3.33 mg/dl	<0.001
Serum Creatinine	10.07±2.77 mg/dl	0.79±0.13 mg/dl	<0.001

[Table/Fig-1]: Baseline characters.

	Normal Values	Group A	Group B	p- value
Arsenic	<5.00 µg/l	4.76±2.28	1.61±0.99	<0.001
Cadmium	<1.50 µg/l	1.012±0.75	0.532±0.30	<0.001
Mercury	<5.00 µg/l	1.2993±0.85	1.3745±0.62	0.656
Lead	<150 µg/l	66.5558±36.62	43.5060±24.68	0.001
Chromium	<30.0 µg/l	5.9947±2.74	1.2655±0.77	<0.001
Barium	<30.0 µg/l	4.5320±2.88	3.6658±1.51	0.096
Cobalt	<4.00 µg/l	1.42±1.04	0.60±0.34	<0.001
Caesium	<5.00 µg/l	1.5432±0.86	1.0023±0.43	0.001
Selenium	60-340	119.15±58.50	134.45±50.46	0.217

[Table/Fig-2]: Mean values of trace elements.

Parameters	Reference value	Group A (%)	Group B (%)	p- value
Arsenic	<5.00 µg/l	23 (57.5)	40(100)	<0.001
	>5.00 µg/l	17(42.5)	0(0)	
Cadmium	<1.50 µg/l	33 (82.5)	40(100)	0.012
	>1.50 µg/l	7(17.5)	0(0)	
Mercury	<5.00 µg/l	40(100)	40(100)	1.00
	>5.00 µg/l	0(0)	0(0)	
Lead	<150 µg/l	37(92.5)	40(100)	0.241
	>150 µg/l	3(7.5)	0(0)	
Chromium	<30.0 µg/l	40(100)	40(100)	1.00
	>30.0 µg/l	0(0)	0(0)	
Barium	<30.0 µg/l	40(100)	40(100)	1.00
	>30.0 µg/l	0(0)	0(0)	
Cobalt	<4.00 µg/l	40 (100)	40(100)	1.00
	>4.00 µg/l	0(0)	0(0)	
Caesium	<5.00 µg/l	40 (100)	40(100)	1.00
	>5.00 µg/l	0(0)	0(0)	
Selenium	60-340	36 (90)	40(100)	0.12
	<60	4(10)	0(0)	

[Table/Fig-3]: The percentage of subjects having altered values of trace elements.

DISCUSSION

A total of 40 subjects were enrolled in both the groups. There were 33 males and 07 females in Group A as compared to 32 males and 08 females in Group B. The average age of subjects in Group A was 48.30±10.95 years as compared to 48.18±9.732 years in Group B.

The BMI in Group A was 20.76±4.249 as compared to24.33±4.465 in Group B. Of the 40 patients in Group A, 15 (37.5%) patients had malnutrition (BMI<18.5Kg/m^2). In a study conducted by Maheshwari N et al., the BMI among patients undergoing HD was 19.83±4.05 as compared to 22.21±3.8 among control group with 48% of patients undergoing HD having malnutrition [3]. This observation suggests a higher prevalence of malnutrition among our patients as compared to their western counterparts.

In the present study, the serum arsenic in Group A was 4.76±2.285 µg/l and as compared to subjects in Group B who had a mean level of 1.61±0.992 µg/l which was statistically significant (p-value =<0.001). De Kimpe J et al., observed more than tenfold increase of arsenic in the serum of HD patients (Median=11.5, p<0.05) [4]. A higher level of arsenic was also seen in hemodialysis patients by Subha Palaneeswari M et al., and Akinobu Ochi et al., [5,6]. Out of 40 subjects in Group A, 17(42.5%) of them had an elevated levels of arsenic as compared to Group B where all the subjects had normal levels, which was found to be statistically significant (p=<0.001) [Table/Fig-2,3]. The ground water, food contamination with pesticides and sea foods are the common source of arsenic. Arsenic is eliminated by kidneys in normal individuals and to a limited extent by hemodialysis in ESRD patients, there by favoring its accumulation.

A higher level of arsenic tends to produce [5,6]:

1. Oxidative stress hastens decline in Glomerular Filtration Rate (GFR) among Chronic Kidney Disease (CKD) patients.

2. Increase the risk of malignancies such as bladder and skin cancer.

3. Neurotoxicity and an increased risk of cardiovascular disease.

In our study the mean cadmium level was 1.012±0.75µg/l in Group A as compared to 0.532±0.30µg/l in Group B which was found to be statistically significant (p<0.001). Out of 40 patients in Group A, 7(17.5%) patients had higher levels of cadmium which was found to be statistically significant (p=0.012) [Table/Fig-2,3]. None of the participants in Group B had an elevated level. Mykola Prodanchuk et al., observed a mean cadmium level of 0.0017±0.0002mg/l amongst their cases as compared to 0.0014±0.00012mg/l amongst their controls, which was statistically significant [7]. In a study from India, Subha Palaneeswari M et al., observed that serum cadmium was higher in hemodialysis patients than in the normal subjects, with a p-value of <0.001 [5]. The primary source of cadmium is from food (liver and kidneys), cigarette smoking and industrial exposure. A higher level of cadmium in ESRD patient is probably due to impaired elimination through kidneys and HD. A sustained marginally higher level of cadmium is likely to produce osteoporosis, osteomalacia, hyperchloraemia, hyperuricaemia and increase the risk of malignancy. Osteomalacia and osteoporosis may contribute to the mineral bone disorder of ESRD and increase the risk of bony pains and fracture.

In our study, the mean mercury level was 1.2993±0.85µg/l in Group A as compared to 1.3745±0.62µg/l in Group B which was not statistically significant (p=0.656). All the participants in both groups had normal levels of mercury [Table/Fig-2,3]. Su-Hui Lee et al., had mean values of 3.17± 2.56µg/l in Group A versus 2.03 ± 1.38µg/l In Group B, which again did not attain statistical significance [8]. Mercury is principally used in manufacturing batteries, latex paint, Poly Vinyl Chloride (PVC), etc. Industrial discharge in to rivers and streams form major source of mercury poison. Higher levels of mercury may produce neurotoxicity, dermatitis, erethism, acrodynia, renal dysfunction and cerebellar ataxia. However, our study did not show elevation in mercury levels.

In our study the mean lead level was 66.5558±36.62µg/l in Group A as compared to 43.5060±24.68µg/l in Group B which was found to be significantly higher (p=0.001). A similar observation was noticed by Su-Hui Lee et al., and Bing Chen et al., [8,9]. Out of 40 patients in Group A, 3 (7.5%) had values of >150 µg/l [Table/Fig-2,3]. None of the healthy individuals had an elevated level. Within normal reference range of lead, HD patients tend to display a high normal value when compared to healthy individuals. The principal source of lead is paint, gasoline, smelting, mining and water through lead pipes. A higher level of lead is incorporated in anaemia, hypertension, renal impairement and toxicity to reproductive organs. Whether a high normal values as observed in our study is capable of producing toxic effects as Stated above needs to be further investigated.

The mean chromium level in Group A was 5.9947±2.74µg/l as compared to 1.2655±0.77µg/l in Group B which was statistically significant (p<0.001). A similar observation was witnessed by Zima T et al., where the mean chromium level was 3.67±0.35µg/l among dialysis patients which was found to be statistically significant [10]. None of the study population had values of >30µg/l [Table/Fig-2,3] raising suspicion whether a high normal values among hemodialysis patient is capable of producing its ill effect on health. A higher value of chromium is incorporated in producing hemolysis, contact dermatitis and malignancies.

The mean barium level in Group A was 4.5320±2.88µg/l as compared to 3.6658±1.51µg/l in Group B which was not found to be significant (p=0.096). Mykolaprodanchuk et al., in his study found a mean value of 0.0030±0.006 mg/l among dialysis patients as compared to 0.0206±0.0052 mg/l in control group which was statistically significant (p<0.00001) [7]. All the study participants in both the groups had normal values of barium [Table/Fig-2,3], except a minimal elevation in hemodialysis patients. Water is the primary source of barium and higher levels are found to produce tremors, anxiety and cardiac abnormalities.

The mean levels of cobalt and caesium in Group A was 1.42±1.048µg/l, 1.5432±0.86µg/l as compared to 0.60±0.34µg/l, 1.0023±0.43µg/l in Group B respectively, both of which was found to be statistically significant (p<0.001 & p<0.001) [Table/Fig-3]. Mykolaprodanchuk et al., observed that mean level of cobalt was 0.00022±0.00011 mg/l in HD patients as compared to 0.00006±0.00010 in non HD patients which was not found to be statistically significant (p=0.501). All the participants in both the groups had a normal value of cobalt and caesium [Table/Fig-3]. We need further studies to elucidate their role in HD patients.

Selenium which is a potent anti-oxidant was found to be 119.15±58.506 in Group A as compared to 134.45±50.465 in Group B, which did not attain statistical significance (p=0.217) [Table/Fig-2,3]. Prodanchuk et al., in his study observed a mean selenium level of 0.121±0.0059 mg/l as compared to 0.139±0.003mg/l in control group which was found to be statistically significant (p=0.0118) [7]. Out of 40 patients undergoing HD in our study, only 4 (10%) had lower levels of selenium [Table/Fig-3]. Selenium is a naturally occurring anti-oxidant which protects cell membrane by preventing free radical generation. It plays a vital role in maintaining endothelial integrity and a lower level of selenium increases endothelial dysfunction and CVD [11-14].

LIMITATION

We were unable to have a multivariate approach for incorporating potentially meaningful factors for modified blood levels of all trace elements due to smaller sample size. Further studies with larger sample size emphasizing on aluminium, zinc and copper are needed to elucidate the role of trace elements and their clinical relevance for better management of ESRD patients on HD.

CONCLUSION

The mean blood levels of biologically significant trace elements were substantially high in ESRD patients undergoing HD when compared to healthy individuals. The trace element correction strategy should be aimed at increasing the selenium intake and elimination of toxic trace elements.

Since, both deficiency and excess of trace elements appear to increase the risk of adverse outcomes and the altered levels of trace elements are potentially amenable for treatment, we warrant further clinical trials with larger sample size.

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REFERENCES

[1] Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B, et al. Trace elements in hemodialysis patients: A systematic review and meta-analysis. *BMC Medicine*. 2009; 7;25:1–12.
[2] Miura Y, Nakai K, Suwabe A, Sera K. Trace elements in renal disease and haemodialysis. *Nucl Instr Meth Phys Res*. 2002;189(1-4):443–49.
[3] Maheshwari N, Ansari MR, Laghari MS, Darshana, Lal K, Ahmed K. Pattern of lipid profile in patients on maintenance hemodialysis. *Saudi J Kidney Dis Transpl.* 2010;21:565–70.
[4] De Kimpe J, Cornelis R, Mees L,Van Lierde S, Vanholder R. More than ten fold increase of arsenic in serum and packed cells of chronic hemodialysis patients. *Am J Nephrol.* 1993;13(6):429–34.
[5] Palaneeswari MS, Rajan PM, Silambanan S, Jothimalar. Blood arsenic and cadmium concentrations in end-stage renal disease patients who were on maintenance haemodialysis. *J Clin Diagn Res*. 2013;7:809–13.
[6] Ochi A, Ishimura E, Tsujimoto Y, Kakiya R, Tabata T, Mori K et al.Trace element in the hair of hemodialysis patients. *Biol Trace Elem Res.* 2011;143(2):825–34.
[7] Prodanchuk M, Makarov O, Pisarev E, Sheiman B, Kulyzkiy M. Disturbances of trace element metabolism in ESRD patients receiving hemodialysis and hemodiafiltration. *Cent Eur J Urol*. 2014;66:472–76.
[8] Lee SH, Huang JW, Hung KY, Leu LJ, Kan YT, Yang CS et al. Trace metals' abnormalities in hemodialysis patients: relationship with medications. *Artificial Organs*. 2000;24(11):841–44.
[9] Chen B, Lamberts LV, Behets GJ, Zharo T, Zhou M, Liu G et al. Selenium, lead and cadmium levels in renal failure patients in China. *Biol Trace Elem Res*. 2009;131(1):1–12.

[10] Zima T, Mestek O, Tesar V, Tesarova P, Nemecek K, Zak A, et al. Chromium levels in patients with internal disease. *Biochem Mol Biol Int*.1998;46(2):365–74.
[11] Zima T, Tesar V, Mestek O, Nemecek K. Trace elements in end stage renal disease, clinical implication of trace elements. *Blood Purif*. 1999;17(4):187–98.
[12] Zima T, Mestek O, Nemecek K, Bartova V, Fialova J, Tesar V, et al. Trace elements in hemodialysis and continuous ambulatory peritoneal dialysis patients. *Blood Purif*. 1998;16(5):253–60.
[13] Hsieh YY, Shen WS, Lee LY, Wu TL, Ning HC, Sun CF. Long-term changes in trace elements in patients undergoing chronic hemodialysis. *Biol Trace Elem Res*. 2006;109(2):115–21.
[14] Zagrodzki P, Barton H, Walas S, Folta M, Stompor T, Janusz-Grzybowska E, et al. Selenium status indices, laboratory data, and selected biochemical parameters in end stage renal disease patients. *Biol Trace Elem Res*. 2007;116(1):29–41.

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