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Serum Level of Trace Elements in Pediatric Patients with End Stage Renal Disease on Hemodialysis

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ABSTRACT

Background: Chronic kidney disease (CKD) represents a significant global health challenge with rising rates that may herald a widespread epidemic.

Objective: This study aimed to evaluate the serum concentrations of copper (Cu), zinc (Zn), selenium (Se), and lead (Pb) in children with end-stage renal disease (ESRD) undergoing long-term hemodialysis.

Patients and methods: Conducted as a case-control study, we included 200 children divided equally into two groups. Group A consisted of children with ESRD, exhibiting a glomerular filtration rate (GFR) of less than 10 mL/min/1.73 m², and undergoing regular hemodialysis 2-3 times per week for 3-4 hours per session, sustained for more than six months. Group B comprised healthy children with normal baseline levels of blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine transaminase (ALT), confirmed through routine clinical visits, medical history, and examinations.

Results: Lead levels showed a positive correlation with the duration of dialysis and a negative correlation with weight and BMI. Zinc levels demonstrated a negative correlation with the duration of dialysis and a positive correlation with weight, height, and BMI. Compared to the control group, children with CKD had significantly higher levels of potassium and phosphorus and lower levels of calcium.

Conclusion: Children with ESRD on regular hemodialysis exhibited decreased serum levels of Cu and Zn, while Pb levels increased, with no significant changes in Se levels. Serum Pb and Zn levels were associated with the duration of hemodialysis, and Zn levels also correlated with anthropometric measurements.

Keywords: Trace elements, Pediatric, End stage renal disease, Hemodialysis.

INTRODUCTION

Chronic kidney disease (CKD) is a significant global health issue with rising incidence and prevalence, potentially leading to an epidemic [1]. Children with end-stage renal disease (ESRD) often face nutritional disturbances affecting their growth and development. Although nutritional elements and electrolytes are routinely monitored in CKD and pediatric dialysis patients, trace elements are typically not examined until complications arise [2].

Trace elements, present in micrograms per milliliter, include heavy metals like cadmium, chromium, nickel, vanadium, copper (Cu), lead (Pb), manganese, selenium (Se), and zinc (Zn). Many are essential for enzymatic pathways and biochemical reactions, though some, like cadmium and nickel, have limited biological roles [3].

Zn, an essential trace element, is crucial for enzyme function and cell division. Zn deficiency can lead to uremic symptoms such as anorexia, growth retardation, and immunological impairment [4]. Copper and Se are also vital trace elements. Copper is necessary for hemoglobin synthesis, connective tissue metabolism, bone development, and the antioxidant defense system. Its deficiency can cause anemia, neutropenia, and osteoporosis [5]. Se is involved in thyroid hormone synthesis and antioxidant mechanisms, with deficiency contributing to cardiovascular disease, immune dysfunction, anemia, and increased cancer risk [6].

The accumulation of Pb has been reported in patients with renal failure. Many of human body functions are affected by Pb toxicity. A variety of symptoms in Pb toxicity [7]. Abnormal levels of trace elements are rarely seen in clinical practice except in patients with ESRD being treated with hemodialysis [8]. Lead accumulation is common in renal failure patients, affecting various bodily functions and causing numerous symptoms. Abnormal trace element levels are rare except in ESRD patients undergoing hemodialysis [9]. In these patients, disturbances can be caused by drugs, the uremic state, dialysis processes, water quality used in dialysis, anemia, and metabolic alterations. Dialysis can lead to the accumulation of trace elements due to impurities in the dialysis fluid or deficiencies as elements are removed from the blood [10]. This study aimed to assess the serum levels of Cu, Zn, Se, and Pb in children with ESRD on long-term hemodialysis.

PATIENTS AND METHODS

This case-control study included 200 children who attended follow-up visits or were admitted to the Pediatric Departments at Benha University Hospital and

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Zagazig University Hospital. The study was conducted from July 2022 to June 2023, with children aged 2-18 years with ESRD and a GFR of less than 10 mL/minute/1.73 m².

Exclusion criteria: Children younger than 2 years or older than 18 years, those with metabolic disorders, malnutrition, malabsorption syndrome, chronic diarrhea and chronic renal failure due to nephrotic syndrome, or those receiving zinc, copper, or selenium supplements.

The participants were divided into two equal groups. Group A included children with ESRD and a GFR of less than 10 mL/minute/1.73 m², who received regular hemodialysis 2-3 times per week for 3-4 hours per session for more than six months. Group B consisted of healthy children with normal baseline levels of BUN, creatinine, AST, and ALT that were confirmed through routine clinical visits, medical history, and examinations. All participants underwent detailed history taking, which included personal information (age, gender, residence), past history (antenatal, natal, postnatal, developmental, family history, consanguinity), and present history (cause of ESRD, duration of the disease, treatment). They also received comprehensive clinical examinations, which covered general examination (vital signs such as pulse, blood pressure, capillary filling time, respiratory rate, temperature, and skin examination) and anthropometric measurements (weight, height, body mass index), along with a local systematic examination.

Routine laboratory investigations were conducted, including complete blood count, serum electrolytes, urea, creatinine, arterial blood gases, serum iron, total iron-binding capacity (TIBC), ferritin, transferrin saturation, parathyroid hormone, random blood sugar, AST, ALT, alkaline phosphatase (ALP), serum albumin, and echocardiography. Additionally, serum levels of Cu, Pb, selenium (Se), and Zn were measured.

Sampling: Venous blood samples of 5 mL were collected from all participants after fasting for 6-10 hours. These samples were drawn using sterile, disposable plastic syringes for routine laboratory tests, blood lead levels, and serum trace element analysis. To prevent contamination, the tubes and syringes were pre-washed with acid. The serum was separated within 2 hours of collection and stored at -20 °C until analysis.

Technique: Plasma levels of copper, zinc, selenium, and lead were measured using an atomic absorption spectrophotometer 210-VGP. The technique involved promoting electrons in the atoms to higher orbitals (excited states) by absorbing a defined amount of energy. This energy absorption is specific to particular electron transitions in each element. The radiation was measured using a detector, and the absorbance was converted to analyte concentration according to the manufacturer's protocol [11].

Ethical considerations: The study was approved by The Research Ethics Committees, Benha University and Zagazig University. All patients provided written informed consents prior to enrolment of their children. The consent form explicitly outlined their agreement to participate in the study and for the publication of data ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were coded, entered, and processed using SPSS version 24. The results were presented in tabular and graphical forms for interpretation. Descriptive statistics included mean, standard deviation, range, frequency, and percentage. The Chi-Square test was employed to assess associations between categorical variables. The student's t-test was used to determine the statistical significance of differences between the means of two independent samples with a normal distribution. Spearman's correlation was used to evaluate the relationship between trace elements and other parameters, with "r" representing the correlation coefficient. A two-tailed P value ≤ 0.05 was considered statistically significant.

RESULTS

Regarding demographic data, there was no significant difference between CKD & control groups regarding age or sex. CKD group had statistically higher frequency of family history of CKD, NICU admission, PICU admission compared to control group. While there was no significant difference between groups regarding gestational age or consanguinity (Table 1).

Table (1): Sociodemographic data, Clinical history and Etiology of kidney disease of the studied groups

		CKD group		Control group		P value
		N=100	%	N=100	%	
Sex	**Male**	57	57.0%	47	47.0%	0.15
	Female	43	43.0%	53	53.0%	
Age (years)		7 ±1.4		6.3±2.3		0.64
Clinical history						
Gestational age (weeks)		37.3±2		37.7±1.7		0.17
Consanguinity	**negative**	59	59.0%	58	58.0%	0.88
	positive	41	41.0%	42	42.0%	
Family history of CKD	**negative**	80	80.0%	94	94.0%	0.003*
	positive	20	20.0%	6	6.0%	
History of NICU admission	**negative**	61	61.0%	79	79.0%	0.005*
	positive	39	39.0%	21	21.0%	
History of PICU admission	**negative**	75	75.0%	99	99.0%	<0.001*
	positive	25	25.0%	1	1.0%	

Etiology of kidney disease			
Duration of kidney disease (years)		3.7±1.8	
Duration of dialysis (years)		2±1.3	
Etiology of CKD	**CAKUT**	31	31.0%
	HUS	11	11.0%
	GN	30	30.0%
	Congenital nephropathy	20	20.0%
	Unknown	8	8.0%

CKD: chronic kidney disease, CAKUT: congenital anomalies of the kidney and urinary tract, HUS: hemolytic uremic syndrome. GN: glomerulonephritis, *Statistically significant $p \leq 0.05$.

CKD group had statistically lower percentiles of weight, height and body mass index compared to control group. CKD group had statistically lower levels of hemoglobin and platelets, and statistically higher levels of TLC compared to control group. While, there was no significant difference between groups regarding RBS. CKD group had statistically higher levels of AST, ALP, urea, creatinine, ALP, PTH, and higher frequency of metabolic acidosis and statistically lower levels of albumin compared to control group (Table 2).

Table (2): Anthropometric measures, complete blood count, random blood sugar and kidney and liver functions of the studied groups

		CKD group		Control group		P value
		N=100		N=100		
Weight (percentile)		23.7±19.2		48.3±21.3		<0.001*
Height (percentile)		37.6±23.4		49.4±19.3		<0.001*
Body mass Index (percentile)		30.6±19.7		47.7±21.7		<0.001*
Complete blood count						
Hemoglobin (g/dl)		10.2±1.3		11.3±1.0		<0.001*
TLC (L)		9±2.4		8.1±2.0		0.005*
Platelets (10^3/l)		305.5±36.4		318.3±44.7		0.028*
RBS (mg/dL)		105.1±20.7		104.4±9.4		0.78
Kidney and liver functions						
AST (U/L)		17.4±1.8		10.7±1.7		<0.001*
ALT (U/L)		21.6±201		12.0±3.9		<0.001*
Albumin (g/dL)		3.4±0.6		4.0±0.5		<0.001*
Urea (mg/dL)		84.2±9.7		17.6±3.1		<0.001*
Creatinine (mg/dL)		2.1±0.36		0.5±0.04		<0.001*
ALP (IU/L)		197.04±4.4		154.2±28.5		0.002*
PTH (pg/mL)		38.8±7.7		29.5±3.1		<0.001*
ABGs	**Metabolic acidosis**	13	13.0%	0	0.0%	0.001*
	Normal	87	87.0%	100	100.0%	

CKD: chronic kidney disease, ALT: Alanine Transaminase, AST: Aspartate aminotransferase, ALP: Alkaline Phosphatase, PTH: Parathyroid hormone, ABGs: arterial blood gases, TLC: total leucocytic count, RBS: random blood sugar, *statistically significant $p \leq 0.05$

CKD group had statistically higher levels of potassium and phosphorus and statistically lower levels of calcium compared to control group. While, there was no statistical difference between groups regarding sodium level. CKD group had statistically higher levels of ferritin and statistically lower levels of iron, TIBC, transferring saturation compared to control group. CKD group had statistically higher levels of lead and statistically lower levels of selenium and zinc compared to control group. While there was no significant difference between groups regarding level of copper (Table 3).

Table (3): Electrolytes, Iron studies, Trace elements and Echocardiography in the studied groups

	CKD group N=100	Control group N=100	P value
Sodium (mEq/L)	141.6±7.6	140.3±3.5	0.11
Potassium (mEq/L)	4.6±0.6	3.9±0.32	<0.001*
Calcium (mg/dL)	9.04±0.67	9.3±0.5	0.005*
Phosphorus (mg/dL)	4.2±0.72	3.5±0.4	<0.001*
Iron studies			
Iron (µg/dl)	92.2±5.3	118.2±23.6	0.001*
Ferritin (ng/mL)	266.4±32.9	106.1±8.9	<0.001*
TIBC (µg/dl)	215.4±5.8	322.3±7.1	<0.001*
Transferrin saturation (%)	31.5±5.8	37.2±8.33	0.001*
Trace elements			
Copper (µg/dl)	115±3.8	121.3±3.6	0.16
Lead (µg/dl)	11.5±2.78	6.68±1.3	<0.001*
Selenium (µg/dl)	81.73±8.4	88.7±22.6	0.017*
Zinc (µg/dl)	77.14±15.48	86.15±11.42	<0.001*

Echocardiography		**CKD group**	
		N=100	**%**
Echocardiography	**Normal**	85	85.0%
	left ventricular hypertrophy/enlargement	5	5.0%
	congestive heart failure/pulmonary edema	3	3.0%
	Cardiomyopathy	2	2.0%
	decreased left ventricular function	5	5.0%

CKD: chronic kidney disease, TIBC: total iron binding capacity, statistically significant $p \leq 05$

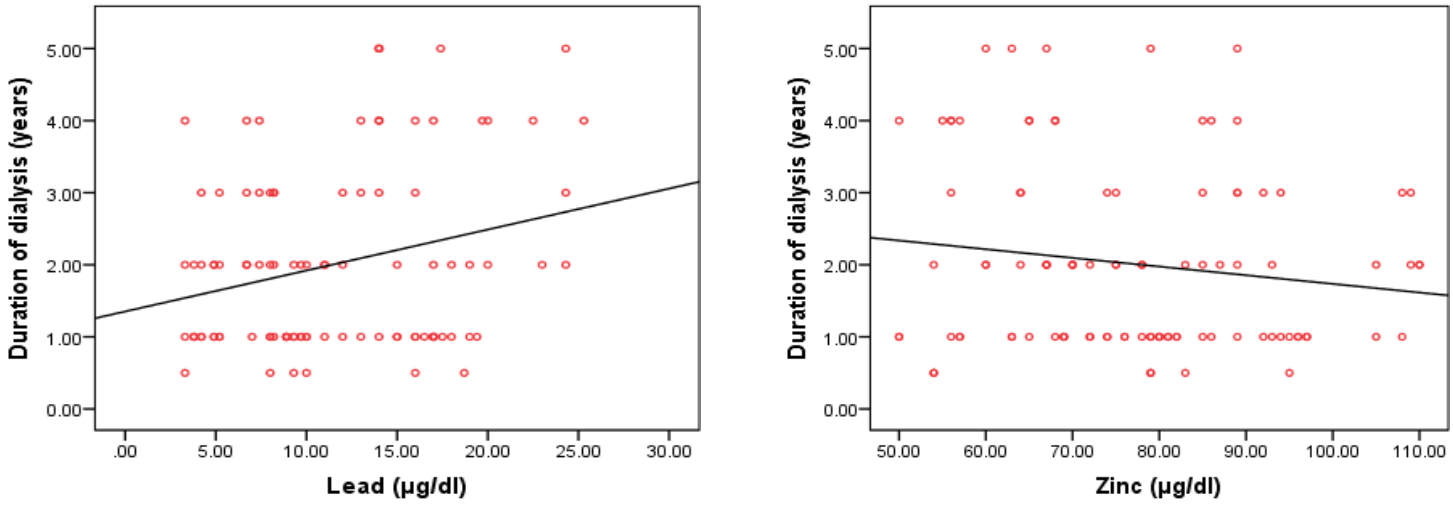
There was no significant difference in copper, lead, selenium, and zinc levels as regards sex or etiology of chronic kidney disease (Table 4).

Table (4): Copper, Lead, Selenium, and Zinc levels according of sex and etiology of kidney disease in the studied cases

		Copper (µg/dl)	**P value**
Sex	**Male**	121.4±32.9	0.15
	Female	114.6±31.4	
Etiology of kidney disease	**CAKUT**	121.65±35.14	0.31
	HUS	122.09±35.71	
	GN	115.4±32.48	
	Congenital nephropathy	110±32.32	
	unknown	97.5±4.82	
		Lead (µg/dl)	
Sex	**Male**	9.6±5.1	0.14
	Female	8.5±4.8	
Etiology of kidney disease	**CAKUT**	11.98±5.39	0.97
	HUS	11.2±6.22	
	GN	11.2±4.81	
	Congenital nephropathy	11.73±6.41	
	unknown	10.55±7.58	
		Selenium (µg/dl)	
Sex	**Male**	83.7±19.4	0.30
	Female	86.8±22.4	
Etiology of kidney disease	**CAKUT**	81.5±19.7	0.73
	HUS	81.7±20.9	
	GN	78.9±18.6	
	Congenital nephropathy	81.6±16.9	
	unknown	89.9±14.4	
		Zinc (µg/dl)	
Sex	**Male**	81.7±15.3	0.88
	Female	81.3±13.1	
Etiology of kidney disease	**CAKUT**	78.5±14.3	0.82
	HUS	76.6±18.6	
	GN	74.3±15.5	
	Congenital nephropathy	76.8±16.9	
	unknown	81.4±10.9	

CAKUT: congenital anomalies of the kidney and urinary tract, HUS: hemolytic uremic syndrome. GN: glomerulonephritis.

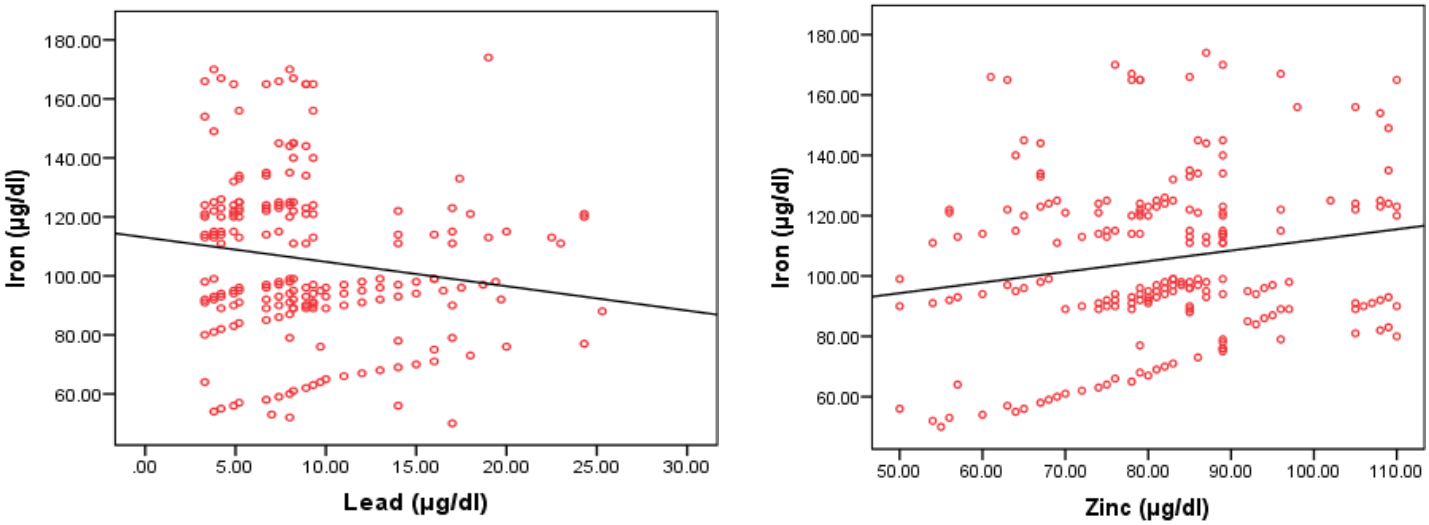
Lead correlated positively with duration of dialysis, and correlates negatively with weight and BMI. Zinc correlated negatively with duration of dialysis ad positively with weight, height and BMI. While there was no significant correlation between copper and selenium with clinical criteria of patients (Figure 1).



(A) **(B)**

Figure (1): Correlation between (A) lead and duration of dialysis and (B) zinc and duration of dialysis.

Copper had a significant positive correlation with sodium, phosphorus and ALP. Lead had a significant positive correlation with potassium, phosphorus & ALP and a significant negative correlation with hemoglobin, albumin and iron. Zinc had a significant positive correlation with iron. Selenium had no significant correlations with other laboratory investigations **(**Figure 2).



(A) **(B)**

Figure (2): Correlation between (A) lead and iron and (B) iron and zinc.

Copper correlated positively with lead, and negatively with zinc. In addition, selenium correlated negatively with lead. No other significant correlations were detected between trace elements (Table 5).

Table (5): Correlations between trace elements

		Copper (µg/dl)	Lead (µg/dl)	Selenium (µg/dl)	Zinc (µg/dl)
Copper (µg/dl)	**r**	1	0.434	-0.086	-0.363
	P value		**<0.001***	0.394	**<0.001***
Lead (µg/dl)	**r**	0.434	1	-0.336	-0.066
	P value	**<0.001***		**<0.001***	0.516
Selenium (µg/dl)	**r**	0.086	-0.336	1	0.087
	P value	0.394	**<0.001***		0.388

r: correlation coefficient, *statistically significant p ≤0.05

DISCUSSION

The mean age in the CKD group was 7±1.4 years, consisting of 43 females and 57 males. There was no significant difference in age or sex between the CKD and control groups. **Silva *et al.*** [12] examined the anthropometric and biochemical profiles of 138 children and adolescents with CKD in a pre-dialysis pediatric interdisciplinary program. The median age at admission was 9 years (interquartile range (IR), 2.3–13.2 years) with a median follow-up time of 58 months (IR, 23.3–94.7 months).

In this study, the CKD group had a significantly higher frequency of family history of CKD, NICU admission, and PICU admission compared to the control group. There was no significant difference between the groups regarding gestational age or consanguinity. This finding aligns with **Lee *et al.*** [13], who reported a mean gestational age of 38.3 ± 3.1 weeks in their study.

In the present study, the mean duration of kidney disease in the studied cases was 3.7±1.8 years and the mean duration of dialysis was 2±1.3 years. The most common cause of kidney disease was CAKUT (31%), followed by GN (30%), then congenital nephropathy (20%), HUS (11%). Our results align with **Silva *et al.*** [12] regarding primary renal disease, with most patients presenting congenital anomalies of the kidney and urinary tract (58%), followed by glomerular diseases (21.7%), cystic diseases (14.5%), and less common renal disorders (5.8%).

In this study, the CKD group had significantly lower percentiles for weight, height, and body mass index compared to the control group. **Sharaf *et al.*** [14] similarly found that HD cases were significantly associated with lower weight, shorter height, and lower BMI compared to the control group.

Additionally, the CKD group showed statistically lower levels of hemoglobin and platelets, and higher levels of TLC, with no significant difference in RBS levels between the groups. Anemia in CKD patients is known to be multifactorial, with its prevalence increasing from 26% to 75% as renal function declines from > 60 ml/min to < 15 ml/min, primarily due to erythropoietin (EPO) deficiency [15]. **Lee *et al.*** [13] observed a bimodal distribution of low hemoglobin levels in CKD patients at ages 0–2 years (11.14 ± 1.64 g/dL) and 6–12 years (11.65 ± 1.79 g/dL). Hemoglobin levels significantly decreased with advancing CKD stages, averaging 12.22 ± 1.94 g/dL ($p < 0.001$).

In the current study, CKD group had statistically higher levels of AST, ALP, urea, creatinine, ALP, PTH, and higher frequency of metabolic acidosis and statistically lower levels of albumin compared to control group. CKD group had statistically higher levels of potassium and phosphorus and statistically lower levels of calcium compared to control group. While there was no statistical difference between groups regarding sodium level. This is in agreement with **Sharaf *et al.*** [14] who reported that HD patient group was significantly associated with higher phosphorus, ALP, PTH and lower albumin concentration when compared to control group.

In this study, the CKD group had significantly higher levels of ferritin and significantly lower levels of iron, TIBC, and transferrin saturation compared to the control group. **Kamal *et al.*** [16] similarly reported decreased levels of serum iron, TIBC, and transferrin saturation (TSAT) in CKD patients, while serum ferritin levels were elevated in patients with CKD and on hemodialysis compared to the control group.

Additionally, the CKD group showed significantly higher levels of lead (Pb) (11.5±5.78 µg/dl) compared to the control group (6.68±2.3 µg/dl, $P<0.001$). This finding is consistent with **Esmaeili & Rakhshanizadeh** [17], who noted significantly lower Pb levels in healthy children and those with CKD under conservative management than in those undergoing hemodialysis or peritoneal dialysis.

There was no significant difference in copper (Cu) levels between the CKD and control groups (115±32.8 and 121.3±31.6 µg/dl, respectively, $p=0.16$). This aligns with **Esmaeili & Rakhshanizadeh** [17] , who found no significant difference in serum Cu concentrations among healthy children, children with CKD under conservative management, and those on hemodialysis or peritoneal dialysis.

In our study, 85% of children had normal echocardiography, while 15% showed abnormalities, including left ventricular hypertrophy/enlargement (5%), congestive heart failure/pulmonary edema (3%), cardiomyopathy (2%), and decreased left ventricular function (5%). These results are in agreement with **Chavers *et al.*** [18] who reported cardiac disease in 24% of patients, left ventricular hypertrophy/enlargement in 17%, congestive heart failure/pulmonary edema in 8%, cardiomyopathy in 2% and decreased left ventricular function in 2%.

In the current study, Lead correlated positively with duration of dialysis, and correlated negatively weight and BMI. Lead had a significant positive correlation with potassium, phosphorus & ALP and a significant negative correlation with hemoglobin, albumin and iron. Similarly, **Rajan & Santhi** [19] found that blood lead levels were higher in ESRD patients on maintenance hemodialysis compared to healthy adults. They also observed that blood lead concentrations increased with the duration of hemodialysis.

In the present study, zinc correlated negatively with duration of dialysis and positively with weight,

height and BMI. Zinc had a significant positive correlation with iron. Our results are in agreement with **Sharaf *et al.*** [14], as zinc level showed significant direct correlation with height, and significant inverse correlation with dialysis duration.

In the current study, copper had a significant positive correlation with sodium, phosphorus and ALP. While, there was no significant correlation between copper and selenium with clinical criteria or other laboratory investigations. In the present study, there was no significant difference in copper, lead, selenium and zinc levels as regards sex or etiology of chronic kidney disease. Copper correlated positively with lead, and negatively with zinc. In addition, selenium correlated negatively with lead. No other significant correlations were detected between trace elements. Our results are consistent with **Nishime *et al.*** [20], who found that hemodialysis patients had lower zinc concentrations compared to healthy individuals. Additionally, zinc and copper levels were inversely correlated. A previous study on rats indicated that lead exposure disrupts copper homeostasis and may mitigate some lead-induced damage [21].

Limitations: This study had several limitations where it was conducted at a single center, lacked a detailed nutritional assessment of the patients, and evaluated trace element levels over a limited period,

CONCLUSION

The children with ESRD on regular hemodialysis showed decreased serum Cu and Zn levels and increased Pd levels with no significant changes in serum Se levels. The serum levels of Pd and Zn were correlated with the hemodialysis duration. The serum levels of Zn were correlated with anthropometric measurements.

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