

Estimation of serum zinc and electrolytes in end-stage renal disease patients on hemodialysis Erbil city

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Abstract

Background and objective: End-stage renal disease (ESRD), particularly in patients undergoing haemodialysis (HD), often results in altered serum mineral and electrolyte levels, which can lead to additional health complications. This study aims to assess serum zinc levels, electrolyte concentrations, and renal function markers in HD, providing a comprehensive analysis of these parameters for the first time in this population.

Methods: This cross-sectional study, which included a comparison group, enrolled 65 ESRD patients undergoing regular HD at the Erbil Dialysis Centre and 65 healthy control subjects individuals from Erbil City. Information on dietary intake, medication use, and demographic factors was gathered through structured interviews, medical record reviews, and serum analysis, which measured kidney function biomarkers, serum zinc levels, and electrolyte levels.

Results: Serum zinc levels were significantly lower, and potassium concentrations were notably higher in HD patients compared to the control group. Zinc depletion was more pronounced in HD patients with hypertension than in those without. These alterations showed a negative correlation with estimated glomerular filtration rate (eGFR) levels among HD patients, with hyperkalaemia being significantly associated with lower eGFR values.

Conclusion: Monitoring serum zinc levels and electrolyte balance is crucial in HD patients, as zinc deficiency appears independently linked to hypertension. Addressing this deficiency may improve patient outcomes, through larger sample-size studies.

Keywords: Serum Zinc; Serum Electrolytes; Chronic kidney disease; Haemodialysis; Hypertension.

Introduction

Chronic kidney disease (CKD) is a progressive and irreversible failure of kidney function and has become one of the most prevalent non-communicable chronic diseases globally. By 2040, the World Health Organization expects that CKD becomes the 5th most common chronic disease.^(1,2)

Several risk factors are involved in CKD aetiologies including diabetes, obesity, hypertension, unhealthy lifestyle, aging, cardiovascular problems, lung disorders, malnutrition, high sodium intake, anaemia, and hypercholesterolemia.⁽²⁻⁵⁾ Among these, diabetes and hypertension are the

more common causes in adults. However, in some regions, other causes such as infection, and herbal and environmental toxification are still common. Among patients with CKD in Erbil, a cohort study revealed a notable association with peripheral artery disease has been observed, indicating that those with impaired kidney function are at increased risk for vascular complications. Highlighting the key risk factors associated with CKD, including older age, hypertension, diabetes, prior coronary artery disease, and advanced CKD stages.⁽⁶⁾

The global prevalence of CKD was 13.4%, it is estimated that around 4.9 to 7 million

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patients often have ESRD, where renal function is severely compromised and requires renal replacement therapy.⁽⁷⁾ One of the main indicators for kidney dysfunction in adults is the glomerular filtration rate (GFR), 60 ml/min/1.73 m² or less of GFR level is considered indicative of CKD. Thus, five stages of CKD have been proposed depending on the GFR level. The first three are mild to moderate, while stages (4 and 5) are considered severe and, consequently, recommended for dialysis treatment.⁽⁸⁾ Thus, at this stage, most ESRD patients highly require HD, the world's most common type of kidney replacement therapy, accounting for approximately 69% of all kidney replacement therapy and 89% of all dialysis.⁽⁹⁻¹¹⁾ Although HD is a life-sustaining therapy that helps manage fluid overload, waste removal, and electrolyte imbalances, it comes with different challenges, including its effects on essential serum minerals and electrolytes, which are crucial for maintaining physiological homeostasis.⁽¹²⁾

Zinc is the second most abundant trace element, after iron, is indispensable for numerous physiological processes,⁽¹³⁾ and acts as a co-factor for over 120 enzymes, influencing cellular signalling pathways, proliferation, apoptosis, and antioxidant defences.⁽¹⁴⁾ Zinc deficiency can potentially lead to a spectrum of nonspecific symptoms, affecting skin integrity, immune function, taste maintenance, and neurological processes. Notably, in ESRD patients, zinc deficiency is highly associated with anaemia, nutritional issues, cardiovascular diseases, and various symptoms like dermatitis and cognitive decline.⁽¹⁵⁾

Overall, the multifaceted functions of zinc underscore its significance in maintaining overall health and well-being. This disruption can be due to abnormal protein metabolism, microelement malabsorption in the gastrointestinal tract, disturbed renal excretion, and anticipated faulty cellular and tissue redistribution. Additionally, zinc

is potentially implicated in the regulation of arterial pressure and the etiopathogenesis of arterial hypertension through the renin-angiotensin-aldosterone system. A decline in blood zinc concentrations with the progression of CKD stages has been evidenced so far.⁽¹⁶⁾ Clinical data has also linked poor outcomes in maintenance HD patients to zinc deficiency.^(12,17)

Not only trace elements but also electrolytes or ions are essential components that perform diverse key functions at cellular and functional levels. Sodium, potassium, calcium, magnesium, chloride, and phosphorus are included among the macro or major electrolytes and are involved in various metabolic and homeostatic functions including enzymatic reactions, bone mineralization, nerve impulse conduction, muscle contraction, and the regulation of osmotic balance.⁽¹⁸⁾

Moreover, electrolyte disturbances are measurable serum biochemical parameters that can be evaluated for renal physiology and pathophysiology.⁽⁴⁾ For instance, body potassium levels were found to be altered in HD patients are associated with an increased risk of hypertension, cardiovascular disease, and eventually death.⁽¹⁹⁾ Despite improvements in dialysis care, the mortality of patients on maintenance HD is persistently high. Abnormal levels of serum electrolytes have a crucial influence on clinical outcomes in HD patients. These severe biochemical derangements in CKD patients can be improved by regular dialysis and renal transplantation.

It has been suggested that potassium management improves and potentially long-term outcomes in HD could be maintained by integrating all factors that determine potassium balance and applying a personalized approach.^(19,20) Not only K⁺ ion but also altered Cl⁻ level in HD is evidenced and associated CVD and high mortality risk.⁽²¹⁾ Serum Cl⁻ as a marker of cardiovascular and all-cause mortality in chronic HD patients: 5-Year follow-up study. Adequate treatment and diagnosis

will minimize complications and can potentially be lifesaving. These complications can exacerbate the already high morbidity and mortality rates among HD patients.

Therefore, this study aims to assess and compare serum zinc levels and electrolyte concentrations in patients with ESRD undergoing regular HD to those of healthy individuals for the first time in Erbil City. It also seeks to evaluate the relationship between these biochemical parameters and renal function, focusing on identifying potential links between zinc depletion and hypertension in the HD population.

Methods

Study design

A cross-sectional study with a comparison between patients with healthy control individuals.

Location setting and duration

This research has been conducted and the data were obtained from Erbil Dialysis Centre in Erbil city from November 2022 to May 2023.

Sample Collection and Biochemical Parameters

A total of 5 ml of venous blood was collected from each individual who participated in this study, including 65 HD patients and 65 healthy subjects. The sample size was determined using power analysis to detect a significant difference in serum zinc levels and electrolyte concentrations between patients and healthy controls, with a desired power of 80% and a significance level of 0.05. Pre-dialysis specimens were taken before the Heparin administration in cases. The blood samples were collected in yellow gel tubes. Consequently, the samples were allowed to clot for 10 to 15 min, and clotted blood was centrifuged for 10 min at 3400 rpm. The serum supernatant was then collected in 1.5 ml Eppendorf tubes and stored at -20°C for the subsequent analysis of serum zinc level, and electrolyte level, including Na⁺, K⁺, and Cl⁻, and for evaluation of several biochemical assays

which included serum creatinine to calculate eGFR. The electrolytes were measured by an Automatic electrolyte analyser EX-D series (JOKOH, Japan). Serum zinc was measured by spectrophotometer, with adding a colorimetric reagent, forming a complex with zinc ions. The sample absorbance at a 560-580 nm wavelength is compared to a standard curve to determine zinc concentration.

Ethical Consideration

The research protocol was positively approved by the ethical committee of the College of Health Sciences/ Hawler Medical University. A complete explanation of the nature and aim of the study was introduced to each participant, and they were reassured about the confidentiality of the data and their anonymity. Additionally, their rights to refuse or participate in the present study were preserved and confirmed, and then direct oral informed consent was obtained for the interview.

Statistical Analysis

The data were analysed by GraphPad Prism8. The continuous variables were tested for normal distribution by the Shapiro-Wilk test and presented as mean ± standard error of the mean (SEM) or median with interquartile ranges (IQR). Categorical variables are presented as the number and percentage. The Chi-square test was used to show the significance of the association between categorical variables. The correlation analysis was performed using Pearson correlation coefficients. A linear regression line is also included to visualize the trend. Comparisons between two independent groups were performed using the unpaired *t*-test or Mann-Whitney test. *P* ≤ 0.05 was considered statistically different.

Results

Baseline Characteristics of Participants

Table 1 presents the sociodemographic characteristics of HD patients and control subjects. A total of 65 HD patients and 65 control subjects were included in the study.

Both groups were age and sex-matched, with the mean age of HD patients being 50.86 ± 1.652 years and control subjects being 49.18 ± 1.742 years. The median body mass index (BMI) was slightly lower in HD patients (26.12 kg/m^2) compared to controls (26.67 kg/m^2). Gender distribution was identical in both groups, with 50.8% males and 49.2% females. Residency diverged notably, with a higher proportion of HD patients living in urban areas (60.0%) compared to controls (27.7%). Economic status varied, with a larger proportion of controls having sufficient economic status (44.6%) compared to HD patients (18.5%). Marital status also

differed, with a higher proportion of married status in the control group (86.2%) compared to HD cases (60.0%). Considering the family history, 26.2% of HD patients had a family history of relevant conditions compared to 7.7% of controls. Most HD patients consumed less than 3 liters of water per day (76.9%), while 75.4% of healthy subjects did so. Smoking and alcohol consumption were higher in HD patients, with 35.4% compared to 12.3% of controls, and 6.2% of HD patients consuming alcohol compared to none in the control group. Dietary habits showed that the proportion of meat-consumers and vegans was equal in both groups.

Table 1 Sociodemographic characteristics of HD patients and controls

Characteristics	Control (n=65)	HD (n=65)
Age/Years (Mean \pm SEM)	49.18 \pm 1.742	50.86 \pm 1.652
Age group, No. (%)		
<50	30 (46.2%)	27 (41.5%)
\geq 50	35 (53.8%)	38 (58.5%)
Body mass index kg/m^2, Median (interquartile range)	26.67 (23.55-30.25)	26.12 (21.70-29.66)
Gender, No. (%)		
Males	33 (50.8%)	33 (50.8%)
Females	32 (49.2%)	32 (49.2%)
Residency, No. (%)		
Urban	29 (44.6 %)	39 (60.0%)
Suburban	21 (32.3%)	13 (20.0%)
Rural	15 (23.1%)	13 (20.0%)
Economic Status, No. (%)		
Sufficient	12 (18.5%)	18 (27.7%)
Barely sufficient	27 (41.5%)	28 (43.1%)
Insufficient	26 (40.0%)	19 (29.2%)
Marital Status, No. (%)		
Single	5 (7.7%)	12 (18.5%)
Married	56 (86.2%)	39 (60.0%)
Widowed/widower.	4 (6.2%)	14 (21.5%)
Family History, No. (%)		
Yes	5 (7.7%)	17 (26.2%)
No	60 (92.3%)	48 (73.8%)
Amount of water in litter/Day, No. (%)		
less than 2 litter	24 (36.9%)	19 (29.2%)
2-3 litter	25 (8.5%)	31 (47.7%)
more than 3 litter	16 (24.6%)	15 (23.1%)
Smoking		
Yes	8 (12.3%)	23 (35.4%)
No	57 (87.7%)	42 (64.6%)
Alcohol Drinking		
Yes	54 (83%)	4 (6.2 %)
No	11(16.9%)	61 (93.8 %)
Type of food		
Meat	33 (50.8%)	40 (61.5 %)
Vegan	32 (49.2%)	25 (38.5 %)

The result is expressed as number (%) and mean \pm SEM.

Clinical Characteristics of HD Patients

Table 2 describes the clinical characteristics of HD patients. A significant majority of HD patients (81.5%) had hypertension, whereas 27.7% had diabetes mellitus. The frequency of dialysis sessions/week varied, with 56.9% undergoing dialysis twice a week, 41.5% three times a week, and 1.5% four times a week. The duration of dialysis treatment showed that 80.0% of the patients had been on dialysis for less than one year, while 20.0% had been on dialysis for more than 5 years.

Low Serum Zinc Level in HD Patients: Comparison of Studied Parameters Between HD Patients and Control Subjects

As shown in Table 3, the median serum zinc level in HD patients was significantly lower than in the control group. 91.87 ± 2.415 for HD patients, 114.5 ± 1.543 in the control subjects, with a highly significant *P*-value of <0.0001 .

This indicates a marked reduction in zinc levels among individuals undergoing HD.

Table 2 Clinical characteristics of HD patients (N=65)

Variables	Number of HD-patients	Percentage
Hypertension		
Yes	53	81.5%
No	12	18.5%
Diabetes mellitus		
Yes	18	27.7%
No	47	72.3%
Days on Dialysis/Week		
Two	37	56.9%
Three	27	41.5%
Four	1	1.5
Period on Dialysis		
<1 Year	52	80.0 %
≥5 Year	13	20.0%

Furthermore, HD patients exhibited significantly higher levels of creatinine (8.098 mg/dL vs. 0.643 mg/dL, $P < 0.001$) and urea (133.1 mg/dL vs. 25.01 mg/dL, $P < 0.001$). The eGFR, a critical biomarker of kidney function, was dropped in HD patients, and significantly lower estimated (7.769 mL/min/m²) compared to the healthy individuals (112.5 mL/min/m², $P < 0.001$).

Altered Serum Electrolyte Levels in HD Patients

The study also examined various electrolyte levels, including, sodium (Na²⁺), potassium (K⁺), and chloride (Cl⁻) in

both HD patients and control subjects (summarized in Table 3). Sodium was not altered HD patients (132.8 mmol/L) compared to the control (134.9mmol/L) ($P = 0.3701$). Similarly, no changes were observed in the serum Cl⁻ level; 95.78 mmol/L for HD patients compared to 95.73 mmol/L in controls ($P = 0.546$). Controversially, serum K⁺ levels were significantly elevated in HD patients (hyperkalemia), 5.017 ± 0.1602 mmol/L, compared to 4.089 ± 0.05083 mmol/L in controls ($P < 0.001$).

Table 3 Comparison of studied parameters between HD patients and control subjects

Groups	Control (n=65)	HD-patients (n=65)	P value
Parameters			
Zinc	114.5 ± 1.543	91.87 ± 2.415	****<0.0001
Creatinine (mg/dl)	0.643± 0.023	8.098± 0.325	****<0.0001
Urea (mg/dl)	25.01±0.908	133.1±5.720	****<0.0001
eGFR (ml/min/m ²)	112.5±1.641	7.769±0.545	****<0.0001
Na ²⁺ (mmol/L)	134.9 ± 1.048	132.8 ± 2.126	0.3701
K ⁺ (mmol/L)	4.089±0.05083	5.017±0.1602	****<0.0001
Cl ⁻ (mmol/L)	95.73 ± 1.866	95.78 ± 0.8163	0.9808

Results are expressed as Mean± SEM. An unpaired *t*-test was used. **** $P \leq 0.0001$.

Correlation Analysis of Zinc, Potassium with Renal Function Parameters Among HD Patients

To understand the interplay and impact on renal function (severity) and following the remark of altered zinc and K^+ levels in HD patients, the potential correlations between serum zinc levels, potassium levels, and estimated eGFR were assessed (Figures 1A and 1B). Interestingly, the comparative analysis between patients and control groups revealed a significant decrease in zinc levels in patients with HD (Table 3). However, this decline was not associated with any of the renal function parameters, specifically the estimated eGFR. Instead,

among the patient cases, a negative correlation between serum zinc levels and eGFR was observed with a slope of -3.239 ($P < 0.0001$).

The comparison related to the relationship between serum K^+ levels and eGFR analysis showed a significant negative correlation with a slope of -0.1064 ($P = 0.0035$) (Figure 1 B). The relationship explains a modest amount of variance in K^+ levels ($R^2 = 0.1273$), indicating a weak but significant inverse association with the study population. This indicates that higher K^+ levels are associated with poorer kidney function, as reflected by the decreased eGFR values in HD patients.

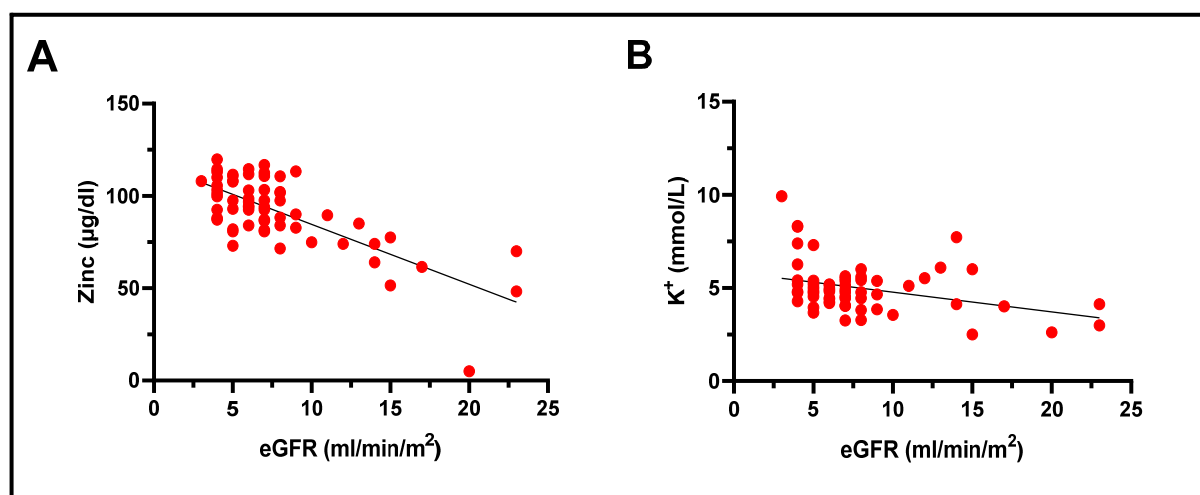


Figure 1 Correlation between Zinc, Potassium, and eGFR among HD patients

A) Relationship between estimated eGFR and serum Zinc levels.

B) The relationship between eGFR and serum K^+ levels. Each point represents an individual patient. The correlation analysis was performed using Pearson correlation coefficients. A linear regression line is also included for visualization.

Low Serum Zinc Level is Associated with Hypertension Among HD Patients

Figure 2 illustrates the comparison between serum zinc levels in HD patients with and without hypertension. The serum zinc level was significantly ($P = 0.0220$) lower in HD patients with hypertension (88.50 ± 2.686 ; $n=53$) compared to HD patients without hypertension (106.7 ± 2.931 ; $n=12$), and the median (interquartile range) was 0.822 (0.589 - 1.139) ng/ml and 0.601 (0.477 - 0.888) ng/ml, respectively. These results indicate that low zinc levels in HD patients might accelerate hypertension and further influence kidney damage.

Discussion

This study assessed the relationship between serum zinc levels, electrolyte balance, and kidney function in patients with CKD undergoing HD in Erbil City. The findings emphasize the significant disturbances in serum zinc levels and electrolyte balance in HD, with particular importance on the association between zinc deficiency and hypertension among the HD group.

Serum Zinc Levels in HD Patients

The distinctly lower serum zinc levels observed in HD patients compared to

healthy controls align with existing literature highlighting zinc deficiency as a common complication in CKD patients.^(15,22) Zinc plays an essential role in different physiological processes, including antioxidant defence and cellular metabolism.⁽¹⁴⁾ The significant reduction in zinc levels among HD patients, as noted in this study, suggests such shortage is prevalent and may contribute to the pathophysiology of CKD. However, despite the lower zinc levels in HD patients, our correlation analysis did not show a significant association between serum zinc levels and eGFR, which is consistent with other studies.⁽²³⁾ In both diabetic CKD patients and our cohort of ESRD patients, lower zinc levels were observed as renal function declined, suggesting that zinc deficiency may be a common issue across different stages of CKD. Furthermore, this suggests that while zinc deficiency is common among HD patients, it may indirectly correlate with the severity of kidney dysfunction as measured by eGFR. Notably, the relationship between serum zinc levels and hypertension analysis revealed that HD patients with hypertension had significantly lower zinc levels than those without hypertension. This finding supports previous research

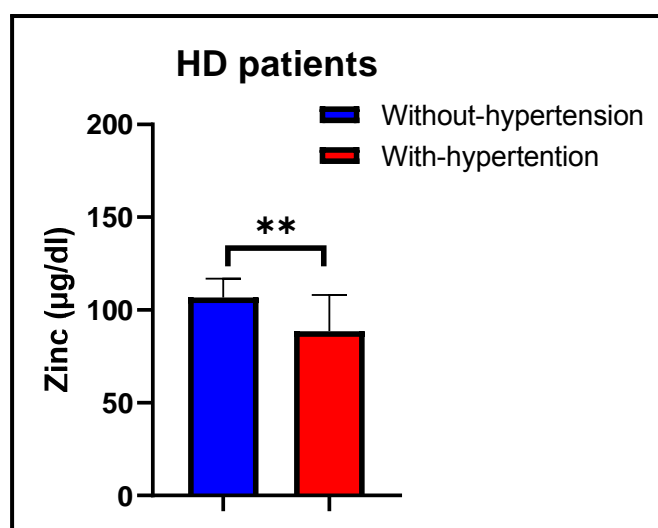


Figure 2 Comparison between serum zinc levels in HD patients with and without hypertension Non-paired student *t*-test is used for the comparison; ** $P < 0.051$.

suggesting a potential role of zinc in blood pressure regulation.⁽²⁴⁾ The inverse relationship between zinc levels and hypertension may indicate that zinc deficiency contributes to the exacerbation of hypertension in HD patients, possibly through its effects on the renin-angiotensin-aldosterone system.⁽²⁵⁾ This highlights the importance of monitoring and potentially supplementing zinc in CKD patients to mitigate hypertension and its associated risks.

Electrolyte Imbalance in HD Patients

This study revealed significant alterations in electrolyte level in HD patients, particularly concerning serum K⁺ levels. Indeed, HD patients exhibited significantly higher K⁺ levels compared to controls, consistent with the known association between hyperkalaemia and CKD progression, as renal function declines, the kidney's ability to excrete potassium diminishes, leading to hyperkalaemia, which might lead to cardiac arrhythmias or cardiac arrest. This is a common issue in HD patients due to their compromised kidney function.^(19,20)

Elevated potassium levels in CKD patients are primarily due to impaired renal excretion, leading to an increased risk of life-threatening complications such as cardiac arrhythmias.⁽¹⁹⁾ The significant negative correlation between serum K⁺ levels and eGFR observed in our study further reinforces the relationship between hyperkalaemia and declining kidney function and implies the cautious use of potassium-lowering therapy and a potassium-restricted diet in patients receiving HD.^(22,26) While serum sodium and chloride levels did not show significant differences between HD patients and controls, the elevated K⁺ levels emphasize the critical need for careful electrolyte management in this patient population. Thus, dietary supplementation therapies can be designed to prevent CKD patients from experiencing electrolyte derangement complications.^(27,28)

Further studies are needed to elucidate

the underlying mechanisms linking zinc deficiency to hypertension and kidney function in CKD patients, and a larger sample size study is essential to further confirm such deterioration.

Conclusion

In summary, this study emphasizes the importance of addressing zinc deficiency and electrolyte imbalances in ESRD patients undergoing HD and underscores the need for comprehensive management strategies that include monitoring and potentially supplementing trace elements like zinc, alongside careful regulation of electrolytes, to improve patient outcomes and reduce the risk of complications such as hypertension and hyperkalaemia.

Competing interests

The author declares that he has no competing interests.

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