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ORIGINAL ARTICLE

Trace Elements in Children With Pre-Dialysis and End-Stage Renal Disease

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Abstract

Background/Aim: Chronic kidney disease (CKD) impacts 11-13 % of world wild population and can lead to end-stage renal disease (ESRD). Paediatric CKD is connected with considerable morbidity and necessity for early management. Trace elements as iron (Fe), zinc (Zn) and copper (Cu) are required for a variety of physiological activities and may influence CKD progression. The main goal of this work was to analyse the amounts of trace elements among children with CKD and ESRD and their potential as disease stage biomarkers.

Methods: The study comprised 40 pre-dialysis CKD patients, 40 dialysis-dependent ESRD patients and 40 healthy controls aged 0 to 19 years. Blood samples were obtained and tested for Fe, Zn and Cu levels utilising flame-atomic absorption spectrophotometry (FAAS). Anthropometric data, such as age, body mass index (BMI) and blood pressure, were also collected. The statistical calculations were done by the utilising of SPSS version 25.0.

Results: Trace element levels varied significantly between groups. Cu levels were higher, while Fe and Zn concentrations were lower in CKD and patients on dialysis compared to controls, with Zn exhibiting the greatest drop. Zn had the highest accuracy as a biomarker for CKD and ESRD, with an the area under the curve (AUC) of 0.999, sensitivity of 100 % and specificity of 98 %.

Conclusion: Zn is a promising biomarker for detecting CKD development and distinguishing between CKD stages and ESRD. Regular trace element monitoring is critical for controlling paediatric chronic kidney disease and improving patients' consequences. Further research is needed to determine the therapeutic potential of trace element management in CKD.

Key words: Renal insufficiency, chronic; Children; Renal dialysis; Trace elements; Zinc.

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Introduction

Chronic kidney disorder (CKD) is a lifelong disease that is connected with significant morbidity and premature death as a result of problems caused by a progressive failure in renal function.[1] It refers to a disorder connected with irreversible kidney impairment, that could proceed to end-stage renal disease (ESRD).[2] This disease affects roughly 11-13 % of the world wild population.[3] The succession and frequency of all phases of CKD in children tend to raises globally. The prevalence of kidney replacement therapy in children aged 0 to 19 years increased by 5.9 % to 15 % for every one million population size, emphasising the necessity of paediatric CKD research.[4] Many

comorbid problems identified in adulthood with CKD, like cardiovascular illness and cognitive impairment, are even very prevalent in the children, subconsciously indicating the critical necessity to initiate therapy earlier to enhance life health outcome in children with CKD.[5] The primary reason of CKD is congenital abnormalities of the urinary tract and kidneys (CAKUT), which is a crucial feature of CKD in children.[6] The prevalence / incidence of CKD among children varies globally. Hypertension and nephropathy are distinct risk indicators for CKD development; other indicators that may influence CKD development include main disease, age, gender, racial/genetic characteristics, urological issues, little birth weight and socioeconomic background.[7] Many surveys using registry data found that female sex, younger age, non-white race, anaemia, non-CAKUT aetiologies, hypoalbuminemia and a high evaluated rate of glomerular filtration (GFR) are risk indicators for morbidity in children with kidney failure taking kidney replacement therapy.[8] When CKD develops to a higher stage and arrives at the end stage, dialysis is the last path to reduce the complications of renal failure. Dialysis is performed in children with renal failure.[9]

Dialysis outcomes are linked to the quality of dialysis provided, determined by the amount (ie dose), frequency and duration of dialysis; management of problems such as anaemia; blood pressure; phosphate control and laboratory monitoring.[10] In haemodialysis, the kind of vascular access influences morbidity and mortality.[11] Trace elements are chemicals in very small concentrations in the human system yet are vital for supporting certain physiological activities. While these elements are minimal, they are essential for various metabolic activities and overall health.[12] Patients that have a disparities of vital trace elements and treatment depending on these is an exciting area for future research. Understanding trace element homeostasis is critical for improving CKD patients' prognoses and slowing disease progression.[13] Although there is much research on individuals with CKD and dialysis in Iraq, there is relatively little focus on children who struggle with these conditions, particularly in terms of monitoring trace element amounts and factoring it in balancing.

This investigation aimed to determine the concentrations of iron (Fe), zinc (Zn) and copper (Cu) in children with kidney disorders and compare them to dialysis patients based on body mass index (BMI), age and gender, as well as to determine whether each mineral can act as a biomarker to estimate the stage of the disease.

Methods

Study population

This study dealt with patients with ESRD who received weekly haemodialysis, offering insight into how reducing dialysis frequency affects patient health outcomes. The samples were collected from the renal centre in different governorates (Baghdad, Anbar, Karbala, Wasit and Arbil) in the period between (August-November) 2023.

The first group comprised of 40 patients with CKD pre-dialysis, aged between 0-19 years old have been collected. The second group comprised of 40 children in dialysis end-stage of CKD. Patients who were getting haemodialysis had their blood samples taken after the procedure. These patients received one dialysis session each week. The adequacy of dialysis was evaluated using two important parameters: Kt/V (urea clearance): aim value of 1.2 or more after every session guaranteed adequate dialysis; and the urea reduction ratio (URR): a goal of 65 % or greater indicated efficient urea elimination during dialysis. All dialysis treatments used reversed osmosis-treated water to maintain the quality of the dialysate, lowering the risk of problems and assuring that treatment was secure and successful for all patients. These two groups were compared with the third group, 40 healthy control children with no medical issues.

Inclusion and exclusion criteria

The current study included two patient groups with two inclusion systems. The first group included patients with CKD in 1 from the first four stages of pre-dialysis and any other chronic diseases were excluded as much as possible. The second group included patients with ESRD who undergo dialysis. Even in this group, all other chronic diseases were excluded as much as possible to isolate the disease and focus the study on kidney patients only.

Anthropometric study

The information on control and patients in all groups was collected in a particular survey to measure gender and age. Then, all participants measured the weight and height for each one to estimate the BMI. BMI calculated by the simplest equation: $BMI = \frac{WT}{H^2}\ (kg/m^2)$. After that, all participants went for blood pressure measuring to estimate systolic and diastolic pressure.[14]

Sample collection

The control and patients had blood drawn by nurses who specialised in dealing with children. Five mL of blood was taken out from every participant and put in a vacuum gel tube. The blood was separated by centrifuge at 4000 rpm for 6 min to separate the serum for the following work. The collected serum was then utilised to evaluate the concentration of the studied parameters (Fe, Zn and Cu).

Flame atomic absorption spectrophotometer (FAAS) Model AA646, *Shimadzu Corporation*, Kyoto/Japan was utilised to test the elements (Cu, Fe and Zn), serum dilutions were produced with deionised water and microwaved before metal analysis. A 1000 µg/dL standard AAS reference of stock solution for the metals was diluted with HCl: HNO_3 (3:1) to obtain (10, 50, 100, 150, 200, and 250) µg/dL. The standards were employed to create calibration curves for metals. Metal calibration curves showed linearity values.[15]

Statistical analysis

The IBM SPSS Statistics programme (IBM Corporation, New York, United States) version 25.0 was used in the analysis. The data were analysed utilising descriptive calculations and given as means ± standard deviation (SD). LSD test was used to compare mean differences among the patients and the control group. Statistical significance was defined as $p < 0.05$ with a 95 % confidence interval and extremely significant at $p \leq 0.01$ with a 99 % certainty interval.[16]

Results

Anthropometric and gender study

A descriptive study was done for gender to show the distribution of diseases among males and females. In first group female to male ratio was 22 (55 %): 18 (45 %). Meanwhile, 23 females represented 57.5 % of dialysis patients and 17 males represented 42.5 %. The percentage of males and females in CKD and dialysis patients is shown in Figure 1.

Age showed a significant difference ($p < 0.001$) between control (7.38 ± 4.76) as compared with dialysis group (8.8 ± 4.46) and CKD (11.8 ± 3.4) as compared with dialysis group (8.8 ± 4.46) ($p = 0.002$). However, there was a non-significant difference ($p = 0.128$) between control and CKD group (Figure 2).

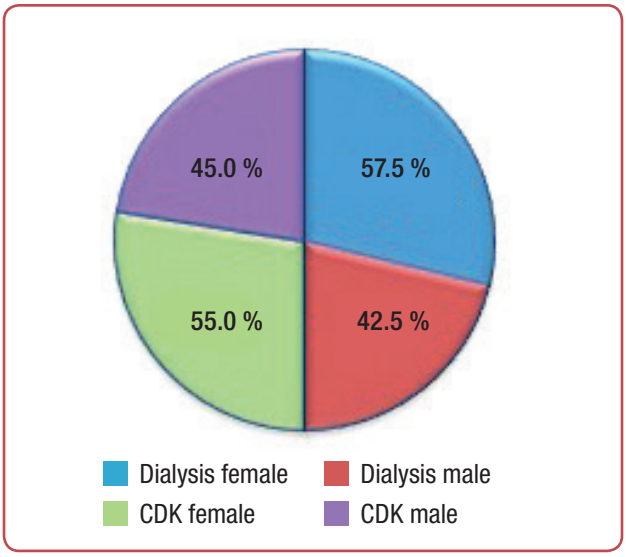

Figure 1: Gender distribution in examined groups

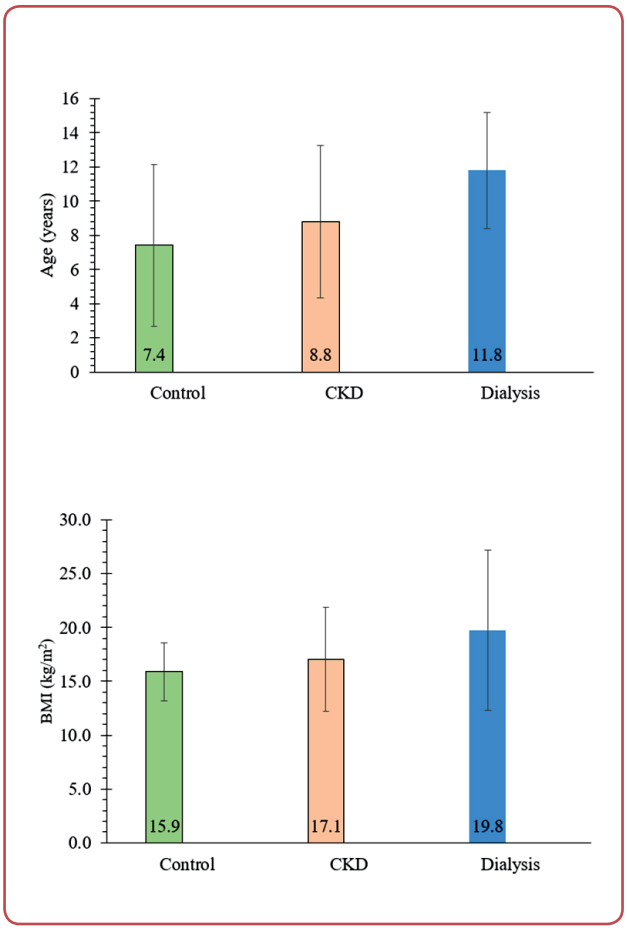

Figure 2: Age and body mass index (BMI) in examined groups

Table 1: Arterial blood pressure (BP) levels in analysed groups

BP (mm Hg)	Control	CKD	Dialysis	p-value
Systolic BP	114.0 ± 12.4	117.0 ± 14.5	123.0 ± 25.3	0.360[a], 0.050[b], 0.053[c]
Diastolic BP	77.7 ± 8.7	74.0 ± 11.9	83.3 ± 18.5	

a: control vs CKD; b: control vs dialysis; c: chronic kidney disease (CKD) vs dialysis;

BMI showed a significant difference between control (15.88 ± 2.67) as compared with CKD (17.05 ± 4.84) (p = 0.027) and dialysis (19.75 ± 7.45) (p = 0.002), but there was a non-significant difference (p = 0.329) between CKD and dialysis (Figure 2). Blood pressure levels were significantly different between control (114.0 ± 12.4 / 77.7 ± 8.7) and dialysis group (123.0 ± 25.3 / 83.3 ± 18.5) (p = 0.050). There was a non-significant difference between control and CKD (117.0 ± 14.5 / 74.0 ± 11.9) ± (0.360) or CKD and dialysis group (p = 0.053) (Table 1).

Trace elements study

Fe showed an extremely significant difference between control (113.8 ± 15.7) and CKD (92.4 ± 28.2) (p = 0.002), as well as dialysis groups (73.8 ± 20.1) (p < 0.001). Significant difference was as well between CKD and dialysis group (p = 0.012). Cu levels were highly significantly different (p < 0.001) among all of the three groups. Cu levels were significantly lower in control group (109.2 ± 16.8), compared to CKD (130.1 ± 20.2) and dialysis group (150.2 ± 9.0).

Zn concentration was higher in control group (96.1 ± 15.1), compared to CKD (71.1 ± 7.6) and dialysis group (61.2 ± 5.0) (p < 0.001). Significant difference was as well between CKD and dialysis group (p = 0.010) (Figure 3).

Receiver operating characteristic (ROC) analysis for trace elements

ROC analysis has been done for trace elements for CKD and dialysis groups to obtain the specificity and sensitivity for the parameters and to find the best parameters to diagnose and monitor gastric cancer. The results of ROC analysis for the CKD group are shown in Table 2 and Figure 4.

The data provided in Table 2 demonstrate the area under the curve (AUC), standard error (SE), p-value, cut-off value, sensitivity and specificity for each parameter. Fe exhibited good discriminatory power with an AUC of 0.630, indicating its ability to differentiate between the two groups

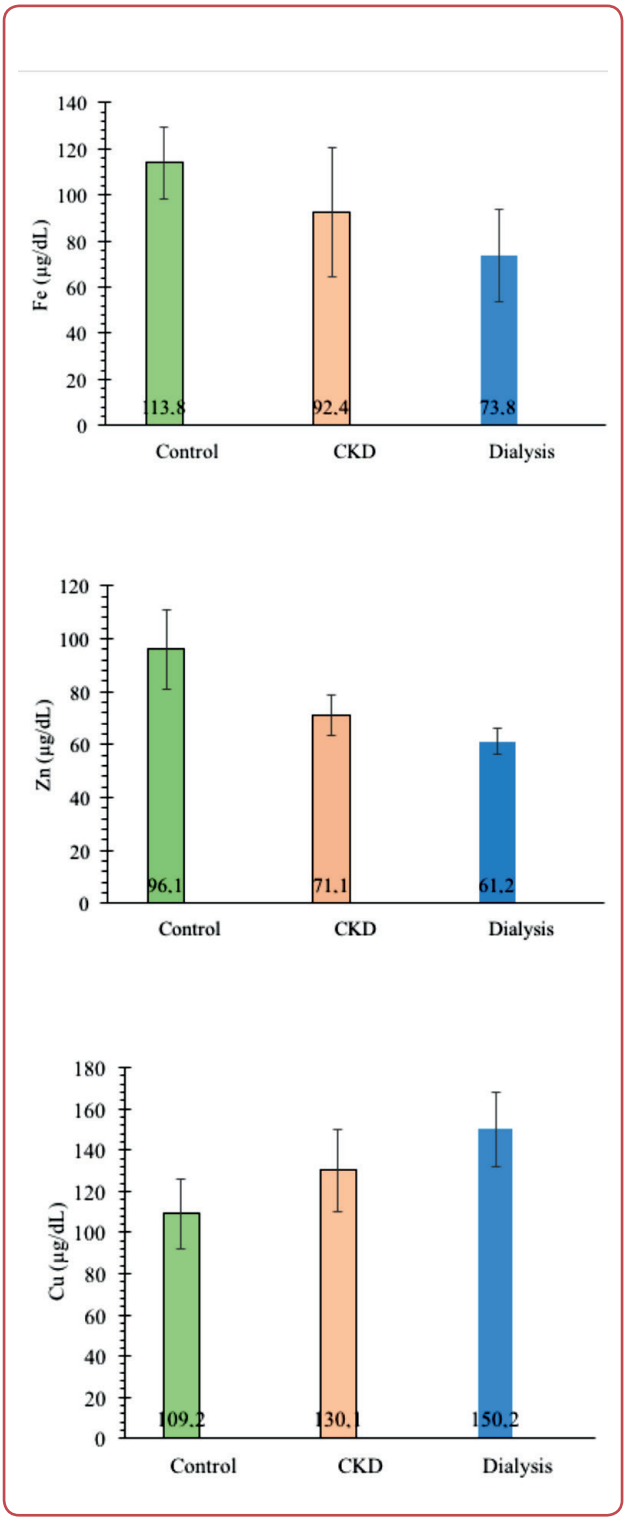

Figure 3: Iron (Fe), zinc (Zn) and copper (Cu) levels in analysed groups

Table 2: Receiver operating characteristic (ROC) analysis of trace elements in chronic kidney disease (CKD) group

Parameter	AUC	SE	p-value	Cut-off value	Sensitivity	Specificity
Fe	0.630	0.063	0.046	101.0	70 %	60 %
Cu	0.830	0.046	< 0.001	123.5	80 %	75 %
Zn	0.962	0.017	< 0.001	79.5	90 %	87 %

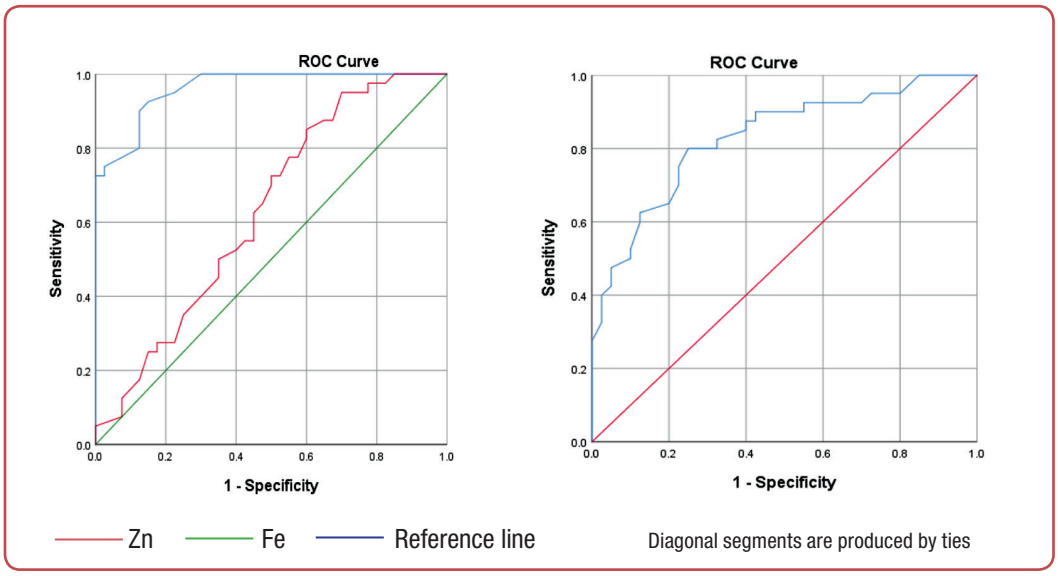

Figure 4: Receiver operating characteristic (ROC) for trace elements in chronic kidney disease (CKD) group

Table 3: Receiver operating characteristic (ROC) analysis of trace elements in dialysis group

Parameter	AUC	SE	p-value	Cut-off value	Sensitivity	Specificity
Fe	0.907	0.033	< 0.001	93.0	85.0 %	84 %
Cu	0.985	0.009	< 0.001	134.5	92.5 %	95 %
Zn	0.999	0.002	< 0.001	73.5	100.0 %	98 %

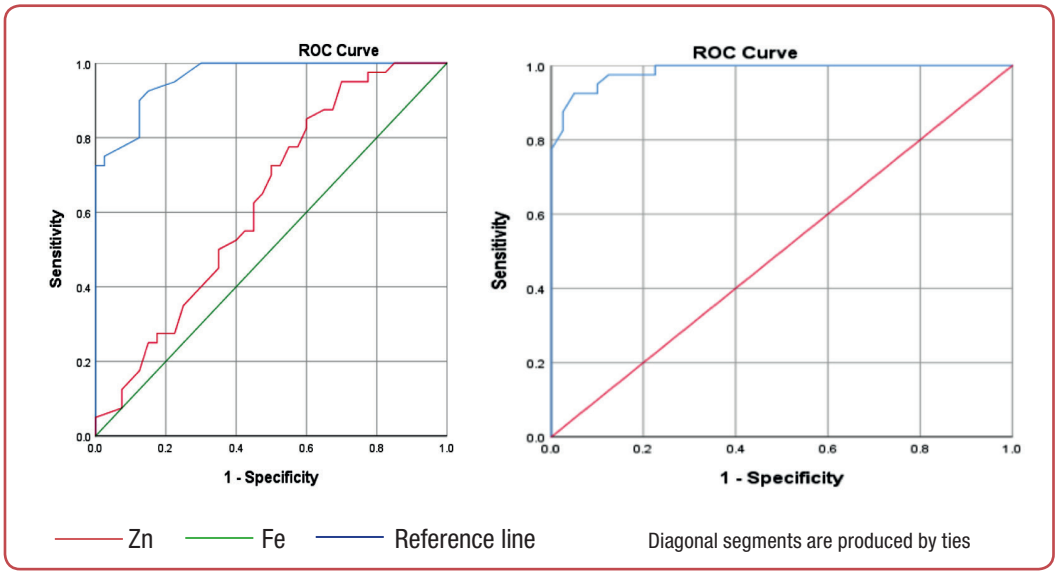

Figure 5: Receiver operating characteristic (ROC) study for trace elements in dialysis group

effectively. Cu demonstrated high accuracy in identifying individuals with CKD at a sensitivity of 80 % and specificity of 75 %. At a sensitivity of 90 % and specificity of 87.5 %, Zn showed excellent accuracy in identifying individuals with CKD.

The results of ROC analysis for dialysis are shown in Table 3 and Figure 5. The data provided in Table 3 demonstrate the area under the curve (AUC), standard error (SE), p-value, cut-off value, sensitivity and specificity for each parameter. Fe exhibited excellent discriminatory power with an AUC of 0.907, indicating its ability to differentiate between the two groups effectively. At a sensitivity of 92.5 % and specificity of 95 %, Cu accurately identified individuals with CKD. At a sensitivity of 100 % and specificity of 98 %, Zn accurately identified individuals with CKD.

Discussion

Gender effect in the current study shows a little difference in distribution among females compared to males in the two conditions of kidney diseases and this result confirmed that kidney diseases in children is less influenced by sex than in adults. Hormonal and lifestyle effects did not represent the leading risk factor in children. Genetic disorders, congenital abnormalities, kidney infections, nephrotic syndrome, immune disease and drug-toxic effects are the main risk factors for CKD in children.

Age analysis showed a non-significant difference between control and CKD patients. These results clarify that CKD began at a very young age, so the age of control and diagnosed CKD children appear nearly in the same age. There was a significant raise in the dialysis children group as compared with control and CKD groups and this was back to the duration of diseases and the time of transformation from CKD to ESRD or dialysis. The current results are in agreement with other studies like Staples et al, who wrote that age is a significant risk indicators for the development of CKD to renal failure and dialysis.[17] Warady and his colleagues confirm that the period between CKD and ESRD depends on different factors like time of diagnosis and type of treatment.[18] However, in the study done on 398 adolescent under 19 years, the calculated period between CKD and ESRD was 3.7 – 5.2 years.

BMI showed a significant increase in the BMI for the CKD and dialysis group matched to the control. Furthermore, blood pressure results showed a slight elevation in the dialysis group as compared with control and CKD groups. Obesity raises the chance of developing CKD and eventually progressing to ESRD. Obesity is a rapidly expanding concern for the global renal community, as a growing number of obese CKD, as well as ongoing dialysis patients, is expected to raise significantly in both developed and low- and middle-income nations.[19] Obesity is linked to albuminuria, hypertension and dyslipidaemia, all of which can affect the course of CKD.[20] Obesity increases the risk of some glomerulonephritis, like FSGS, compared to lean persons.[18] Hypertension combined with proteinuria has been shown to be a significant risk factor for the appearance of primary kidney disorders in children as well as adults and the renoprotective activity of renin-angiotensin system (RAS) inhibitors, which is slightly independent of blood pressure levels, is readily apparent in animal studies and adults with gained nephropathies.

In contrast, both ACE inhibitors and blockers of angiotensin receptors have been demonstrated to diminish proteinuria among children with CKD.[21] Unlike many CKD consequences, hypertension can be evident from the beginning of the disorder and increases in prevalence as GFR drops.[22] A recent study conducted through the CKD in children study group revealed that hypertension had been detected in 54 % of the subjects at the time of enrolment and possibly more strikingly, 48 % of the children suffered high blood pressure quantities despite the use of antihypertensive drugs, which generally consisted of renin-angiotensin-aldosterone system inhibitors (RAAS-I).[23]

Fe is a critical transitory element that provides flexibility. Fe plays an essential role in catalysing redox processes and serves as a co-factor in a lot of enzymes. It is crucial for fundamental cellular activities and biological processes and these include oxygen transport, aerobic respiration and intermediate and xenobiotic metabolism.[24] Fe level decreased for dialysis and CKD groups compared to control. There was also a significant decrease in Fe for dialysis compared to CKD. The results obtained in the current study agree with previous studies about Fe deficiency anaemia in CKD patients. Batchelor et al showed an apparent decrease in the level of Fe in CKD children and state that anaemia is a consequence that occurs in the majority of people with severe CKD.[25] Al-

though a relative lack of erythropoietin manufacturing is the primary cause of anaemia in CKD, Fe deficiency is one of the processes contributing to decreased erythropoiesis in the context of lower renal function. Fe deficiency contributes significantly to anaemia in CKD.[25] This could be because of an actual scarcity of Fe stores (absolute Fe deficit) or a relative (functional) insufficiency that hinders the utilise of existing Fe stores.[26] Several risk indicators lead to absolute and functioning Fe deficiency in CKD, such as blood loss, poor Fe absorption and chronic inflammation.[27] For dialysis patients, Fe deficiency is one of the most famous signs.[28] Chronic haemodialysis patients frequently suffer from Fe shortage, necessitating Fe replacement therapy.[25] Many individuals have both absolute and functional Fe insufficiency, as evidenced by a poor response to erythropoietin-stimulating drugs (ESAs).[29] Anaemia in CKD patients is caused by diminished erythropoietin manufacturing and reticuloendothelial Fe blockage due to chronic renal inflammation.[30] Hepcidin regulates plasma concentrations of Fe by binding to ferroproteins, leading to Fe internalisation in the reticuloendothelial system. Kidney failure causes higher hepcidin levels due to impaired renal clearance and inflammation, reducing plasma Fe availability and anaemia.

Zn, the second among the most critical trace elements in the human body, is crucial in regulating cellular and subcellular processes across various tissues. Zn deficiency is linked to the advancement of CKD and related consequences. As CKD progresses to ESRD, dialysis may be necessary.[31] Zn level significantly decreased for dialysis and CKD groups compared to control. Furthermore, there is a significant difference between CKD as compared with dialysis. These results agree with Elgenidy et al which reported that serum Zn concentrations were decreased in CKD and haemodialysis patients relative to control and appear to be more prevalent than recorded in daily clinical practice. Anorexia, food limitations and haemodialysis can all cause alterations in Zn homeostasis in CKD patients.[32] Zn homeostasis changes could expose CKD and HD patients to certain adverse effects, including erythropoietin-resistant anaemia, oxidative stress-related atherosclerosis and heart disease. Because blood concentrations of Zn are rarely examined in CKD and patients with HD, Zn supplementation is not a conventional treatment for them.[33] Zn concentrations are decreased in CKD, which is not balanced by decreased renal Zn excretion. The inverse relationship among urinary Zn outflow and uromodulin may indicate reduced tubular function, which could explain Zn imbalance in CKD. These data imply that Zn level is related to renal function deterioration.[34] In some situations, Zn insufficiency is caused not only by the disease but also by a lack of a Zn-rich diet, which leads to a drop in Zn in patients with CKD.[35] As a result, more research is needed to add Zn to therapeutic supplements for renal failure patients.

Cu is a crucial trace element derived primarily from meals; however, recent research reveals that circulation Cu amounts are also genetically determined.[36] Trauma-related mortality has been linked to changes in flowing trace elements in a lot of organs, such as the heart, brain, liver and kidney. Excessive dietary Cu intake can cause nephrotoxicity, resulting in proximal tube necrosis, oxidative stress, cellular injury and impaired kidney function.[37] Cu concentration significantly increased in dialysis and CKD groups as matched with control. This result is in agreement with previous studies. Cu and renal disorders have a bi-directional relationship, with imbalances in flawing Cu concentrations caused by impaired renal excretion and protein metabolism in CKD patients. Regulating Cu levels is crucial to prevent complications.[38] Previous investigations have linked higher circulation Cu levels to CKD. Traditional empirical epidemiological studies are prone to ambiguity and reverse causality; therefore, it is questionable if greater body levels of Cu cause kidney injury, faster loss of renal function and a greater likelihood of CKD.[39] Circulating Cu was linked to an increased risk of CKD and lower GFR levels. Cu is a crucial human transition metal, acting as a cofactor for multiple enzymes engaged in various physiological activities. Cu circulating in the body is influenced by genetics, but it can also be ingested through diet and enter the bloodstream.[40] Cu in the kidneys produces highly reactive hydroxyl radicals, which can lead to proximal tube necrosis due to oxidative stress. Observational epidemiological research has linked higher Cu intake to abnormal GFR and ESRD.[41]

ROC analysis confirmed that Zn is the best parameter to diagnose stage of CKD because it has an AUC of 0.962, sensitivity of 90 %, and specificity of 87.5 %. This data could work as an excellent parameter. On the other hand, Zn represents the best parameter to differentiate between CKD stages and dialysis because it shows an AUC of 0.999, a sensitivity of 100 % and a specificity of 98 %.

Conclusion

This study found substantial differences in trace element concentrations between children with CKD, ESRD (dialysis group) and normal controls. Fe and Zn concentrations were significantly decreased in CKD and dialysis patients than in controls and Cu concentrations were increased in patients. Zn showed the most dramatic drop. Zn demonstrated the highest accuracy in distinguishing between CKD stages and dialysis, with an AUC of 0.999, sensitivity of 100 % and specificity of 98 %, indicating its potential as a dependable biomarker for disease development. The study emphasises the significance of monitoring trace element levels in paediatric CKD for better disease treatment and outcomes.

Ethics

The study was approved by the Ethics Committee of the University of Fallujah, College of Applied Sciences, decision No 38432, dated 18 July 2023. All procedures performed in studies involving human participants followed the ethical standards of the ethical committee in the "University of Fallujah, College of Applied Sciences" and with the 1964 "Helsinki Declaration" and its later amendments or comparable ethical standards. Written informed consent was obtained from patients and/or their legal guardians prior to their participation in the study and for publishing of the anonymised data.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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