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Assessment of Trace elements (Zinc, Copper) in Iraqi Patients with Chronic Kidney Disease on Dialysis

Ahmed Alaa Saleem Alturfi[1] and Mohammed Imran Hamzah[2]

[1]*Al-Hakim General Hospital, Najaf, Iraq.*

[2] *College of Medicine, University of Nahrain, Baghdad, Iraq.*

E-mail: ahmedaltorfi45@gmail.com

ABSTRACT

Background: *In the context of insufficient healthcare accessibility for a substantial segment of the global populace, chronic kidney disease (CKD) has emerged as a significant contributor to mortality, ranked subsequent to cardiovascular disease and neoplasia, demonstrating a notable increase over the preceding two decades. This rising burden of CKD is further exacerbated by a deficient understanding of its underlying pathogenesis. Therefore, it was important to study all the variables in the human body that contribute to monitoring the patient's condition or preventing the patient's condition from deteriorating. In this study, we highlighted some trace elements (zinc and copper), and monitored the change in these elements between patients and healthy people. We indicated the possibility of monitoring the results of tests for these elements to predict the condition of patients from the first stage to the final stages of chronic renal failure patients on dialysis.* ***purpose****: To assess the trace elements (zinc, copper) in Chronic kidney disease patients compared with healthy control.* ***Methods****: A total forty (40) patient with chronic kidney disease were studied among them twenty (20) female and twenty (20) male patients and forty (40) healthy as control of them were eighteen (18) females and twenty-two (22) males. Their ages (patients and controls) were ranged from (18 – 70). Blood samples were collected from patients and control to evaluate serum levels of serum trace elements (zinc, copper) and evaluate the routine markers (urea, creatinine, Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) and this was done by spectrophotometry.* ***Results*** *The Zinc levels in the patients (80.69±51.30 µg/dl) were lower than in the control group (97.42±38.61 µg/dl) (p=0.10773) and The Copper levels in the patients are significantly higher (116.33±71.20 µg/dl) than in the control group (74.77±46.16 µg/dl) (p=0.00304). while The Alanine Aminotransferase and Aspartate Aminotransferase levels in the patients are lower than in the control group, but the difference is not statistically significant for ALT (p=0.13235) and is significant for AST (p=0.02982). the Alkaline Phosphatase, Urea, and Serum Creatinine levels in the patients were all significantly higher than in the control group (p<0.00001 for all).* ***Conclusion:*** *A notable elevation in alkaline phosphatase and copper levels is observed in chronic kidney disease patients, alongside a modest decrease in serum zinc in those with end-stage chronic kidney disease compared to healthy individuals, indicating these biomarkers' potential diagnostic utility in advanced stages of the disease. The correlation between AST/ALT and CKD progression highlights the impact of liver enzyme alterations during chronic kidney disease.*

Keywords:Chronic Kidney Disease, Serum Trace Elements, Zinc, Copper, Hemodialysis.

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Article Information

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INTRODUCTION

Chronic kidney disease (CKD) exerts a considerable and profound impact on the concentrations of essential trace elements, specifically zinc and copper, both of them play pivotal roles in a wide array of physiological processes that are vital for maintaining overall health and homeostasis. A plethora of studies has demonstrated that individuals undergoing dialysis treatment frequently present with diminished levels of zinc and elevated levels of copper when compared to their healthy counterparts who do not suffer from such renal impairments. The resultant imbalance of these critical trace elements can precipitate a variety of complications, including but not limited to anemia and cardiovascular disorders, thereby underscoring the imperative need for regular clinical monitoring and the potential consideration of dietary supplementation strategies aimed at restoring equilibrium (Xie *et al*., 2022) (Fukasawa *et al*., 2023).

Zinc is recognized as an indispensable element for the proper functioning of the immune system and for the process of erythropoiesis, a deficiency in this vital trace element can manifest in various adverse symptoms, including dermatitis and cognitive decline, thus highlighting its importance in human health (Fukasawa *et al*., 2023). Regarding the levels of copper in patients with CKD, it is noteworthy that elevated copper concentrations are frequently observed among this population, and excessive amounts of this trace element can lead to toxic effects, thus necessitating careful monitoring and management (Ahmed & Ahmed, 2024).

However, several scholarly investigations have suggested that copper may serve a protective function under specific circumstances, thus indicating that the relationship between these trace elements and the progression of chronic kidney disease is characterized by a certain degree of complexity and nuance (Xie *et al*., 2022).

METHODS

This case control study was carried out on an 80 participants age ranged from 18 to 70 years, consist of patients diagnosed as CKD, all patients are under hemodialysis compare to 40 healthy persons as controls were enrolled serially in the study. The control subjects were taken from the same socioeconomic population who matched for their age and body mass index (BMI) with the cases. All persons in control group were have normal kidney function. All the participants notified about the goals of the study, and informed. All patients were attended from Al-Hakim General Hospital (dialysis unit) and Al-najaf Teaching Hospital in alnajaf. Patients and controls were with a comparable age.

•Exclusion Criteria: patients with; 1.Cardiovascular disease 2. Liver disease 3. diabetes disease 4. thyroid disease 5. Leukemia 6. Elderly patient above 70 years .

Sample collection:5ml of blood were taken from each patient and control, serum was centrifuged at 2000 rpm for 5-10 minutes. The levels of serum zinc, copper, Urea, Creatinine, Alkaline, Phosphatase, Alanine Aminotransferase and Aspartate Aminotransferase measured

Kits and Instruments:

The methods used to measure the markers were way according to the substance that was measured as listed in Table (1).

Chemicals	Type	Suppliers
Urea	spectrophotometry	Snibe, china
Creatinine	spectrophotometry	Snibe, china
LDH	spectrophotometry	Bioresearch, Germany
Zinc	spectrophotometry	Bio labo, France
Copper	spectrophotometry	Spectrum, Egypt
ALT	spectrophotometry	Snibe, china
AST	spectrophotometry	Snibe, china
Alkp	spectrophotometry	Snibe, china

Table (1): Kits and their suppliers.

Statistical analysis:

Data analysis was performed using SPSS software Windows, version 22 (SPSS Inc. Chicago, Illinois, United States). The Shapiro normality test was used Wilk to determine whether the studied parameters follow a Gaussian distribution. Categorical variables were expressed as frequencies and proportions. Proportions were compared using the chi-square (x2) test. Expressed Report data as mean standard deviation (SD) For continuous variables. Tukey's Post Hoc tests were applied for multiple comparisons after ANOVA tests. Scores were analyzed Correlation between variables by Pearson correlation analysis. In addition, ROC was used to evaluate the area under the curve (AUC). The best cut-off point for the studied signs was also calculated sensitivity and specificity. A p value less than 0.05 was considered significant Statistical (Forthofer et al., 2014).

RESULTS

Sex: The sex distribution in both groups was balanced. The patient group exhibited an equal gender ratio. The control group indicated a male predominance of 55% males to 45% females. Nonetheless, the sex distribution between groups was statistically insignificant ($P > 0.05$). This information is depicted in figure (1).

Age: The mean age of the patients (44.68±16.19 years) and the control group (46.95±15.03 years) does not differ significantly (p=0.52200), suggesting that age does not significantly influence the differences observed in other parameters. as in figure (2)

BMI: The patients exhibited a significantly reduced Body Mass Index (23.79±3.97) compared to the control group (27.19±3.82) (p=0.00023). This disparity may be attributed to dietary limitations and metabolic alterations related to CKD and hemodialysis. Refer to figure (3) for visual representation.

Biochemical parameters

Biochemical variables were assessed between two cohorts. This investigation elucidates the physiological alterations in CKD patients receiving hemodialysis. The marked disparities in BMI, Copper, AST, ALP, Urea, and S. Cr. levels between CKD patients and controls emphasize the metabolic and physiological burdens imposed by CKD and hemodialysis. These results accentuate the necessity for tailored and comprehensive medical management for CKD patients to address these alterations and enhance their quality of life.

Zinc: The Zinc levels in the patients (80.69±51.30 µg/dl) were lower than in the control group (97.42±38.61 µg/dl), but the difference is not statistically significant (p=0.10773). Refer to figure (4)

Copper: The Copper levels in the patients are significantly higher (116.33±71.20 µg/dl) than in the control group (74.77±46.16 µg/dl) (p=0.00304). This could be due to altered mineral metabolism in CKD. Refer to figure (5)

AST&ALT: The Alanine Aminotransferase and Aspartate Aminotransferase levels in the patients are lower than in the control group, but the difference is not statistically significant for ALT (p=0.13235) and is significant for AST (p=0.02982). These enzymes are markers of liver function, and their levels can be affected by CKD and hemodialysis. Refer to figure (6), (7)

Blood urea & Serum Creatinine & Alkaline phosphatase:

The Alkaline Phosphatase, Urea, and Serum Creatinine levels in the patients were all significantly higher than in the control group ($p<0.00001$ for all). These are all markers of kidney function and their elevation is expected in CKD patients. Refer to figure (8), (9), (10).

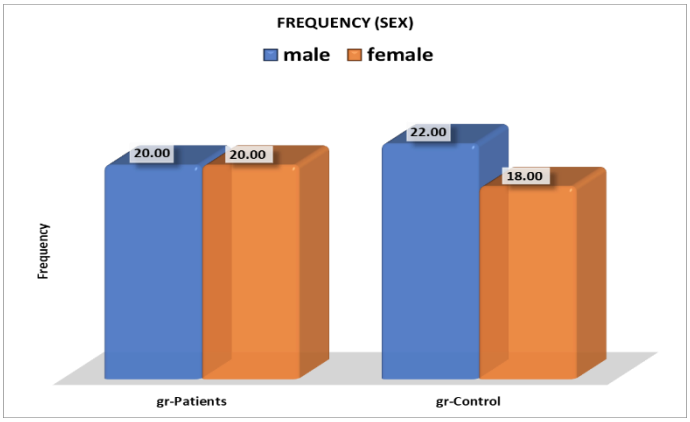

Figure (1) Show the comparisons of sex frequency between the groups

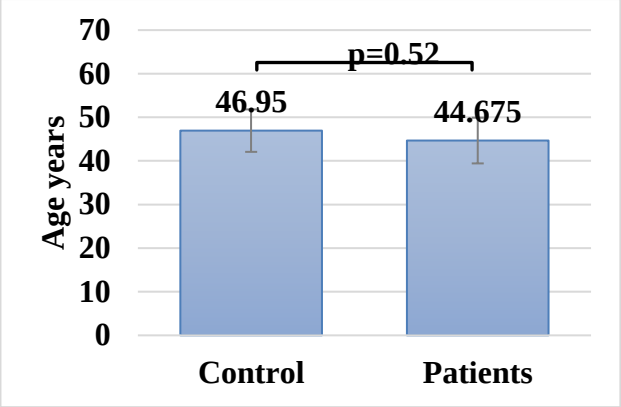

Figure (2) Bar chart for Means & 95%Confidence interval error bars of (Age) by groups

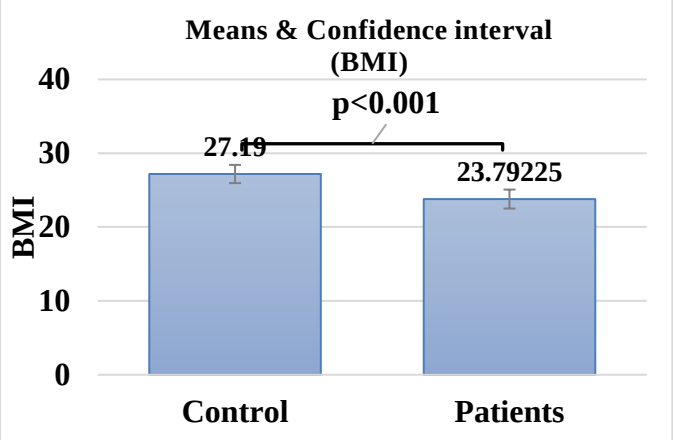

Figure (3) Bar chart for Means & 95%Confidence interval error barsof (BMI) by groups

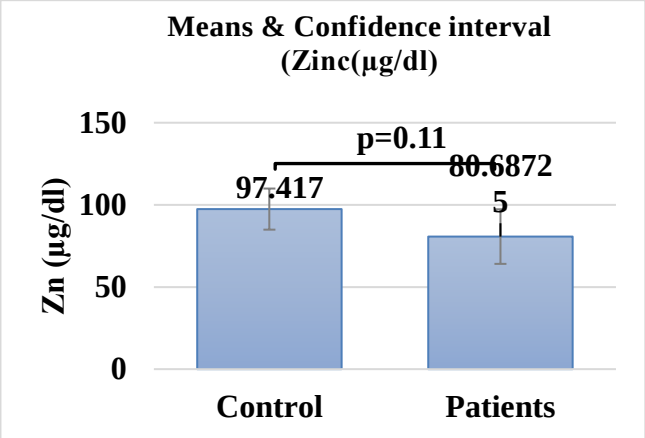

Figure (4) Bar chart for Means & 95%Confidence interval error bars of (Zn) by groups

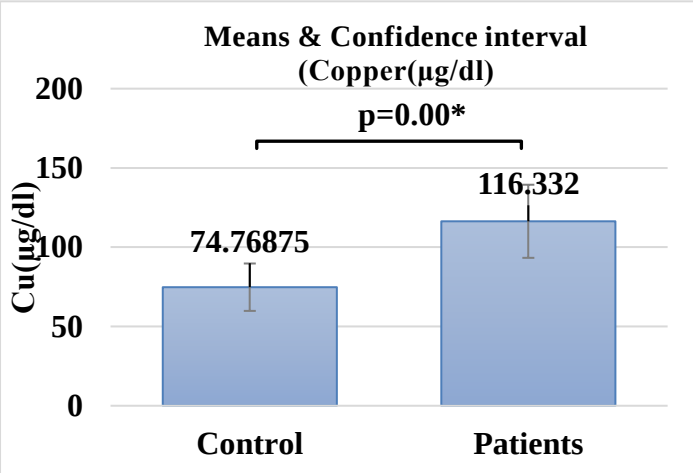

Figure (5) Bar chart for Means & 95%Confidence interval error bars of (Cu) by groups

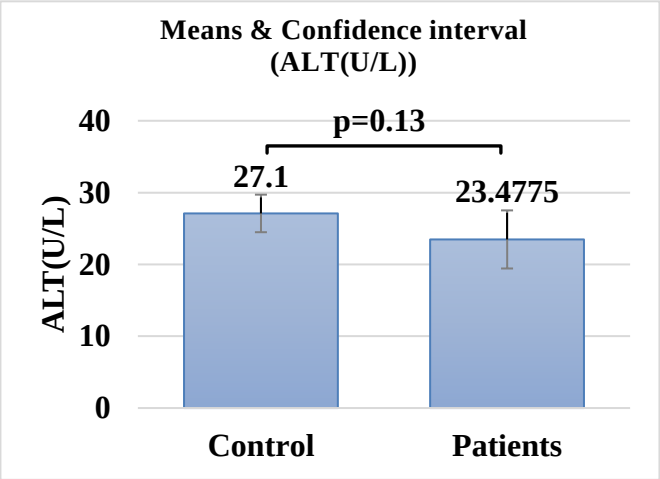

Figure (6) Bar chart for Means & 95%Confidence interval error bars of (ALT) by groups

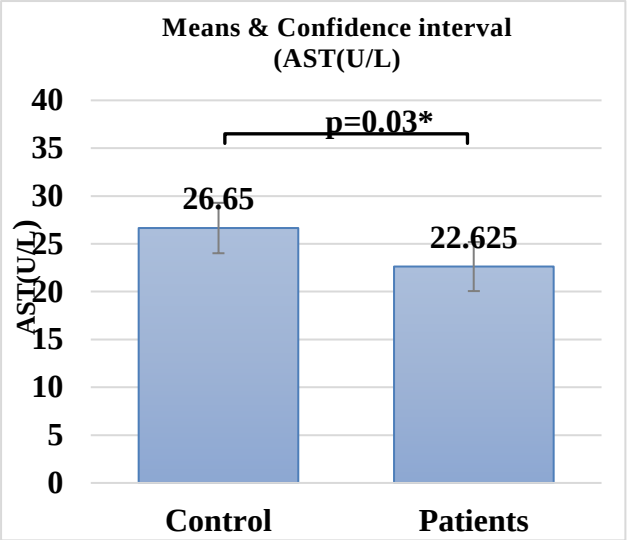

Figure (7) Bar chart for Means & 95%Confidence interval error bars of (AST) by groups

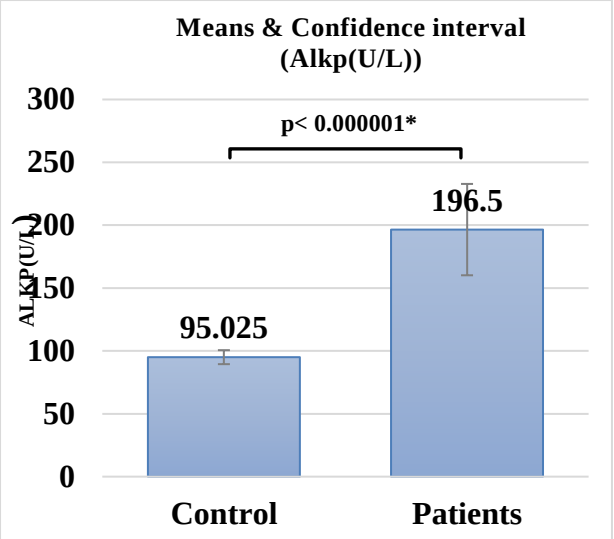

Figure (8) Bar chart for Means & 95%Confidence interval error bars of (ALP) by groups

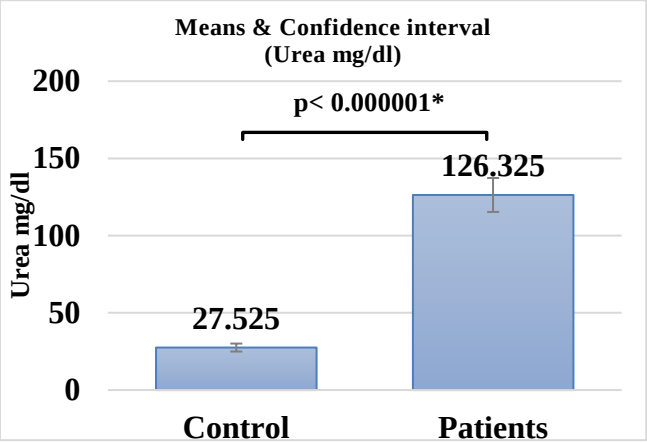

Figure (9) Bar chart for Means & 95%Confidence interval error bars of (Urea) by groups

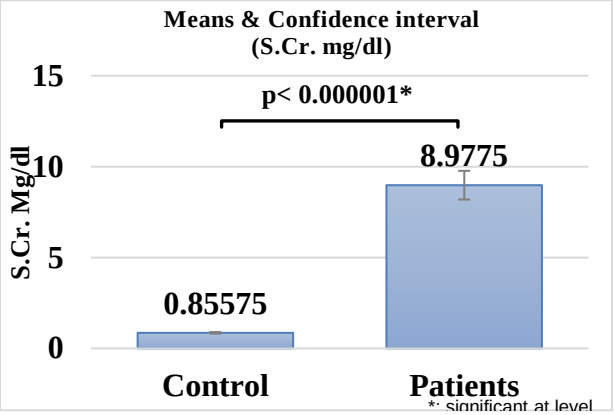

Figure (10) Bar chart for Means & 95%Confidence interval error bars of (Creatinine) by groups.

Table (2) Pearson correlation coefficient between the studied variable in patients.

		Age (year)	Weight (Kg)	Height (cm)	BMI (Kg/h^2)	LDH (U/L)	Zinc (µg/dl)	Copper (µg/dl)	ALT (U/L)	AST (U/L)	Alkp (U/L)	Urea (mg/dl)
Age (year)	r	1.00										
	P											
Weight (Kg)	r	0.42	1.00									
	P	0.01										
Height cm	r	0.38	0.75	1.00								
	P	0.02	<0.0001									
BMI (Kg/h^2)	r	0.35	0.88	0.35	1.00							
	P	0.03	<0.0001	0.03								
Zinc (µg/dl	r	-0.30	-0.33	-0.30	-0.24	0.10	1.00					
	P	0.06	0.04	0.06	0.14	0.55						
Copper (µg/dl)	r	0.09	0.04	0.03	0.02	-0.07	0.03	1.00				
	P	0.59	0.83	0.85	0.92	0.68	0.86					
ALT (U/L)	r	0.07	0.17	0.12	0.19	-0.02	-0.18	-0.11	1.00			
	P	0.67	0.30	0.48	0.25	0.91	0.27	0.48				
AST (U/L)	r	-0.25	0.02	-0.03	0.06	-0.19	-0.13	0.04	0.58	1.00		
	P	0.12	0.89	0.84	0.69	0.25	0.42	0.81	0.00			
Alkp (U/L)	r	-0.15	-0.18	-0.13	-0.15	0.30	0.36	0.12	-0.08	-0.07	1.00	
	P	0.37	0.26	0.44	0.34	0.06	0.02	0.45	0.63	0.65		
Urea (mg/dl)	r	0.07	0.10	0.16	0.03	-0.02	-0.12	-0.18	0.07	-0.11	0.00	1.00
	P	0.68	0.56	0.33	0.85	0.89	0.46	0.28	0.69	0.49	0.99	
S.Cr (mg/dl)	r	-0.14	-0.05	0.06	-0.10	-0.06	0.05	-0.06	-0.14	-0.01	0.07	0.62
	P	0.38	0.77	0.72	0.54	0.70	0.76	0.71	0.38	0.96	0.66	<0.0001

Table (3) Pearson correlation coefficient between the studied variable in Control group.

		Age (year)	Weight (Kg)	Height (cm)	BMI (Kg/h^2)	LDH (U/L)	Zinc (µg/dl	Copper (µg/dl)	ALT (U/L)	AST (U/L)	Alkp (U/L)	Urea (mg/dl)
Age (year)	r	1.00										
	p											
Weight Kg	r	0.10	1.00									
	p	0.53										
height cm	r	-0.32	0.18	1.00								
	p	0.05	0.26									
BMI (Kg/h^2)	r	0.31	0.75	-0.51	1.00							
	p	0.06	<0.0001	0.00								
Zinc (µg/dl	r	0.06	0.16	-0.09	0.19	0.09	1.00					
	p	0.69	0.32	0.56	0.24	0.58						
Copper (µg/dl)	r	-0.14	0.04	0.21	-0.11	-0.19	0.13	1.00				
	p	0.38	0.83	0.19	0.49	0.24	0.42					
ALT (U/L)	r	0.14	0.08	0.33	-0.17	-0.01	0.00	0.21	1.00			
	p	0.41	0.62	0.04	0.29	0.95	0.98	0.19				
AST (U/L)	r	0.15	0.13	0.32	-0.12	-0.05	-0.06	0.25	0.93	1.00		
	p	0.36	0.41	0.04	0.48	0.75	0.71	0.13	<0.0001			
Alkp (U/L)	r	0.22	0.00	0.13	-0.10	0.00	0.01	0.27	0.45	0.50	1.00	
	p	0.16	0.98	0.43	0.55	1.00	0.93	0.09	0.00	0.00		
Urea mg/dl	r	0.23	0.03	0.05	-0.03	0.06	-0.02	-0.17	0.23	0.27	0.06	1.00
	p	0.15	0.85	0.74	0.86	0.70	0.90	0.30	0.16	0.09	0.72	
S.Cr. mg/dl	r	0.31	-0.04	0.25	-0.21	0.02	0.02	0.07	0.36	0.40	0.31	0.68
	p	0.05	0.81	0.13	0.19	0.91	0.90	0.68	0.02	0.01	0.05	<0.0001

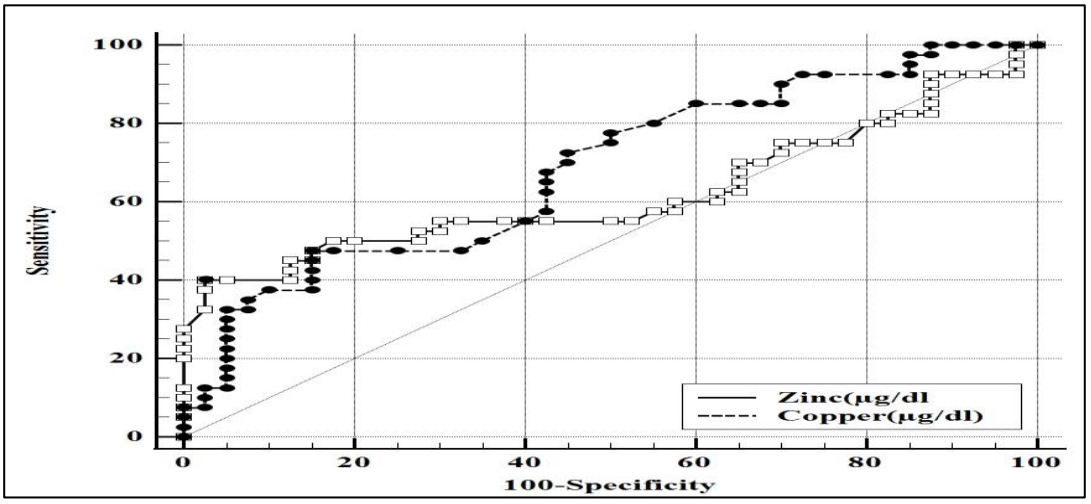

Figure (11) ROC curve comparison between Zn and Cu .

DISCUSSION

Zinc is a vital trace element in the human body. Zinc deficiency contributes to the onset and progression of chronic kidney disease (CKD) and related complications, including anemia and cardiovascular issues (Hirotaka *et al*.,2023). This study indicated that serum zinc levels were significantly lower in CKD patients (80.69±51.30 µg/dl) compared to controls (97.42±38.61 µg/dl) (p value 0.10773) as shown at Figure (4), suggesting a strong link between zinc deficiency and CKD. The findings emphasize the importance of zinc supplementation during various stages of kidney disease, corroborating previous research also agreement with (Adaku *et al*.,2022). CKD patients typically exhibit diminished zinc levels, which may be aggravated by urinary zinc loss also agreement with (Danfeng *et al*.,2023). Research indicates that zinc deficiency can exacerbate renal dysfunction and increase the risk of end-stage kidney disease (ESKD)also agreement with (Tokuyama *et al*., 2021).

Copper is significantly influences chronic kidney disease (CKD) and renal health. Research indicates a correlation between elevated blood copper levels and CKD prevalence (Shafqat et al.,2022). This study revealed a notable increase in serum copper levels among CKD patients (116.33±71.20 µg/dl) compared to controls (74.77±46.16 µg/dl), with statistical significance (p value 0.00304) as shown at figure (5). Excessive copper exposure may cause nephrotoxicity through kidney copper deposition, impairing renal function also agreement with (Guido et al.,2022). These results underscore the complex interplay between copper concentrations and kidney health in CKD, highlighting the necessity of maintaining an optimal balance of copper and essential elements for renal function and overall well-being.

Furthermore, serum AST and ALT levels were notably reduced in CKD patients both with and without ESRD compared to controls (Asmita *et al*.,2023). Recent studies further corroborate that serum ALT levels are diminished in CKD patients relative to those with normal renal function (Celestin *et al*.,2021). This study found that serum aspartate aminotransferase levels were significantly lower in CKD patients (22.63± 7.93 U/L) than in control groups (26.65± 8.13 U/L) with (p-value of 0.02982), as shown at figure (7). Additionally, this study indicated that serum alanine aminotransferase levels were significantly lower in CKD patients (23.48± 12.49 U/L) compared to control groups (27.10± 8.07 U/L) with a (p value < 0.13235), as shown at figure (6). These findings imply that AST, ALT, and the AST/ALT ratio could function as biomarkers for renal dysfunction and CKD progression, aligning with (Gjin *et al*.,2021) (Asmita *et al*.,2023), which suggests that renal impairment adversely affects liver enzyme levels in non-dialyzed CKD patients.

Urea serves as an indicator of uremic retention in chronic kidney disease (CKD) and the effectiveness of solute removal during dialysis. Recent experimental findings indicate urea's toxicity at CKD-representative concentrations. Numerous studies reveal that urea precipitates molecular alterations associated with insulin resistance, free radical generation, apoptosis, and intestinal barrier disruption (Vanholder *et al*., 2018). This study demonstrated that serum urea levels in control groups (27.53± 7.97 mg/dl) were significantly lower than in patients (126.33± 33.94 mg/dl), with a highly significant increase (p < 0.000001) in CKD patients compared to controls, as shown at figure (9). This suggests that chronic kidney disease correlates with the accumulation of metabolic waste products and multi-organ involvement, manifesting as elevated blood urea, creatinine levels, electrolyte and various

disorders, consistent with findings by (Vanholder *et al*.,2018).

The assays that measure blood levels of creatinine are widely recognized as the most prevalent and clinically significant indicators of renal function in a medical setting, as noted by (Onuigbo and Agbasi.,2015) in their study. This current investigation has revealed that the serum creatinine levels in the control groups were recorded at an average of (0.86± 0.13 mg/dl), whereas in the cohort of patients suffering from chronic kidney disease (CKD), the measured serum creatinine level was alarmingly elevated at (8.98± 2.44 mg/dl), with a statistically profound increase that reached a level of significance indicated by a (p value <0.000001) when compared to the control group, as shown at figure (10). This finding aligns with the conclusions drawn by (LAIBI *et al*.,2023) research, further corroborating the results obtained in this study.

Alkaline phosphatase (ALP) serves as a biomarker linked to chronic kidney disease (CKD) and its associated complications. Increased concentrations of ALP have been correlated with adverse outcomes in individuals diagnosed with CKD (Smout *et al*., 2023). This current investigation revealed that the serum alkaline phosphatase level in the control group was (95.03± 17.17 U/L), while in the CKD patient cohort, it was markedly elevated at (196.50± 112.21 U/L), demonstrating a statistically significant increase (p value < 0.000001) in CKD patients compared to the control subjects, as shown at figure (8). This finding suggests that non-skeletal ALP, in particular, is associated with inflammatory processes and an increased risk of all-cause mortality among CKD patients. Furthermore, research has indicated that CKD is characterized by the buildup of uremic toxins, which contribute to the pathophysiological processes underlying CKD-related comorbidities. These observations imply that both the role of ALP and the accumulation of metabolic waste products are integral to the multi-organ manifestations of CKD. This aligns with the assertions made by (Mathias *et al*.,2022), which indicated that chronic kidney disease (CKD) is associated with the accumulation of metabolic waste products and the involvement of multiple organ systems, including alkaline phosphatase (ALP).

CONCLUSION

A significant increase in the levels of alkaline phosphatase and copper concentrations is distinctly noted among patients suffering from chronic kidney disease, while concurrently there is a slight reduction in serum zinc levels observed in individuals who are in the end-stage of chronic kidney disease when compared to their healthy counterparts, thereby suggesting that these specific biomarkers may possess significant diagnostic potential and utility particularly in the advanced stages of this debilitating disease. The observed correlation between the serum levels of aspartate aminotransferase and alanine aminotransferase in conjunction with the progression of chronic kidney disease serves to underscore the considerable influence and implications of alterations in liver enzyme levels throughout the course of chronic kidney disease.

Ethical approval

The present study Which is conducted by authors ((Ahmed Alaa Saleem Alturfi, Mohammed Imran Hamzah) was approved by the local Department of Najaf Health Department committee.

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