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Correlation of the trace elements (Zinc & Copper) in type-2 diabetic patients with and without nephropath

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Abstract
Background: Trace elements have a significant impact on diabetes, and an imbalance in trace element levels in diabetes mellitus (DM) contributes to the occurrence of diabetic nephropathy (DN). The objective of this work was to examine alterations in concentrations of copper (Cu) and zinc (Zn) in serum and their correlation with the occurrence of DN among individuals with type 2 DM.
Methods: This observational work was performed on 80 participants aged above 20 years old, both sexes, diagnosed with type 2 DM with or without out DN. Participants were categorized into three groups: Group 1 (n=20): subjects with type 2 diabetic mellitus without DN, Group 2 (n=40): subjects with type 2 DM and DN which subdivided into two equal group according to urinary albumin to creatinine ratio (ACR) [Microalbuminuria group (n =20): (ACR 30 to 300 mg/g) and macroalbuminuria group (n=20) (ACR > 300 mg/g)] and Group 3 (n =20): healthy control group.
Results: Mean serum Zn level is higher in the microalbuminuria group than macroalbuminuria group 121.7, and 51.6, respectively. In addition, there is significant positive correlation between the two groups which means that the more microalbuminuria in the group the more Zn precipitate. A substantial variation was existed among both groups which means that serum Cu level increase in microalbumiuria than macroalbuminuria. The Zn and Cu was substantially distinct among three groups (p<0.05).
Conclusion: Serum Zn level decrease significantly while serum Cu level increase in type 2 DM. Serum Zn level and Cu increase with microalbuminuria than macroalbuminuria.

Keywords: Trace elements, zinc, copper, type-2 diabetic, nephropathy

Introduction
Diabetes mellitus (DM) is a metabolic condition defined by hyperglycemia, that is the presence of excessively high levels of glucose in the bloodstream [1].
Diabetic nephropathy (DN) is a significant microvascular consequence of DM. DN is the main trigger of chronic renal failure, accounting for 30-40% of all instances of end-stage renal disease (ESRD) [2]. Zinc (Zn) and copper (Cu) are vital trace elements that are necessary for the proper functioning of our bodies. They serve as cofactors for several enzymes and are necessary for biochemical processes [3].
Zinc has a crucial role in the activity of hormones, and healing of wound in addition to synthesis of proteins, Zn has an impact in insulin synthesis, storage and secretion and its metabolism is affected in DM. deficiency of Zn is associated with insulin resistance. DN has been related to oxidative stress. Antioxidant deficiency may result from reduction in the enzymes production, which includes glutathione peroxidase due to deficiency of Zn [4, 5].
Copper is a crucial micronutrient for the functioning of cytochrome C oxidase in mitochondria, as well as for superoxide dismutase, deficiency of Cu minimizes the activities of these enzymes, and thus consequently negatively impacts the regular physiological functions. Evidence was existed about indicating that the Cu metabolism is changed in people with DM and may play particular functions in the development and progression of diabetes and its complication. Also, urinary Cu play's role in the progression of DN among individuals with advanced nephropathy [6-8].
Lastly, Research has demonstrated that trace elements have a significant impact on combating diabetes, and disturbance in trace element level in DM contribute to development of DN [9].

This work aimed to evaluate alterations in Zn and Cu serum levels and their relationship with the occurrence of DN among individuals with type 2DM.

Patients and Methods

This observational work was performed on 80 participants aged above 20 years old, both sexes, diagnosed with type 2 DM with or without out DN. The work was performed from June 2022 to May 2023, following permission from the Ethics Committee Tanta University Hospitals, Tanta, Egypt. The participants provided a well-informed written consent.

Criteria for exclusion were existence of non-DN as the presence of rapid reductions in eGFR (>5 mL/min/year) or the sudden start of albuminuria aren't characteristic of DN, particularly when there is an active urinary sediment. Microscopic hematuria isn't a typical characteristic of DN; however, it can occur, and family history of non-diabetic renal disorders, usage of Zn and/or Cu supplementation during the last three-month period, secondary causes of renal insufficiency such as obstructive renal disease, urolithiasis, and acute urinary tract infection, autoimmune diseases, cardiovascular and cerebrovascular diseases, type 1 diabetes and malignancy.

Participants had been categorized into three groups: Group 1 (n=20): Participants with type 2 DM without DN, Group 2 (n=40): Participants with type 2 DM and DN which subdivided into two equal groups according to urinary ACR [Microalbuminuria group (n =20): (ACR 30 to 300 mg/g) and macroalbuminuria group (n=20) (ACR > 300 mg/g)] and Group 3 (n =20): healthy control group.

Each participant had been exposed to taking of history, clinical examination, ophthalmology examination (fundus examination) to detect diabetic retinopathy, laboratory investigations [measurement of blood glucose levels while fasting and two hours after a meal, glycated hemoglobin (HbA1c), serum creatinine and blood urea, estimated glomerular filtration rate (eGFR) by CKDEPI equation and urinary albumin/creatinine ratio (ACR)] and specific laboratory investigations [Zn and Cu (assessed using a varian atomic absorption spectrometer. Reference range for Zn: (60-125 µg/L), total Cu (63.5-158.9 µg/L)]. The concentration of metals in each sample was determined using a calibration curve and sample dilution.

The HR-ICP-MS equipment (Thermo Finnigan model Element 2, Bremen, Germany) was used to analyze trace element concentrations. This instrument is considered the most effective commercially available technique for determining levels of trace element because of its low limits of detection and ability to process samples quickly. The power of radio frequency had been adjusted to 1350 watts. The samples have been administrated with a prep-FAST sample injecting technique. The instrument had been fitted with a concentric PFA-ST nebulizer, connected to a quartz cyclonic micromist spray chamber, sample cones and aluminum skimmer, and a detachable quartz torch with a guard electrode. The instrument was calibrated by utilizing a solution of a multielement standard provided by ESI. The solution was matrix matched to ensure the same acid strength (0.6 M), sodium concentration (160 mg/L), and potassium concentration (115 mg/L).

Curves of calibration were generated by utilizing four distinct concentrations of a multi-element standard in order to encompass the required concentration ranges for the study. Instrumental drift corrections were performed by repeatedly measuring one of the multielement standards.

The instrument's stability was assessed by examining the argon signal and doing measures of 1 g/L rhenium, which was introduced as an internal reference using the prep FAST method. In order to reduce the impact of analytical interferences, trace elements had been measured using varying levels of resolution. The low-resolution level included cesium, cadmium, gold, indium, mercury, lead, thallium, tantalum, and timedium. The medium resolution level included boron, calcium, copper, chromium, gadolinium, magnesium, iron, manganese, molybdenum, rubidium, nickel, strontium, silver, and zinc. The high-resolution level included bromine, arsenic, and selenium. The precision of the trace element measurements was assessed by analyzing the certified reference material Seronorm Level 1 (Sero, Norway). Furthermore, a specimen obtained from a medically healthy participant was subjected to many analyses in order to evaluate the consistency of the procedure across time.

Fasting plasma glucose (FPG)

Performed using the Cobas-400 automated analyzer with the appropriate kits provided by Roche Diagnostics. This test evaluates your levels of glucose in the bloodstream after a period of fasting. Fasting refers to abstaining from consuming any kind of drink or food (with the exception of water) for a minimum of 8 hours prior to the test. This test is often conducted early in the morning.

Oral glucose tolerance test: The OGTT is a diagnostic procedure that measures your blood glucose levels prior to and two hours following consuming a standardized 75 g glucose solution. It provides the doctor with information about your body's glucose metabolism.

Albumin-Creatinine Ratio (ACR)

Second morning urine fresh sample in sterile cups were collected for measurements of urinary albumin and urinary creatinine for ACR estimation.

GFR estimation

The national kidney foundation suggests utilizing the CKD-EPI creatinine equation of 2021. eGFR =142*min (standardized Scr/K, 1)α *max(standardized Scr/K, 1) 1.200 *0.9938Age *1.012 [if female]. The value of Scr represents the serum creatinine level. For females, κ is 0.7 and α is -0.241. For men, κ is 0.9 and α is -0.302 [10].

Statistical analysis

The statistical analysis had been performed employing SPSS v26 software (IBM Inc., Chicago, IL, USA). The mean and standard deviation (SD) of the quantitative parameters were analysed and contrasted among both groups using ANOVA test with a post hoc test (Tukey). The qualitative parameters were displayed as frequencies and percentages (%) and were examined using the Chi-square test. The correlation among different parameters was calculated utilizing the Pearson moment correlation equation. A two tailed P value < 0.05 was considered statistically significant.

Results

Age, gender, weight and height were insignificantly different among studied groups. BMI, SBP, DBP and

diabetic retinopathy DR grade was significantly distinct among three studied groups (p<0.05). Table 1.

Table 1: Comparison between groups under study based on demographic data, blood pressure and fundus examination

		DM only (n=20)	DM + CKD (n=40)	Control (n=20)	P
Age (years)		46.0±16.0	57.0±19.0	45.0±15.0	0.08
Sex	Male	12(60.0%)	22(55.0%)	10(50.0%)	0.07
	Female	8(40.0%)	18(45.0%)	10(50.0%)	
Sig. bet. grps		**p1=0.07*, p2=0.06*, p3<0.065***			
Weight (Kg)		80.80± 15.76	81.95± 16.05	79.15± 15.98	0.075
Height (m)		162.75± 5.40	163.82± 5.15	160.21± 4.98	0.071
BMI (kg/m^2)		29.11±3.19	29.94±3.56	27.11±3.64	0.001*
SBP (mmHg)		141.50±13.34	145.50±15.42	126.05±10.35	0.001*
DBP (mmHg)		82.0±14.36	85.88±13.05	74.74±9.05	0.001*
Fundus examination					
Normal		2(10.0%)	5(12.5%)	20(100.0%)	0.001*
Grade I		10(50.0%)	14(35.0%)	0(0.0%)	
Grade II		6(30.0%)	12(30.0%)	0(0.0%)	
Grade III		2(10.0%)	4(10.0%)	0(0.0%)	
Grade IV		0(0.0%)	5(12.5%)	0(0.0%)	

Data are presented as mean ± SD or frequency (%). *Significant p< 0.05. p1: p value for comparing between DM only and DM + CK, p2: p value for contrasting between DM only and Control, p3: p value for comparing between DM + CKD and Control., CKD: chronic kidney disease, DM: diabetes mellitus, BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

The FBG, 2-h PPG, HbA1c, urea, creatinine and GFR distribution was substantially distinct among three groups. Table 2.

Table 2: Comparison between studied groups according to FBG, 2-h PPG, HbA1c, urea, creatinine and GFR

	DM only (n=20)	DM + CKD (n=40)	Control (n=20)	P
FBG (mg/dl)	130.85±21.79	161.30±18.58	76.2±9.2	0.001*
2h- PPG (mg/dl)	206.30±40.17	240.25±61.15	111.7±8.8	0.001*
HbA1c %	8.56±2.36	10.59±1.18	---	0.001*
Urea (mg/dl)	28.1±6.3	65.1± 25.3	25.2±8.3	0.001*
Creatinine (mg/dl)	0.87±0.14	1.9±0.51	0.7±0.14	0.001*
GFR (ml/min/1.73m^2)	95.2±7.2	55.4± 10.4	106.02±13.8	0.001*

Data are presented as mean ± SD.*Significant p< 0.05. p1: p value for comparing between DM only and DM + CK, p2: p value for comparing between DM only and Control, p3: p value for comparing between DM + CKD and Control., DM: diabetes mellitus, FBG: fasting blood glucose, CKD: chronic kidney disease, 2h- PPG: post prandial blood glucose, GFR: glomerular filtration rate

The Zn and Cu was substantially distinct among three groups (p<0.05). Table 3.

Table 3: Comparison between studied groups according to Zn and Cu

	DM only (n=20)	DM + CKD (n=40)	Control (n=20)	P
Zn (µg/dL)	62.25±10.34	52.27±12.39	188.25±26.21	0.001*
p1=0.077, p2<0.001*, p3<0.001*				
Cu (µg/dL)	175.95±34.99	164.33±22.89	112.50±30.27	0.001*
p1=0.049*, p2<0.001*, p3<0.001*				

Data are presented as mean ± SD. *Significant p< 0.05. p1: p value for contrasting between DM only and DM + CK, p2: p value for contrasting between DM only and Control, p3: p value for contrasting between DM + CKD and Control., DM: diabetes mellitus, CKD: chronic kidney disease, Zn: zinc, Cu: cupper

A substantial variation was existed among both groups which means that serum Cu level increase in microalbumiuria than macroalbuminuria. Table 4.

Table 4: Correlation t-Test between Cu level in both micro and macro albuminuria groups

	Macro	Micro
Mean	106.7	121.6667
Variance	408.9579	607.2941
Observations	20	18
Hypothesized Mean Difference	0	--
Df	33	--
t Stat	-2.0332	--
P(T<=t) one-tail	0.02507	--
t Critical one-tail	1.69236	--
P(T<=t) two-tail	0.05014	--
t Critical two-tail	2.034515	--

t-Test: Two-Sample Assuming Unequal Variances

Mean serum Zn level is higher in the microalbuminuria group than macroalbuminuria group 121.7, and 51.6, respectively. In addition, there is significant positive correlation between the two groups which means that the more microalbuminuria in the group the more Zn precipitate. Table 5.

Table 5: Correlation t-Test between Zn level in both micro and macro albuminuria groups

	Macro	Micro
Mean	51.66667	121.7368
Variance	172.9333	573.6491
Observations	21	19
Hypothesized Mean Difference one-tail	0 df 27 t Stat P (T<=t)	-11.3036 4.81E-12
t Critical one-tail	1.703288	
P(T<=t) two-tail	9.62E-12	
t Critical two-tail	2.051831	

t-Test: Two-Sample Assuming Unequal Variances, Zn: zinc.

Discussion

There has been a consistent rise in interest about the biochemical and clinical effects of metabolism of trace elements. Trace elements exert significant physiological impacts when found at amounts different from those linked to extreme deficiency or classical toxicity [11]. An increasing evidence was existed, that the metabolism of many trace elements is changed in individuals with DM.

In the assessment of risk factors of our participants our data showing that the SBP and DBP distribution of the different groups in which mean SBP distribution is 141.5±13.34, 145.5±15.42, 126.05±10.25 in group one, group two and group three respectively, where SBP was higher among diabetic patients more than the control group but with statistically substantial variation. The mean DBP distribution 82±14.36, 80.88±13.05, and 74.74±9.05 in group one, group two and group three respectively with statistically significant difference between diabetic and control group which mean that DBP has effect on all group results. That agreed with Maklouph *et al.* [12] reported that BP was higher among diabetic group than the control group. We found the mean FBG distribution 130.85±21.79, 161.3±18.58, 76.2±9.2 in group one, group two and group three respectively with statistically significant difference. Which means that FBG higher in DN patients than diabetic patients without nephropathy. The mean 2-hour PPBG distribution 206.30±40.17,240.25± 61.15,111.7±8.8 in group one, group two and group three respectively with statistically significant difference which means that the mean 2-hPP higher in DN patients more than another group. The mean HbA1C distribution 8.56±2.36, 11.59±1.81 in group one, group two respectively with statistically significant difference, which mean higher HbA1C in DN patients. Lin *et al.* [13] revealed a substantial association among HbA1c variation and DN. Furthermore, Wang *et al.* [14] discovered a correlation between elevated glucose variability and a decline in eGFR, as well as an increased likelihood of CKD in individuals with inadequate glycemic management.

Possible mechanisms that might clarify the influence of higher levels of glucose and toxicity in the kidneys encompass advancements in the permeability of the glomeruli, circulating concentrations of inflammatory cytokines, accumulation of lipids in the mesangial region, production of matrix by mesangial and tubulointerstitial cells, expression of markers associated with fibrinogenesis, impairment of the function of endothelial cells, and the production of free radicals that initiate consequences of diabetes [15, 16].

On measuring the values of Cu and Zn in the participants the mean Zn distribution is 62.25±10.34, 52.27±12.39, 188.25±26.21 in group one, group two, and group three respectively with statistically significant difference which means that the mean Zn has significant effect on all group results. This was supported by A cross-sectional work was performed in Saudi Arabia 2018 by Farooq *et al.* [17] showed that Diabetic individuals have deficiency in Zn contrasted to normal individuals. Also, Meta analysis done by Sanjeevi *et al.* [18] found that Zn concentrations were decreased in type 2 diabetic individuals contrasted to nondiabetic controls.

In our study Correlation t-Test between Zn level in both micro and macro albuminuria groups demonstrated that a substantial correlation was existed among both groups which mean that serum Zn increases in microalbuminuria than macroalbuminuria. Similarly, Makhlouph *et al.* [19] showed a substantial difference in blood Zn levels among individuals with macro and microalbuminuria, with microalbuminuria patients having significantly higher serum Zn concentrations than patients with macroalbuminuria.

According to our study findings, Zn serum levels were greater in microalbuminuria group contrasted to the macroalbuminuria group which was in coherence with the results found by Feng *et al.* [20] discovered that the concentration of serum Zn was considerably lower in individuals with macroalbuminuria or renal failure than it was in those with microalbuminuria. Additionally, a negative correlation was existed among 24-hour urine albumin loss and serum Zn content in individuals with DN. This shows that in DN patients, Zn homeostasis is linked to both inflammatory reactions and renal functional impairment caused by DN. Zhang *et al.* [21] discovered that restriction of dietary Zn dramatically decreased the concentrations of Zn in mice's plasma and kidneys, and that it aggravated tubulointerstitial fibrosis in mice with diabetes. Which mean that Zn associated with pathogenesis of DN. Tang *et al.* [22] demonstrated that adding zinc to the diet can protect against renal fibrosis caused by diabetes and reduce the amount of protein lost in urine over a 24-hour period.

The elevated concentration of zinc in the urine may be associated with excessive urine production, high levels of blood glucose, the presence of glucose in the urine, and/or the presence of protein in the urine. The concentrations of zinc in urine steadily declined as DN progressed, and this reduction became considerable when individuals with DN had an eGFR <15 ml min^{-1} 1.73 m^{-2}. This can be attributed to a reduction in volume of urine or even anuria among individuals experiencing kidney failure, and aberrant zinc

metabolism is more prevalent in individuals at this stage of diabetic nephropathy development [20].

Copper is essential for the production of erythrocytes, as well as for maintaining the integrity of blood vessels, neurons, immune system, and skeletal structure. A work revealed a direct association among the levels of copper in the blood serum and the occurrence of DM.

The mean Cu distribution 175.95±34.99, 164.33±22.89, 186.5±40.27, 112.50±30.27 in group one, group two, and group three respectively with statistically significant difference which means that the mean Cu has a significant effect on all group results.as serum Cu increase in diabetic group contrasted to other groups. Comparable findings were stated by Hussain *et al*. [23] found serum Cu levels had been observed to be comparatively greater among individuals with T2DM. Also, with agreement of our result Zhixin *et al*. [24] high plasma Cu concentration was correlated with raised prevalence of DM in Chinese hypertensive adults.

In addition, Correlation t-Test between cooper level in both micro and macro albuminuria groups showing that significant correlation between two groups which indicates that serum Cu level increase in microalbuminuria than macroalbuminuria. This comes in agreement with Maklouph *et al*. [19] observed a notable disparity in serum copper levels among individuals who had macro and microalbuminuria. Specifically, individuals with microalbuminuria had significantly elevated serum Cu values.

Limitations of this work were the relatively limited sample size. The study was conducted at a solitary center. We suggest conducting large-scale clinical trials to establish the correlation between DM and serum levels of Zn and Cu. Adding other trace elements as Mg, Iron, and selenium. Screening of prediabetic patients for trace elements level.

Conclusion

Serum Zn level decrease significantly while serum Cu level increase in type 2 DM. Serum Zn level and Cu increase with microalbuminuria than macroalbuminuria.

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Conflict of Interest: Nil.

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