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Impact of Copper/Zinc Ratio in Diabetic Retinopathy and Nephropathy: A Cross-Sectional Study

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ABSTRACT

Background & Objective: Understanding copper/zinc (Cu/Zn) ratio's influence on diabetic complications could lead to more targeted therapeutic interventions, and preventive measures. This study compared serum Zn, Cu, and Cu/Zn ratios among T2DM individuals with and without retinopathy and nephropathy.

Materials & Methods: In this cross-sectional study, the individuals with T2DM participated between 2021 and 2022 at the Yazd Diabetes Research Center. A control group consisted of 30 people with T2DM without microvascular problems, whereas 30 people with diabetic retinopathy (DR) and 30 people with diabetic nephropathy (DN) were recruited.. Blood samples were analyzed for Zn and Cu levels. Statistical analysis was conducted with SPSS, utilizing Pearson correlation and ANOVA. Statistical significance was established with a p-value of ≤ 0.05.

Results: 41.76% of men and 58.24% of women were included in this study. No significant differences were found in terms of age. (P=0.128), BMI (P=0.210), and gender (P=0.057). Results revealed lower Zn levels in the patients with DR compared to T2DM (P=0.033). Cu/Zn ratio in the DR was higher than in the other groups (P=0.046). Cu/Zn ratio correlated positively with HbA1c (P=0.001, r=0.321). Furthermore, negative correlations were observed between the duration of diabetes, and Zn levels (r=-0.195, P=0.05), and between the Cu/Zn ratio and glomerular filtration rate (GFR) levels (r=-0.182, P=0.05).

Conclusion: The research identified correlations between HbA1c and GFR levels and the Cu/Zn ratio, indicating a potential relationship between trace element imbalances and the progression of diabetes. Thus, Zn levels decreased and Cu/Zn ratio increased across the DR group compared to the control.

Keywords: Copper/Zinc Ratio, Diabetic Retinopathy, Diabetic Nephropathy

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is globally increasing, making it a serious global health concern (1, 2). Among its array of complications, diabetic retinopathy (DR) and diabetic nephropathy (DN) stand out as formidable microvascular manifestations, often leading to severe visual impairment and renal dysfunction (3-5). These difficulties not only reduce the quality of life for affected individuals, but also impose significant fiscal burdens on healthcare systems worldwide (6-8).

T2DM and its related microvascular problems have a complex etiology that includes metabolic abnormalities, environmental variables, and genetic predispositions (9, 10). Among underlying mechanisms, oxidative stress and dysregulation of essential mineral elements, such as zinc (Zn) and Cu (Cu) garnered attention for their pivotal roles in exacerbating diabetes and diabetic complications (11-13).

Zn, a crucial micronutrient, plays vital roles in maintaining cellular homeostasis, modulating immune responses, and regulating gene expression (14-16). Regarding DN, zinc's antioxidant and anti-inflammatory characteristics were implicated in ameliorating renal damage and mitigating the progression of nephropathy (17, 18). Moreover, Zn exerts renoprotective effects by attenuating oxidative stress, inhibiting profibrotic pathways, and preserving endothelial function, thereby safeguarding against renal injury in diabetic individuals (18-20).

Cu, another crucial trace element, is involved in a number of redox and enzymatic activities that are necessary for cellular activity (21). Nevertheless, DN progression may be exacerbated by dysregulated Cu metabolism, which may increase oxidative stress and inflammation (22). Elevated Cu levels were linked to endothelial dysfunction, glomerular injury, and renal fibrosis, highlighting its detrimental effects on kidney health in the context of diabetes (23, 24).

Similarly, in DR, Zn appears to be a promising therapeutic agent because of its anti-angiogenic, anti-inflammatory, and antioxidative properties (24).

Conversely, dysregulated Cu metabolism was implicated in the pathogenesis of DR, where elevated Cu levels exacerbate retinal oxidative stress, promote angiogenesis, and contribute to the development of microvascular abnormalities (25, 26).

The imbalance between Cu and Zn levels, reflected by alterations in Cu/Zn ratio, may serve as a critical determinant of complications of diabetes (27). Clarifying the dynamics and interactions of zinc and copper within these microvascular problems is crucial for therapeutic approaches and disease management methods, since these elements play complex roles in influencing the development of diabetic nephropathy and retinopathy (13, 21). Although some studies evaluated the level of Cu and Zn in diabetes, less research was conducted on the Cu/Zn ratio concerning the microvascular complications of diabetes, especially in the Iranian population. Therefore, most existing studies have focused on comparing these elements between diabetic and non-diabetic individuals. Therefore, the present study aimed to compare serum Zn, Cu, and Cu/Zn ratios among patients with T2DM, stratified based on the presence or absence of retinopathy and nephropathy.

2. Materials and Methods

This cross-sectional study was conducted from February 2021 to May 2022, focusing on individuals aged 30 to 70 years who were diagnosed with T2DM and referred to the Yazd Diabetes Research and Treatment Center.

Based on electronic records and documented complications from ophthalmological examinations and laboratory tests for microalbuminuria, the participants were categorized into three groups: 1) 30 individuals with T2DM without microvascular complications, 2) 30 patients with only diabetic retinopathy (DR), and 3) 30 patients with only diabetic nephropathy (DN).

Microalbuminuria was defined as persistent albuminuria (>30 mg/g) observed on two or more occasions (28).

Patients who had infections within the previous three weeks, those with Type 1 diabetes mellitus (T1DM), those with inflammatory diseases, pregnant or lactating women, and those who had taken vitamin and mineral-containing supplements during the previous three weeks were all excluded. Sampling was conducted based on purposive sampling, focusing on the patients with electronic health records available at Yazd Diabetes Center. Sample size determination employed the formula to compare two means, with an alpha level of 0.05, a beta level of 20%, and a mean Cu/Zn ratio of 0.8, resulting in a target sample size of 30 individuals per group. Group matching was done based on age, sex, and BMI.

Participants' blood samples were taken to assess serum levels of Zn and Cu using specialized kits and a BA400 autoanalyzer. Hence, age, gender, diabetes duration, glomerular filtration rate (GFR), and HbA1c levels were recorded.

2.1 Statistical Analysis

SPSS v.24 software was used to analyze all of the data. Pearson correlation was employed to assess the relationships among variables, while one-way ANOVA was used to compare means among the different groups. Statistical significance was considered as a p-value ≤ 0.05.

3. Results

This study included 90 participants, 41.76% of whom were men and 58.24% of whom were women. Of them, 30 patients had DR (33.33%) and 30 patients had DN (33.33%). 30 patients (33.33%) with T2DM without any complication were included as a control group. Furthermore, 24 individuals (80%) suffered from non-proliferative diabetic retinopathy (NPDR) and 6 individuals (20%) from proliferative diabetic retinopathy (PDR) in the DR group. The gender distribution of the participants was as follows: 53.3% were male in the control group of T2DM, 33.8% in DR, and 38.2% in DN. No notable difference was observed between the groups due to gender (P=0.057).

As shown in Table 1, there were not any significant differences among groups based on age and BMI (P=0.128 and P=0.210 respectively). Moreover, HbA1c level and the duration of diabetes were remarkably higher in DR groups than in the T2DM (P=0.001).

The results of Table 2 showed that Zn level in the serum of the patients with DR was significantly lower than T2DM (P=0.033). Moreover, Cu/Zn ratio in the retinopathy group was significantly greater compared to the other groups (P=0.046).

As shown in Table 3, after adjusting data for age, gender, and BMI, there was still a significant difference between the mean of Zn level and Cu/Zn ratio between DR and T2DM (P=0.037 and P=0.048 respectively).

Table 4 shows a positive correlation between the serum Cu/Zn ratio and HbA1c (P=0.001, r=0.321). Furthermore, a significant positive correlation was observed between Cu/Zn ratio and HbA1c levels in the DR group (r=0.311, P=0.01). Additionally, a significant negative correlation was found between the duration of diabetes and Zn levels (r=-0.195, P=0.05),

as well as between the Cu/Zn ratio and GFR levels (r= -0.182, P=0.05).

Table 1. Comparison of demographic data among studied groups

Parameters	Groups			P-value*
	T2DM (Control) (n=30)	DR (n=30)	DN (n=30)	
Age (years)	54.23(±11.11)	56.32(±9.25)	57.87(±7.19)	0.128
BMI (kg/m2)	25.90(±2.70)	25.63(±2.67)	24.98(±2.60)	0.210
GFR (ml/min/1.72m2)	87.47(±13.69)	83.55(±15.51)	75.150(±16.06)	0.0021
HbA1c (%)	7.20(±1.09)	8.43(±1.64)	8.12(±1.45)	0.001
Duration (years)	8.75(±5.80)	14.32(±6.69)	11.78(±7.26)	0.001

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; DN, diabetic nephropathy. The variables are described as mean (standard deviation). * One-way ANOVA was used

Table 2. Comparison of serum levels of Zn and Cu and the ratio of them among groups

Parameters	Groups			P-value*
	T2DM (Control) (n=30)	DR (n=30)	DN (n=30)	
Serum Cu (µg/dL)	82.07(±36.31)	91.08(±24.9)	89.8586.38(±24.25)	0.076
Serum Zn (µg/dL)	91.63(±29.19)	73.23(±22.45)	87.13(±31.76)	0.033
Cu/Zn ratio	0.94(±0.44)	1.25(±0.64)	0.99(±0.68)	0.046

Abbreviations: Cu, Cu; Zn, zinc. The variables are described as mean (standard deviation). T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; DN, diabetic nephropathy. * One-way ANOVA was used

Table 3. Comparison of serum levels of Zn and Cu and the ratio of them among groups after adjusting for age, gender, and BMI among groups

Parameters	Groups			P-value*
	T2DM (Control) (n=30)	DR (n=30)	DN (n=30)	
Serum Cu (µg/dL)	82.91(±40.56)	90.98(±37.23)	86.59(±32.3)	0.0651
Serum Zn (µg/dL)	89.33(±29.5)	74.79(±24.56)	88.01(±34.53)	0.037
Cu/Zn ratio	1.00(±0.58)	1.21(±0.67)	0.98(±0.32)	0.048

Abbreviations: Cu, Cu; Zn, zinc. The variables are described as mean (standard deviation). T2DM, type 2 diabetes mellitus; DR, diabetic retinopathy; DN, diabetic nephropathy. * One-way ANOVA was used

Table 4. The correlation of serum Cu/Zn ratio with HbA1c level in participants

Parameters	Groups			Total (n=90)
	T2DM (Control) (n=30)	DR (n=30)	DN (n=30)	
r	0.029	0.311	0.352	0.321
P-value	0.880	0.001	0.011	0.001

4. Discussion

This study has revealed substantial results regarding trace element imbalances in individuals with T2DM. Specifically, it has demonstrated a substantial increase in the Cu/Zn ratio and a significant decrease in serum Zn levels among patients with DR in comparison to the control group. Thus, we identified meaningful correlations between the Cu/Zn ratio and HbA1c and GFR and a significant correlation between serum Zn levels and the duration of diabetes.

A significant increase in Cu/Zn ratio among patients with DR in our study indicates that this ratio may effectively reflect systemic metabolic disturbances associated with DR; however, there was no association of this ratio with DN. A study by Takao et al. found that an elevated Cu/Zn ratio was linked to a higher prevalence of DN in the individuals with T2DM (29). The findings, in particular, show that changes in the characteristics of the examined populations, the length of diabetes, and the degree of kidney and eye involvement may account for the discrepancy between the present study's findings and those of previous research. Therefore, it is suggested that future studies investigate trace elements in diabetic patients with different severity of complications.

Furthermore, we found that serum Zn level decreased significantly in DR compared to T2DM without complication. A study by Luo et al. which assessed the relationship between serum Zn level and each microvascular complication of diabetes revealed that the Zn level was lower in DN, DR, and diabetic neuropathy compared to those with T2DM who do not have any microvascular problems (30). Similarly, Mor et al. found that serum Zn levels were significantly lower and Cu levels were higher in DR, DN, and macrovascular complications of diabetes than in T2DM without difficulties (31). In contrast, Abu Zaid et al. found no correlation between serum Zn levels and DR severity (32).On the other hand, although we observed an increase in Cu levels in the people with DR and DN compared to those without complications, this increase was not statistically significant. This discrepancy may be attributed to variations in disease severity among participants. The variation in the severity of diabetes complications could be one reason for this observation. Ito et al. compared urinary and serum levels of Cu in 41 patients with T2DM in various stages of nephropathy (microalbuminuria, macroalbuminuria, and normoalbuminuria) with 10 non-diabetic patients. The results showed that the serum Cu levels of participants were not significant, but a significant difference in urinary Cu levels was observed exclusively in the macroalbuminuria group when compared to the other groups (33). Nephropathy group studied in our study were all microalbuminuria and this difference in the studies could be the result of the difference in severity of the disease. Hyperglycemia, which can promote glycosylation and the release of Cu ions from proteins, is thought to be the cause of rise in Cu ions in diabetic individuals (34). Oxidative stress is increased when Cu ions are released into the circulation. Ceruloplasmin and albumin plasma contain the primary Cu-binding proteins. Chronic hyperglycemia causes changes in the binding properties of these proteins (35).

The potential effect of disease stage on elemental profiles provides valuable context for interpreting the study findings and underscores the multifactorial nature of diabetic microvascular complications. Future research should include stratifying study groups based on disease stage and severity to better understand the complex interactions between trace elements and diabetes complications. Incorporating these concerns into future studies may provide further insight into the processes driving Cu dysregulation and its implications for the development and progression of DR and DN. Moreover, exploring the interplay among disease stage, metabolic parameters, and elemental profiles may inform personalized therapeutic strategies aimed at mitigating diabetic complications and improving patient outcomes.

Therefore, we observed significant associations between Cu/Zn ratio and HbA1c levels, as well as GFR. The findings indicated that while serum Cu levels did not show significant differences among groups, Cu/Zn ratio was positively correlated with HbA1c levels, suggesting a link to systemic oxidative stress and metabolic dysregulation characteristic of diabetes (36). Increased oxidative stress is frequently linked to higher HbA1c levels, which may result in alterations in the Cu/Zn ratio as the body attempts to counterbalance oxidative damage (36, 37). This relationship underscores the potential utility of Cu/Zn ratio as a marker for glycemic control and oxidative stress burden in diabetic patients.

Furthermore, the negative correlation between Cu/Zn ratio and GFR suggests that this ratio may reflect renal function in diabetic individuals. As renal function declines, modifications in copper and zinc metabolism may result in variations in their respective ratios (38, 39). Hamasaki et al. analyzed the ratio of Zn to Cu rather than Cu to Zn, and consistent with our results, they showed that in patients with T2DM, after controlling for gender and BMI, the Zn to Cu ratio exhibited a significant negative connection with HbA1c. Also, they showed a positive correlation between the Zn/Cu ratio and GFR (38). Therefore, these results support the hypothesis that Cu/Zn ratio can be a better indicator of DN compared with Zn or Cu levels alone (23).

The single-center setting may restrict the generalizability of our findings to broader diabetic populations. There is a need for larger-scale, multicenter studies to confirm our findings and explore potential ethnic or regional variations in the elemental

profiles and their associations with diabetic complications.

5. Conclusion

This study demonstrated important correlations between vital metabolic markers and the Cu/Zn ratio, including HbA1c and GFR, in individuals with T2DM and a significant correlation between serum Zn levels and the duration of diabetes. Notably, we found that patients with DR had considerably greater Cu/Zn ratios and lower serum Zn levels than the control group. These findings highlight the complex relationship between trace elements, glycemic management, renal function, and diabetes complications. Additional investigation is required to elucidate the fundamental mechanisms, and explore therapeutic interventions targeting trace element imbalances to enhance diabetic care and outcomes.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This study received approval code (IR.SSU.MEDICINE.REC.1401.172) from the ethics committee of Shahid Sadoughi University of Medical Sciences.

6.3 Authors' Contributions

M.M. was in charge of gathering information and composing the initial draft of the manuscript. R.A. monitored the clinical aspects of the research. The data analysis and interpretation were done by N.N. The research approach was developed and studied under the supervision of M.A.A. The final manuscript was read and approved by all of the authors.

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest.

6.5 Fund or Financial Support

This research received no specific grant from any funding agency in the public, commercial, or not for profit sector.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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