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Concentration of Selected Serum Trace Elements in Male Patients With Diabetic Erectile Dysfunction: A Case–Control Study

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Abstract

Identifying novel risk factors for erectile dysfunction (ED) is crucial for developing targeted intervention. This study aimed to investigate the potential impacts of serum trace elements (TEs) concentration on the risk of diabetic ED. A retrospective case–control study was conducted involving 51 patients with diabetic ED and 51 control subjects. Serum levels of copper (Cu), zinc (Zn), magnesium (Mg), iron (Fe), and calcium (Ca) were measured using inductively coupled plasma-mass spectrometry (ICP-MS). While most selected TEs showed no significant differences, Cu levels were notably higher in patients with diabetic ED. In addition, the Cu/Zn ratio (CZr) was significantly elevated in the diabetic ED group compared to controls (1.3 vs. 1.2 mg/L, $p < .001$), reflecting its potential relevance to oxidative stress. Receiver operating characteristic curve analysis revealed that CZr exhibited better diagnostic performance for ED than the single parameter. These findings suggest disruptions in Cu homeostasis and a high probability of elevated CZr in diabetic ED. Further studies are warranted to validate our findings and elucidate the underlying mechanisms.

Keywords

erectile dysfunction, diabetes, trace elements, copper, zinc

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Introduction

Erectile dysfunction (ED) is defined as the inability to obtain sustainable penile erection necessary during sexual activity. Reasonably data suggest that approximately 322 million men worldwide will experience varying degrees of ED by 2025 (Ayta et al., 1999). Established risk factors for ED include diabetes, advancing age, obesity, poor lifestyle, lower testosterone (T) levels, and mental status (Xiong et al., 2024). Among these, diabetes is particularly significant, with the prevalence of ED being approximately twice as high in diabetic men as compared with nondiabetic counterparts (Pellegrino et al., 2023). Despite the widespread use of phosphodiesterase type 5 inhibitors (PDE5i) as first-line therapy, men with diabetic ED often exhibit suboptimal responses (Swiecicka, 2023).

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Hence, identifying novel risk factors for diabetic ED is required and potentially beneficial for targeted intervention.

Trace elements (TEs), though present in the human body in minute amounts (less than 0.01%), are essential for maintaining physiological homeostasis. The primary sources of these elements include dietary patterns as well as environmental and occupational exposures (Mohammadifard et al., 2017). Both excessive and inadequate levels of TEs have been linked to adverse health effects, especially in cardiovascular system. Increased serum copper (Cu) levels are positively associated with cholesterol and cardiovascular mortality (X. Chen et al., 2023). Zinc (Zn) deficiency is known to correlate with elevated blood pressure, dyslipidemia, diabetes, and oxidative stress (Nakatani et al., 2021). Magnesium (Mg) deficiency may cause reversible diastolic cardiomyopathy, driven by mitochondrial dysfunction and oxidative modification of myosin-binding protein C (M. Liu et al., 2021). Higher iron (Fe) status has been linked to an increased risk of cardioembolic ischemic stroke (Barad et al., 2024). However, evidence regarding the long-term impact of TEs exposure on overall cardiovascular mortality remains inconsistent (M. Wang et al., 2014). Given the shared risk factors and pathophysiological links between ED and cardiovascular disease (CVD), such as endothelial dysfunction and low testosterone (T) (Terentes-Printzios et al., 2022), ED is regarded as an independent, early indicator of subclinical CVD. However, the relationship between these TEs and ED remains largely unexplored.

It was recently suggested that exposure to TEs may contribute to the pathogenesis of ED, though the supporting data remain limited. An analysis of TE concentration in serum showed an association between T and levels of Cu, Zn, and Mg (Ryl et al., 2024). In addition, dietary consumption of Mg, Zn, and Cu have been inversely linked to ED in studies of the U.S. population (Deng et al., 2024; R. J. Liu et al., 2022). However, no explorative study has examined the relationship between TEs and diabetic ED specifically. To address this gap, this study aims to provide insights into possible impacts of five common and easily detected TEs (Cu, Zn, Mg, Fe, and Ca) on the risk of diabetic ED.

Materials and Methods

Ethics Approval

This study was approved by the Research and Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (Approval No. IRB-2023-15). Written informed consent was obtained from all participants.

Study Population

Following institutional review board approval, electronic medical records from October 2023 to May 2024 were retrospectively reviewed. All patients had engaged in sexual activities within the past 3 months. ED was confirmed using the International Index of Erectile Function short form (IIEF-5) questionnaire. Patients with an IIEF-5 score of 21 points or less and a diagnosis of type 2 diabetes were included in the study. According to the latest advanced epidemiologic study, middle age (50 years) has been identified as a peak period for ED prevalence, with a subsequent decline in older populations (Pellegrino et al., 2023). In addition, a recent umbrella review demonstrated that age above 40 years is a significant risk factor for ED in diabetic patients (Kitaw et al., 2024). Taken together, to minimize the influence of age-related factors and ensure more accurate results, only participants aged 18 to 45 were included. The exclusion criteria were as follows: (a) other endocrine diseases, such as type 1 diabetes and hypogonadism; (b) neurologic conditions, including spinal cord injury or pelvic trauma; (c) severe CVD, including heart failure and stroke; (d) anatomical penile deformities; (e) malignancies; and (f) current use of medications known to affect erectile function.

Laboratory Measurements

Fasting venous blood samples were collected from all participants and stored at $-80°C$ until further processing. Total testosterone (tT) levels were measured using chemiluminescent immunoassays (cobas e; Roche Diagnostics, USA). Glycated hemoglobin (Hb1Ac) levels were determined by immunoturbidimetric assay (Integra 400-plus; Roche Diagnostics, USA).

Serum concentrations of the Cu, Zn, Mg, Fe, and Ca were assessed using inductively coupled plasma-mass spectrometry (ICP-MS, Agilent 7900, Agilent Technologies, CA, USA) following the manufacturer's instruction.

Statistical Analysis

Statistics were depicted as mean $\pm$ standard deviation (*SD*), median (interquartile range, IQR), and number (proportion), as appropriate. Normality of parameters was assessed by the Shapiro–Wilk test. For variables

Table 1. Comparison of Demographic and Clinical Features Between Diabetic ED and Control Group

Characteristics	Diabetic ED (n = 51)	Control (n = 51)	P
Age, yrs	34.1 ± 6.3	34.2 ± 4.5	.957
BMI, kg/m^2	25.7 ± 3.7	25.3 ± 3.8	.595
Current smoker, n (%)			.112
Yes	5 (9.8)	7 (13.7)	
No	46 (91.2)	44 (86.2)	
Current drinker, n (%)			1.0
Yes	6 (11.8)	6 (11.8)	
No	45 (88.2)	45 (88.2)	
Hb1Ac,%	9.5 (9.2–9.8)	5.5 (5.2–5.7)	<.001
Testosterone, ng/mL	3.6 (3.0–4.5)	3.7 (2.8–4.7)	.973
IIEF-5 score	13 (7–15)	–	
Zn, mg/L	6.6 ± 0.7	6.8 ± 0.8	.213
Fe, mg/L	526.7 ± 49.9	526.4 ± 43.8	.972
Mg, mg/L	41.5 ± 4.3	42.0 ± 4.3	.562
Ca, mg/L	56.8 ± 6.2	56.2 ± 6.5	.640
Cu, mg/L	8.6 ± 1.5	7.9 ± 0.8	.005
CZr	1.3 ± 0.2	1.2 ± 0.2	<.001

Note. Data were expressed as mean ± standard deviation, number (proportion), and median (interquartile range) as appropriate. ED, erectile dysfunction; IIEF-5, International Index of Erectile Function short form questionnaire; Cu, copper; Zn, zinc; Mg, magnesium; Fe, iron; Ca, calcium; CZr, copper/zinc ratio.

with normal distributions, group comparisons were performed using the independent t-test. Associations between categorical variables and group levels were evaluated using the chi-square test or Fisher's exact test as applicable. For variables that did not follow a normal distribution, such as HbA1c and tT levels, group comparisons were conducted using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of the index parameters in distinguishing between groups. All statistical analyses were performed by SPSS, version 25.0 (IBM Corp., Chicago, USA) and a P value $< .05$ (two-tailed) was considered statistically significant.

Results

The study included 51 male patients with diabetic ED and 51 healthy controls. The demographic and clinical characteristics of the study population are summarized in Table 1. No statistically significant difference was observed between groups in terms of age, body mass index (BMI), cigarette and alcohol consumption, or tT concentration.

Regarding selected TEs, Cu was the only element that differed significantly between the two groups, with diabetic ED patients showing higher Cu levels compared with controls. While zinc (Zn) levels were lower in the diabetic ED group, this difference did not reach statistical significance. To further explore the interaction between Cu and Zn, a comparison pertaining to Cu/Zn ratio (CZr) was performed between groups to evaluate the synergistic and combined effects of these TEs. As expected, CZr exhibited a significant increase in patients with diabetic ED compared with controls.

ROC curve analysis demonstrated that CZr had a higher area under the curve (AUC) value compared with Cu alone, indicating superior discriminatory performance in distinguishing diabetic ED patients from controls (Figure 1 and Table 2).

Discussion

Exploring novel risk factors for diabetic ED poses a demand, particularly in the post-PDE5i era. A major achievement of this study is the novel identification of significantly elevated serum Cu levels and CZr in men with diabetic ED. Notably, CZr demonstrated superior discriminative performance compared to Cu alone in identifying diabetic ED, suggesting its potential as a more effective biomarker.

Many chronic diseases are associated with abnormal Cu and Zn metabolism. Cu excess and Zn deficiency are associated with an increased risk of diabetic complications and CVD (Laouali et al., 2021; Takao et al., 2021), Given the influence of Cu levels on Zn metabolism, the CZr have been established as a better indicator of various diseases compared with either element alone. However, few studies have demonstrated

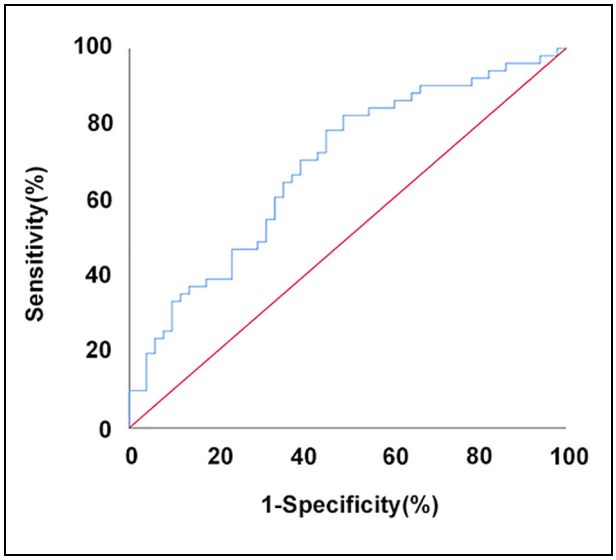

Figure 1. *Receiver Operating Characteristic (ROC) Curve Analysis of Copper/Zinc Ratio in the Prediction of Diabetic ED*

the interaction between Cu and Zn metabolism and erectile function. A study involving 152 ED patients found no significant correlation between blood Cu or Zn levels and ED incidence (Ryl et al., 2024). Another epidemiologic study reported compromised sexual function and lower testosterone levels among copper miners (Musa Obadia et al., 2023). Zinc deficiency, however, has not been identified as a reversible cause of sexual dysfunction (Lartey et al., 2024). In contrast, findings from the National Health and Nutrition Examination Survey (NHANES) revealed a negative, nonlinear correlation between dietary Cu or Zn intake and ED prevalence (R. J. Liu et al., 2022). These conflicting outcomes highlight the need for further research to elucidate the role of TEs in relation to ED. This study contributes to this understanding by demonstrating that elevated circulating Cu level but not Zn level is negatively associated with erection in diabetic participants. In addition, CZr may play a crucial role in the development of ED under diabetic conditions.

As an essential TE, systemic Cu levels are maintained within a narrow range to ensure normal biochemical processes (L. Chen et al., 2022). Excessive Cu accumulation has been associated with proteotoxic stress-mediated endothelial dysfunction, a critical process for diabetic ED. One proposed mechanism involves Cu is involved in maintaining a balanced cycle of oxidation and anti-oxidation. Studies have shown that the Cu chaperone for superoxide dismutase (SOD) delivers Cu to SOD1, while the Cu-ATPases couple with extracellular Cu/Zn SOD (SOD3) to detoxify reactive oxygen species (Ozumi et al., 2012). In addition, Cu and Zn are significantly associated with other antioxidant enzymes like catalase and malondialdehyde (Li et al., 2023). Second, Cu accumulation has been linked to cuproptosis, a novel form of cell death (Tsvetkov et al., 2022). Although recent findings suggested no direct binding of Cu to lipoylated components of the tricarboxylic acid cycle in corpus cavernosum (Y. Wang et al., 2023), larger sample sizes were required to reduce biases and further in-depth experiments were needed to verify this finding. Third, Cu possesses pro-angiogenic properties and is required for the activation of hypoxia-inducible factor 1, a major transcription factor that regulates angiogenesis (Urso & Maffia, 2015). Collectively, the current evidence suggests that oxidative stress, mitochondrial damage, and vascular growth as the primary mechanisms by which Cu accumulation contributes to endothelial dysfunction.

Preclinical and clinical studies in conditions involving nonclassical copper overload, such as Wilson disease, have suggested promising therapeutic benefits. For example, the application of trientine, a Cu chelator, is associated with improvements in cardiac structure and function in an open-label study in patients with diabetic cardiomyopathy (Farrant et al., 2023; Gong et al., 2008). Despite the precise influence of Cu overload on erection remains uncertain, some animal studies have carried out the potential of Cu chelation therapy for ED. Khan et al. demonstrated that Cu exacerbates homocysteine levels, which in turn inhibits nitric oxide-mediated cavernosal smooth muscle relaxation (Khan et al., 1999). Furthermore, tetrathiomolybdate and penicillamine have been shown to alleviate ED in mammalian models of diabetes (Yin et al.,

Table 2. Receiver Operating Characteristic Curve of Trace Elements for Predicting Diabetic ED

Variables	AUC	95% CI	*P*	Cut-off value	Sensitivity (%)	Specificity (%)
Cu	0.672	0.565–0.780	.003	8.191	58.8	82.4
CZr	0.689	0.586–0.791	.001	1.135	82.4	51.0

Note. Cu, copper; CZr, copper/zinc ratio.

2022) and hyperhomocysteinemia (Koupparis et al., 2006). In some way, our study adds growing clinical evidence supporting the potential use of Cu chelators in treating ED. However, further research is needed to determine the optimal Cu concentration within the cavernous cavernosum, as well as the organ- and cell-specificity effects of Cu chelation.

Other TEs, such as Fe, Mg, and Ca, have shown varied associations with ED. For instance, while ferroptosis has been implicated in animal studies (Tan et al., 2023; Xu et al., 2023), clinical results on Fe homeostasis and ED remain inconclusive (Ryl et al., 2024). Mg deficiency may contribute to ED by affecting T in elderly patients with advanced chronic kidney disease (Maggio et al., 2014; Toprak et al., 2017). However, this association appeared to be weaker in the general population (R. J. Liu et al., 2022). Similarly, numerous studies have explored the potential link between intracellular Ca signaling in corpus cavernosum (Rasmussen et al., 2015; Thornbury et al., 2019), and Ca consumption was found to be inversely correlated with ED (Deng et al., 2024). However, our results suggested that no significant association was found between serum Ca levels and the risk of ED.

This study has several limitations. First, although the severity of ED can be categorized as mild, mild to moderate, moderate, and severe based on IIEF-5 scores, the limited sample size prevented stratified or subgroup analyses based on these classifications. Second, the study design could not identify a causal relationship. Third, we did not take exposure sources such as dietary patterns and residential environment into consideration, which can influence in part the variations of the circulating levels of these TEs. Finally, the exclusion of patients with aging and other comorbidities, which are prevalent in patients with ED, may have restricted the generalizability of our findings and limited insights into the broader interplay between these factors and TE concentrations.

Conclusion

Our findings suggest disruptions in Cu homeostasis and a high probability of elevated CZr in patients with diabetic ED. Additional studies are needed to validate these findings, explore their correlation with ED severity, and elucidate the underlying biological mechanisms contributing to these effects.

Author Contributions

Conception and design, ZY; Materials ZY; Acquisition of data, ZLP and LBC; Analysis and interpretation of data, YZX; Correcting, XLH and JXW; Drafting the manuscript, ZY; Revising the manuscript JYZ. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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