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Evaluation of Relationship between Copper and Insulin Resistance by Hyperinsulinemic Clamp

Dear Editor,

Trace elements are essential micronutrients required for the normal functioning of the body. Patients on hemodialysis (HD) exhibit altered levels of essential trace elements, predisposing them to oxidative stress, inflammation, and immune abnormalities. In particular, patients undergoing HD have disruption of zinc (Zn) and copper (Cu) levels, which has been suggested as a cause of clinical deterioration and adverse outcomes in HD patients.[1] Zn and Cu have been suggested to affect oxidative stress and to be associated with abnormal glucose tolerance and diabetes mellitus.[2] Cu is an essential trace element and a major constituent of the respiratory enzyme complex cytochrome *c* oxidase; Cu is also found in superoxide dismutase, which decreases oxidative stress. Oxidative stress is thought to promote the development of insulin resistance (IR) and diabetes.[2] IR is considered a substantial risk factor for the development of excessive vascular stiffening and consequent adverse cardiovascular disease events.[3] Strategies aimed at preventing or improving IR may represent novel interventions to improve poor clinical outcomes in HD patients. The hyperinsulinemic euglycemic clamp is the gold standard for the index of IR, but the technique is complicated because it requires time for equipment and inspection, making it difficult to use in daily medical treatment and large-scale clinical studies.[4] Since there is a lack of evidence in this area, we evaluated the relationship between IR and trace elements such as Zn and Cu in HD patients using an artificial pancreas.

The hyperinsulinemic euglycemic clamp was performed with an artificial pancreas (STG-55; Nikkiso, Shizuoka, Japan). In brief, human regular insulin was automatically injected intravenously by the artificial pancreas at a rate of 1.25 mU/kg/min to achieve a blood glucose level of 95 mg/dL. The mean glucose infusion rate (GIR; mg/kg/min) over the last 30 min of the 120-min clamp represents insulin sensitivity. The high GIR means low IR because insulin is functioning well.

This study and all its protocols were reviewed and approved by the International University of Health and Welfare Ethics Committee (approval no. 21-NR-060). Written informed consent was obtained from the patient for this study. In seven HD patients, GIR was measured by the hyperinsulinemic euglycemic clamp on two occasions, 6 weeks apart, before dialysis at the beginning of the week. The hyperinsulinemic euglycemic clamp requires two catheters, one for continuous blood collection and the other for glucose and insulin administration. In this study, the two indwelling needles used in subsequent HD were used as routes.

Normality of data was evaluated with the Shapiro–Wilk test. Data are presented as the mean ± standard deviation (SD) or the median (25%–75% interquartile range), unless otherwise indicated. The relation between two variables was assessed with Pearson's correlation coefficient for normal distribution and Spearman's rank correlation coefficient for non-normal distribution. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software. A P value of <0.05 was considered statistically significant.

Table 1 summarizes the demographic and clinical characteristics of the seven patients included in this study. Results showed correlation between Cu and GIR (r = −0.55, P = 0.042), but no correlation between Zn and GIR (r = 0.31, P = 0.280) [Figure 1]. Trace elements have received increasing attention in relation to the prevalence of diabetes, and Cu is one such element. Cu is a crucial component of a variety of metalloenzymes and plays an important role in the redox reaction. Cu contributes to increased oxidative stress by enhancing the formation of reactive oxygen species (ROS) through Haber–Weiss and Fenton-like reactions and by catalytically participating in the generation of hydroxyl radicals by hydrogen abstraction.[5] These consequences are thought to lead to IR, and our results are consistent with this hypothesis. Zn is an essential micronutrient in the metabolism, which regulates more than 300 enzymes for protein folding, gene expression, and the

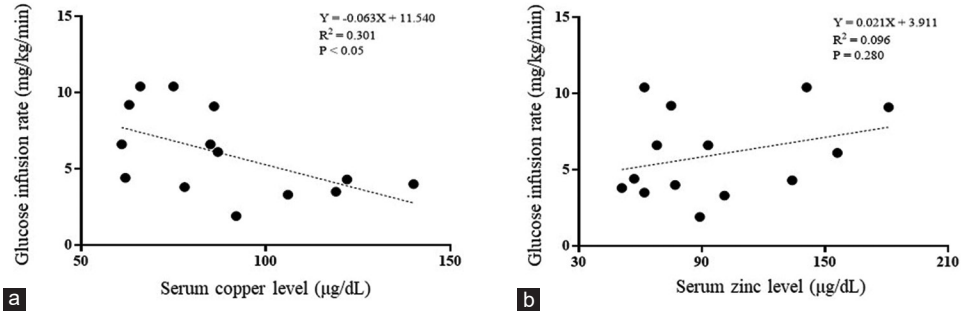

Figure 1: Correlation analysis for glucose infusion rate and either (a) copper or (b) zinc.

Table 1: Clinical characteristics and laboratory data of the study participants (*n*=7)

Parameters	Results
Clinical characteristics	
Age, years	66.8±8.5
Men, *n* (%)	4 (57.1%)
Body weight, kg	70.1±24.6
Body mass index, kg/m^2	26.3±8.2
Diabetes mellitus, *n* (%)	5 (71.4%)
Laboratory data	
Glucose infusion rate, mg/kg/min	6.3±2.9
Copper, µg/dL	80.3±20.9
Zinc, µg/dL	62.5±8.4
Fasting plasma glucose, mg/dL	122.3±48.3
Fasting immunoreactive insulin, µU/mL	7.0 (4.0–10.5)
HOMA-IR	2.0 (0.8–3.28)
HbA1c, %	6.1±1.4
Glycoalbumin, %	18.6±3.2

HbA1c=Glycated hemoglobin

production and neutralization of ROS. Zn is required for the processing and storage of insulin. In particular, the zinc transporter ZnT8 is vital for the biosynthesis and secretion of insulin, the uptake of zinc into insulin secretory granules, and Zn co-secretion with insulin. Disruption of Zn homeostasis has been associated with diabetes and IR.[2] There have been several studies examining the association between Zn and IR, but they were inconclusive. In the present study results, no association was found between Zn and IR, but this could be due to insufficient number of cases. HOMA-R did not correlate with GIR, Zn, or Cu, possibly related to the fact that HOMA-R does not accurately reflect IR, especially in high fasting blood glucose.

To our best knowledge, this is the first report suggesting an association between Cu and GIR. In the area of basic research, it has been reported that Cu chelators reduced IR and ameliorated glucose intolerance in type 2 diabetic mice.[6] However, there have been no reports in clinical studies. Our results support the investigation of whether Cu chelators contribute to IR improvement.

Conflicts of interest

There are no conflicts of interest.

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