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Research Article

Serum Trace Element Levels in Type 2 DM Patients and its Correlation with Glycemic Control

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ABSTRACT

Background: Type 2 diabetes mellitus, a chronic metabolic disorder, is known to impact serum trace element levels. **Objectives:** to investigates the association between serum trace elements (Co, Cr, and Cu) and glycemic control in individuals with type 2 diabetes. **Material and Methods:** A 209 type 2 diabetes patients from Dr. H. Abdul Moeloek Hospital in Bandar Lampung and Hasan Sadikin Hospital in Bandung participated in the study. Patients underwent assessments for serum trace element levels (Co, Cr, and Cu) and glycemic control indicators (FBG and HbA1c). **Results:** Results indicated significantly lower Co levels in uncontrolled diabetes versus controlled cases (P<0.05). Co, Cr, and Cu levels displayed a significant negative correlation with HbA1c (P<0.05), while Cr and Cu showed a significant negative correlation with FBG (P<0.05). Age did not show significant correlations with serum trace element levels. **Conclusion:** serum trace element levels (Co, Cr, Cu) are inversely linked to glycemic control in type 2 diabetes individuals.

Keywords: type 2 diabetes mellitus, fasting blood glucose, glycemic control, HbA1c, trace element serum.

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INTRODUCTION

Diabetes mellitus (DM), particularly type 2 diabetes, is a non-communicable disease with an increasing global prevalence each year.[1] In 2021, the estimated global incidence of DM was 537 million cases, with diagnoses occurring at progressively younger ages.[2] In Indonesia, the prevalence of diabetes has also risen annually,[3] affecting approximately 8.5% of the population, predominantly women.[4] Beyond its prevalence, DM is notable for its association with organ damage affecting the heart, liver, blood vessels, eyes, nerves, and kidneys.[5] If unmanaged, this condition can substantially impair the quality of life for affected individuals and may lead to adverse socio-economic consequences for Indonesia in the future. Consequently, diabetes mellitus constitutes a major healthcare concern requiring urgent attention from the Indonesian government.[6]

Various risk factors contribute to the development of type 2 diabetes, including obesity, genetics, and poor dietary habits. The complex interplay of these factors necessitates a comprehensive treatment approach.[7] An unhealthy diet, common among individuals with diabetes, can disrupt essential nutrient balances, including trace elements.[8,9] These trace elements play crucial roles in various physiological processes, such as glucose regulation and insulin secretion.[10,11]

Among these trace elements, copper (Cu), chromium (Cr), and cobalt (Co) have been identified as having significant effects on glucose metabolism.[10-15] Copper, primarily obtained through daily consumption of foods like seafood, meat, and wheat, plays a vital role in energy production, erythropoiesis, glucose metabolism, and radical scavenging.[16] Copper has been implicated in the activation of insulin signaling,[17] and its deficiency can result in insulin resistance.[18] Elevated serum copper levels have also been associated with an increased risk of diabetes mellitus.[19] Chromium, typically found in its trivalent form (Cr3+) in the human body, plays an important role in the regulation of fat and glucose metabolism.[20] It activates insulin receptors, enhances insulin signal transduction and sensitivity, and regulates glucose homeostasis.[14] In type 2 diabetes, chromium deficiency has been linked to insulin resistance and hyperlipidemia.[20] Similarly, cobalt is an essential trace element that plays a vital role in the body. Cobalt is a component of vitamin B12, which acts as a coenzyme in various metabolic processes, including glucose metabolism.[21]

Studies exploring the impact of these trace elements on insulin sensitivity and resistance have produced conflicting results, underscoring the need for further investigation into their role in type 2 diabetes pathophysiology, particularly in relation to glycemic control.[10,11,22] Effective glycemic control is crucial for preventing complications in individuals with type 2 diabetes. Achieving glycemic control requires a comprehensive approach, including both pharmacological and non-pharmacological strategies, such as lifestyle modifications, physical activity, and dietary and nutritional improvements, including trace mineral intake.[23-25]

Research focusing on the Indonesian population in this context is limited, highlighting the need to investigate the association between serum trace elements and glycemic control in type 2 diabetes patients. This study aims to address this gap by examining the relationship between serum trace elements (cobalt, chromium, and copper) and glycemic control in individuals with type 2 diabetes.

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METHODS

Study Participant

This cross-sectional study was conducted at the internal medicine polyclinic and clinical pathology laboratory of Dr. H. Abdul Moeloek Hospital in Bandar Lampung and Hasan Sadikin Hospital in Bandung. The study included 209 eligible patients with type 2 diabetes mellitus who provided informed consent. Inclusion criteria include Indonesian patients with type 2 diabetes mellitus. Exclusion criteria included pregnancy, breastfeeding, chronic conditions such as liver, cardiovascular, kidney, or endocrine diseases, malignancies, and the use of vitamin or mineral supplements.[26-28] Participants were selected using a consecutive sampling technique. Ethical approval was obtained from the Research and Health Ethics Committee at the Faculty of Medicine, University of Lampung, in accordance with the Helsinki Declaration for medical research. Participants voluntarily consented to participate after a comprehensive understanding of the study's objectives

Antrophometric Parameter Measurement

Anthropometric data, including weight (kg) and height (cm), were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height in meters (m^2).[9] BMI classifications were defined as follows: normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (>30.0 kg/m^2).[29]

Blood Parameter Measurement

A 5 ml fasting blood sample was obtained from the patient's vein using a disposable syringe and placed into a plain tube. The blood was allowed to clot at room temperature for approximately 30 minutes before being centrifuged at 3.000 rpm for 10 minutes to separate the serum from the whole blood. Fasting blood glucose levels were measured using the hexokinase method on a COBAS Integra 400 plus chemistry autoanalyzer. HbA1c levels were assessed through the immunoturbidimetric method using a BioRad D-100 instrument. Serum trace element levels were analyzed using the inductively coupled plasma mass spectrometry (ICP-MS) method.

Data Analysis

Differences in serum trace element levels between the two groups of type 2 diabetes mellitus, controlled and uncontrolled, were analyzed using either the t-test or Mann-Whitney test. The relationship between serum trace element levels and glycemic control was assessed using the Spearman Rank correlation test. Comparisons involving frequencies were conducted using the chi-squared or Fisher's exact test. All statistical analyses were performed at a significance level of $\alpha = 0.05$ using SPSS version 23.0 software (IBM Corporation, Armonk, NY, USA).

RESULTS

Initially, 221 individuals with type 2 diabetes mellitus were recruited for the study, with 209 participants meeting the research criteria. The majority of subjects exhibited uncontrolled glycemic status (70.3%). No significant differences were observed in mean age, gender distribution, or BMI between the controlled and uncontrolled type 2 diabetes groups (P>0.05). However, a higher frequency of obesity was noted in the uncontrolled type 2 diabetes group (Table 1).

In this study, the controlled type 2 diabetes group exhibited significantly lower levels of fasting blood glucose (FBG) and HbA1c compared to the uncontrolled group. Cobalt levels were markedly lower in the uncontrolled group. Although chromium (Cr) and copper (Cu) levels were also lower in the uncontrolled group compared to the control group, these differences were not statistically significant (P>0.05) (Table 2).

Table 1: Subject Characteristics.

Characteristics	Glycemic Status		P-value
	Controlled n=62	Uncontrolled n=147	
Age, years	58.35±9.69	58.81±11.24	0.781[a]
Gender			
-. Male (%)	38 (61.3%)	71 (48.3%)	0.086[b]
-. Female (%)	24 (38.7%)	76 (51.7%)	
BMI, kg/cm^2	25.84 (19.36-37.27)	25.50 (18.61-42.91)	0.854[c]
-. Normal (%)	23 (37.7%)	68 (47.2%)	
-. Overweight (%)	30 (49.2%)	49 (34.0%)	
-. Obesitas (%)	8 (13.1%)	27 (18.8%)	

Note: [a] t-test P-value; [b] Chi Square P-value; [c] Mann Whitney P-value

Table 2: Glycemic Control Status and Levels of Serum Trace Element.

Parameters	Glycemic Status		P-value
	Controlled n=62	Uncontrolled n=147	
FBG, mg/dL	104.50 (72-185)	143.00 (78-366)	0.000*
HbA1c, %	6.4 (3.2-7.0)	8.7 (7.1-14.5)	0.000*
Cobalt (Co), µg/L	0.76 (0.01-3.90)	0.56 (0.01-2.90)	0.008*
Chromium (Cr), µg/L	0.15 (0.01-0.70)	0.10 (0.05-0.90)	0.107
Copper (Cu), µg/L	0.44 (0.01-1.05)	0.28 (0.03-0.99)	0.096

Note: * P<0,05 based on Mann Whitney test

Table 3. The association between age, BMI, glycemic control and levels of serum trace element.

Trace Element	Age	BMI	FBG	HbA1c
Co	0.112	-0.080	-0.128	-0.241*
Cr	0.064	0.022	-0.216*	-0.204*
Cu	-0.181	-0.043*	-0.204*	-0.149*

Note: *P<0.05 based on Rank Spearmann test

The level of serum trace elements was also compared in patients with diabetes according to difference age and BMI. Further analysis of serum trace element levels among type 2 diabetes patients based on age and BMI did not reveal significant differences (P>0.05).

To evaluate the association between glycemic control and serum trace elements in patients with type 2 diabetes mellitus, a Spearman rank correlation test was performed. The results indicated a significant negative correlation between fasting blood glucose (FBG) levels and the trace elements chromium (Cr) and copper (Cu). Additionally, HbA1c levels showed a significant negative correlation with cobalt (Co), chromium (Cr), and copper (Cu) (Table 3). These findings suggest that as glycemic control deteriorates in individuals with type 2 diabetes mellitus, levels of cobalt, chromium, and copper tend to decrease

DISCUSSION

In this study, we investigated the modulation of serum trace elements (Co, Cr, Cu, and Se) among patients with type 2 diabetes mellitus. Our findings revealed significantly lower serum Cobalt levels in uncontrolled type 2 diabetes cases compared to controlled cases.

Cobalt, often underappreciated, is a critical component of vitamin B12 and serves as an essential coenzyme in various metabolic pathways.[21] Research suggests that cobalt may contribute to lowering blood glucose levels by enhancing GLUT-1 expression, suppressing gluconeogenesis, and regulating liver glycogen levels.[30] Our study showed decreased cobalt levels in uncontrolled type 2 diabetes patients and observed

negative correlations between cobalt levels and glycemic control parameters such as fasting blood glucose (FBG) and HbA1c. This study establishes a novel link between cobalt levels and glycemic indicators in type 2 diabetes patients, revealing an inverse relationship where lower cobalt levels are associated with poorer glycemic control. This aligns with findings from Chen et al. (2021),[31] who reported a negative association between cobalt levels and insulin resistance in adult women, closely related to HbA1c levels as a glycemic indicator.[32,33] Cobalt supplementation has shown potential for enhancing endothelial function and insulin sensitivity by modulating oxidative stress, improving the balance of eNOS/iNOS expression, increasing HO-1 levels, and increasing TBARS levels and antioxidant enzyme activity.[34,35] However, its efficacy appears more significant in women than in men.[35] Therefore, the therapeutic potential of cobalt in managing type 2 diabetes warrants further investigation with larger sample sizes to fully evaluate its clinical utility.

Chromium (Cr) is another crucial trace element for regulating glucose and fat metabolism and enhancing insulin signaling.[36-38] Our study found a negative correlation between chromium levels and FBG and HbA1c levels in type 2 diabetes patients, suggesting that higher chromium levels may reduce these markers. This finding is consistent with the observations of Rajendran et al. (2015),[39] who reported a negative correlation between serum chromium levels and HbA1c in type 2 diabetes patients. Previous research has shown that chromium supplementation can significantly improve glycemic control by enhancing insulin sensitivity through mechanisms such as increasing insulin binding sites, reducing protein tyrosine phosphatase 1B (PTP1B) levels, and enhancing β-cell sensitivity in Langerhans' islets.[40,41] While chromium supplementation shows promise for managing type 2 diabetes,[14,42,43] further research with larger cohorts is necessary to validate its efficacy and long-term impact, especially in diabetic populations.

Copper (Cu) is another essential trace element, with studies reporting increased copper levels in uncontrolled type 2 diabetes cases.[44] Copper is vital for various biological processes, acting as a catalyst for the antioxidant enzyme superoxide dismutase (SOD) and playing a key role in activating cytochrome oxidase in mitochondria. Our study, while not statistically significant, observed lower copper levels in uncontrolled type 2 diabetes patients compared to controlled cases. These findings align with previous research indicating decreased copper levels in type 2 diabetes patients,[45,46] despite contrasting results indicating a significant negative correlation between copper levels and glycemic control, contrary to findings from studies in Iran,[47] and Saudi Arabia.[48] These discrepancies underscore the potential influence of demographic factors on copper homeostasis in individuals with type 2 diabetes, emphasizing the complexity of copper regulation in this population.

CONCLUSION

Our study on Indonesian patients with type 2 diabetes mellitus demonstrates significant alterations in the metabolism of trace elements Cobalt (Co), Chromium (Cr), and Copper (Cu). We observed reduced levels of Co, Cr, and Cu in patients with uncontrolled type 2 diabetes, which correlated inversely with glycemic control. These findings underscore the potential significance of these trace elements in the pathophysiology of type 2 diabetes and suggest a possible link between their levels and glycemic regulation in this patient population. Further research is warranted to elucidate the mechanisms underlying these observations and to investigate the therapeutic potential of modulating these trace elements in the management of type 2 diabetes mellitus.

DISCLOSURE

The authors report no conflict of interest in this paper.

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