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The Role of Trace Elements in the Development of Disorders of Carbohydrate Metabolism

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Abstract This study investigates the serum levels of zinc and calcium in individuals with various carbohydrate metabolism disorders, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (T2DM), across rural (Markhamat district) and urban (Andijan city) populations in the Andijan region. A cross-sectional epidemiological survey was conducted among adults aged 35–75 years. Biochemical analyses revealed significant regional differences in trace element status. Zinc levels were consistently higher in rural residents across all groups, while calcium levels showed variable trends depending on the glycemic status. These findings highlight the potential role of trace elements, particularly zinc, in the pathogenesis of prediabetes and T2DM and suggest the need for monitoring micronutrient status in at-risk populations.

Keywords Zinc, Calcium, Type 2 Diabetes Mellitus, Prediabetes, Andijan region, Micronutrient Deficiency

1. Introduction

Assumptions about the role of micronutrients in human disease were published in 1929 when Glaser E and Halpern G. observed that yeast extracts enhanced the action of insulin. [1]. Further, Mertz W.et al. in 1959 demonstrated the existence of glucose tolerance factor and the role of chromium in relation to health and disease including DM 2. [2].

Direct associations of micronutrients and macronutrients with type 2 DM have been shown in many studies. The action of insulin on blood glucose lowering has been reported to be potentiated by some elements such as chromium, magnesium, zinc, manganese, molybdenum and selenium. The putative mechanism of micronutrients enhancing insulin action involves activation of insulin receptor sites that serve as cofactors or components for enzyme systems involved in glucose metabolism. Zinc is required for insulin synthesis and storage, and insulin is secreted as zinc crystals; it maintains the structural integrity of insulin. Magnesium is a cofactor in mechanisms transporting cell membrane glucose and various enzymes in carbohydrate oxidation. It is also involved at several levels in insulin secretion, binding and enhancing the ability of insulin to activate tyrosine kinase. According to the authors, it is unknown whether micronutrient deficiencies contribute to the development of the disease. [3]. According to Masood N., serum zinc levels were significantly lower in patients with type 2 DM. There was no association of age, sex, glycemic status and duration of type 2 DM with serum concentrations of these micronutrients in patients with type 2 DM [3].

Numerous studies have demonstrated the necessary role of trace elements (chromium, zinc, magnesium, selenium, vanadium, molybdenum) in insulin action and carbohydrate metabolism [4]. The observed changes in the status of these elements in patients with type 2 DM were associated with hyperglycemia and increased protein glycosylation [5].

In the studies, it was observed that the mean serum zinc levels were significantly low in the diabetic group compared to control subjects. Similar observations are reported by Al-Maroof RA, et al, who also observed significantly lower serum zinc levels in type 2 DM patients than in control subjects [6].

In connection with the above, This study aimed to evaluate serum levels of zinc and calcium among individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes mellitus in different regions of the Andijan region.

2. Materials and Methods of Research

To realize the goal and objectives of the dissertation research we conducted a one-stage epidemiological study with the inclusion of men and women from 35 to 75 years old, living in rural and urban areas. The survey was conducted in 1800 persons over 40 years old in Markhamat district of Andijan region and in 1600 persons over 40 years old in Andijan city. The survey was conducted in 3 stages. The stage-by-stage approach in the realization of monitoring provides that at the first stage data on the main risk factors are collected

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by means of questionnaires (stage 1). Then, at the second stage, the simplest physical examinations are performed (stage 2), and only then it is recommended to perform blood sampling for biochemical studies (stage 3). Prediabetes was diagnosed based on WHO criteria and recommendations by the Russian Association of Endocrinologists (2017), EASD, and ADA (2015, 2018). Prediabetes was defined as IFG (Impaired Fasting Glucose) or IGT (Impaired Glucose Tolerance). Hyperglycemia included a diagnosis of diabetes or prediabetes.

The parameters of carbohydrate metabolism were evaluated on the basis of capillary blood glycemia levels using glucometers. HbAlc level was determined using a set of reagents from "HUMAN" company with automatic determination of blood hemoglobin level and calculation of the percentage of HbAlc from the total, the levels of trace elements were determined using the following reagents: calcium - HUMAN (Germany), Zinc - "DAC-SpectroMed" company (on a semi-automatic biochemical analyzer Mindray BA-88A).

For adult women, the reference values for blood zinc are between 10.7- 17.5 µµmol/ and for men between 11.1 - 19.5 µmol/. In the blood of healthy individuals, the observed concentration of ionized calcium corresponds to the level of 1.17 - 1.29 mmol/L.

Statistical processing of the study results was performed using the Statistica 6.0 application program package. Spearman's rank correlation method was used to calculate correlation coefficients. To assess the significance of the difference between the shares, Pearson's x^2- square criterion will be used. Differences at the significance level of p<0.05 are taken as reliable.

3. Results and Discussion

Analysis of average values of blood calcium level in patients with various carbohydrate metabolism disorders living in Markhamat district and Andijan city revealed a number of regularities (Table 1).

The most pronounced differences were recorded in the group of patients with impaired fasting glycemia (IFG): calcium levels were significantly lower in the Markhamat district (0.98 mmol/L vs. 1.03 mmol/L; P<0.05). A similar trend was found in the control group without carbohydrate metabolism disorders, where calcium levels were also significantly higher in the Markhamat district compared to the urban population (1.05 mmol/L. vs. 0.95 mmol/L.; P<0.05).

The group of patients with diabetes mellitus (DM) deserves special attention, where, on the contrary, calcium level was found to be higher in Markhamat district (0.93 mmol/L.) compared to the city (0.84 mmol/L.) and this difference was statistically highly significant (P<0.01).

In the groups with impaired glucose tolerance (IGT) and combined form (IFG+ IGT), no statistically significant differences were observed between the study populations (P>0.05).

Thus, the most pronounced regional differences in calcium levels are observed in patients with MND, DM and controls, which may indicate the influence of environmental factors, lifestyle and socioeconomic status on mineral metabolism.

Table 1. Average calcium value

Group	Average calcium level (mmol/l)	
	Markhamat	Andijan city
IFG	0,98±0,020	1,03±0,020
IGT	1,05±0,022*	1,04±0,018
IFG+ IGT	0,97±0,017**	1,07±0,015
DM 2 type	0,84±0,036$^{**\wedge\wedge\wedge\&\&\&}$	0,93±0,030$^{*\wedge\wedge\&\&\&}$
without carbohydrate metabolism disorders	1,09±0,018$^{\wedge\&\&\#}$	1,08±0,015$^{\#\#}$

Note: *- significantly compared to the IFG group (*-P<0.05, P<0.01))
^- significantly compared to the IGT group values (^-P<0.05,^ ^-P<0.01;)
&- significantly compared to the indicators of the IFG+ IGT group (&-P<0.05&&&-P<0,001)

Table 2. Average zinc value

Group	Average zinc level (µmol/l)	
	Markhamat	Andijan city
IFG	11,4±0,76	16,8±0,94
IGT	12,7±0,78	15,5±0,83
IFG+ IGT	11,6±0,55	13,6±0,48$^{**\wedge}$
DM 2 type	13,3±0,74	14,7±0,63*
without carbohydrate metabolism disorders	14,4±0,90$^{*\&}$	18,1±0,81$^{\&}$

Note: *- significantly compared to the IFG group (*-P<0.05, P<0.01))
^- significantly compared to the IGT group values (^-P<0.05,^^-P<0.01;)
&- significantly compared to the indicators of the IFG+ IGT group (&-P<0.05)

Table 2 shows the average blood zinc level in patients with different carbohydrate metabolism disorders. In Markhamat district zinc level was 15.5 µµmol/, which is significantly higher compared to the urban group, where it was 11.4 µµmol/. This difference is statistically significant (P<0.05). In Markhamat district, the mean zinc level was 12.7 µµmol/. which is also higher than the value in the urban group (11.6 µµmol/.), and the difference between the groups was statistically significant (P<0.01). In the combined IFG+ IGT group, zinc level in Markhamat district was 13.6 µµmol/. and in urban group was 11.6 µmol/., which was also statistically significant (P<0.01). This confirms the trend of higher zinc level in Markhamat district. The zinc level in the group with diabetes mellitus was 14.7 µµmol/. in Markhamat district group and 13.3 µµmol/. in the city. The difference in zinc levels between the groups was also statistically significant (P<0.05). In the group without carbohydrate metabolism disorders, Markhamat district group showed an average zinc level of 15.5 µqmol/. while in the city it was slightly lower at 14.4 µqmol/. The difference in values is statistically significant (P<0.05), which confirms the general trend of higher zinc level in Markhamat district.

The study data show that blood zinc levels in Marhamat district are significantly higher than in urban areas in all patient groups considered.

The findings demonstrate the influence of regional factors on trace element metabolism in patients with various carbohydrate metabolism disorders. Higher levels of zinc and specific fluctuations in blood calcium levels may play a role in the development and progression of carbohydrate metabolism disorders, which requires further studies to establish causal relationships.

To date, the question of whether micronutrient metabolism disorders are the cause of insulin resistance has not been sufficiently investigated. However, new experimental data suggest the presence of certain correlation: the results of the study show that the level of most of the analyzed trace elements remains stable, but the concentration of zinc in the serum of women with prediabetes decreases by 10%. This trace element is known for its important role in the synthesis of insulin by pancreatic beta-cells and in increasing tissue sensitivity to this hormone [7].

Changes in serum magnesium and ionized calcium levels in glucose tolerance disorders were first described in 1990 by Czech authors [8]. In a group of 58 people with strictly defined glucose tolerance (38 with normal glucose tolerance - nGT, 10 with impaired glucose tolerance - IGT, 10 type 2 DM patients treated by diet), the authors investigated the relationship between changes in blood sugar and serum insulin levels in relation to changes in calcium, ionized calcium, magnesium and total protein.

Another study conducted in India reported a significant decrease in serum calcium levels in diabetic patients compared to non-diabetic controls. Elevated plasma glucose levels were negatively correlated with serum calcium levels [9]. A cross-sectional study involving 40 patients with DM2 and healthy individuals was conducted in Khartoum, North Sudan to evaluate serum calcium and glycated hemoglobin (HbA1c) levels. The results showed that there was a significant decrease in serum calcium levels in the group of DM2 patients with elevated Hb1Ac levels compared to the control group with normal HbA1c levels. This negative correlation between serum calcium and HbA1c levels in DM 2 patients suggests that patients with uncontrolled hyperglycemia in DM 2 patients are at risk for hypocalcemia compared to control patients [10].

There are no cohort studies examining the role of elevated serum calcium levels as markers of impaired glucose metabolism. One such study demonstrated an increased risk of diabetes in individuals with elevated serum calcium concentrations.

Another study confirmed the prevalence of metabolic syndrome and diabetes with higher serum calcium levels in 1329 middle-aged and elderly Korean individuals ($p < 0.001$). This association was independent of age, sex, body mass index (BMI), serum creatinine, phosphorus, parathyroid hormone (PTH), 25-OHD levels, smoking, alcohol consumption, exercise, total energy intake, and calcium and sodium intake [11]. Studies have shown a complex relationship between calcium levels and the pathogenesis of DM 2. Decreased β-cell function has been associated with abnormal calcium regulation [12], which may be related to altered glucose homeostasis and oxidative stress [13].

4. Conclusions

The study revealed that calcium and zinc levels in serum are statistically significantly different in rural (Markhamat district) and urban population (Andijan city) of Andijan region. In the group of patients with impaired fasting glycemia (IFG) and in the control group without carbohydrate metabolism disorders calcium level was lower in rural population compared to urban population, while in patients with type 2 diabetes mellitus (DM2) calcium level, on the contrary, was significantly higher in rural area. In all studied groups, the level of zinc in blood was statistically significantly higher in patients from Markhamat district, which is probably associated with the peculiarities of nutrition, environmental conditions and lifestyle of the rural population.The obtained data confirm the role of trace elements, especially zinc, in the pathogenesis of carbohydrate metabolism disorders, including pre-diabetic states and type 2 diabetes mellitus, which emphasizes the need to control the trace element status in the risk group.

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