ORIGINAL ARTICLE

Relationship between glycaemic control with microalbuminuria and trace metals in patients with type 2 diabetes mellitus: A cross-sectional study from University of Ilorin teaching hospital, Nigeria

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Abstract

Background: Low serum levels of some trace metals have been associated with the severity of diabetes mellitus. An increase in Urinary Albumin Excretion (UAE) has also been identified as one of the risk factors that contribute to morbidity and mortality among patients with Type 2 Diabetes Mellitus (T2DM). Aim and *Objective*: This study aims to determine the relationship between serum trace metals (Mg, Zn, Mn, and Cr), UAE, and glycaemic control among patients with Type 2 Diabetes Mellitus (T2DM). *Materials and Methods*: This cross-sectional analytical study was carried out over three months. There were 304 participants, comprising 152 patients with T2DM and 152 age and sex-matched controls without Type 2 Diabetes mellitus. The Fasting Plasma Glucose (FPG), Glycated Albumin (GA), Glycated Serum Albumin (GSA), Glycated haemoglobin (HbA1c), UAE, and trace metals (Mg, Zn, Mn, and Cr) were analyzed. The data analysis in this study was done using SPSS Inc., Chicago, IL, USA. Parameters with $p < 0.05$ were statistically significant. *Results*: This study found reduced serum Mg and Zn in patients with T2DM. There was a positive correlation between markers of glycaemic control and UAE. Negative correlation exists between markers of glycaemic control and serum Mg and Zn. Also, the study demonstrated a negative correlation between UAE and serum Mg and Zn. *Conclusion*: This study demonstrated that the poorer the glycaemic control, the higher the urinary albumin level. The poor glycaemic levels were also adversely correlated with Mg and Zn serum levels.

Keywords: Glycaemic control, Serum Trace metals, Urine Albumin Excretion, Type 2 Diabetes mellitus

Introduction

Diabetes Mellitus (DM) is a long-term metabolic condition with various causes, marked by persistent high blood sugar levels and disruptions in the metabolism of carbohydrates, fats, and proteins resulting from problems with insulin production, its effectiveness, or a combination of the two [1]. The common health issues and fatalities among patients with Type 2 Diabetes mellitus (T2DM) arise from the long-term complications of T2DM, which impact numerous organ systems and create significant challenges for both individuals with diabetes and the healthcare system. Therefore, maintaining good blood sugar control is essential for preventing or postponing diabetes-related complications.

In clinical practice, serum glycaemic biomarkers have been effectively used to monitor glycaemic control [2]. Traditionally, Glycated haemoglobin

(HbA1c) has been used as the standard measure of long-term glycaemic control. In addition, the role of HbA1c was further highlighted as part of the guidelines for the diagnosis of DM in 2009 by the American Diabetes Association (ADA) [3] and the World Health Organisation (WHO) [4].

The HbA1c has several benefits when compared with the Fasting Plasma Glucose (FPG) and Oral Glucose Tolerance Test (OGTT); these advantages include increased convenience (as fasting is not required), improved preanalytical stability, and reduced variability due to day-to-day changes during periods of stress and illness[3]. As a result of some drawbacks to HbA1c like factors that influence Red Blood Cells (RBC) survival, increasing interest on other non-traditional glycaemic biomarkers as alternatives to HbA1c have started evolving, and these alternative biomarkers of glycaemic control include: Fructosamine, Glycated Albumin (GA), and 1, 5-Anhydroglucitol (1, 5-AG) [2].

Several studies have reported that the imbalance of some of trace metals like chromium (Cr), magnesium (Mg), vanadium (V), Zinc (Zn), Manganese (Mn), Copper (Cu), molybdenum (Mo), Iron (Fe) and Selenium (Se) can negatively impact pancreatic islets and lead to the onset of diabetes [5]. Some of the proposed mechanisms of how trace elements enhance insulin action include activation of insulin receptor sites [6], serving as cofactors or components of enzyme systems that are involved in glucose metabolism [7], increasing insulin sensitivity, and acting as antioxidants for preventing tissue peroxidation [8].The basis of the screening for microvascular complications among patients with diabetes is to correctly identify and then put appropriate and effective measures in place to prevent the progression of the disease. An example of earlier biomarkers widely used clinically in screening microvascular complications in type 1 and type 2 diabetes is the determination of microalbuminuria. Studies have linked excessive loss of urinary albumin to cardiovascular morbidity and mortality as well as progression of kidney disease in DM [9]. However, microalbuminuria has been noticed in non-diabetic-related conditions such as urinary tract infection, hematuria, heart failure, febrile illness, severe hypertension, diet, and vigorous exercise [9].

Several similar works have shown a close relationship between serum trace metal levels and glycaemic control in T2DM. This has also been linked with the severity of microvascular complications among patients with T2DM. The paucity of data in this environment necessitates this study. This study determined whether there is any correlation between glycaemic control, microalbuminuria, and some serum trace metals among patients with type 2 diabetes.

Material and Methods

The study was a hospital-based, analytical study carried out over three months. A total of 304 participants, comprising 152 participants with Type 2 Diabetes Mellitus and 152, age and sex matched, healthy adults without diabetes as controls, were recruited for this study. The Fasting Plasma Glucose (FPG) was analyzed using the glucose oxidase method, Glycated Albumin (GA) was analysed using two methods that include ELISA for determining Glycated Serum Albumin (GSA) and colourimetry for estimation of serum albumin. The HbA1c and UAE were assayed using the nephelometry method. The trace metals (Mg, Zn, Mn, and Cr) were analyzed using the atomic absorption spectrophotometry.

The study population included consenting diabetic patients who attended General Outpatient

Department (GOPD) and Medical Outpatient Department (MOPD) clinics and were referred to the Department of Chemical Pathology and Immunology to estimate their FPG and/or HbA1c status as part of measures to determine their glycaemic control level. The controls were healthy adults, age and sex-matched, recruited from the GOPD and staff clinics.

Statistical analysis was done with the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Data that followed a normal distribution were represented as mean ± SD, whereas data that were not normally distributed were indicated as median and inter-quartile range, or converted logarithmically. Categorical data were shown as percentages. For non-normally distributed data, comparison was performed employing Spearman's rho. The analysis of normally distributed data was carried out using Analysis of Variance (ANOVA). Parameters that had a *p*-value under 0.05 were deemed statistically significant.

Results

A total of 304 participants, comprising 152 patients with T2DM and 152 age and sex matched healthy adults without diabetes as controls, were recruited for this study. There were 125 males (61 diabetic and 64 non-diabetic) and 179 females (91 diabetic and 88 non-diabetic) with a male: female ratio of 1:1.4. There was no significant difference in the distribution of gender between the diabetic and

Table 1: Age and sex wise distribution of study participants

Variable	Diabetic N (%)	Non-diabetic N (%)	Total N (%)	χ^2	*p*
Age (years)					
40-45	23 (15.1)	26 (17.1)	49 (16.1)	0.503	0.973
46-50	22 (14.5)	23 (15.1)	45 (14.8)		
51-55	24 (15.8)	25 (16.4)	49 (16.1)		
56-60	32 (21.1)	28 (18.4)	60 (19.7)		
61-65	51 (33.6)	50 (32.9)	101 (33.2)		
Mean ± SD	55.27 ± 7.16	54.57 ± 8.63	54.92 ± 7.90	0.767^t	0.444
Range	40-65	40-68	40-68		
Gender					
Male	61 (40.1)	64 (42.1)	125 (41.1)	0.122	0.727
Female	91 (59.9)	88 (57.9)	179 (58.9)		

χ^2: Chi square test, N: Number, %: Percentage

non-diabetic groups (p = 0.727). The age of the study population ranged from 40 to 68 years, with a mean of 54.92 ± 7.90 years. The mean age of diabetic participants (55.27 ± 7.16 years) and non-diabetic participants (54.57 ± 8.63 years) was similar and not statistically significant (p = 0.444). The majority of the participants were within the age group of 61-65 years (33.2%). Also, there was no significant statistical difference in the age groups of the study participants (p = 0.973), Table 1.

Table 2 compares the biochemical parameters' mean concentrations between the diabetic and non-diabetic participants. The mean values of HbA1c among the diabetic group (7.51 ± 2.50%) when compared to those of the non-diabetic group (5.40 ± 0.51%) were significantly higher (p < 0.001). The mean FPG in the diabetic group was significantly higher (8.53 ± 3.11) compared to (5.35 ± 0.39) the control groups, p < 0.001. The mean %GA (23.48 ± 6.58) was significantly higher in the diabetic group compared to the control group (12.49 ± 1.98) (p < 0.001). The result of UAE for both groups was skewed to the right, and log-transformation was applied to the values obtained. The mean concentration of UAE was significantly higher in the diabetic study group (197.69 ± 2.50 mg/g) compared to the control group (23.71 ± 2.50 mg/g) (p < 0.001). The mean serum Mg concentration for the diabetic participants (0.69 ± 0.09 mmol/L) was significantly lower than that of control participants (0.86 ± 0.12 mmol/L), p < 0.001. The mean serum concentration of Zn (14.49 ± 2.10 µmol/L) was significantly lower in the diabetic group compared to the control group (16.21 ± 2.23 µmol/L) (p < 0.001). The mean concentration of Mn in the diabetic group (19.14 ± 1.56 nmol/L) was not significantly different compared to the control group (19.51 ±10.69 nmol/L) (p = 0.237).

Table 2: Comparison of the mean concentrations of biomedical parameters between diabetic participants and the controls

Variables	Diabetic (Mean ± SD)	Non-diabetic (Mean ± SD)	t	*P*
HbA1C (%)	7.51 ± 2.50	5.40 ± 0.51	10.187	<0.001*
FPG (mmol/L)	8.53 ± 3.11	5.35 ± 0.39	12.510	<0.001*
GA (%)	23.48 ± 6.58	12.49 ± 1.98	11.987	<0.001*
UA (mg/g)	197.69 ± 2.50	23.71 ± 2.50	24.672	<0.001*
Mg (mmol/L)	0.69 ± 0.09	0.86 ± 0.12	-14.101	<0.001*
Zn (µmol/L)	14.49 ± 2.10	16.21 ± 2.23	-6.918	<0.001*
Mn (nmol/L)	19.14 ± 1.56	19.51 ± 1.69	1.194	0.237

*t: Independent Samples T test; *: p value <0.05, HbA1c: Glycated Haemoglobin, FPG: Fasting Plasma Glucose, GA: Glycated Albumin, UA: Urinary Albumin, Mg: Magnesium, Zn: Zinc, Mn: Manganese*

Table 3 revealed the average serum concentration for Mg, Zn, and Mn among the diabetic participants (male and female groups) concerning their levels of glycaemic control using FPG. There is a significant negative correlation between serum concentrations of magnesium and zinc and the levels of glycemic control in both groups, but no significant association between the levels of glycemic control and the serum concentration of Mn in both groups.

Table 4 revealed the average serum concentration for Mg, Zn, and Mn among the diabetic participants (male and female groups) concerning their levels of glycaemic control using HbA1c. Both groups have a significant negative correlation between serum concentrations of Magnesium and Zinc and glycaemic control levels. However, there is no significant association between the levels of glycaemic control and the serum concentration of Mn in both groups.

Table 5 shows the correlation between the levels of urinary albumin and serum concentrations of trace metals (Mg, Zn, and Mn) among diabetic participants. It shows a negative correlation between the levels of urinary albumin and serum Mg (p = 0.009) and the serum Zn (p = 0.001). However, there was no significant correlation between the levels of urinary albumin and Serum Mn (p = 0.283). Therefore, as the levels of urinary albumin increased in the diabetic participants, the serum Mg and Zn decreased, but there was no effect on the serum Mn.

Table 3: Relationship between levels of glycaemic control and serum trace metals (Mg, Zn, and Mn) in respect to FPG among diabetic participants

Variables	Good FPG group (Mean ± SD)	Poor FPG group (Mean ± SD)	t	*p*
Male				
Mg (mmol/L)	0.71 ± 0.09	0.68 ± 0.10	1.981	**0.035***
Zn (umol/L)	15.41 ± 2.29	14.14 ± 1.85	2.378	**0.021***
Mn (nmol/L	19.41 ± 2.04	19.38 ± 1.82	0.966	0.092
Female				
Mg (mmol/L)	0.69 ± 0.08	0.64 ± 0.10	2.110	**0.027***
Zn (umol/L)	15.09 ± 1.47	13.76 ± 2.40	3.169	**0.002***
Mn (nmol/L	18.68 ± 1.04	18.62 ± 0.99	0.349	0.731

*t: Independent Samples t tests; *: p value <0.05; Fasting Plasma Glucose (FPG), Magnesium (Mg), Zinc (Zn), Manganese (Mn)*

Table 4: Relationship between levels of glycaemic control (Using HbA1c) and serum trace metals (Mg, Zn, and Mn)

Variables	Good HbA1c (Mean ± SD)	Poor HbA1c (Mean ± SD)	t	*P*
Male				
Mg(mmol/L)	0.71 ± 0.07	0.66 ± 0.09	2.672	**0.010***
Zn (mmol/L)	15.06 ± 1.96	14.03 ± 2.19	2.447	**0.026***
Mn (nmol/L)	19.42 ± 2.04	19.36 ± 1.06	1.373	0.184
Female				
Mg (mmol/L)	0.70 ± 0.08	0.66 ± 0.10	-0.273	**0.021***
Zn (µmol/L)	14.88 ± 1.57	13.89 ± 2.47	2.294	**0.024***
Mn (nmol/L)	18.68 ± 0.99	18.52 ± 1.04	-0.349	0.731

*t: Independent samples t tests; *: p <0.05; Magnesium (Mg), Zinc(Zn).Manganese(Mg),Glycated Haemoglobin (HbA1c)*

Table 5: Correlation between urinary albumin excretion and serum trace metals (Mg, Zn, and Mn)

	UAE	
Variables	**r**	***p***
Mg	-0.079	**0.009***
Zn	-0.268	**0.001***
Mn	0.167	0.283

r: Spearman's rank Correlation Coefficient;
**: p value <0.05; Urinary Albumin Excretion (UAE), Magnesium (Mg), Zinc(Zn), Manganese (Mn)*

Discussion

The investigation showed that individuals with diabetes had decreased serum Mg levels compared to the control group. Moreover, there was a notable negative correlation between serum Mg levels and glycaemic control among the diabetic patients. Other researchers have also identified a similar Magnesium deficiency [7].

In this study, there was a significant decrease in serum Mg in both diabetic males and females compared with the controls, and serum Mg was found to be significantly lower in the diabetic group with poor glycaemic control compared with those with reasonable control. Similar losses in serum Mg of type 2 diabetic males and females, concerning the respective controls, were reported by other researchers [7]. Research indicates that hypomagnesemia affects between 13.5% and

47.7% of individuals with type 2 diabetes. In the early stages of non-insulin-dependent diabetes mellitus, serum Magnesium and plasma glucose levels are inversely related [7].

Deficiency of Mg in patients with T2DM can be related to the alteration in Mg metabolism by autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, osmotic diuresis, recurrent metabolic acidosis, decreased absorption, hypophosphataemia, hypokalaemia, and an inadequate dietary intake [8]. Previous studies [11] indicated that the urinary Mg excretion of subjects with T2DM was more than that of control subjects. The studies also reported further that the metabolic control mechanisms of type 2 diabetic patients need additional Mg. However, this absorbed Mg seemed not to be utilized and, thus, excreted in the urine.

This study also supported other findings [7, 12] that observed an inverse relationship between serum Mg levels and the degree of urinary albumin in patients with T2DM. This study demonstrated lower serum Mg levels among diabetic groups with microalbuminuria and macroalbuminuria than those with normoalbuminuria. Some of the highlighted causes of lower serum Mg among T2 diabetic patients stated above could also cause low serum Mg in those subjects with microalbuminuria and macroalbuminuria.

To sum up, the low serum Mg concentrations in diabetic participants compared to controls suggest the need for Mg supplementation because this trace metal helps to reduce oxidative stress and glucose levels in diabetic subjects [13].

Studies have identified that an unbalanced level of Zn in the body can reduce the activity of the antioxidant enzymes and contribute to the tissue damage observed in diabetes [14-16]. It has been reported that in T2DM, the impaired intestinal reabsorption of endogenous Zn and the increase in excretion of Zn into the intestine during the digestive process may lead to a low serum Zn level [16]. Another investigation reported that the urinary excretion of Zn was increased in T2DM. Research indicates that hyperglycemia disrupts the active transport of zinc into the renal tubular cells, leading to lower blood levels of zinc in affected patients [14, 16]. Many studies established that diabetes was strongly associated with Zn deficiency, [7, 17-18]. In contrast, some studies found unchanged serum Zn levels [19-20], while a study [21] reported increased plasma levels of Zn in T1 diabetic patients. This report may be due to the lower sample size used in the study and the characteristics of the study population.

Considering the low blood Zn levels in the diabetic patients examined in this study, Zn supplementation might provide significant protection against diabetes-induced complications. Some authors found beneficial effects in Zn-supplemented T2 diabetic patients with improved glycaemic control [18].

In this study, the data obtained revealed no statistically significant difference in the mean values for serum Mn in both control and diabetic groups. Also, concerning gender, there was no significant difference in serum Mn levels among male and female diabetic participants compared to their control groups. Similar findings have also been reported in a study [20], where they found no significant relationship between serum Mn and diabetes; thus, altered Mn metabolism may not be pronounced in diabetes.

Available data on humans do not seem conclusive concerning Manganese's role in diabetes. Though some authors have reported Mn deficiency between type 2 diabetic patients and non-diabetic controls, [22-23] others found elevated Mn in type 2 diabetic subjects [20]. It has been reported that appropriate Mn levels are required to develop normal insulin synthesis and secretion [24]. In this context, Manganese deficiency can result in glucose intolerance in some animal species.

Some studies have demonstrated chromium's role in carbohydrate metabolism and its essential function as a cofactor in insulin action [25, 29]. However, the direct measurement of chromium status in human samples has not been adequately standardized. In the present study, repeated attempts to measure serum chromium in both groups were unsuccessful, and chromium could not be detected.

Consistent with other studies [26, 30], this study revealed a significant positive relationship between urinary albumin levels and markers of glycaemic control. The causes of this relationship among the various groups of type 2 diabetic patients may be attributed to altered insulin metabolism, chronic hyperglycaemia, glomerular dysfunction, or osmotic diuresis [27-28].

In this study, the progression of UAE was associated with poor glycaemic control. Other authors have reported similar findings. In addition to poor glycaemic control, several studies have revealed that the length of time a person has been diagnosed with diabetes plays a crucial role in the progression of urinary albumin. However, in this study, there was no significant relationship between the duration of DM and the degree of albuminuria and glycaemic control. This can probably be explained by the paucity of knowledge in the duration of DM, especially among the less educated diabetics, who accounted for about two-thirds of the total diabetic population studied. Though this work is not entirely novel, it offers an important African perspective to previously established research, predominantly carried out in Western populations.

Conclusion

This study has demonstrated that the degree of glycaemic control correlates with the level of urinary albumin, a well-known predictor of poor renal outcomes in patients with T2DM. Both the degree of glycaemic control and urinary albumin levels correlate negatively with the serum levels of Mg and Zn among diabetic patients. This study revealed reduced serum Mg and Zn levels in diabetic patients. The cause of lower serum Mg and Zn levels cannot be demonstrated in this study. This study revealed that lower serum Mg and Zn can be associated with the progression of poor glycaemic control and increased urinary albumin excretion.

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