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RESEARCH ARTICLE **CLINICAL BIOCHEMISTRY**

The Association between Serum Magnesium Level and Microalbuminuria in Diabetic Patients Attending Sebha Diabetic and Endocrine Centre, Sebha-Libya

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A B S T R A C T

Background: Magnesium is one of the essential elements for various vital processes in the human body and has an important role in glucose metabolism. Magnesium deficiency may play a role in poor glycemic control and the development of diabetic complications.

Objective: This study aimed to investigate the potential association between magnesium deficiency and elevated microalbuminuria levels.

Method: This study was conducted during the period from June 2023 to January 2024 at the Diabetes and Endocrinology centre in Sabha-Libya. We studied 124 diabetic patients and 44 healthy individuals as controls in the Sebha Diabetic and Endocrine Centre. Blood samples were collected for the analysis of Fasting Blood Sugar (FBS), hemoglobin A1c (HbA1C), lipid profile (Triglyceride (TG), Cholesterol (CHOL), Low –Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL), Urea, Creatinine (CREA), and Magnesium (Mg) concentrations by standard methods. The uthors also collect urine samples for microalbuminuria (MAU) and creatinine tests.

Results: The research results showed that Mg^{2+} level was lower in DM patients (Mean±SD Mg^{2+} mg\dl=1.75±0.22), compared to control group (Mean±SDMg^{2+}mg\dl=1.98±0.15).and the different was statically significant (p=0.000), Mg^{2+} has shown negative correlation with FBS (r= -0.261, p=0.033), and with HbA1C (r= -0.142, p=0.003). Also there was a significantly negative correlation between Mg^{2+} and MAU(r= -0.445, p=0.000).

Conclusion: In the present study we found a significantly negative correlation between serum Mg^{2+} and MAU in diabetic group.

العلاقة بين المغنيسيوم في المصل والمايكرو البومين لدي مرضي السكريالمترددين علي مركز السكري والغدد الصماء في مدينة سبها

أبوالقاسم علي ابكر[1,*]، إبراهيم علي أبواشناف[2]

الكلمات المفتاحية
مرض السكري
المغنيسيوم
الميكروألبومين
اعتلال الكلي السكري
مركز السكري والغدد الصماء-سبها

الملخص

يعتبر المغنيسيوم من العناصر الأساسية في العمليات الحيوية التي تتم داخل جسم الإنسان، و خصوصا في عملية استقلاب الجلوكوز وقد يرتبط نقص الماغنيسيوم في ضعف التحكم في مستوي السكر في الدم وتطور مضاعفات مرض السكري.

الهدف من الدراسة: تهدف هذه الدراسة إلي دراسة العلاقة المحتملة بين نقص المغنيسيوم وارتفاع مستويات الميكروالبومين لدى مرضي السكري .

المواد والطرق:-أجريت هذه الدراسة خلال الفترة من يونيو 2023 إلي يناير 2024 في مركز السكري والغدد الصماء بمدينة سبها في ليبيا. شارك فيها 124 مريضا بالسكري و 44 شخصا سليما كمجموعة ضابطة، جمعت منهم عينات دم لإجراء التحاليل التالية لكل المشاركين في الدراسة، تحليل سكر الدم (FBS) تحليل السكر التراكمي (HbA1C)تحليل الكوليسترول(CHOL) تحليل الدهون الثلاثية (TG) تحليل البروتين الدهني عالي الكثافة (HDL) تحليل البروتين الدهني منخفض الكثافة (LDL) تحليل نسبة اليوريا في الدم (UREA) تحليل نسبة الكرياتينين في الدم (CREA) تحليل الماغنيسيوم (Mg). كما تم جمع عينات البول لإجراء تحاليل الميكروالبومين (MAU) و الكيرياتين(CREA in urine) لكل المشاركين.

النتائج: أظهرت نتائج الدراسة أن مستويات المغنسيوم منخفضة لدي مرضي السكري(المتوسطmg\dl± الانحراف المعياري = 0.22±1.75) مقارنة مع الأصحاء(المتوسطmg\dl± الانحراف المعياري =1.98 ±0.15) ، وكان الفرق ذو دلالة إحصائية (P=0.000) ، كما تبين من خلال النتائج وجود علاقة ارتباط سلبي بين تركيزالمغنسيوم ونسبة الجلوكوز في الدم لدي مرضي السكري ,r= -0.261) (p=0.033، وكذلك كان الارتباط سلبيا أيضا بين تركيز المغنيسيوم و مستوي السكر التراكمي(r= -0.142, p=0.003). كما وجدنا علاقة عكسية بين مستويات الماغنسيوم والميكروالبومين لدي مرضي السكري(r= -0.445, p=0.000).

الخلاصة: خلصت هذه الدراسة إلي وجود ارتباط بين انخفاض تركيز المغنيسيوم وارتفاع مستوي الميكروالبومين لدى مرضى السكري.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycaemia due to a defect in insulin production or action. The World Health Organization (WHO) reported in 2014 that 8.5% of persons over the age of 18 had diabetes, and in 2019 1.5 million deaths due to diabetes, 48% of which happened before the age of 70 [1]. According to

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Libya's 2009 National Non-Communicable Disease Study, 16.4% of Libyans had diabetes. In2009, the international Diabetes Federation (IDF) estimate the prevalence of diabetes in Libya to be around 9.7% [2]. Diabetic renal disease also caused an additional 460,000 fatalities. There was a 3% increase in diabetes-related standardized death rates between 2000 and 2019, diabetes was linked to a 13% rise in mortality in lower middle-income countries [1]. The national diabetes committee indicated that, if left untreated, diabetes can lead to a variety of serious health problems affecting both small and large blood vessels [3]. Diabetes causes pathognomonic changes in the microvasculature, increasing the thickness of the capillary basement membrane and damaging arterioles in the glomeruli, retina, heart, skin, and muscle. This causes diabetic microangiopathy [4].

Diabetic Nephropathy (DN) is one of the severe and most concerning complications of most diabetics, 45% of Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus(T2DM) patients suffer from this microvascular issue [5]. In most nations that reported to the US Renal Disease Registry in 2006, 20% to 44% of diabetic patients started renal replacement therapy (RRT). Between 1996 and 2006, the number of Americans with diabetes who needed RRT grew by 50% [6]. Globally, DM is considered the main cause of End-Stage Kidney Disease (ESKD), DM affects between 23% and 39% of ESKD patients [7]. DN is a primary factor in end-stage renal disease, and it's excessively linked to a higher risk of cardiovascular death [8]. DN is characterized by a gradual rise in microalbuminuria (MAU = 30–300 mg/day), over many years, accompanied by slowly rising in blood pressure, and a normal or mildly decreased glomerular filtration rate (GFR) (GFR = 60–89 mL/min/1.73 m^2). These changes typically occur during the course of the disease in both types of diabetes [6], with or without manifested nephropathy [9]. The detection and management of DN have become increasingly dependent on the combined use of Estimated Glomerular Filtration Rate (e-GFR) and Albumin Creatinine Ratio (ACR). This combined approach gives clinicians a more comprehensive assessment of kidney function and damage in diabetic patients. Research suggests that using both e-GFR and ACR improves the sensitivity and specificity of detecting early stages of DN compared to using either marker alone [10]**.**

Magnesium (Mg) is the second most prevalent intracellular cation after potassium, and the fourth most abundant mineral in the human body [11]. It plays an important role in glucose metabolism and insulin action [12]. In addition, it has an important role in the action of many enzymes participating in glycolysis, such as hexokinase, phosphofructokinase, aldoses, phosphoglycerate kinase, and pyruvate kinase, Mg is a cofactor for ATP, and Mg-ATP is essential for those enzyme activities [13].

Many studies have suggested that hypomagnesaemia is commonly associated with metabolic disorders, especially diabetes mellitus [14]. The most common mechanisms leading to Mg reduction in diabeticpatients are a low Mg^{2+} intake and increasing Mg urinary loss [15]. Urinary Mg excretion may rise in both hyperglycaemia and hyperinsulinemia. Serum magnesium levels have been observed to be inversely correlated with fasting blood glucose and urinary magnesium excretion. As a result, hyperglycaemia reduces tubular reabsorption of $Mg^{2+}$from the glomerular filtrate [16].

Accordingly, a low magnesium level may play a role in the development and progression of diabetes complications by increasing insulin resistance. Insulin receptors are tyrosine kinase receptors [13]. It is formed by two alpha and two beta subunits, with insulin binding to the alpha subunit to activate the tyrosine kinase (TK) in the beta subunit and auto-phosphorylation [17]. The binding of two Mg^{2+} ions is required for kinase function by acting as a cofactor. Mg^{2+} is also necessary for the auto phosphorylation of the β-subunit of the insulin receptor, so it increases tyrosine kinase receptor affinity for ATP [18].

Mg^{2+} deficiency is associated with oxidative stress and inflammation, andMg^{2+} deficiency has been linked to indirectly enhancing oxidative stress, the decrease in Mg^{2+} to Calcium ratio stimulate catecholamine release which increase Reactive Oxygen Species (ROS).Moreover, Mg^{2+} deficiency induces the activation of the renin-angiotensin system. It has been shown that patients with diabetes showed elevated levels of oxidized low-density lipoprotein (LDL) in correlation with decreased serum magnesium levels[19]. Individuals with normal serum magnesium levels did not show this rise in amounts of oxidized low-density lipoproteins[19]. Hypomagnesaemia results in the activation of inflammation and elevated levels of certain inflammatory biomarkers, such as C-reactive protein and tumor necrosis factor-α[20].

Diabetic nephropathy is one of the most serious and widespread complications of diabetes. In this study, we seek to investigate whether magnesium plays a role in the occurrence and development of this disease.

The main objective of this study is to investigating the association between serum magnesium and microalbuminuria levels in diabetic patients, in addition to assess the relationship between magnesium levels, blood sugar and HbA1c.

Materials and methods

Participants

One hundred and sixty-eight persons, 124 diabetic patients (44 males and 80 females), their Mean±SDage 56.29±12.73 years, were recruited from the Sebha Diabetic and Endocrine Centre, between June 2023 and January 2024. In addition, 44 (21 male and 23 female), their Mean±SD age 56.36±10.13 years, healthy individuals who underwent check-ups at a physical examination centre as control, verbal consent were obtained from all participants in this study.

Clinical data and biochemistry parameters

Clinical data were collected from the participants using a questionnaire containing sex, age, body mass index (height and weight), duration of diabetes, history of hypertension, and medical history.

Glycated hemoglobin (HbA1C) concentration was measured using a turbid metric inhibition immunoassay (TINIA) (quantitative) on Cobas Integra 400 Plus. Fasting blood sugar (FBS), triglyceride (TG), cholesterol (CHOL), high-density lipid (HDL), low-density lipid (LDL), magnesium (Mg), and urine creatinine concentration were measured using enzymatic colorimetric methods on Cobas Integra 400 Plus. Albumin in urine (Microalbumin) concentration was measured using an immunotubidimetric assay on Cobas Integra 400 Plus.

Albumin \ creatinine ratio (ACR) calculation

The following formula was used for calculation of ACR is:

$ACR=\frac{Albumin}{creatinine}$, [21].

eGFR calculation

2021 CKD-EPI Creatinine Equation, Expressed as a single equation [22]

For Males:-

$eGFR_{cr}$= 142 x $\min(S_{cr}/K,1)^{A}$ x $\max(S_{cr}/K,1^{)-1.200}$ x 0.9938^{Age}

where :K = 0.9

S_{cr} = Serum creatinine in mg\dl

Serum creatinine ≤ 0.9 A=0.9 and B= -0.302

Serum creatinine> 0.9 A=0.9 and B= -1.2

For Females:-

$eGFR_{cr}$=142 x $\min(S_{cr}/K,1)^{a}$ x $\max(S_{cr}/K,1^{)-1.200}$ x 0.9938^{Age} x 1.012 [if female]

where: K = 0.7

S_{cr} = Serum creatinine in mg\dl

Serum creatinine ≤ 0.7 A=0.7 and B= -0.241

Serum creatinine> 0.7 A=0.7 and B= -1.2

Statistical Analysis

Statistical analysis was performed using the Statistical Package for social sciences (SPSS) version 18. Data between the two groups were compared using the student's t-test if the distribution was normal, and otherwise, the Mann- Whitney test was used.

The relationship of Mg concentration with MAU was analyzed using Pearson's correlation for normally distributed data and Spearman's correlation for non-normally distributed data. P < 0.05 was regarded as statistically significant.

Results

Comparison between the DM group and control group

The results of this study include 168 participants, of whom 124 had DM: 44 males (35.5%) and 80 females (64.5%) with a mean age of 56.29±12.73, and 44 healthy individuals as the control group: 21 males (47.7%) and 23 females (52.3%) with a mean age of 56.36±10.13.

Results of BMI, FBS, and HbA1C

As shown in Table 1, in the DM group, the mean of BMI, FBS, and HBA1C were significantly higher than in the control group (P < 0.000).

Table 1: Comparison between the two groups in Body Mass Index (BMI), FBS, and HBA1C, SD = Standard Deviation

	Diabetic group	Control group	
Parameter	Mean ± SD		**P**
BMI kg\m^2	27.13±4.51	21.40±2.38	0.000
FBS mg\dl	219±79.97	97.84±11.75	0.000
HbA1C %	9.60±1.68	5.65±0.355	0.000

Results of lipid profile

As shown in Table 2, the concentrations of TG, CHOL, LDL, and HDL were significantly higher in the DM group when compared with the control group; with a P -value <0.005.

Table 2:Results of lipid profile

	Diabetic group	Control group	
Parameter	Mean ± SD		**P**
TG mg\dl	166.4±141.4	96.81±35.36	0.000
CHOL mg\dl	182.9±44.6	145.9±23.19	0.000
HDL mg\dl	56.1±14.4	51.06±11.65	0.015
LDL mg\dl	121.0±35.1	76.15±15.63	0.000

Results of kidney function

There is no significant difference in the mean concentration of UREA (p = 0.627) and CREA (p=0.061) between the two groups. As shown in Table 3.

Table 3:Result of the kidney function.

	Diabetic group	Control group	
Parameter	Mean ± SD		**P**
UREA mg\dl	27.56±7.99	27.8±8.15	0.627
CREA mg\dl	0.778±0.176	0.72±0.134	0.061

Results of ACR, MAU, and e-GFR:-

The result of ACR and MAU was significantly higher in the DM group compared with the control group, with a p-value of 0.000. The e-GFR was lower in the DM group with P = 0.000, as shown in Table 4.

Table 4: Results of (ACR), (MAU), and e.GFR.

	Diabetic group	Control group	
Parameter	Mean ± SD		**P**
ACR mg\g	82.34 ±200.4	4.90±2.35	0.000
MAUmg\l	42.71±72.88	5.11±2.16	0.000
e GFR ml\min\1.73m^2	105.2±21.50	120.2±18.67	0.000

Results of Mg

As shown in Figure (1) the Mg^{2+} concentration was significantly lower in the DM group with P-value 0.000.

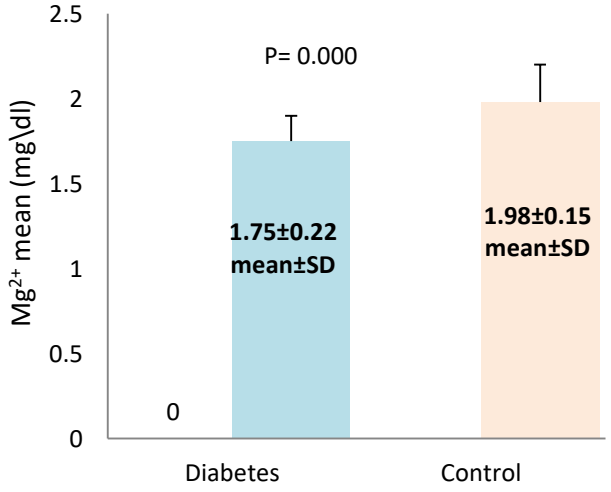

Fig.1: Comparison of mean Mg concentration between the diabetic group and the control group

Comparison between DM patient groups

Correlation between duration of diabetes and other variables

The mean duration of diabetes in the diabetic group was 11.14±7.82 years, there was a negative correlation between duration of diabetes and Mg^{2+} concentration. There was a positive correlation between the duration of diabetes and MAU (p = 0.023), and ACR (p= 0.000), and no correlation with e GFR.as shown in Table 5.

Table 5: Correlation between duration of diabetes and other variables

	Duration of diabetes	
Variable	Correlation coefficient (r)	P value
Mg2+ mg\dl	-0.178*	0.048
MAUmg\l	0.204*	0.023
ACR mg\g	0.331*	0.000
e GFRml\min\1.73m2	0.133	0.141

* Correlation is significant at the 0.05, P<0.05 means statically significant

Comparison between DM group according to MAU level

Diabetic group was divided into two groups: group I with normal MAU (n =88, 71%) and group II withhigh MAU (n=36, 29%). The means of FBS and HBA1C were higher in group II than in group I, but there was no significant difference; on the contrary, the mean of Mg was significantly lower in group II, as shown in Table 6.

Table 6:Comparison between group I (DM patients with normal MAU) and Group II (DM patients with MAU)

Parameter	Group I Without MAU	Group II With MAU	P value
N	88	36	
FBS mg\dl Mean±STD	217±78.5	225±84.2	0.519
HbA1C % Mean±STD	9.53±1.71	9.78±1.62	0.449
Mg^{2+} mg\dl Mean±STD	1.82±0.20	1.62±0.16	0.000

The correlation between magnesium concentrations and indices of biochemical parameters of DM

Table 7 shows, that there was a significant negative correlation between Mg, HBA1C, and FBS, but no significant correlation were found between Mg^{2+}, LDL, TG, CHOL, and HDL.

Table 7: Correlation between Mg and biochemical parameter

Parameter	Mg^{2+} mg\dl Correlation coefficient (r)	P value
HbA1C %	-0.142*	0.033
FBS mg\dl	-0.261*	0.003
TG mg\dl	0.064	0.477
CHOL mg\dl	0.149	0.100
LDL mg\dl	0.164	0.068
HDL mg\dl	0.100	0.269

*Correlation is significant at the 0.05, P<0.05 means statically significant

The correlation between Mg concentration and kidney indicators (MAU, ACR, e GFR, UREA, and CREA)

As shown in Table 8, a significant negative correlation between Mg^{2+}, MAU, and ACR. a significant positive correlation with eGFR. There is no correlation between Mg, UREA, and Creatinine (CREA).

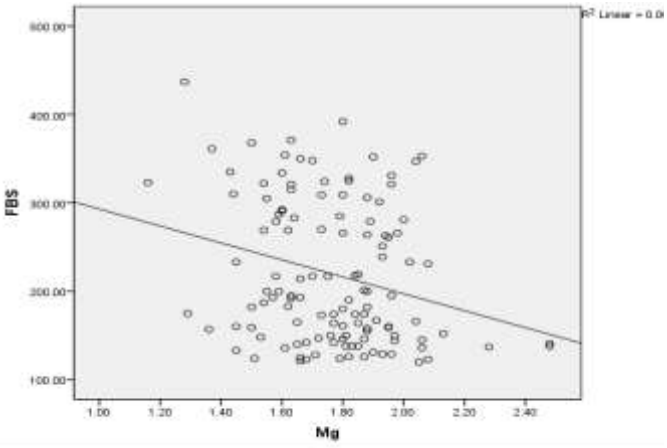

Fig.2: Scatter diagram shows the correlation between serum magnesium and FBS

Discussion

Hypomagnesaemia is common in DM patients, and is linked to the development of diabetes complications [23]. In the present study, the mean Mg^{2+} concentration was significantly lower in the DM group compared tothe control group (P= 0.000). This result is consistent with the results of the studies of Pasula[24], Myke et al. [25] and Hussain et al. [26]. In contract, in study of Mamza et al. [27], and Tiwari et al. [28], the results were different, they found no significant different in Mg^{2+} concentration between diabetics and control subjects. Diabetic hypomagnesaemia has multiple underlying causes, One possible cause is the increased loss of urinary magnesium due to a defect in renal tubular reabsorption, this defect may result from the osmatic action of glycosuria and hyperglycaemia [23,28]. Malabsorption of Mg^{2+}or reduce Mg2+ intake can play a role in hypomagnesaemia in DM patients [27,15].

Table 8: the correlation between, Mg, and kidney indicators.

Variable	Mg^{2+} mg\dl Correlation coefficient (r)	P value
MAU mg\l	-0.445*	0.000
ACR mg\g	-0.254*	0.004
e GFRml\min\1.73m^2	0.238*	0.008
Urea mg\dl	0.146	0.106
CREA mg\dl	0.009	0.917

*Correlation is significant at the 0.05, P<0.05 means statically significant

In this study, there was a weak significantly negative correlation between Mg^{2+} concentration and HbA1Cand between $Mg^{2+}$and FBS levels in the DM patient's group, this was accordance with funding of Ashok et al study, who found strong negative correlation between Mg^{2+} and FBS (R= -0.801, P= 0.000), and between $Mg^{2+}$and HbA1C (R= -0.804, P= 0.000) [30], Hassan et al study also obtained the same results, which were as follows:correlation between Mg^{2+} and FBS (R= -0.534, P= 0.000), and between $Mg^{2+}$and HbA1C (R= -0.556, P= 0.000) [31]. This association between $Mg^{2+}$and diabetes indicators (FBS and HbA1C) can be explained by Mg^{2+}role as a cofactor in glucose transporting mechanism and enzymes that important in glucose oxidation[32].In additional, the role of Mg^{2+} in insulin function Yadav et al. has reported that Mg^{2+} deficiency is associated with the hyperinsulinaemia and insulin resistance in pre-diabetes subjects [33].

There is no correlation between Mg^{2+} concentration and lipid profile tests (CHOL, TG, HDL, and LDL). This finding differs the study by Mishra et al. in India [34]. In a study in Ethiopia by Wolide et al our findings regarding CHOL, LDL and HDL no agree, while there is agreement concerning TG. The difference in results may be attributed to variations in lifestyle and diet [35].

MAU is one of the most important markers in the diagnosis and monitoring of DN. Early structural alterations seen on kidney biopsy have been linked to changes in MUA [36].

According to our finding, MAU level was higher in the DM group compared to the control group (p = 0.000), which is consistent with the finding of Mosbah et al. [37]. Among our diabetes group, there were 71% with normal-albuminuria and 29% with high micro-albuminuria.

In present study, there was a significant negative correlation between Mg^{2+} concentration and MAU. In the a study conducted by Nasreen et al. found a significant negative correlation (r= -0.353, P =0.006) [38].Ferdoushi et al. also found statistically significant negative correlation (r= - 0.402,

p= 0.001) between Mg^{2+}ans MAU[39]. In the Baihui et al. study found that MAU level was inversely correlated with serum magnesium levels[40].

Also found a significant negative correlation between Mg, ACR in the DM patient group and a significant positive correlation between Mg^{2+} concentration and e-GFR. This findings consistent with clinical trials suggest the Reno-protective effects of Mg^{2+} in DN. Mg^{2+} has several properties that enable it to play this role, including direct antioxidant properties, acting as a cofactor for several antioxidant enzymes, and several of proteins involved in the control of oxidative stress are influenced by Mg^{2+} in terms of expression and function [41].

Conclusion

Based on the results obtained from this study, magnesium deficiency is associated with high microalbumin in diabetic patients, so magnesium should be included in the nutritional supplements prescribed for diabetic patients.

Recommendations

Based on the results obtained, we recommend regular testing of magnesium levels in diabetic patients, especially those who have been diagnosed with the disease for more than seven years, due to the correlation found between magnesium levels and microalbuminuria in diabetic patients.

We also recommend conducting further studies in this field that include a larger number of patients and taking more than one urine sample (three random samples) to obtain more accurate results.

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