

Depression and Serum Magnesium Level in Patients with Type 2 Diabetes Mellitus

Fawzi M¹, Said NS², Fawzi M³

¹Department of Psychiatry, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

²Department of Internal Medicine, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

³Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

ABSTRACT

Background: The link between magnesium deficiency and the increased risk for Type 2 diabetes mellitus (T2DM) is well known. High serum magnesium levels, on the other hand, have been frequently reported in patients with depression. Although the association between T2DM and depression is common, it is not known whether the presence of depression in patients with T2DM would lead to hypermagnesemia. **Objectives:** This cross-sectional study aimed to test the hypothesis that T2DM patients with depression have higher serum magnesium level than those without depression. **Subjects and method:** Two groups of T2DM patients, with and without depressive symptoms (50 patients in each group) assigned according to their score on the Beck Depression Inventory (BDI). Serum magnesium level was measured in patients and control. **Result:** No significant differences were found between the two groups except for their serum magnesium level, with a mean ($\pm$ SD) of 0.70 ($\pm$ 0.060) in patients with depression and 0.75 ($\pm$ 0.071) in those without depression ($p=0.002$). Overall, 31% of the participants had significant hypomagnesemia below (0.69mmol/l). Twenty three (46%) patients with depression and 8 (16%) patients without depression exhibited hypomagnesemia ($p=0.001$). Correlation between serum magnesium and glucose levels was negative but modest ($r=-0.201$, $p=0.05$) while a highly significant negative correlation was found between serum magnesium level and BDI score for the depressed group ($r=0.66$, $p=0.005$). **Conclusion:** Results did not support our hypothesis that T2DM patients with depression have higher serum magnesium level than those without depression. Instead, our results might support an alternative hypothesis that low serum magnesium levels are a risk factor for development of depression. If this is so, we are wondering whether magnesium treatment could be effective in the management of depression in people exhibiting hypomagnesemia as in many patients with T2DM.

Key words: Depression, Magnesium, Type 2 diabetes, Egypt.

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INTRODUCTION

Diabetes, which was described for the first time in human history in Egypt (~1500 BC) has now become one of its major and

emerging clinical and public health problems¹⁻². By the year 2025, Egypt is expected to be among the top ten countries

that have the highest prevalence rates of diabetes in the world, notably Type 2 diabetes mellitus (T2DM)³. For many decades T2DM, formerly referred to as non-insulin-dependent, was regarded a less dangerous type of disease by both the patients and their doctors. It has now been realized, however, that T2DM is a leading cause of premature death, mainly due to cardiovascular causes, and of occurrence of complications that can lead to blindness, amputations, and renal insufficiency⁴.

The mechanism by which hyperglycemia causes these complications appears to be multifactorial. Apart from the various known factors, a growing number of recent evidences indicate that magnesium deficiency may play a novel role in the development of diabetic complications⁵⁻⁶. Magnesium, the second most common intracellular cation, acts as a mild calcium antagonist on vascular smooth muscle tone, and on postreceptor insulin signaling; it is critically involved in energy metabolism, fatty acid synthesis, glucose utilization, ATPase functions, release of neurotransmitters, and endothelial cell function and secretion⁷. In the presence of diabetes, it is observed that inadequate metabolic control can affect the corporal concentrations of magnesium, developing hypomagnesemia. Excessive urinary magnesium loss associated with glycosuria is probably the most important factor in the genesis of hypomagnesemia in the diabetic patient⁸. Linkage between magnesium deficiency and insulin resistance, carbohydrate intolerance, accelerated atherosclerosis, dyslipidemia, hypertension and adverse outcomes in pregnancies complicating diabetes have been observed or postulated⁹⁻¹⁰.

Another significant problem among patients with diabetes is the increased risk of comorbid depression¹¹. This commonly overlooked comorbidity has an estimated prevalence of 15–20%, compared with 2–9% in the general population¹². Depression is not only common in patients with T2DM but it is also associated with a 2.3-fold increase in mortality, and minor or "subclinical" depression is associated with a 1.7-fold increase¹³⁻¹⁴. Studies have shown a significant and consistent association of depressive symptoms with a variety of diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction)¹⁵. However, the pathways that mediate this association have not yet been ascertained. Depression has been found to increase the risk of poorer diabetes-specific outcomes such as hyperglycemia¹⁶ and an increase in diabetes complications¹⁵. These poorer outcomes have been partly explained by the impact of depressive symptoms on diabetes self-care, adherence to diet, exercise and medication regimens, functioning, and health care costs¹⁷⁻²¹. Few investigators, however, have tried to explain the poorer diabetes-specific outcomes in the presence of depression by terms other than psycho-social or more specifically to examine the relationship between magnesium level and depression in patients with T2DM.

Numerous studies, on the other hand, have been performed on magnesium metabolism in depressed patients-without concomitant T2DM, showing, though inconsistently, elevated magnesium blood serum/plasma or CSF levels²². The high serum magnesium levels noted in patients with mood disorders are thought to be related to the underlying disorder itself and are not influenced by clinical background factors²³. Researchers

found that hypermagnesaemia might lead to hypoactivity and psychomotor retardation which is so often observed in depressed patients²⁴. It is interesting to note that these studies sharply contrast with those reporting hypomagnesemia at an increased frequency among patients with T2DM. The conflicting data may perhaps reflect different study designs and populations studied. It is not known, however, whether hypermagnesaemia would still be the case should T2DM patients get depressed. Although bivariate relationships between depressive symptoms, diabetes, and serum magnesium level have been identified, the complex relationship among these three constructs has not been explicated.

In this cross-sectional study we aimed to test the hypothesis that T2DM patients with depression have higher serum magnesium level than those without depression.

SUBJECT AND METHODS

Participants:

Two groups of consecutive unrelated patients were selected from those attending the Diabetes Clinic, Department of Internal Medicine, Zagazig University Hospitals, Zagazig: Group (A): T2DM patients with depressive symptoms. Group (B): T2DM patients without depressive symptoms but matching for age and gender.

Fifty patients were enrolled in each group fulfilling the following inclusion criteria:

- Suspected clinical diagnosis: T2DM.
- Age at diagnosis: ≥ 30 years.
- Duration of disease: ≥ 12 months since diagnosis.

In addition, patients in group (A) were required to have a score of ≥ 10 on Beck Depression Inventory (BDI), whereas

patients in group (B) were required to have a score of < 10 on BDI.

Exclusion criteria were:

- History of ketonuria or ketoacidosis.
- Insulin therapy.
- Pregnancy or lactation.
- Magnesium supplementation or magnesium containing antacids (laxatives).

Diseases or drugs that are known to cause depressive symptoms or hypo- or hypermagnesemia such as renal failure, hypo- or hyperthyroidism, chronic diarrhea, use of diuretics (e.g., thiazide, loop diuretics), lithium, reserpine, methyl dopa, clonidine, propranolol, corticosteroids, or levodopa. Other known causes for depression such as loneliness, recent loss of a partner or close relative, and debilitating health conditions including those caused by the chronic diabetic complications (e.g., blindness and amputation). Informed consent was obtained from all participants.

Clinical assessment:

Data evaluated included full history and physical examination. Body height was measured without shoes to the nearest 0.5 cm; body weight was measured with light clothes to the nearest 0.1 kg; body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the level of the umbilicus, at the end of a normal expiration to the nearest 0.1 cm. Blood pressure was computed as the mean of two measurements in supine position recorded, with an interval of 5 min of resting between measurements, from the right arm, using a mercury sphygmomanometer by auscultatory methods. Blood pressure was considered raised if systolic blood pressure was or exceeded 130 mmHg or diastolic blood pressure was or exceeded 85 mmHg.

or treatment of previously diagnosed hypertension was obtained. Each participant was privately and independently subjected to a semi-structured interview to collect demographic and clinical data. Toward the end of the interview the participant was asked to complete the BDI. Although this is a self-rating instrument, it was administered verbally in a face-to-face manner since a number of patients were illiterate. A brief description of the instrument is given below.

Beck Depression Inventory (BDI):

The original version of the BDI was introduced in 1961²⁵ and its reliability and validity have been established across a broad spectrum of clinical and non-clinical populations²⁶. It is, however, regarded as an effective screening test for major depression in diabetic patients¹⁶. The inventory was translated into and validated in many different languages. The Arabic version²⁷ was used in this study. Each of the 21 items on the BDI measures the presence and severity of a symptom of depression by requiring a self-rating from 0 to 3. A score is determined by summing the ratings for the individual items. To separate depression symptoms that might be confounded by diabetes, items on the BDI were subdivided into cognitive and somatic subsets (Items 1-13 and 14-21, respectively) following the procedures set forth¹⁶. None of the symptoms in the cognitive set is recognized as being a common feature of diabetes. In contrast, many of the symptoms in the somatic set (e.g., fatigue, loss of interest in sex) occur in both depression and diabetes. To identify individuals with at least mild to moderate symptoms of depression, a cut-off score of 10 or above on BDI was used here as recommended²⁸ which discriminate depressed from non-depressed in physically ill patients²⁹⁻³⁰.

Laboratory Investigations:

All participants were asked to return next morning for laboratory investigations after an overnight fast. Blood samples (10 ml, in two aliquots - one aliquot in EDTA and another without anti-coagulant for each participant) were collected by venipuncture for the analysis of serum creatinine, albumin and lipids [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL)] by using standard automated clinical chemistry techniques, and for glycemia by the hexokinase method with a Dade Behring reagent on a Dimension (Dade Behring) instrument. Glycated hemoglobin (HbA1c) was measured by microparticle enzyme immunoassay (Abbot AxSYM System, Alameda CA). Serum magnesium concentrations were measured by colorimetric method with values for normal magnesium concentration between 0.70 to 1.02mmol/l. Hypomagnesemia was, therefore, defined as a serum magnesium level of 0.69mmol/l or less and hypermagnesemia was defined as 1.03mmol/l or more.

Statistical Analysis:

Data are presented as the arithmetic mean $\pm$ 1 standard deviation ($\pm$ SD) for continuous variables, and as absolute values for categorical measures. Differences between groups were assessed by unpaired Student T test or chi-square (χ^2) test. Correlations between data were analyzed using Pearson's coefficient. Two-tailed *p* values <0.05 were considered statistically significant. All data were analyzed using the Statistical Program for Social Sciences 11.0.1 software³¹.

RESULTS

Sixty per cent of the samples studied were women. Hypertension was detected in 29 (58%) and 21 (42%) in patients with and without depression respectively. This

difference, however, was not statistically significant ($\chi^2 = 3.241$; $df=1$; $p=0.072$) $p=0.249$.

Table (1): Characteristics of participants

	Group (A)*	Group (B)**	Analysis
Gender:			
Male: N	19	20	$\chi^2 = 0.042$; $df=1$; $p=0.838$
Female: N	31	30	
Age (years):			
Mean ($\pm$ SD)	45.4 ($\pm$ 10.238)	44.9 ($\pm$ 9.605)	$t= 0.272$; $df= 98$; $p=0.786$
Residency:			
Urban: N	30	36	$\chi^2 = 1.604$; $df=1$; $p=0.205$
Rural: N	20	14	
Education (years):			
Mean ($\pm$ SD)	9.2 ($\pm$ 3.183)	9.6 ($\pm$ 3.226)	$t= 0.593$; $df= 98$; $p=0.555$
Employment:			
Employed: N	21	28	$\chi^2 = 1.961$; $df=1$; $p=0.161$
Unemployed/ Retired: N	29	22	
Marital status:			
Married: N	28	26	$\chi^2 = 0.161$; $df=1$; $p=0.688$
Unmarried [§] : N	22	24	
Smoking:			
Current smoker: N	16	11	$\chi^2 = 1.268$; $df=1$; $p=0.260$
Not current smoker: N	34	39	
Duration of illness (years):			
Mean ($\pm$ SD)	7.2 ($\pm$ 3.371)	6.4 ($\pm$ 3.621)	$t= 1.058$; $df= 98$; $p=0.293$
BP			
Systolic	159.9 ($\pm$ 31.241)	154.8 ($\pm$ 29.735)	$t= 0.820$; $df= 98$; $p=0.414$
Diastolic			
BMI	96.3 ($\pm$ 11.434)	92.9 ($\pm$ 12.861)	$t= 1.395$; $df= 98$; $p=0.166$
Male (kg/m^2)			$t= 0.618$; $df= 37$; $p=0.541$
Mean ($\pm$ SD)			
Female (kg/m^2)	27.9 ($\pm$ 2.942)	27.4 ($\pm$ 2.560)	$t= 0.885$; $df= 59$; $p=0.380$
Mean ($\pm$ SD)	27.0 ($\pm$ 2.708)	26.4 ($\pm$ 2.581)	
Total (kg/m^2)			
Mean ($\pm$ SD)	27.3($\pm$ 2.804)	26.8 ($\pm$ 2.589)	$t= 1.037$; $df= 98$; $p=0.302$

* T2DM patients- with depression

** T2DM patients- without depression

§ Unmarried= total number of never-married, divorced, separated and widowed.

Table (2): Laboratory results

	Group (A)*	Group (B)**	Analysis
Total cholesterol (mmol/l) Mean (± SD)	6.3 (± 1.406)	6.1 (± 1.015)	t= 0.775; df= 98; p=0.440
HDL-cholesterol (mmol/l) Mean (± SD)	1.0 (± 0.179)	1.1 (± 0.207)	t= 1.781; df= 98; p=0.078
LDL -cholesterol (mmol/l) Mean (± SD)	3.5 (±0.432)	3.6 (±0.328)	t= 1.096.; df= 98; p=0.276
Triglycerides (mmol/l) Mean (± SD)	2.0 (±0.199)	1.9 (±0.248)	t= 1.818; df= 98; p=0.072
Fasting glucose (mmol/l) Mean (± SD)	9.4 (± 0.281)	9.3 (±0.301)	t= 1.546; df= 98; p=0.125
HbA1c (%) Mean (± SD)	8.7 (±0.587)	8.5 (±0.590)	t= 1.447; df= 98; p=0.151
Albumin (mmol/l) Mean (± SD)	49. 4 (±0.623)	49.2 (±0.702)	t= 1.145; df= 98; p=0.255
Creatinin (mmol/l) Mean (± SD)	97.7 (±1.402)	97.3 (±1.577)	t= 1.300; df= 98; p=0.197
Mg (mmol/l) Mean (± SD)	0.70 (±0.060)	0.75 (±0.071)	t= 3.260; df= 98; p=0.002 [§]

* T2DM patients- with depression ** T2DM patients- without depression[§] Significant

Table (3): Beck Depression Inventory (BDI) scores

	Group (A)*	Group (B)**	Total
Cognitive subscore	13.7 (± 3.436)	3.3 (± 0.658)	8.5 (± 5.579)
Somatic subscore	6.1 (±1.157)	3.3 (± 0.886)	4.7 (± 1.874)
Total score	19.8 (± 4.569)	6.6 (± 1.289)	13.2 (± 7.391)

* T2DM patients- with depression

** T2DM patients- without depression

Table (4): Frequency of hypomagnesemia

	Group (A)*	Group (B)**	Total	χ^2	p
With hypomagnesemia	23	8	31	10.519	0.001 [§]
Without hypomagnesemia	27	42	69		
Total	50	50	100		

* T2DM patients- with depression ** T2DM patients- without depression

[§] Significant

Table (5): Correlation of serum magnesium with glucose and BDI scores in the diabetic patients with depression (group-A), without depression (group-B) and the total sample.

	Serum magnesium					
	Group (A)* (N=50)		Group (B)** (N=50)		Total (N=100)	
	r	p	r	p	r	p
Fasting serum glucose level	-0.273	0.05 [§]	-0.274	0.05 [§]	-0.201	0.05 [§]
BDI score	-0.372	0.001 [§]	-0.225	0.12	-0.259	0.01 [§]

* T2DM patients- with depression * T2DM patients- without depression

§ Significant

There were also no statistically significant differences between the two groups in antihypertensive treatment (which was mainly based on the use of captopril and nifedipin) or in the hypoglycemic treatment (based mainly on the use of glybenclamid alone or in combination with metformin) (14.5 vs. 9.1%). Patients receiving insulin were not included in the study. Other main characteristics of the participants are presented in table (1).

There were no significant differences between diabetic patients with and without depressive symptoms along all variables studied. Table (2) shows the laboratory results. There were no significant differences between the two groups except for the serum magnesium level which was lower in patients with depression ($p=0.002$). The mean total BDI score was 19.8 (± 4.569) and 6.6 (± 1.289), $t=19.539$, $df=98$, $p=0.000$ for the patients in group (A) and group (B) (table 3). Differences between the two groups along cognitive and somatic subscores were similarly highly significant.

The frequency of hypomagnesemia among participants is given by table (4). Overall, 31% of the participants had significant hypomagnesemia having serum magnesium level less than 0.69mmol/l. Twenty three (46%) patients in group (A) and 8 (16%) patients in group (B) exhibited hypomagnesemia ($p=0.001$).

Correlation analyses of serum magnesium with glucose and BDI scores are shown in (table 5). Although modest negative correlation was found between serum magnesium and glucose ($r=-0.201$, $p=0.05$) and this relationship was maintained for each sub-group individually, a highly significant negative correlation was observed between serum magnesium and BDI for group (A) ($r=0.66$, $p<0.005$) but not for group (B).

DISCUSSION

Results did not support our hypothesis that T2DM patients with depression have higher serum magnesium level than those without depression. They were also in disagreement with a number of previous studies that reported elevated magnesium levels in patients with depression²². To the contrary, we found that serum magnesium level was significantly lower in patients with depression. This is, however, more in keeping with the recent study³² found that serum magnesium levels were significantly lower among type 2 diabetic patients with depression, aged 65 years or older, than an age and gender matched control diabetic subjects.

Interestingly, a Korean study of outpatients with T2DM, classified into two groups according to their mode of therapy, found

that diabetics who were treated with insulin showed a significantly higher frequency of depression compared to those treated with oral anti-diabetic drugs³³. Although there have been reports indicating that insulin induces hypomagnesemia³⁴⁻³⁵ long before the Korean study was performed, the idea that hypomagnesemia could explain the results was not explored by Noh and colleagues. Deficiencies of micronutrients including trace elements are associated with psychological symptoms³⁶, and concentrations of magnesium have long been noted to decrease in the cerebrospinal fluid (CSF) of subjects with depression, particularly in those with suicide attempts³⁷. In this regard, our results support an alternative hypothesis that low serum magnesium levels are a risk factor for development of depression. Hypomagnesemia could be speculated to be the cause of low CSF magnesium levels that correlates with CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA)³⁷⁻³⁸, which play a significant role in dopamine metabolism and brain serotonin synthesis and are linked to development of depression³⁹⁻⁴⁰. Moreover, it has been shown that magnesium exhibits antidepressant-like effects in animal models of depression⁴¹. Recent research indicates the involvement of NMDA/glutamate pathway in the antidepressant-like activity of magnesium in mouse forced swim test⁴².

Therefore, as a therapeutic implication of our results, we venture to suggest that magnesium treatment could be effective in the management of depression in people exhibiting hypomagnesemia as in many patients with T2DM. Indeed, antidepressant drugs are not always effective and some have been accused of causing an increased number of suicides particularly in young

people⁴³. In support of this implication, it may be noted that some case reports are emerging to show rapid recovery (mostly in less than 7 days) from major depression using around 125-300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime⁴⁴. Though appropriate magnesium supplementation might prove beneficial in ameliorating some physiological deficiencies associated with diabetes and prevent or retard the development of secondary complications, well designed trials need to be performed before the rationales for such therapy are developed.

Our study shares others of similar design their many limitations. First, because of the cross-sectional nature of the data, inferences about causality are inevitably compromised. Thus, it cannot be ascertained whether hypomagnesemia is a causative factor for depression or merely an associated epiphenomenon. Second, the diagnosis of depression was based on the BDI, a depression symptom inventory, rather than on a clinical diagnostic interview. Thus, there is a possibility of having overdiagnosed depression. Third, because we did not measure hemoglobin or hematocrit, we are uncertain about the possible association between hypomagnesemia and anemia and about the effect that anemia could exert on development of depression. Furthermore, although serum creatinine levels were similar and within normal values in both groups, we do not have data on glomerular filtration rate; therefore, we cannot adjust serum magnesium levels according to renal function. Finally, thyroid hormones were not measured. There is an experimental evidence that hyperthyroidism can increase the renal excretion of magnesium and thus cause hypomagnesemia⁴⁵. Subclinical

hyperthyroidism, however, can be difficult to exclude since it may present without or with minimal symptoms of thyroid hormone excess, or may present with psychological symptoms such as nervousness, reduced feeling of well-being, fear, hostility, and inability to concentrate, which could be confounded with depressive symptoms. On the other hand, poor glycaemic control produces symptoms similar to hyperthyroidism, such as weight loss despite increased appetite as well as fatigue. Thus, we are uncertain whether our results could have been biased by a presence of subclinical hyperthyroidism. Further research is needed.

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Address of Correspondence:

Fawzi M. Department of Psychiatry,
Faculty of Medicine, Zagazig University,
Zagazig, Egypt

e-mail: mohabfawzi@yahoo.com