Depression and serum magnesium level in patients with type 2 diabetes mellitus

Fawzi M., Said N. S. and Fawzi M.

Abstract

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. This cross-sectional study aimed to test the hypothesis that T2DM patients with depression have higher serum magnesium level than those without depression. 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). No significant differences were found between the two groups except for their serum magnesium level, with a mean (± SD) of 0.70 (±0.060) in patients with depression and 0.75 (±0.071) in those without depression (*p*= 0.002). Overall, 31% of the participants had significant hypomagnesemia below (0.69 mmol/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). 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. Further research is needed.

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 problems (Herman et al., 1995; 1998). 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) (King et al., 1998). 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 insufficiency (Morrish et al., 2001).

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 complications (Rodríguez-Morán and Guerrero-Romero,

2001; Sharma et al., 2007). 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 secretion (Iannello and Belfiore, 2001). 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 patient (Sheehan, 1991). Linkage between magnesium deficiency and insulin resistance, carbohydrate intolerance, accelerated atherosclerosis, dyslipidemia, hypertension and adverse outcomes in pregnancies complicating diabetes have been observed or postulated (Pham et al., 2007; Sales and Pedrosa, 2006).

Another significant problem among patients with diabetes is the increased risk of comorbid depression (Ali et al., 2006). This commonly overlooked comorbidity has an estimated prevalence of 15–20%, compared with 2–9% in the general population (Anderson et al., 2001). 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 increase (Katon et al., 2005; Zhang et al., 2005). 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) (de Groot et al., 2001). 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 hyperglycemia (Lustman et al., 2000) and an increase in diabetes complications (de Groot et al., 2001). 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 costs (Ciechanowski et al., 2000; Egede et al., 2002; Eren et al., 2008; Kalsekar et al., 2006; Park et al., 2004). 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 levels (Widmer et al., 1992). The high serum magnesium levels noted in patients with mood disorder are thought to be related to the underlying disorder itself and are not influenced by clinical background factors (Imada et al., 2002). Researchers found that hypermagnesaemia might lead to hypoactivity and psychomotor retardation which is so often observed in depressed patients (Barra et al., 2007). 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.

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: Type 2 diabetes (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, methyldopa, 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 thorough 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 Beck Depression Inventory (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 1961 (Beck et al., 1961) and its reliability and validity have been established across a broad spectrum of clinical and non-clinical populations (Beck et al., 1988). It is, however, regarded as an effective screening test for major depression in diabetic patients (Lustman et al., 1997). The inventory was translated into and validated in many different languages. The Arabic version by Abdel-Khalek (1996) 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 forth by Lustman et al (1997). 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 recommended by Beck and Steer (1993) and by other investigators who found it to discriminate depressed from non-depressed in physically ill patients (Kronish et al., 2006; Lespérance et al., 2000).

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 1.02 mmol/l. Hypomagnesemia was, therefore, defined as a serum magnesium level of 0.69 mmol/l or less and hypermagnesemia was defined as 1.03 mmol/l or more.

Statistical Analysis:

Data are presented as the arithmetic mean ±1 standard deviation (±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 software (SPSS for Windows, 2001).

Results

Sixty per cent of the sample 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 5 0.249. 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).

Table (1): Characteristics of participants

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

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).

As shown in table (3) 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). 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 0.69 mmol/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).

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

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 depression (Widmer et al., 1992). 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 study by Barragan-Rodríguez et al. (2007) which 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 drugs (Noh et al., 2005).) Although there have been reports indicating that insulin induces hypomagnesemia (Matsumura et al., 2000; Ratzmann and Zöllner, 1985) long before the Korean study was performed, the idea that hypomagnesemia could explain the results was not explored by Noh and colleagues (2005). Deficiencies of micronutrients including trace elements are associated with psychological symptoms (Kaplan et al., 2007), and concentrations of magnesium have long been noted to decrease in the cerebrospinal fluid (CSF) of subjects with depression, particularly in those with suicide attempts (Banki et al., 1985). 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) (Banki et al., 1986; 1985), which play a significant role in dopamine metabolism and brain serotonin synthesis and are linked to development of depression (Stuerenburg et al., 2004; Williams et al., 1999). Moreover, it has been shown that magnesium exhibits antidepressant-like effects in animal models of depression (Poleszak et al., 2004). Recent research indicates the involvement of NMDA/glutamate pathway in the antidepressant-like activity of magnesium in mouse forced swim test (Poleszak et al., 2007).

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 people (Seemüller et al., 2008). 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 bedtime (Eby and Eby, 2006). 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 hypomagnesemia (Gilroy et al., 2006). 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.

References

Abdel-Khalek A. (1996): *Beck Depression Inventory: The Arabic version*. Cairo: The Anglo- Egyptian Bookshop.

Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. (2006): The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*; 23(11):1165- 1173.

Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. (2001)*:* The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*; 24:1069–1078.

Banki CM, Arato M, Kilts CD. (1986): Aminergic studies and cerebrospinal fluid cations in suicide. *Ann NY Acad Sci*; 487: 221e230.

Banki CM, Vojnik M, Papp Z, Balla KZ, Arató M. (1985): Cerebrospinal fluid magnesium and calcium related to amine metabolites, diagnosis, and suicide attempts. *Biol Psychiatry*; 20(2):163- 171.

Barra A, Camardese G, Tonioni F, et al. (2007): Plasma magnesium level and psychomotor retardation in major depressed patients. *Magnes Res*; 20(4): 245- 249.

Barragan-Rodríguez L, Rodríguez-Morán M, Guerrero-Romero F. (2007): Depressive symptoms and hypomagnesemia in older diabetic subjects. Arch Med Res; 38(7): 752- 756.

Beck AT, Steer RA, Garbin MG (1988): Psychometric properties of the Beck Depression Inventory. Twenty-five years of

evaluation. *Clinical Psychology Review*; 8: 77-100.

Beck AT, Ward CH, Mendelson Met al (1961): An inventory for measuring depression. *Archives of General Psychiatry*; 4: 53-63.

Ciechanowski PS, Katon WJ, Russo JE. (2000): Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med.* 2000 Nov 27;160(21):3278- 3285.

de Groot M, Anderson R, Freedland KE, et al (2001): Association of depression and diabetes complications: a meta-analysis. *Psychosom Med*; 63:619–630.

Eby GA, Eby KL. (2006): Rapid recovery from major depression using magnesium treatment. *Med Hypotheses*; 67(2):362- 370.

Egede LE, Zheng D, Simpson K. (2002): Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. *Diabetes Care*.; 25(3):464- 470.

Eren I, Erdi O, Sahin M. (2008): The effect of depression on quality of life of patients with type II diabetes mellitus. *Depress Anxiety*; 25(2):98-106.

Gilroy CV, Horney BS, Burton SA, MacKenzie AL. (2006): Evaluation of ionized and total serum magnesium concentrations in hyperthyroid cats. *Can J Vet Res.*; 70(2):137- 142.

Herman WH, Ali MA,. Aubert RE, et al . (1995): Diabetes mellitus in Egypt: risk factors and prevalence. *Diabet Med*;12(12): 1126- 1131.

Herman WH, Aubert RE, Engelgau MM, et al (1998): Diabetes mellitus in Egypt: glycaemic control and microvascular and neuropathic complications. *Diabet Med*; 15(12):1045-1051.

Iannello S, Belfiore F. (2001): Hypomagnesemia. A review of pathophysiological, clinical and therapeutical aspects. *Panminerva Med.*; 43(3):177-209.

Imada Y, Yoshioka S, Ueda T,et al (2002): Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. *Psychiatry Clin Neurosci.*; 56(5):509- 514.

Kalsekar ID, Madhaven SS, Amonkar MM,et al (2006): Depression in patients with type 2 diabetes: impact on adherence to oral hypoglycemic agents. *Ann Pharmacother*; 40: 605–611.

Kaplan BJ, Crawford SG, Field CJ, et al (2007): Vitamins, minerals, and mood. *Psychol Bull*; 133(5):747- 760.

Katon WJ, Rutter C, Simon G, Lin EH, (2005)*:* The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*; 28:2668–2670.

King H, Aubert RE, Herman WH. (1998): Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*; 21(9): 1414-1431.

Kronish IM, Rieckmann N, Halm EA, et al. (2006): Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. *J Gen Intern Med*; 21(11): 1178- 1183.

Lespérance F, Frasure-Smith N, Juneau M, et al. (2000): Depression and 1-year prognosis in unstable angina. *Arch Intern Med*; 160(9):1354- 1360.

Lustman PJ, Anderson RJ, Freedland KE, et al RE (2000): Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 23:934–942.

Lustman PJ, Clouse RE, Griffith LS, et al (1997): Screening for depression in diabetes using the Beck Depression Inventory. *Psychosom Med.*; 59(1):24-31

Matsumura M, Nakashima A, Tofuku Y. (2000): Electrolyte disorders following massive insulin overdose in a patient with type 2 diabetes. *Intern Med*; 39(1): 55- 57.

Morrish NJ, Wang SL, Stevens LK, et al (2001): Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*; 44(Suppl 2):S14–S21.

Noh JH, Park JK, Lee HJ, et al (2005): Depressive symptoms of type 2 diabetics treated with insulin compared to diabetics taking oral anti-diabetic drugs: a Korean study. *Diabetes Res Clin Pract*; 69(3): 243- 248.

Park HS, Hong YS, Lee HJ, et al (2004): Individuals with type 2 diabetes and depressive symptoms exhibited lower adherence with self-care. *J Clin Epidemiol*; 57:978–984.

Pham PC, Pham PM, Pham SV, et al (2007): Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Nephrol.; 2(2):366- 373.

Poleszak E, Szewczyk B, Kedzierska E, et al (2004): Antidepressant- and anxiolytic-like activity of magnesium in mice. *Pharmacol Biochem Behav*; 78(1):7-12.

Poleszak E, Wlaź P, Kedzierska E, et al (2007): NMDA/glutamate mechanism of antidepressant-like action of magnesium in forced swim test in mice. *Pharmacol Biochem Behav*; 88(2): 158- 164.

Ratzmann GW, Zöllner H. (1985): Hypomagnesemia and hypokalemia in the insulin hypoglycemia test. *Z Gesamte Inn Med.*; 40(19):567- 570. English abstract. [Article in German].

Rodríguez-Morán M, Guerrero-Romero F. (2001): Low serum magnesium levels and foot ulcers in subjects with type 2 diabetes. Arch Med Res.; 32(4): 300- 303.

Sales CH, Pedrosa Lde F. (2006): Magnesium and diabetes mellitus: their relation. *Clin Nutr*; 25(4):554- **5**62.

Seemüller F, Riedel M, Obermeier M, et al (2008): The controversial link between antidepressants and suicidality risks in adults: data from a naturalistic study on a large sample of in-patients with a major depressive episode. *Int J Neuropsychopharmacol*:1-9 [Epub ahead of print].

Sharma A, Dabla S, Agrawal RP, Barjatya H, Kochar DK, Kothari RP. (2007): Serum magnesium: an early predictor of course and complications of diabetes mellitus. *J Indian Med Assoc.*; 105(1):16- 20.

Sheehan DV, Lecrubier Y, Sheehan KH, et al (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*; 59 (Suppl 20): 22-33.

Sheehan JP. (1991): Magnesium deficiency and diabetes mellitus. *Magnes Trace Elem.*; 10(2-4):215- 219.

SPSS for Windows (2001): *Statistical Package for the Social Sciences, version 11.0.1.* SPSS Inc., Chicago.

Stuerenburg HJ, Ganzer S, Muller-Thomsen T. (2004): 5-Hydroxyindoleacetic acid and homovanillic acid concentrations

in cerebrospinal fluid in patients with Alzheimer's disease, depression and mild cognitive impairment. *Neuro Endocrinol Lett*; 25:435- 437.

Widmer J, Bovier P, Karege F, et al (1992): Evolution of blood magnesium, sodium and potassium in depressed patients followed for three months. *Neuropsychobiology*; 26(4):173- 179.

Williams WA, Shoaf SE, Hommer D, et al (1999): Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. *J Neurochem*; 72:1641-1647.

Authors

Fawzi M
Lecturer of Psychiatry
Department of Psychiatry
Faculty of Medicine
Zagazig University

Said N.
Lecturer of Internal Medicine
Department of Internal Medicine
Faculty of Medicine
Zagazig University

Fawzi M.
Lecturer of Clinical Pathology
Department of Clinical Pathology
Faculty of Medicine
Zagazig University

Address of Correspondence
Fawzi M.
Department of Psychiatry
Faculty of Medicine
Zagazig University
Zagazig
Egypt
e-mail: mohabfawzi@yahoo.com