Hypomagnesemia in Iraqi Diabetic Patients and Healthy Controls: An Exploratory study

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Abstract

Background: Diabetes mellitus has been suggested to be the most common metabolic disorder associated with magnesium deficiency, and because available data suggest that adverse outcomes are associated with hypomagnesemia, it is prudent that routine surveillance for hypomagnesemia be done and the condition be treated whenever possible**.**

Aim of the study: To explore the serum Mg concentrations of diabetic patients and healthy controls in our locality.

Mehtods: One hundred and forty four diabetic patients (22 with type I and 122 with type II diabetes mellitus) recruited from the outpatient diabetes clinic at the Specialized Center For Endocrine Diseases-Baghdad (62 patients), National Diabetes Center-Al Mustansiria University (20 patients), and from private endocrinologic practice clinics in Baghdad (62 patients), during the period from 1st October 2005 to 30th April 2006. Ninety non-diabetic healthy controls matched for age and sex were participated in this study. Exclusion criteria for both groups included diarrhea and loop diuretics. None were taking Mg supplements**.** Level of Mg and Albumin were determined spectrophotometerically in the same serum samples**.**

Results: Mean serum Mg concentrations of the diabetics was significantly lower than in controls ($p<0.001$). Serum albumin was not a significant predictor of serum Mg neither among diabetic patients ($r = 0.005$) nor control subjects ($r = 0.139$). In 88.9% of the diabetic patients and 11.1% of the control subjects serum Mg concentrations were below the normal reference range of 0.70 mmol/L. The prevalence is increased when hypomagnesemia is defined by a reference limit of 0.75 mmol/L (98.6% and 28.9 % for diabetics and controls, respectively), a further higher prevalence among controls (91.1 %) was noted when 0.80 mmol/L is adopted as the lower normal limit. All diabetics (100%) and controls (100%) were identified as hypomagnesemic with a lower reference limit of 0.90 mmol/L**.**

Conclusion: The tremendous hot climate of ours, can be suggested as an influential cause for increased Mg losses, and may provide a coherent explanation for the exceedingly high prevalence of hypomagnesemia observed in diabetic and control subjects participated in this study. Which therefore may suggest an inevitable requirement for magnesium supplementation to avert hypomagnesemia, not only among diabetics, but as well for controls, particularly through the hot summer episode

Key words: Hypomagnesemia , Albumin, Diabetes, Iraqi.

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Introduction

Until recently, the function of magnesium in biological processes waslargely ignored to the point where it was described as the 'forgotten' ion. In recent years, there has been an explosion of interest in the physiological and therapeutic properties of this essential element[1], and despite numerous reports linking hypomagnesemia to chronic diabetic complications, attention to this issue is poor among clinicians[2].Diabetes mellitus has been suggested to be the most common metabolic disorder associated with magnesium deficiency. Hypomagnesemia, in children with insulin-dependent diabetes and through the entire spectrum of adult type I and type II diabetics, were reported in several European countries including Austria, Germany, Italy, France, Sweden and Switzerland[3-8]. Similar findings were described in American[9,10], Asian[11-13] and African[14,15] countries.

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type II diabetes [16], as well as on the development of complications such as retinopathy, thrombosis and hypertension [17-19]. Moreover, low serum Mg is a strong independent predictor of the development of type II diabetes [20]. Preventing low Mg status in diabetics may therefore be beneficial in the management of the disease.

The mechanism responsible for magnesium deficiency in patients with diabetes is not completely known. Osmotic diuresis clearly accounts for a portion of the magnesium loss. It is believed that glucosuria which accompanies the diabetic state, impairs renal tubular reabsorption of magnesium from the glomerular filtrate. Dietary magnesium intake may also be a factor in deficiency, as the individuals do not consume the fully-recommended daily allowance for magnesium [21].Although controversies still exist as to how hypomagnesemia is best judged, the current understanding on the clinical effects of hypomagnesemia in human is influenced by studies that have relied predominantly on the measurements of serum magnesium concentration. Traditionally, hypomagnesemia refers to a low serum Mg level. Clinically, hypomagnesemia may be defined as a serum Mg level <0.7 mmol/l (<1.70 mg/dl) or >2 SD below the mean of the general population [9, 22]. In the literature, 0.75 mmol/l and 0.8 mmol/l (1.82 mg/dl and 1.95 mg/dl, respectively) were among the different lower normal limits cited for serum Mg[23]. Hypomagnesemia has been reported to occur in 13.5 to 47.7% of nonhospitalized patients with type 2 diabetes compared with 2.5 to 15% among their counterparts without diabetes[3,8,9,22]. The wide range in the reported incidence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia and techniques in Mg measurements[2].

Recently, the Self-Help Organization on Mineral Imbalances (Berlin, Germany), analysis the different lower limits of serum Mg mentioned in the literature, and reported that the reason patients with symptoms of Mg deficiency do not get Mg therapy is the acceptance of an inappropriate reference values for serum Mg concentration, which seems to be selected from values obtained for symptomatic patients. They recommend a Mg serum value of 0.9 mmol/l to be considered as the lower reference limit, in evaluating symptoms or diseases suspected as being associated with Mg deficiency [24].

Because available data suggest that adverse outcomes are associated with hypomagnesemia, it is prudent that routine surveillance for hypomagnesemia be done and the condition be treated whenever possible [2]. Reviewing the literature, there are no reported data for Iraq. Therefore, the aim of this study was to explore the serum Mg concentrations of diabetic patients and healthy controls in our locality.

Methods

One hundred and forty four diabetic patients (22 with type I and 122 with type II diabetes mellitus) recruited from the outpatient diabetes clinic at the Specialized Center For Endocrine Diseases-Baghdad (62 patients), National Diabetes Center-Al Mustansiria University (20 patients), and from private endocrinologic practice clinics in Baghdad (62 patients), during the period from 1st October 2005 to 30th April 2006. Ninety non-diabetic healthy controls matched for age and sex were participated in this study. Exclusion criteria for both groups included diarrhea and loop diuretics, known to be associated with higher fecal and urinary Mg losses, respectively. None were taking Mg supplements. Characteristics of the study groups are presented in **Table-1.**

Venous blood samples were drawn, with the least haemostasis, and transferred into 10 ml plain tubes. Serum was separated from blood cells by centrifugation at 3000 rpm for 15 minutes. Serums with any trace of hemolysis were discarded and a new fresh sample was obtained. Aliquots were stored in plastic vials at –20 °C until analysis.

Serum level of Mg was determined spectrophotometerically, using the Blue Xilidil method (Giesse Diagnostics, Roma-Italy). Normal ambit-test serum (Giesse Diagnostics, Roma-Italy) was employed for quality control. Albumin concentration was measured in the same serum samples utilizing the Bromocresol Green method (Randox Laboratories Ltd., Antrim-UK). All samples were analyzed in duplicate and

repeated if the difference between individual values relative to the mean was >5%.
Data processing and statistical analysis were done using Excel 2003 (Microsoft, Seattle WA, USA). Normal distribution of data was verified by calculating the quotient of the skewness; normal distribution was assumed if the quotient was between –2.5 and +2.5. Normally distributed data were expressed as arithmetic means ± SD. Differences between groups were evaluated using unpaired Student's t-test and considered statistically significant at $p<0.05$. ANOVA was aimed to test for association of serum albumin with Mg concentration as the dependent variable.

Result

Skewness quotient for serum Mg (-2.35 and 0.80 for controls and diabetics, respectively) and albumin (0.71 and -0.45 for controls and diabetics, respectively), indicates normal distribution in both study groups. Mean serum Mg concentrations of the diabetics was significantly lower than in controls (0.569±0.09 vs. 0.758±0.05 mmol/L; $p<0.001$), serum albumin levels of both groups (43.0±4.52 and 41.5±4.81 g/L for diabetics and controls, respectively) were comparable **(Table- 2)**. Serum albumin was not a significant predictor of serum Mg neither among diabetic patients ($r = 0.005$) nor control subjects ($r= 0.139$). Moreover, no significant differences in serum Mg were observed when related to sex, age, type of antidiabetic medication, duration or type of diabetes.
In 88.9% of the diabetic patients and 11.1% of the control subjects serum Mg concentrations were below the normal reference range of 0.70 mmol/L. The prevalence is increased when hypomagnesemia is defined by a reference limit of 0.75 mmol/L (98.6% and 28.9 % for diabetics and controls, respectively), a further consonant with the findings of Pickup et al.[27] and Corsonello et al.[28].Analogous to the previous worldwide observations[3-15], mean serum Mg concentration of diabetics was significantly lower than in controls. However, two striking manifestations are quite evident in the population sample of the exploratory study presented herein; [1] The prevalence of hypomagnesemia among the diabetics and controls are extremely higher than any other reported study, even with a cut-off point of 0.70mmol/L: [2] Among controls, the higher prevalence among controls (91.1 %) was noted when 0.80 mmol/L is adopted as the lower normal limit. All diabetics (100%) and controls (100%) were identified as hypomagnesemic with a lower reference limit of 0.90 mmol/L **(Table- 3).**

Discussion

Magnesium in serum represents less than 0.3% of total body Mg, nevertheless, serum or plasma Mg measurement is the most readily available and widely used test of Mg status. Yet, normal serum Mg concentrations have been reported in association with low Mg values in various blood cells and tissues, which makes serum Mg measurement an insensitive, but highly specific indicator of low Mg status[25].
Around 55% of the total Mg in serum is present as free ionized Mg^{+2}, 15% is complexed to anions (e.g. bicarbonate, citrate, sulfate) and 30% is bound to proteins, mainly albumin[26]. It could therefore be argued that in diabetics with microalbuminuria, serum Mg might be reduced because of lower serum albumin concentration[8]. The comparable serum albumin concentrations observed in the present study for both groups, as well as its failure as a predictor of serum Mg level, may excludes any substantial artefact effect on serum Mg measurement. This is in

distribution of serum Mg, although statistically normal, have a propensity to negatively skew (skewness quotient = -2.35) and may point to a higher tendency to develop hypomagnesemia. These may indicate the presence of a common cause(s) affecting the whole population with further contribution to the diabetic patients.
Recently, Franz et al. have recognized that climate associated with increased

temperature can result in increased sweat losses of magnesium, which may not be easily compensated by a normal diet[29]. Magnesium content in sweat induced by exercise in a hot environment in healthy young men and women was estimated as 0.5 ± 0.5 mmol/L[30]. Thus, two liters daily sweat would result in a mean Mg loss of 1mmol /day (24 mg/day).

In a balance study for whole diets, only 21–27% of magnesium was absorbed from self-selected daily diets containing 234-323mg Magnesium[31]. Moreover, fractional magnesium absorption is highly dependent on the amount of magnesium in the meal; the larger the amount, the lower the fractional absorption [32]. Hence, as a minimum, an extra 120 mg of Mg would be needed, if the above mentioned sweat Mg losses are to be compensated by diet or water intake. Further increases in these sweat losses could compromise the already limited Mg intake and may contribute to Mg deficiency[29]. In human, sweat volumes as large as 14 liters/day have been recorded[33]. Accordingly, the tremendous hot climate of ours, can be suggested as an influential cause for increased Mg losses, and may provide a coherent explanation for the exceedingly high prevalence of hypomagnesemia observed in diabetic and control subjects participated in this study.Although, the present study is of an exploratory nature, based on a relatively small number of subjects and should be interpreted with care. Reanalysis of serum Mg results with respect to the date of sampling may provide a cogent insight when attempting to test the above hypothesis. For controls, the lowest mean was recorded in samples acquired during October and November, while February and March scores the highest levels; however, none of these differences were statistically significant. Additionally, the increments in mean serum Mg were paralleled with a reduction in the prevalence of hypomagnesemia (Table 4). Since October and/or November represent the shift point from the extreme hot climate of summer in our district, their results may reflect a continuous Mg depletion during the earlier preceding months. This seems to be partially corrected within the following months as indicated by the results of February and March.

On the other hand, in diabetics, the date of sampling has a less discernible effect on the mean of the estimated serum Mg levels (data not shown). This could be attributed to the persistence Mg losses known to be associated with diabetes mellitus[21], and thus the failure of diabetics to compensate for the Mg depletion by their normal diet. Which therefore may suggest an inevitable requirement for magnesium supplementation to avert hypomagnesemia, not only among diabetics, but as well for controls, particularly through the hot summer episode. Amendment of low serum Mg levels has never been proved to be protective against chronic diabetic complications, however, intervention is justified because hypomagnesemia has been linked to many adverse clinical outcomes. Liebscher and Liebscher [24], have cited that many patients with so-called exclusion diagnoses (as for example, attention deficit hyperactivity disorder or chronic fatigue syndrome) would have their symptoms improved through Mg therapy. Similarly, patients with diagnoses of depression, epilepsy, diabetes mellitus, tremor, Parkinsonism, arrhythmias, circulatory disturbances, hypertension, migraine, cluster headache, cramps, neuro-vegetative disorders, abdominal pain, osteoporosis, asthma, stress dependent disorders, tinnitus, ataxia, confusion, preeclampsia, weakness, might also be consequences of the magnesium deficiency syndrome. In addition, Mg supplementation is inexpensive and, with the exception of diarrhea, a relatively benign medication[2].

Though, to our knowledge, no study has ever documented an optimal serum Mg concentration in patients with diabetes, Pham et al. have speculated that a level between 0.82 and 1.03 mmol/L (2.0 and 2.5 mg/dl) may be favorable. Their suggestion was based on previous findings that patients who had serum Mg levels within this range had the least degree of renal function deterioration and best glycemic control [2]. Similarly, magnesium supplementation was generally recommended with Mg serum values lower than 0.90 mmol/L, and become necessary starting when values drops lower **than 0.80 mmol/L.**

When Mg substitution is started, the minimum dose to be applied is 600 mg Mg per day, proceed for more than one month, and then continue with a dose that holds the serum Mg value not lower than 0.9 mmol/l [24].Endeavor to apply the above perceptions, magnesium supplementation is suggested for the whole population sample of the present study, whereas it become necessary starting only in 91.1 % of controls and 98.6% of diabetics. However, the exploratory nature of our study, should be again stressed out, and a more comprehensive investigations are required to validate these recommendations. Future studies should concerned with individual variations, including sex, age, occupation, physical activity, as well as Mg contents of food and drinking water.

Conclusion

The tremendous hot climate of ours, can be suggested as an influential cause for increased Mg losses, and may provide a coherent explanation for the exceedingly high prevalence of hypomagnesemia observed in diabetic and control subjects participated in this study. Which therefore may suggest an inevitable requirement for magnesium supplementation to avert hypomagnesemia, not only among diabetics, but as well for controls, particularly through the hot summer episode.

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Table 1: Characteristics of study groups.

Characteristic	Controls	Diabetics	P
N	90	144	_
Age (years)	47.6±16.2	50.1±14.6	NS
BMI (Kg/m^2)	26.7±3.8	28.3±5.1	NS
Gender (M/F)	34/56	58/86	NS
Type of DM : NIDDM	_	122	_
IDDM	_	22	_
Duration (years)	_	8.9±8.0	_
Treatment : Oral agents	_	92	_
Insulin	_	52	_

Table 2: Serum Mg and Albumin concentrations of the study groups.

Parameter		Controls	Diabetics	P
Serum Mg (mmol/L):	Mean ± SD	0.758±0.050	0.569±0.093	<0.001
	Range	0.531- 0.835	0.436- 0.889	_
	Skewness quotient	-2.35	0.80	_
Serum Albumin (g/L):	Mean ± SD	41.5±4.81	43.0±4.52	NS
	Range	35.6- 50.8	30.2- 51.6	_
	Skewness quotient	0.71	-0.45	_

Table 3: Prevalence of Hypomagnesemia among Diabetics and Controls.

Cut-off point	Controls	Diabetics
0.70 mmol/L	10/90 (11.1%)	128/144 (88.9%)
0.75 mmol/L	26/90 (28.9 %)	142/144 (98.6%)
0.80 mmol/L	82/90 (91.1 %)	142/144 (98.6%)
0.90 mmol/L	90/90 (100 %)	144/144 (100%)

Table 4: Prevalence of Hypomagnesemia among Controls in relation to date of sampling.

Date of sampling	Serum Mg in mmol/L (Mean±SD)	Prevalence of Hypomagnesemia (cut-off=0.75mmol/L)
October	0.742±0.06	7/18 (38.9%)
November	0.744±0.07	5/13 (38.5%)
December	0.760±0.03	6/21 (28.6%)
January	0.757±0.05	3/12 (25.0%)
February	0.776±0.03	2/9 (22.2%)
March	0.776±0.04	3/17 (17.6%)
April	---	---
All	0.758±0.05	26/90 (28.9%)

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