Hypomagnesemia in type 2 diabetic Omani patients

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ABSTRACT

الأهداف: دراسة مستويات مصل المغنيسيوم (Mg) لدى مرضى السكري العمانيين من الدرجة الثانية و إيجاد العلاقة بين مستويات المغنيسيوم (Mg) و (HbAIc) و(BMI) وعمر المريض.

الطريقة: أجريت هذه الدراسة بعيادات بوشير الشاملة – مسقط – عمان، ما بين الفترة يناير 2008م حتى أكتوبر 2008م. تمت مقارنة 34 مريض مصاب بالدرجة الثانية من داء السكري مع أفراد غير مصابين بداء السكري وفقاً لمصل المغنيسيوم الكامل. قمنا بتقييم حالة مرضى السكري وفقاً للسن ونوع الجنس و(HbAIc) و(BMI) وأدويتهم. تم استبعاد الأفراد الذين لديهم اسباب خطر الاصابة الواضحة لتدني المغنيسيوم في الدم او ارتفاع المغنيسيوم في الدم.

النتائج: بلغ متوسط مستوى مصل المغنيسيوم الكامل 0.92 ملليمول / لتر (SD 0.06) لدى مجموعة التحكم و 0.81 ملمول / لتر (SD 0.08) في مجموعة السكري وعلى الرغم من أن معظم مرضى السكرلدينا لا يعانون من نقص المغنيسيوم في الدم، إلا ان مستويات مصل المغنيسيوم الكامل لهم كانت منخفضة بشكل معقول أكثر من أفراد مجموعة التحكم. أظهر فحص (T) أن مرضى السكري لدينا لديهم مستوى المغنيسيوم الكامل منخفض بشكل ملحوظ مع اختلاف (0.12 ملمول / لتر) (p=0.000) بغض النظر عن العمر ونوع الجنس. كانت مستويات المغنيسيوم مرتبطة بشكل إيجابي مع العمر ولكن لم يكن هنالك صلة مع (HbAIc) و (BMI).

خاتمة: على الرغم من كون مستويات المغنيسيوم متشاردة وأكثر استناداً من مصل المغنيسيوم الكامل في تقييم نقص المغنيسيوم إلا أنه تم ملاحظة تكرار مستويات مصل المغنيسيوم الكامل المنخفض بين الأفراد الذين يعانون من داء السكري من الدرجة الثانيه. يوصى بالقيام بالمزيد من الدراسات على دور عنصر المغنيسيوم في الوقاية من داء السكري من الدرجة الثانيه ومضاعفاته وكذلك الدراسات المشابهة لداء السكري من الدرجة الأولى.

Objectives: To study serum total magnesium (Mg) levels in type 2 diabetic Omani patients, and to find the relation between Mg levels and glycosylated hemoglobin (HbA1c), body mass index (BMI), and age of the patient.

Methods: This work was carried out at the Bousher Polyclinic, Muscat, Oman from January to October 2008. We compared 34 type 2 diabetic patients with non-diabetic subjects as regards serum total Mg. We assessed diabetic patients in terms of age, gender, HbA1c, BMI, and their medications. Subjects at risk for apparent causes of hypomagnesemia or hypermagnesemia were excluded.

Results: The mean serum total Mg level was 0.92 mmol/L (SD 0.06) in the control subjects, and 0.81 mmol/L (SD 0.08) in the diabetic group, and although almost all our diabetic patients have no hypomagnesemia, their levels of serum total Mg were significantly reduced compared with control subjects. T-test shows that our diabetics have significantly lower total Mg levels with a difference of 0.12 mmol/L (p=0.000) irrespective of age and gender. The Mg levels are positively correlated with age, but no correlation with HbA1c and BMI.

Conclusions: Although ionized and intracellular Mg levels are more reliable than total serum Mg in assessing Mg deficiency, low total serum levels of Mg are frequently seen in individuals with type 2 diabetes. Further studies on the role of Mg supplementation in the prevention of type 2 diabetes mellitus and its complications and similar studies in type 1 diabetes mellitus are recommended.

Saudi Med J 2009; Vol. 30 (7): 897-901

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Received 18th February 2009. Accepted 19th May 2009.

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Magnesium (Mg) is essential for life. Half of total body Mg is found in bone, the other half is found in cells of body tissues and organs and only 1% is found in the blood.[1] It is normally kept in a narrow range from 0.7-1.1 mmol/L,[2] exerts a vasodilator effect,[3] and

it has an important role in neuromuscular transmission.[4] It is an important co-factor in enzymatic reactions involving energy metabolism, glucose transporting, and carbohydrate oxidation, and it is involved in insulin secretion, binding, and activity.[5] It keeps bones strong, supports a healthy immune system, regulates blood sugar, blood pressure, and heart rhythm, and is involved in protein synthesis. Dietary Mg is absorbed in the small intestine and excreted by the kidneys.[6] Green vegetables, some legumes (beans and peas), nuts, seeds, whole unrefined grains, and hard water are good sources of Mg.[7] Magnesium depletion can result from impaired gastrointestinal absorption as in Crohn's disease, chronic vomiting and diarrhea, excessive loss of Mg in urine due to drugs like, diuretics, antibiotics (gentamicin, and amphotericin) and anti-neoplastic medication, such as cisplatin, or due to osmotic diuresis caused by glucosuria, mannitol, and urea.[8] Low blood levels of Mg occur in 30-60% of alcoholics, and in nearly 90% of patients experiencing alcohol withdrawal.[9] Endocrinal causes of Mg depletion include pregnancy, primary aldosteronism, hypoparathyroidism, hyperthyroidism, and hungry bone syndrome. Other causes include excessive lactation, extracellular volume expansion, IV fluid administration, or increased Mg requirement as in aging, stress, and various disease states.[8] Magnesium plays an important role in carbohydrate metabolism. It may influence the release and activity of insulin. Hypomagnesemia is frequently seen in individuals with type 2 diabetes,[10] and both mean plasma, and intracellular free Mg (IC Mg) levels are lower in patients with diabetes than in the general population.[11] Magnesium deficiency in obese children is associated with the development of insulin resistance.[12] It had been observed that nearly 25% of diabetic patients had hypomagnesemia, which had been correlated with both poor diabetic control and insulin resistance in nondiabetic elderly patients.[13] This link is strengthened by the fact that some antidiabetic drugs appear to increase Mg levels. Metformin, for example, raises Mg levels in the liver and pioglitazone, increases free Mg concentration in adipocytes.[14] Other authors concluded that up to 80% of type 2 diabetics have a Mg deficiency.[15] Reasons for hypomagnesemia in diabetic patients include low magnesium in the diet, high renal excretion of Mg, insensitivity to insulin that affects Mg transport, diuretics that promotes Mg wasting,[14] glucose-induced osmotic diuresis and insulin therapy in the course of diabetes ketoacidosis (DKA),[16] and it is associated with severe retinopathy,[17] and proteinuria.[18] According to the American Diabetes Association (ADA), serum Mg levels should be measured in patients who have diabetes and suffer heart attacks, heart failure, DKA, calcium deficiency, potassium deficiency or pregnancy, or with ethanol abuse, long-term parenteral nutrition, long-term use of certain drugs (such as diuretics, digoxin, or aminoglycosides).[14] Magnesium depletion is common in poorly controlled type 2 diabetic patients, especially those with neuropathy or coronary artery disease.[19] The Mg depletion leads to a more rapid decline of renal function in type 2 diabetic patients,[18] and is associated with development of neuropathy and abnormal platelet activity, both of which are risk factors for feet ulcers.[20] A higher intake of Mg reduces the risk of type 2 diabetes, especially in overweight women.[21,22] More prolonged use of higher doses of Mg is needed to improve control or prevent chronic complications in type 2 diabetic patients.[19] Magnesium supplementation improved metabolic control of diabetes, as suggested by lower glycosylated hemoglobin (HbA1C) levels,[23] and had excellent therapeutic effects in all forms of arterial diseases as peripheral vascular disease, angina, heart attack, and non-hemorrhagic cerebral vascular disease.[24] The purpose of this study is to compare serum total Mg levels between type 2 diabetic patients and healthy control subjects, and to study the relation between Mg levels and glycemic control, body mass index (BMI), and age of the patient.

Methods. This work was carried out at Bousher Polyclinic, Muscat, Oman from January to October 2008. This was an ex-post-facto study, where we studied 34 Omani patients with type 2 diabetes mellitus (men 17, women 17) treated by diet or diet plus oral antidiabetic drugs or insulin during follow up at the Bousher Polyclinic, and compared them to 40 Omani healthy subjects (men 20, women 20) with no history of any chronic illness as a control group. Patients in the study group were the eligible patients seen at the clinic during the defined study period. In the study, we compared diabetic patients with non-diabetic control subjects in terms of serum total Mg. Inside the diabetic group, we assessed them in terms of age, gender, serum MG, glycemic control (HbA1c), BMI, and medications for diabetes, hypertension, and hypercholesterolemia as well as other medications. Venous whole blood samples were taken, for measurement of serum Mg using the colorimetric method. The normal range of Mg in our laboratory is 0.65-1.25 mmol/L, and hypomagnesemia was defined as serum Mg levels <0.66 mmol/L (1.6 mg/dL). To reduce source of bias, patients at risk for apparent causes of hypomagnesemia, or with reduced renal function were excluded. In addition, subjects receiving Mg supplementation (antacids or laxatives) were not included. The study is ethically approved by the Regional Research and Ethics Committee, after getting the patient's informed consents. Results were presented using the means and standard deviations or proportions as appropriate. Comparison of the independent groups was performed using Student's t-test, or Chi-square test (x^2) as appropriate, and a p-value of <0.05 defined

the level of statistical significance. Regression analysis was used to adjust the differences between groups for other co-variables. Pearson correlation coefficient was estimated to test correlations among variables of the study.

Results: There were no significant demographic distinctions between the type 2 diabetic (n=34) and control (n=40) subjects. The age of diabetic patients ranged from 22-73 years, with a mean of 51.06 years and standard deviation of 11.87 years. While the age of controls ranged from 15-78 years, with a mean of 47.75 years and a standard deviation of 13.63 years. The difference of age between the 2 groups was 4.3 years (95% confidence interval of the difference was -10.3 to 1.7 years, showing no statistical significant difference as regards to age [p=0.606] (**Table 1**). Also, both groups were similar with regards to gender distribution (p=1.0). The mean Mg level in the control subjects was 0.92 mmol/L (SD 0.06). The mean Mg level in the diabetic group was 0.81 mmol/L (SD 0.08). The difference of Mg between the 2 groups was 0.12 mmol/L (95% confidence interval of the difference was 0.08-0.15 mmol/L), and the student's t-test showed that diabetics have significantly lower Mg level (p=0.000) irrespective of age and gender (**Figure 1**). The Mg levels are positively correlated with age (n=34, r=0.359, p=0.037), but there was no correlation with glycemic control (n=29, r=0.049, p=0.799), and BMI (n=31, r=0.2, p=0.281), as shown in **Table 2** and **Figures 1 & 2**.

Table 1 - Comparison between Type II diabetics and controls (mean ± standard deviation).

Variables	Controls (n=40)	Type II diabetics (n=34)	Significance t-test	*P*-value*
Magnesium (mmol/l)	0.92 ± 0.065	0.81 ± 0.076	t = 7.18	0.000†
Age (years)	46.8 ± 13.6	51.05 ± 11.9	t= -1.347	0.606
Gender (males) (%)	50	50	X^2 = 0	0.1

*Significant, †Significance testing was performed using student's t-test for magnesium and age and chi-square for gender.

Table 2 - Regression analysis using magnesium levels as the outcome variable.

Variables	β coefficient ± standard error	*P*-value
Constant	0.865 ± 0.032	
Diabetics versus controls	-0.123 ± 0.016	0.000 *
Age (years)	0.001 ± 0.001	0.033 *
Gender	-0.012 ± 0.016	0.471

R^2 = 0.456, *significant. Results of regression show that both type of patient (diabetic versus controls) and age significantly affects magnesium levels

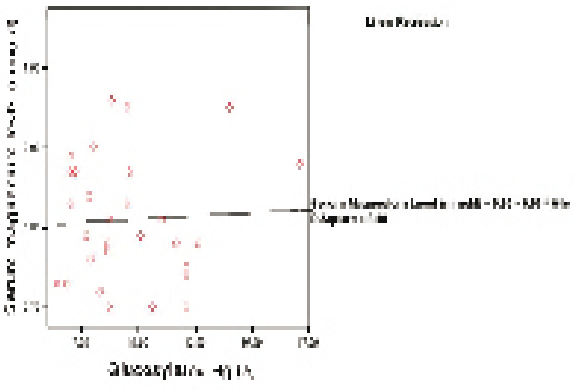

Figure 1 - The relations between serum magnesium and hemoglobin Alc.

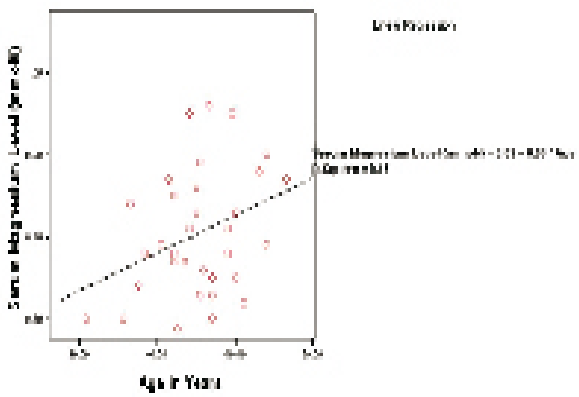

Figure 2 - The relations between serum magnesium and age.

Discussion. Magnesium deficiency decreases insulin-mediated glucose disposal in non-diabetic subjects, which is consistent with insulin resistance,[25] has been associated with type 2 diabetes, and may reduce insulin sensitivity and impair glucose tolerance.[26] Many studies have shown that diabetic patients have lower mean plasma and IC Mg levels than the general population, but most have lower levels of free intracellular Mg only, and this can be explained by the fact that intracellular free Mg is a more sensitive marker in people with diabetes and insulin resistance than plasma Mg levels.[14] The serum Mg level is not a reliable way to determine total body Mg depletion because only a small fraction of Mg in the body is extracellular, and an ionized Mg level should be considered in assessing Mg depletion. So, the total body Mg may be depleted markedly before the serum level drops,[27] and Mg deficiency can exist even when Mg is normal.[28] In one study, the levels of serum ionized Mg and IC Mg were significantly lower in 22 untreated patients with type 2 diabetes and mild hyperglycemia than they were in 30 healthy control subjects (p<0.001). The serum total Mg was not reduced. Furthermore, a close relationship was observed between serum ionized Mg and IC Mg (r=0.728, p<0.001). The investigator contributes that Mg may be a strong predisposing factor for the development of the excess cardiovascular morbidity associated with diabetes.[11] Another study evaluated 27 patients with poorly controlled type 2 diabetes. It had been observed that decreased serum was found in 75% and IC Mg depletion found in 30.8% of patients. The IC Mg was negatively correlated with BMI and HbA1c. The homeostasis model assessment for insulin resistance was higher than 3.0 in 59.2% of patients, and it was negatively correlated with IC Mg levels, although statistically insignificant. Despite the small number of patients, this study concluded that Mg depletion is frequent in patients with diabetes and its correlation with insulin resistance should be studied further.[29] In our study, the mean serum total Mg level was lower in the diabetic group, and although almost all our diabetic patients have no hypomagnesemia, their levels of serum total Mg were significantly reduced compared with levels in control subjects. T-test shows that our diabetics have significantly lower total Mg levels, irrespective of age and gender. As mentioned before, some studies showed depleted serum Mg levels in type 2 diabetic patients[29] like our study, and others mentioned deficiency of ionized and IC Mg only.[11] In our study, serum total Mg levels in diabetics are not correlated with HBA1c, however, in another study although there were negative correlations between IC Mg levels and HBA1c, the same study did not report any correlation between serum total Mg and HbA1c.[29] This difference is because serum total Mg was assessed in our study, and IC Mg was assessed in the other study. The IC Mg is a more sensitive marker in people with diabetes and insulin resistance than plasma Mg levels. The Mg levels in our type 2 diabetic patients are positively correlated with age, although it was mentioned that Mg becomes depleted with aging.[8] This difference can also be attributed to measurement of total serum Mg, and not IC Mg, and Mg deficiency can exist even when Mg is normal.[28] Our study is limited as ionized and IC Mg was not assessed, and the effects of Mg supplementation were not studied.

In conclusion, although ionized and IC Mg levels are more reliable than total serum Mg in assessing Mg deficiency, low total serum levels of Mg are frequently seen in individuals with type 2 diabetes. Similar studies in type 1 DM are recommended. Further studies on Mg supplementation in the prevention of type 2 diabetes mellitus and its complications are warranted.

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Related topics

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