Iraq JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: Iraqi_jms_alnahrain@yahoo.com
http://www.colmed-alnahrain.edu.iq/

Hypomagnesemia and Obesity in Relation to Insulin Resistance and Glycemic Control in Type 2 Diabetic Patients

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Abstract

Background Obesity and diabetes mellitus are the most common health problems with both macro- and micro-vascular complications and consequences of end organ damage. The alteration in trace elements could have deleterious effects on the health of the diabetic patients. Magnesium (Mg) is an important factor for enzymes involved in carbohydrate metabolism and good evidence suggests the presence of an important role for hypomagnesaemia in insulin resistance and metabolic control.

Objective To evaluate the relation of hypomagnesaemia with insulin resistance (IR), and glycemic control in obese and non obese diabetic people.

Methods The study included 65 patients with type 2 diabetes mellitus (Type 2 DM) who were all on oral hypoglycemic drugs only. They were divided according to their body mass index (BMI) and the presence or absence urinary protein, into three groups. The results were compared with those of another 52 normal controls grouped on the same bases.

Fasting venous blood specimens were aspirated for the measurement of glycated hemoglobin (HbA1c) by A1c variant reader, glucose, urea, creatinine, protein and albumin by routine enzymatic chemical and colorimetric methods, insulin by immuno-enzymometric assay and magnesium by atomic absorption spectrophotometer, while Mg ions and Quicki test (for IR) were estimated by calculations. Morning urine specimens from each subject were examined for the presence of protein by dip Stick.

Results As compared with the healthy controls the study reveals a significant reduction in Quicki test (increased IR) and low serum Mg^{2+} in all diabetic patients, with the presence of a significant positive correlation between the two parameters. Serum Mg^{2+} was significantly lower in the normal weight non proteinuric diabetics than the normal weight controls. In diabetic patients the presence of proteinuria caused a further reduction in serum Mg^{2+}. Glycated hemoglobin (HbA1c) negatively correlated with total serum Mg^{2+} in all diabetics and their controls.

Conclusions Insulin resistance and poor glycemic control are important events associating hypomagnesaemia in type 2 DM. Proteinuria is an additional factor which may aggravate hypomagnesaemia, which involves both ionized and total Mg to the same degree.

Key words type 2 diabetes mellitus, magnesium, Insulin resistance, HbA1C, proteinuria

Introduction

Obesity is the most common cause of insulin resistance (IR) which does not necessarily lead to diabetes [(1,2)].

Magnesium (Mg) is an important factor for enzymes involved in carbohydrate metabolism. A strong relationship between Mg^{2+} and insulin action has been reported in adults [(3)], where low serum and intracellular where low serum and intracellular Mg^{2+} concentrations were found to be associated with IR, impaired glucose tolerance and increased insulin secretion with increased risk of Type 2 DM [(4)].

The present study deals with phenomenon of hypomagnesaemia and its relation to insulin

resistance in obesity and diabetes mellitus with special reference to the effect of proteinuria.

Methods

A- Patients:

Sixty five type 2 diabetics with age range of 19-53 years attending the National Diabetes Centre (NDC) during the periods from June to September 2008 were enrolled in the study. They were all on oral hypoglycemic drugs only.

They were divided according to their body mass index (BMI) and urinary protein into 3 groups:

1. Normal weight diabetics (BMI < 25) with no proteinuria (N-NPU) included 31 patients.
2. Over weight - obese diabetics (BMI > 25) with no proteinuria (O-NPU) included 24 patients.
3. Over weight - obese diabetics (BMI > 25) with proteinuria (O–PU) included 10 patients.

B- Controls:

Comprised 52 healthy subjects of matching age (20 -50 years) and sex were included in the study and grouped as in the patient group into:

1. Normal weight controls (NC) included 26 patients.
2. Overweight - obese controls (OC) included 26 patients.

C- Blood specimens:

Ten milliliters (10 ml) of venous blood were aspirated from each subject involved in the study after an overnight fast. Two mls were added to an EDTA tube for the measurement of glycated hemoglobin (HbA1c) and the rest was used for the measurement of other study parameters.

D- Methods:

Serum glucose, urea and creatinine were measured by routine enzymatic method, total protein by Biuret method [5], insulin by immunoenzymometric assay, HbA1c by ion exchange high performance liquid chromatography using Bio-Rad Variant HbA1C program, and total Mg^{2+} by Atomic Absorption Spectrophotometer after dilution by Lanthinium chloride (1:20), while serum Mg ions were calculated from the chart of (Willis & Sunderman 1952) [6]. Insulin resistance (IR) was estimated by Quicki test (the reverse index of IR) through the following formula:

Quicki test = 1/ [log (FI) + log (FG) 7.

Where FI = fasting insulin, and FG = fasting glucose.

Results

Table 1 shows significantly higher serum glucose in the diabetics as compared with their controls, significantly higher serum insulin in the diabetics than their controls and in the overweight-obese than the normal weight diabetics.

Quicki test (the reverse index of IR) shows a significant reduction in the diabetics being lower in the overweight-obese than the normal weight diabetics.

For serum total Mg and Mg^{2+}, there was a significant reduction in the diabetics as compared with their controls, with no significant change in the ratio of Mg^{2+}/ Mg.

Serum protein was significantly lower in the proteinuric diabetic group as compared with others.

Serum total Mg shows clearly a significant positive correlation with Quicki test, and a significant negative correlation with HbA1C in both control and diabetic groups (Figures 1 and 2).

Table 1: Serum fasting glucose(FG), insulin, glycated hemoglobin(HbA1c), QUICKI test, total Mg, Mg^{2+}, Mg^{2+}/ Mg ratio and total protein in type 2 diabetics (T2DM) and their healthy controls

Blood tests	Controls, n=52		T2DM , n=65		
	NC n=26	OC n=26	O- NPU n = 31	N -NPU N= 24	O - PU N = 10
FG mg / dL	80.7±18.89	96.8±9.73	184.84±75.4**	237.6±96.64**	188.3±38.9**
Insulin (µmol/L)	5.73±1.73	8.6±1.53	19.46±13.94**	9.195±9.73**	14.85±11.4**
QUICKI test	0.382±0.029	0.343±0.009	0.297±0.033**	0.328±0.047**	0.307±0.038*
HbA1c %	4.71±0.75	5.45±0.59	8.43±2.29**	8.43±2.29**	10.97±2.93**
Total Mg mmo/l	0.901±0.092	0.79±0.093	0.56±0.11*	0.666±0.112*	0.501±0.106**
Mg^{2+} (mmo/l)	0.602±0.064	0.54±0.093	0.38±0.09	0.451±0.073	0.352±0.084*
Mg^{2+}/Mg ratio	0.672±0.074	0.693±0.094	0.68±0.09	0.68±0.057	0.7±0.047
TP (g/dl)	6.72±0.42	6.45±0.45	6.44±0.46	6.36±0.45	5.56±0.53*

NC: Normal weight controls, OC: Overweight – obese controls, N- NPU: Normal weight non proteinuric diabetics, O-NPU: Over weight – Obese non proteinuric diabetics, O-PU = Over weight - obese proteinuric diabetics, TP: total protein, * $p < 0.05$, ** $p < 0.01$

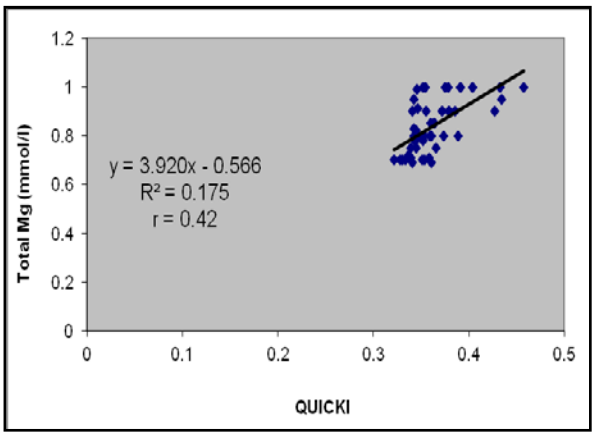

Figure 1a. Correlation between serum total Mg and QUICKI test in control group (n=52), r = 0.42, $p < 0.001$

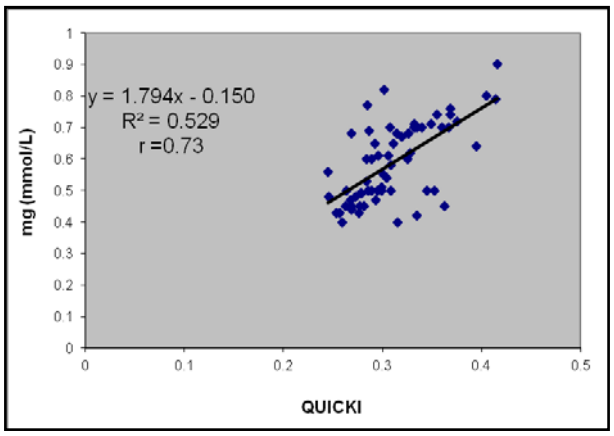

Figure 1b. Correlation between serum total Mg and QUICKI test in the diabetic group (n=65) r= 0.73, $p < 0.001$

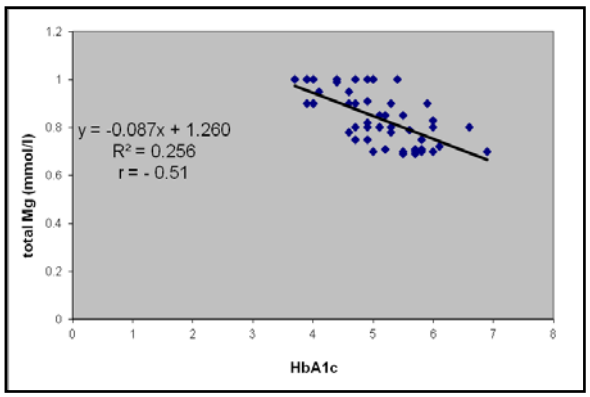

Figure 2a. Correlation between serum total Mg and QUICKI test in control group (n = 52) r= 0.51, $p < 0.001$

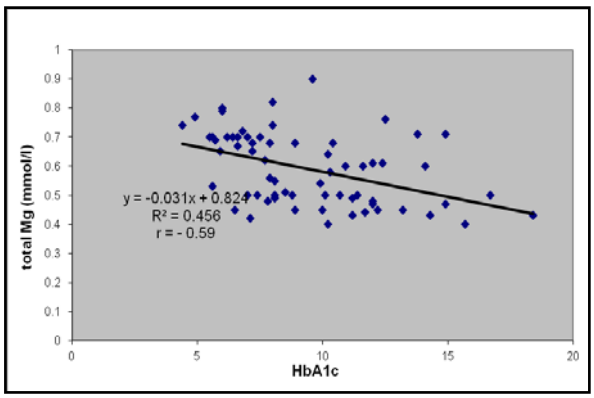

Figure 2: (b) Correlation between serum total Mg^{2+} and HbA1c in diabetic group (n=65), r = 0, 59, $p < 0.001$

Discussion

In the present results the significant increase in IR (presented by the decrease in QUICKI test) with increasing BMI of the obese Type 2DM patients when compared with their matching control groups agrees with previous reports [1,8].

Perhaps the common cause of insulin resistance is an excessive amount of fat in the body [1]. In obese person, however, too much fatty acid is released and tissues become overloaded with fat. Thus obese people acquire excess fat in their tissues, particularly muscle and liver as well as in adipose tissues. This excess tissue fat leads to IR [9].

Increased fatty acid concentration has also been implicated to increase the rate of their oxidation resulting in an increase in the production of acetyl-COA in the mitochondria and this, in turn, will inhibit pyruvate dehydrogenase, the rate limiting enzyme of glucose oxidation, and so interferes with glucose utilization in addition to the suppressive effect of fatty acids on pancreatic cell insulin secretion [10,11].

Hypomagnesaemia in patients with diabetes may result from poor oral intake, poor gastrointestinal absorption and enhanced renal magnesium excretion [12,13].

Reduced tubular reabsorption may be another cause, because insulin has been implicated in enhancing Mg reabsorption at the thick ascending loop (TAL), insulin deficiency or resistance in the diabetic state can promote Mg wasting at this nephron segment [14,15] .

In addition to the above causes various metabolic disturbances that are associated with diabetes also have been previously suggested to promote urinary Mg excretion [16].

Metabolic acidosis, In addition to its role in increasing serum ionized Mg concentration and, hence, ultra filterable Mg load for renal excretion, has been also suggested to enhance protonation of the Mg channel in the distal convoluted tubules and subsequent inhibition of cellular Mg uptake [16,17]. The common use of diuretics, and their type, among patients with diabetes also may contribute to magnesuria and its degree [18].

Finally, the more common use of antibiotics and antifungal agents such as amino glycosides and amphotericin in patients with diabetes may also contribute to renal Mg wasting ([19].

The interrelation of serum Mg and diabetes has been reported by many previous studies. Some showed that Caucasian men with serum Mg (0.58 mmol/L) had a two fold increase in incidence of T2DM compared to those with Mg concentration (0.78 mmol/L) [20]. The mechanism by which Mg deficiency may lead to IR has not been fully elucidated; however, Mg is a cofactor for multiple enzymes involved in carbohydrate metabolism [21].

The presence of a significant positive correlation between QUICKI test and total serum Mg may be secondary to a decrease in dietary intake of Mg [22]. However this low Mg may be associated with hyperinsulinemia, decreased insulin mediated glucose disposal and metabolic syndrome [23, 24].

The association of low Mg^{2+} with IR in the present T2DM patients confirms previous study [25], who suggested that a loss in Mg^{2+} and Hypomagnesaemia would contribute to the cardiovascular disease. This study seems to be in agreement with this (ionic hypothesis) and further confirmed that an alteration in Mg metabolism play a key pathophysiological role in the metabolic syndrome or IR [22,26] but was in contrast with others who showed that obesity was not associated with hypomagnesaemia [24].

Other reports showed that oral Mg supplementation had improved insulin sensitivity and metabolic control in T2DM [27].

Moreover the present study shows a negative association between Mg^{2+}/Mg ratio and serum total protein in the control and T2DM groups. One of the reports [28] showed that an increased serum protein will lead to reduced

serum Mg^{2+} and cause low Mg^{2+}/Mg ratio as seen in this study.

As concerning the negative correlation of serum Mg^{2+} with HbA1c in this study, HbA1c was found to decrease Mg^{2+} when it was above 7% and, hence, will lead to a decrease in Mg^{2+}/Mg ratio. This result is in agreement with a report suggested that putative role of increased urinary Mg loss may be linked to a prolonged hyperglycemic control state [(29)], and also in agreement with others who showed the benefits of oral supplementation of Mg as an adjuvant therapy for fasting glucose and HbA1c [(27)]. Moreover, the group of T2DM with proteinuria who had an increased Mg loss could be invoked to explain the low concentration of serum Mg^{2+} observed in patients with HbA1c greater than 7% in this case, consequently hypomagnesaemia was claimed to associate with coronary heart disease [(30)], or to promote a decline in renal function of the diabetics [(28)], which makes it an important factor to be considered in various metabolic studies.

At last it could be concluded that changes in total and ionized Mg in diabetics associate insulin resistance and glycemic control, while proteinuria is an additional factor which aggregates or worsen Mg loss and hypomagnesaemia.

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Received: 5th May 2010, Accepted: 6th