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Serum and Urine in a Cohort of Adult Patients with *Diabetes Mellitus*

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ABSTRACT. This is a cross-sectional study on 37 randomly selected patients with *Diabetes mellitus*. Serum magnesium, calcium, potassium, and HbA_{1c}, together with 24 hour urine collection for magnesium (MG) were obtained from these patients. Fifteen healthy non-diabetic subjects served as control. The mean serum Mg in this diabetic cohort was 0.74 mmol/L, compared to 0.91 mmol/L of the non-diabetic control subjects (P value < 0.001). Nine patients (24%) from the diabetic cohort were significantly hypomagnesemic range. The low mean serum Mg was associated with poor glycemic control; mean HbA_{1c} was 11.2%. The mean 24 h urinary Mg in this diabetic cohort was 4.15 mmol which is relatively high for the level of hypomagnesemia present suggesting increased urinary Mg excretion as the cause for such hypomagnesemia. These patients had no symptoms attributable to hypomagnesemia, and they had no associated abnormalities in serum potassium and calcium. Mean serum potassium was 4.49 mmol/L & mean serum calcium of 2.42 mmol/L (<0.70 mmol/L) while none of the controls had serum Mg outside the normal range. Our study shows high prevalence of asymptomatic hypomagnesemia with increased urinary Mg excretion in a cohort of poorly controlled diabetics. This was not associated with abnormalities in serum potassium or calcium as it is the case in other causes of hypomagnesemia.

Keywords: *Diabetes mellitus*, Hypomagnesemia, Magnesium, Saudi Arabia.

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Introduction

Magnesium (Mg^{++}) is a vital intracellur cation involved in many enzymatic reactions as a co factor to ATPase. It is the second most abundant intracellular cation, next only to potassium[1]. Hypomagnesemia was found in at least 25% of diabetics[2] and becomes more evident after correction of diabetic ketoacidosis, as it may occur in up to 55% of treated cases[3]. Moreover, a low ionized and a low, free intracelular Mg were found in diabetic patients despite a normal serum Mg level[4], suggesting a state of Mg deficiency in diabetics. There is an inverse relationship between the height of blood sugar level and the degree of hypomagnesemia[5]. This is clearly shown by the "surrogate" of glycemic control, *i.e.*, glycosylated hemoglobin (HbA_{1c})[6]. There are different factors which interplay to cause Mg deficiency and hypomagneseia in diabetics[1], such as, decrease intake and vomiting in diabetic gastroparesis, diarrhea due to automomic neuropathy and most importantly, excessive renal Mg wasting[5,7].

Diabetes mellitus is a prevalent disease in Saudi Arabia. In a recent study in Riyadh, Saudi Arabia[8], it accounted for 16% of the male and 12.3% of the female population above 30 years of age. To the best of our knowledge, there is no local data which indicates the prevalence of hypomagnesemia in the Saudi diabetic population.

This cross-sectional study was conducted to study the prevalence of hypomagnesemia in a cohort of Saudi diabetic population and to determine whether this is related to the degree of glycemic control. This study will also look to whether hypomagnesemia is associated with an increase in urinary Mg secretion.

Patients and Methods

A cohort of 37 randomly selected diabetics, 15 years of age and older, who were attending a diabetes clinic in a tertiary care hospital in Jeddah. Prior to enrollment, all patients were subjected to a thorough history and physical examination together with preliminary investigations to confirm the eligibility criteria. Patients were excluded from the study if they were known to have hypomagnesemia, and or if they have any risk factor for hypomagnesemia, other than being diabetic. Patients were also entered in the study if they were on Mg supplementation. All patients entered in the study should have normal liver enzymes, bilirubin, creatinine, T4 and TSH.

Patients who consented to be in the study were subjected to undergo the following laboratory investigations: serum magnesium, calcium, potassium, glucose, total protein, albumen, creatinine and HbA_{1c}. These tests were done while the patients were fasting and before taking their morning dose of insulin or oral hypoglycemic drugs. Twenty-four urine collections were obtained for magnesium and creatinine. Spot urine analysis for ketones were obtained from all patients.

A control group of 15 healthy non-diabetic volunteers who fulfilled the inclusion criteria were selected. Fasting blood for Mg, calcium, potassium, and creatinine were ob-

tained from this control group. Serum and urinary Mg and calcium were analyzed using Cynchron CX(R) of Beckman. Glycosylated Hemoglobin (HbA_{1c}) assay is measured with iron capture assay of Abbot IMx(R). Data was collected prospectively and were analyzed using the SPSS version 7.5. The significance (P value) between means of continuous variables were examined by the t-test. The relation between serum magnesium level and urinary magnesium excretion and between serum Mg level and Hgb_{1c} were ascertained by the Pearson's correlation coefficient (r). $P < 0.05$ was considered statistically significant.

Results

Sixteen male (43%) and 21 female (57%) patients were included in the study with the mean age being 54 years SD+/- 6 (range 6-27 years). Twenty-two (59%) were normotensive while 15 (39%) were known to be hypertensive. None of these patients were receiving medication that interfered with their Mg metabolism or excretion.

The mean serum Mg in this diabetic cohort was 0.74 mmol/L (range 0.57-0.86) (Table 1). The mean serum Mg in the control group was 0.91 mmol/L (range 0.85-1.11). The difference between both groups was highly statistically significant (P value < 0.001). Significant hypomagnesemia (<0.70 mmol/L) was found in 9 patients (24%) in the diabetic group, while none of the control group had serum Mg which is outside the normal range (0.70-1.15 mmol/L). This diabetic cohort was found to have poor glycemic control as indicated by the high mean HbA_{1c} of 11.2% (range 7.5-18.1%). There was no correlation between the serum Mg and HbA_{1c}, r = 0.09 and this was not statistically significant (P=0.32).

TABLE 1. Summary of clinical and laboratory data of the diabetic cohort.

Variable	Mean	Range
Age (years)	54 year (SD +/- 13)	21-80
Duration of diabetes	12 year (SD +/- 6)	6-27
Serum Mg	0.74 mmol/L (+/- 0.068)	0.57-0.86
Urine Mg	4.15 mmol/L (+/- 1.8)	1.75-11.0
Serum potassium	4.16 mmol/L (+/- 0.36)	3.9-5.2
Serum calcium	2.42 mmol/L (+/- 0.10)	2.26-2.69
HbA_{1c}	11.2 (SD +/-2.6)	7.5-18.1

All patients underwent 25 hour urinary collection for Mg. The mean urinary Mg excretion was 4.15 mmol/24h SD +/-1.8 (1.75-11.02 range). No correlation could be found between the level of serum Mg and the level of urinary Mg excretion as r =0.016, which is statistically not significant (P-value = 0.46). All of the diabetic patients had negative urinary ketones and none of them required hospital admission for treatment of

diabetic ketoacidosis. None of the diabetic patients had symptoms which could be attributed to hypomagnesemia. Similarly, there were no associated abnormalities in serum potassium and serum calcium. Mean serum potassium was 4.49 mmol/L SD=/- 0.36 (3.9-5.2 range) and mean serum calcium was 2.42 mmol/L SD=/- 0.1 (2.26-2.69 range).

Discussion

Our study showed a high prevalence of hypomagnesemia in this cohort of randomly selected diabetics, occurring in 24% of the patients. Mather *et al*[2]showed similar results, while other investigators[5] reported a higher prevalence rate of 39%. The possible explanation of this difference is the conflict on what cut-off serum Mg level which represents hypomagnesemia. Nevertheless, mean serum Mg in our diabetic cohort was significantly lower than the non-diabetic control subjects. As serum Mg only constitutes 0.3% of the total body Mg content, there is significant controversy regarding the best method to assess magnesium status in patients with Mg deficiency. It is fact that patients could have normal serum Mg levels while they are Mg deficient [1,9]. There is also controversy regarding the cut-off level which constitutes a low serum Mg. Nevertheless, the presence of low serum Mg<0.70 mmol/L usually indicates significant Mg deficiency[1]. Attempts to find an inverse correlation between the level of serum Mg and the level of Hb_{1c} was not successful. This is probably due to the fact that all of our patients had poor glycemic control making inter-group comparison difficult. This is best explained by the fact that none of our diabetic patients had normal HbA_{1c}.

The causes of hypomagnesemia in diabetics are of a multifactorial nature. The passive magnesium re-absorption in the Thick Ascending Loop of Henle (TAL) is dependent on the positive transmembrane potential created by the active NaCl absorption [10,11]. Conceptually, abolishment of this potential by the osmotic diuresis brought abut by the hyperglycemia, will result in an excessive renal magnesium loss. Furthermore, insulin administration was found to increase the urinary excretion of Mg in normal non-diabetic volunteers[12]. This has been achieved in the absence of hyperglycemia. Through unclear mechanisms, acidosis and phosphate depletion may enhance the urinary excretion of magnesium[1,11], and these two conditions are frequently encountered in diabetics. Recent works[13,14] have suggested that insulin enhances free Mg entry into the cells. This might explain the higher prevalence of hypomagnesemia in patients treated for diabetic ketoacidosis[3].

The kidney is capable of conserving the urinary Mg to less than 0.5 mol/24 hour if faced with decreased intake of Mg or loss of Mg from sites other than the kidneys [1,11,13]. Sutton and Domorongkitchaiborn[15] have suggested that if a hypomagnesemic patient excretes more than 1.0 mol of Mg in 24 hours urine collection, the cause of hypomagnesemia has to be the excessive renal wasting of Mg. In our patients the mean 24 hour urinary excretion of Mg is significantly high (4.15 mmol) for the degree of hypomagnesemia they have, suggesting enhanced renal Mg wasting. Fur-

thermore, all of our patients were studied while they were visiting the out-patient department and none of them had ketosis or were treated for diabetic ketoacidosis. This might imply that the excessive renal wasting of Mg is probably the main mechanism for the hypomagnesemia.

Electrolyte disturbance in the form of hypokalemia and hypocalcemia are frequently seen in hypomagnesemic patients and correction of such abnormalities is not possible unless magnesium is first replenished[1]. Hypocalcemia has been reported in 33% of hypomagnesemic ICU patients[16]. It probably results from the combination of impaired release of PTH and the end-organ resistance to PTH[1]. Hypokalemis is highly predicative of the hypomagnesemia, and 42% of hospitalized patients with hypokalemia has concomitant hypomagnesemia[17]. Experimental human magnesium deficiency has resulted in hypokalemia and the increase of urinary potassium excretion [18]. These studies were done on a non-diabetic population. Serum potassium and calcium were normal in our diabetic cohort. To the best of our knowledge, this has not been reported on such a population. The cause of unexpected normal serum calcium and potassium in our diabetic patients is not clear. Diabetes is a well known cause for hyporeninemic hypoaldosteronemic renal tubular acidosis, which usually manifests with hyperkalemia. Despite that all of our patients had normal serum creatinine, and we did not intend to investigate the tubular function in this cohort of patients, we cannot rule out a possible compensatory role played by a sub-clinical tubular dysfunction. So it is tempting to speculate abnormal renal handling of potassium and calcium in diabetics as a plausible explanation for such findings. Hypomagnesemia and magnesium deficiency are known to cause a wide variety of symptoms and clinical presentations resulting from neuromuscular irritability and cardiac arrhythmia[1]. Our patients were totally asymptomatic, and had no abnormal manifestations attributable to magnesium deficiency. Symptomatic hypomagnesemia was thought to occur if hypocalcemia and or hypokalemia are present[19] and this might explain the absence of symptoms in our patient population.

Mg deficiency was implicated in the development of many vascular disorders which include: ischemic heart disease[20], hypertension[21], and pre-eclampsia[22]. Similarly, *Diabetes mellitus* is a major risk factor in many vascular disorders which includes ischemic, cerebral and peripheral vascular disease. Some investigators[23] suggested that reduced intracellular Mg is the missing link to explain the epidemiological association between NIDDM and hypertension. In a recent review by Altura & Altura[24] extending this link between diverse cardiovascular risk factors and atherosclerosis to be related to Mg defiency. This is probably explained by the fact that experimental Mg deficiency has resulted into vasospasm, increased vascular reactivity, elevated $[Ca^{2+}]i$, formation of proinflammatory agents and free oxygen radicals, and enhanced platelets aggregation[24]. Furthermore, insulin resistance and diabetic complications have been linked to the state of magnesium deficiency. These facts prompted the American Diabetic Association to publish a consensus statement suggesting that diabetic patients with hypomagnesemia are to receive magnesium supplementation[25]. For all of these, it is imperative to consider measuring serum Mg levels in diabetic patients as hypo-

magnesemia might have some impact on diabetes control or on diabetic complications.

We conclude that hypomagnesemia is present in a significant number of diabetics probably resulting from enhanced renal Mg loss due to the osmotic effect of hyperglycemia. To the best of our knowledge, this is the first study in Saudi Arabia which tackles this problem. Further studies are needed to elucidate the association between this cation abnormality and the different diabetic complications. Further studies are needed to study the impact of magnesium supplementation on the degree of glycemic control and on the associated diabetic complications.

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مستوى المغنزيوم في المصل والبول لدى طائفة من مرضى داء السكري البالغين

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المستخلص. تهدف هذه الدراسة إلى تحديدانتشار مستوى انخفاض المغنيزيوم في الدم لدى طائفة من المرضي البالغين والمصابين بمرض الداء السكري والبحث فيما إذا كان سببه زيادة إفراغ المغنزيوم في البول. تم إجراء دراسة مقطعية جزئية على سبعة وثلاثون مريضاً تم اختيارهم بطريقة عشوائية وذلك من المرضى الذين يراجعون عيادة الداء السكري في مستشفى الملك فهد العسكري بجدة. لقد تم قياس مستوى المغنزيوم والكالسيوم والبوتاسيوم وغليكوزيد خضاب الدم مع قياس مستوى المغنزيوم في البول المجمع لمدة ٢٤ ساعة. وجد أن متوسط مستوى المغنزيوم في الدم لدى طائفة مرضى الداء السكري هو ٠,٧٤ مللي مول لكل لتر مقارنة بالأشخاص الطبيعيين والغير مصابين بمرض الداء السكري حيث وجد المتوسط لديهم ٠,٩١ مللي مول لكل لتر وهذه النتيجة ذات قيمة إحصائية معتدة عالية. كما وجد أن عدد المرضى والذين لديهم انخفاض في مستوى المغنزيوم في الدم هو ٩ مرضى أي ما يساوي ٢٤٪ من العينة العشوائية، كما وجد أن العينة تعاني من عدم انضباط مستوى السكر في الدم لزيادة نسبة غليكوزيد خضاب االدم إلى متوسط ١١,٢٪. أما متوسط افراغ المغنزيوم في البول فقد كان مرتفعاً نسبياً إلى ٤,١٥ مول في خلال الأربع وعشرين ساعة. إن هؤلاء المرضى لم يكونوا يعانوا من أعراض ناتجة عن انخفاض مستوى المغنزيوم في الدم كما كان متوسط مستوى البوتاسيوم ٤,٤٩ مللي مول لكل لتر ومتوسط

مستوى الكالسيوم ٢,٤٢ مللي مول لكل لتر. تشير النتائج إلى زيادة انتشار انخفاض مستوى المغنزيوم في الدم لدى مرضى الداء السكري والغير مصحوبة بأعراض سريرية أو انخفاض في مستوى البوتاسيوم والكالسيوم في المصل. كما آوضحت الدراسة ارتفاع متوسط إفراغ المغنزيوم في البول مما قد يعتبر مسبباً لانخفاض مستوى المغنيزيوم في المصل لمرضى الداء السكري.