ORIGINAL ARTICLE

Frequency and Risk Factors Associated with Hypomagnesaemia in Hypokalemic Type-2 Diabetic Patients

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ABSTRACT

Objective: To determine the frequency and factors associated with hypomagnesaemia in hypokalemic type-2 diabetic patients presenting at Civil Hospital, Karachi.

Study Design: A cross-sectional study.

Place and Duration of Study: Department of Medicine and Diabetic Clinic of Civil Hospital and Dow Medical College, Karachi, from November 2010 to May 2011.

Methodology: A total of 358 adult type-2 diabetics with hypokalemia were selected for this study. With aseptic measures, venous blood was collected for serum magnesium, potassium, HDLc, LDLc Triglyceride (TGs) and glycosylated hemoglobin (HbA1c) from each subject after an overnight fasting and was analyzed on Roche Hitachi 820 Photo Spectrometry. The data was analyzed on SPSS version 17 to determine the factors associated with hypomagnesaemia like duration of diabetes, Body Mass Index (BMI), diabetic nephropathy, HDLc, LDLc Triglyceride (TGs) and glycosylated hemoglobin (HbA1c) level.

Results: Mean age of study population was 55.62 ± 9.9 years. Most of them (n=228, 63.7%) were males. Out of the 358 subjects, 198 (55.3%) had hypomagnesaemia. There was significant association between hypomagnesaemia with duration of diabetes, Body Mass Index (BMI), diabetic nephropathy, HDLc, LDLc Triglyceride (TGs) and glycosylated hemoglobin (HbA1c) level.

Conclusion: Hypomagnesaemia is very common in type-2 diabetic hypokalemic patients. Therefore, it should be routinely sought by the clinicians. Early recognition and subsequent treatment of hypomagnesaemia may help in better glycemic control, may delay the chronic complications and decrease the mortality in diabetic hypokalemic patients.

Key Words: *Hypokalemia. Hypomagnesaemia. Type-2 diabetes. Glycosylated hemoglobin (HbA1c). Body Mass Index. Diabetic nephropathy. Triglyceride.*

INTRODUCTION

Diabetes mellitus is a metabolic disease of growing concern that is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Most of these patients are obese and are at increased risk of developing macro and micro vascular complications.[1,2] An estimated 285 million people worldwide lived with diabetes in 2010 and the number is expected to grow to 438 million by 2030.[3] In 2005, an estimated 1.1 million people died from diabetes and WHO projects this figure will double between 2005 and 2030.[4] A cross survey conducted in rural and urban areas of Pakistan showed 19% prevalence of diabetes mellitus.[5]

Magnesium (Mg), the second and fourth most common divalent cation in the cell and body respectively, has been the recent focus of much clinical and scholarly interest. It is distributed into three compartments of the body. Approximately 65% of the total body magnesium is found in the bones, 34% is found predominately inside the cells of tissues and organs. Only 1% of magnesium is in the extracellular fluid. Previously underappreciated, this ion is now established as a central electrolyte in large number of cellular metabolic reactions, including DNA and protein synthesis, neurotransmission and hormone receptor binding. It is a component of GTPase and a co-factor for Na^+ /K^+ ATPase, adenylate cyclase and phosphofructokinase. It is needed for more than 300 biochemical reactions in the body. Magnesium also plays an important role in the carbohydrate metabolism. It may influence the release and activity of insulin, the hormone that helps to control blood glucose levels.[6-8]

The role of hypomagnesaemia in the pathophysiology of insulin resistance, diabetes mellitus, hypertension and dyslipidemia has been observed in several studies. The Atherosclerosis Risk in the Community (ARIC) study showed significant association between hypo-magnesaemia and the incidence of type-2 diabetes mellitus (DM). Furthermore, Mg depletion may also affect the onset and progression of chronic diabetic complications.[9]

Hypokalemia is also common in diabetes and impairs both insulin release and organ sensitivity resulting in

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worsening of hyperglycemia. When hypomagnesaemia co-exist with hypokalemia the chances of complications significantly increases in diabetic patients. In addition, the correction of hypokalemia becomes difficult as magnesium is required for adequate processing of potassium.[10]

Several studies have investigated the relationship between Mg and type-2 diabetes mellitus and risk factors that showed wide range of prevalence (13.5 - 65%)[11-13] of hypomagnesaemia in type-2 diabetic patients but not much research has been done to show the relationship between hypomagnesaemia and hypokalemic type-2 diabetic patients. The authors could find only one small study (sample size=30) from Bangladesh that showed the 63.3% patients had hypomagnesaemia in diabetic hypokalemic patients.[10]

The objective of this study was to evaluate the frequency of hypomagnesaemia in type-2 diabetic patients who are hypokalemic and to determine the factors associated with hypomagnesaemia in these patients.

METHODOLOGY

This cross-sectional study was carried out at Civil Hospital, Karachi, from November 2010 to May 2011. Three hundred and fifty eight adult type-2 diabetic patients with hypokalemia, visiting the medical OPD, medical wards and Diabetic Clinic of Civil Hospital, Karachi and fulfilling the selection criteria were selected for this study. Inclusion criteria were patients aged > 35 years of either gender who were diagnosed cases of type 2 diabetes mellitus of ≥ 1 year duration and having hypokalemia. Exclusion criteria were patients with acute pancreatitis, diarrhea, vomiting or nasogastric suction, taking diuretics (loop or thiazides), on antimicrobials (amphotericin B, aminoglycosides, pentamidine, capreomycin, vancomycin, and foscarnet) and on chemotherapeutic (cisplatin) or immunosuppressant agents (tacrolimus and cyclosporine). A sample size of 358 was calculated, using 5% level of significance, margin of error as 5% and expected prevalence of 63.3%. Patients were explained about the purpose, the risk/benefit of the study and informed consent was taken. Demographic data and history including age, gender, marital status, duration of diabetes and type of treatment was collected. Weight (kilograms) and height (meter square) were measured in all patients for calculation of Body Mass Index (BMI). BMI of less than 23 taken as normal, 23.1 - 25 was taken as overweight and greater than 25 was considered as obese. Patients were called after 12 hours overnight fasting and with aseptic measures 10 ml venous blood was collected in each BD vacutainer serum bottle (red topped) and vacutainer EDTA bottle (purple topped) for serum magnesium, potassium, high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), triglyceride (TGs) and glycosylated hemoglobin (HbA1c). All samples were analyzed on Roche Hitachi 820 Photo Spectrometry. Serum magnesium level less than 1.7 mg/dl was considered as hypomagnesaemia and serum magnesium level between 1.7 - 2.7 mg/dl was considered as normal. Serum potassium less than 3.5 mEq/L was considered as hypokalemia. Serum triglyceride (TGs) more than 150 mg/dl, serum Low density lipoprotein cholesterol (LDLc) more than 100 mg/dl, serum high density lipoprotein cholesterol (HDLc) less than 40 mg/dl in males and less than 50 mg/dl in females were considered as abnormal. Glycosylated hemoglobin (HbA1c) less than 7% was considered as good diabetic control, 7 - 11% poor control and more than 11% very poor control of diabetes.

While Random Blood sugar (RBS) was checked through on call gluco-meter, diabetic nephropathy was determined by presence of microalbuminuria or proteinuria in the urine samples. For this, Quik Check™ urinalysis reagent strips (ACON Biotech, Co; Ltd) were used in urine samples. Patients exhibiting proteinuria by colour change were labeled nephropathy. Those with negative proteinuria with reagent strips were again screened for the presence of microalbuminuria (mg/l) in urine samples by MALB method.

The data was entered by two different analysts to control the bias and was analyzed with the help of Statistical Package for Social Sciences (SPSS) version 17. Mean and standard deviation of continuous variables like age, duration of diabetes mellitus, serum magnesium, body mass index and glycosylated hemoglobin were calculated. Frequency and percentage was computed for categorized variables like gender, age group, marital status, duration of diabetes, serum magnesium, body mass index, glycosylated hemoglobin (HbA1c), nephropathy and type of treatment. Binary logistic regression analysis was used to find out odd ratio, 95% confidence interval and observing the relationship between hypomagnesaemia and gender, age group, duration of diabetes, body mass index, nephropathy and glycosylated hemoglobin (HbA1c). Median, inter quintile range, mean and standard deviation were calculated for biochemical variables like serum magnesium, potassium, RBS, HDLc, LDLc, TGs and for the comparison of biochemical value between the two groups (hypomagnesaemia and non-hypomagnesaemia) Mann-Whitney U-test was used. P-value less than 0.05 was taken as significant. Stratification technique was used to control effect modifiers like age and gender to observe an outcome.

RESULTS

A total of 358 diabetic hypokalemic patients were selected for this study. Out of them, 228 (63.7%) were males and 130 (36.3%) were females. The male and

female ratio was 1.7:1. The mean age of study population was 55.62 ± 9.9 (range 36 to 78 years). Most of the study population (n=164, 45.8%) had age between 56 - 65 years. The mean body mass index, duration of diabetes, glycosylated hemoglobin (HbA1c), serum magnesium, blood sugar, potassium, LDLc, HDLc and TGs of the study population are given in Table I. One hundred and fourteen (n=114, 31.9%) patients had normal Body Mass Index (BMI), [120, 33.5%] were overweight and 124 (34.6%) patients were obese. The duration of diabetes was more than 10 years in 174 (48.6%) patients. Most of the patients (n=254, 70.9%) were on oral hypoglycemic agents alone. Seventy nine (22%) patients had glycosylated hemoglobin (HbA1c) less than seven percent (HbA1c < 7%), 219 (61.1%) patients had HbA1c between 7 - 11% and 60 (16.9%) patients had HbA1c more than 11%. One hundred ninety six (54.74%) patients had diabetic nephropathy.

Out of the total type-2 diabetic hypokalemic patients, 198 (55.3%) had hypomagnesaemia. Frequency of hypomagnesaemia was higher in males. Out of 228 males, 129 (56.6%) and out of 130 females, 69 (53.1%) had hypomagnesaemia respectively (p=0.522, Table II).

Body Mass Index (BMI) showed significant association with hypomagnesaemia in adult type 2 diabetic hypokalemic patients. Hypomagnesaemia was present in 35.5% of patients with normal BMI, 58.3% of overweight patients and 67.8% of obese patients (p < 0.001, Table II).

Table I: Baseline characteristics of study population.

Characteristics	Mean	Standard deviation	Minimum	Maximum
Age (years)	55.62	±9.9	36	78
BMI (kg/m^2)	25.36	±4.02	18	39
Duration of diabetes (years)	12.44	±5.02	1	25
HbA1c (%)	8.82	±1.83	6	14
Serum magnesium level (mg/dl)	1.86	±0.34	1.1	2.9
Serum potassium level (mEq/L)	2.84	±0.37	1.6	3.4
Random blood sugar level (mg/dl)	188.6	±55.2	75	333
Serum triglyceride level (mg/dl)	215.65	±74.43	89	452
Serum high density lipoprotein-cholesterol level (mg/dl)	115.67	±28.32	56	199
Serum high density lipoprotein-cholesterol level (mg/dl)	42.59	±8.88	23	63

Table III: Different biochemical parameters in hypomagnesaemia and non-hypomagnesaemia diabetic hypokalemic patients.

Biochemical parameters	Hypomagnesaemia (n = 198)		Non-hypomagnesaemia (n = 160)		p-value
	Median	IQR	Median	IQR	
Serum magnesium level (mg/dl)	1.43	1.32 - 1.5	1.9	1.76 - 2.1	< 0.001
Serum potassium level (meq/l)	3.0	2.8 - 3.1	2.9	2.6 - 3.1	0.549
Random blood sugar level (mg/dl)	199.0	145 - 234	198	136.75 - 233.50	0.736
Serum triglyceride level (mg/dl)	234.50	154 - 268	169	150 - 258	0.001
Serum low density lipoprotein-cholesterol level (mg/dl)	123	100 - 143.50	105	89 - 130	< 0.001
Serum high density lipoprotein-cholesterol level (mg/dl)	39	35 - 45	46	37.25 - 53	< 0.001

Table II: Risk factors and hypomagnesaemia.

Factors	Hypomagnesaemia		Total	Odd ratio	95% CI	p-value
	Yes (n=198)	No (n=160)	(n=358)			
Gender						
Male	129 (56.6%)	99 (43.4%)	228 (100%)	1.152	0.747 - 1.776	0.522
Female	69 (53.1%)	61 (46.9%)	130 (100%)			
Duration of diabetes (years)						
Less than 5 years	36 (41.9%)	50 (58.1%)	86 (100%)			< 0.001
5 to 10 years	42 (42.9%)	56 (57.1%)	98 (100%)	1.042	0.580 - 1.872	
More than 10 years	120 (69.0%)	54 (31.0%)	174 (100%)	3.086	1.807 - 5.272	
Age group						
36 - 45 years	13 (38.2%)	21 (61.8)	34 (100%)			0.087
46 - 55 years	59 (54.1%)	50 (45.9%)	109 (100%)	1.906	0.867 - 4.19	
56 -65 years	92 (56.1%)	72 (43.9%)	164 (100%)	2.064	0.968 - 4.402	
More than 66 years	34 (66.7%)	17 (33.3%)	51 (100%)	3.231	1.308 - 7.979	
HbA1c						
Less than 7% (good)	20 (25.3%)	59 (74.7%)	79 (100%)			< 0.001
7 - 11% (poor)	138 (63%)	81 (37%)	219 (100%)	5.026	2.824 - 8.946	
More than 11% (very poor)	40 (66.6%)	20 (33.4%)	60 (100%)	5.900	2.819 - 12.347	
BMI						
Less than 23	44 (35.5%)	70 (64.5%)	124 (100%)			< 0.001
23 - 24.9	70 (58.3%)	50 (41.7%)	120 (100%)	2.227	1.320 - 3.759	
25	84 (67.8%)	40 (32.2%)	124 (100%)	3.341	1.961 - 5.692	
Nephropathy						
Yes	125 (63.8%)	71 (36.2%)	196 (100%)	2.146	1.403 - 3.283	< 0.001
No	73 (45.1%)	89 (54.9%)	162 (100%)			

Longer duration of diabetes also showed significant association with frequency of hypomagnesaemia. Hypomagnesaemia was present in 41.9% of patients having diabetes of less than 5 years duration, in 42.9% of patients having diabetes of 5 - 10 years duration and in 69% of patients having diabetes of more than 10 years ($p < 0.001$, Table II).

Glycosylated hemoglobin (HbA1c) also showed significant relationship with frequency of hypomagnesaemia. Hypomagnesaemia was present in 25.3% of patients with good glycemic control (HbA1c less than 7%), sixty three percent (63%) of patients having poor glycemic control (HbA1c 7 - 11%) and in 66.6% patients having very poor glycemic control (HbA1c > 11%) [$p < 0.001$, Table II].

Diabetic nephropathy also showed significant relationship with frequency of hypomagnesaemia. Out of 196 diabetic nephropathy patients, 125 (63.8%) had hypomagnesaemia ($p < 0.001$).

On comparing patients with hypomagnesaemia and normal magnesium level, there was significant differences of serum magnesium ($p < 0.001$), triglycerides ($p=0.001$), LDLc ($p < 0.001$) and HDLc ($p < 0.001$) but no significant difference of serum potassium ($p=0.549$) and RBS ($p=0.736$). Details were given in Table III.

DISCUSSION

Hypomagnesaemia among diabetic patients is multifactorial in etiology including poor metabolic control, glycosuria induced osmotic diuresis, altered insulin metabolism and insulin resistance, poor dietary intake, autonomic neuropathy induced vomiting and diarrhea, glomerular hyperfiltration, recurrent metabolic acidosis, hypophosphatemia, and hypokalemia.[12]

Hypomagnesaemia has been reported to occur at an increased frequency among patients with type-2 diabetes compared with their counterparts without diabetes. Despite numerous reports linking hypomagnesaemia to chronic diabetic complications, attention to this issue is poor among clinicians.[12,14]

The mean age of this study population was 55.62 ± 9.9 (36 - 78 years). Almost similar mean age has been reported in other studies, a study from Bangladesh[10] showed mean age of study population was 52.3 ± 12.9 years and a study from Ethiopia[13] reported mean age of study population as 51.3 ± 1.3 years.

A wide range of prevalence of hypomagnesaemia (13.5 - 65%) among diabetic patients has been reported in various studies.[11-13] In this study, frequency of hypomagnesaemia in hypokalemic type-2 diabetic patients is 55.3%. The study from Bangladesh showed that 63.3% diabetic hypokalemic patients had hypomagnesaemia.[10]

In this study, the mean serum magnesium level in hypomagnesaemia group was 1.42 ± 0.13 mg/dL which is significantly low while in non-hypomagnesaemia group was 1.97 ± 0.26 ($p=0.001$ mg/dL). These results are in accordance with the observations of Sharif,[7] Kao[15] and Chamber[16] but much lower than Rasheed's observation that showed mean serum magnesium level was 1.6 ± 0.23 mg/dL in diabetic patients.[11]

Mean random blood sugar level in hypomagnesaemia group was 189.42 ± 55.88 mg/dL and 187.37± 54.4 mg/dL in non-hypomagnesaemia group, which was not significant ($p=0.698$). This is similar to studies done by Corica *et al*. and Masood *et al*.[9,17] On spot RBS level, HbA1c greater than 7% showed significant ($p=0.001$) association with hypomagnesaemia in hypokalemic type-2 diabetic patients. A poor glycemic control is a well known entity of hypomagnesaemia in diabetic patients. Hyperglycemia and glycosuria may interfere with renal magnesium handling, mainly by reducing the tubular reabsorption of the cation. Although Mg excretion was not measured in the present study, an increased urinary Mg loss could explain the low concentration of serum Mg observed in patients with HbA1c values greater than 7%. So, it is worth noting that HbA1c, but not plasma glucose, showed a significant association to hypomagnesaemia. Plasma glucose measurement reflects the actual glucose concentration at the time of the test and HbA1c values represent the adequacy of glycemic control during the last 2 - 3 months, which seems to influence more the serum Mg level. This difference is likely to explain the lack of association between plasma glucose and magnesium status in this and previous studies and suggests that the putative role of increased urinary Mg loss may be linked to a prolonged, more than actual, hyperglycemic state.[9]

There was significant association of hypomagnesaemia with duration of diabetes which is consistent with Mishra *et al*.,[8] but inconsistent with other studies.[10,13,17] The longer duration of diabetes is associated with poor glycemic control and this causes increase risk and severity of hypomagnesaemia.

Diabetic nephropathy is the leading cause of death that affects more than 40% of diabetic patients. It is mostly associated with electrolyte imbalances. Diabetic nephropathy showed strong association ($p=0.001$) with hypomagnesaemia in hypokalemic type-2 diabetic patients. Dewitte *et al*. showed that diabetic patients with chronic renal insufficiency have low serum ionized Mg (i-Mg) levels as compared to non-diabetic chronic renal insufficiency patients. Furthermore, declining creatinine clearance is not associated with increase in serum i-Mg concentrations in diabetic chronic renal insufficiency patients and this suggested that the progression of renal dysfunction may increase the risk of hypomagnesaemia in diabetic patients.[18] Both micro-albuminuria and

clinical proteinuria have been previously reported to be associated with a significant reduction in circulating i-Mg.[9,19] The results from the study of Shahid *et al*. further confirmed hypomagnesaemia is potential risk factor for the development of diabetic nephropathy.[20]

In this study, the authors found a strong association between serum TGs, LDLc, HDLc and hypomagnesaemia. Hypomagnesaemia has also been a well known factor of dyslipidemia, which constitutes for the complication of DM as well as atherosclerosis.[21] Altura in experimental model, showed that hypomagnesaemia is associated with increase in serum lipid concentration.[22] A significant inverse correlation of serum Mg with TGs, LDLc, VLDLc and a positive correlation with HDLc in type-2 diabetic patients has been discussed by Mishra *et al*.[8] Finally, oral replacement of magnesium in type-2 diabetic patients showed a significant reduction in serum total cholesterol, TGs, LDLc, VLDLc and improvement in HDLc level.[23-25]

Hypomagnesaemia was more common with higher BMI. Thirty five percent of normal BMI had hypomagnesaemia as compared to 67.8%, (p=0.001) in obese patients, which is almost twice more frequent. A significant relationship between BMI and hypomagnesaemia was also reported among Ethiopian[13] and Indian diabetic patients.[8]

In this study, the mean serum potassium level of patients in hypomagnesaemia group was 2.86 ± 0.34 mEq/L while in non-hypomagnesaemia group was 2.82 ± 0.40 mEq/L that was statistically insignificant (p=0.549). Similar relation was reported from Bangladesh.[10]

There was no significant relationship between hypomagnesaemia and age noted in this study, which is consistent with results by Walti *et al*. and Masood *et al*.,[14,17] but inconsistent with other studies.[8,9,13] In this study, the mean age of patients in hypomagnesaemia group was 56.52 ± 9.9 years while in non-hypomagnesaemia group was 54.51 ± 10.0 years that was statistically significant (p=0.026).

There were some limitations in this study. Firstly, the study population consisted of type-2 diabetic hypokalemic patients visiting Civil Hospital, Karachi, which mainly caters people from very low socio-economic status. Thus, it cannot be considered representative of all Pakistani population. Secondly, this study cannot propose any prognostic role for hypomagnesaemia in diabetic hypokalemic patients. So there is a need for longitudinal cohort study to the cause and effect of hypomagnesaemia on diabetic complications and control.

CONCLUSION

Hypomagnesaemia was very common in the studied type-2 diabetic hypokalemic patients, therefore, should be routinely sought by the clinicians. An early recognition and subsequent treatment of hypomagnesaemia may help in better glycemic control, may delay the chronic complications and decrease the mortality in diabetic hypokalemic patients.

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