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Original Article

Comparison of Serum Magnesium Levels among Type 2 Diabetic Patients with and without Microalbuminuria

Tahir Hanif, Usama Bin Khalid*, Aatir Hanif, Sana Ashraf***, Jamal Azfar****, Irfan Khattak******

Department of Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,*Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,**Liaquat University of Medical and Health Sciences, Jamshoro Pakistan,***Department of Radiology, Armed Forces Institute of Radiology and Imaging/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,****Department of Nephrology, PNS Shifa, Karachi Pakistan

ABSTRACT

Objective: To compare hypomagnesemia among type II diabetic patients with and without microalbuminuria.
Study Design: Cross-sectional comparative study
Place and Duration of Study: Department of Medicine, Pak-Emirates Military Hospital, Rawalpindi, Pakistan, from Nov 20 to Oct 21.
Methodology: 160 adult type 2 diabetic patients were categorized into two groups based on spot urine protein-to-creatinine ratio (Group-A: Diabetic patients with microalbuminuria & Group-B: Diabetic patients without microalbuminuria). Descriptive variables were measured as mean, median, and standard deviation. Chi-square test was used to determine association of hypomagnesemia between the two groups, taking $p \leq 0.05$ as statistically significant. Independent sample t-test was employed to determine statistical difference among HbA1c, serum magnesium and other lab parameters between Group-A and Group-B.
Results: The mean age of the sample stood at 44.19±8.33 years. Out of 160 total patients, 95(59.4%) were male while 65(40.6%) were female. The mean serum magnesium levels and mean glycated hemoglobin (HbA1c) levels were 1.36±0.24 mg/dl and 8.66±1.23% for Group-A and 1.62±0.28 mg/dl and 7.43±0.58 for Group-B, respectively. There was a statistically significant difference observed between Group-A and Group-B for Random Plasma Glucose, HDL Cholesterol, LDL cholesterol, HbA1c, and Serum Magnesium Levels. A strong association between hypomagnesemia and albuminuria was found ($p<0.001$).
Conclusion: Hypomagnesemia is associated with microalbuminuria among diabetic patients. Incidence of hypomagnesemia and microalbuminuria also coincided with higher glycated hemoglobin (HbA1c) levels and poorer glycemic control.
Keywords: Diabetes Mellitus, Diabetic Nephropathy, Glycated Hemoglobin (HbA1c), Hypomagnesemia, Microalbuminuria

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INTRODUCTION

Diabetes mellitus is a metabolic syndrome characterized by raised blood glucose levels due to relative or absolute deficiency of insulin, and can lead to long-term complications like damage to vital organs, especially the eyes, renal, neurological, and cardiovascular systems.[1] The global regional prevalence of diabetes in the world is reported as: Africa (2.1 - 6.7%), Europe (6.8% - 13%), Middle East and North Africa (6.3% - 12.2%), North America and Caribbean (10.8% - 14.5%), South and Central America (8% - 11.3%), Western Pacific (8.2% -11.4%) and South East Asia (6.8% -10.8%).[2]

The renal involvement in diabetes can lead to diabetic nephropathy, which is the long-term complication of uncontrolled diabetes mellitus and is defined by increased excretion of urinary albumin in the absence of other renal disorders.[3] The existence of microalbuminuria in the diabetic population indicates non-compliance with treatment and poor glycemic control, while the low serum magnesium level suggests and predicts the presence of long-term microangiopathic complications due to type 2 diabetes mellitus.[4,5]

Magnesium is the element that plays a vital role in metabolism and DNA synthesis in the human body, and its deficiency leads to endothelial cell malfunction, oxidative stress, and inflammatory processes; this all leads to the initiation of the process of atherosclerosis.[6] The low magnesium (hypomagnesemia) observed in type 2 diabetes mellitus impairs insulin sensitivity, glycemic status, and contributes to the development of complications such as cerebrovascular and cardiovascular disease, nephropathy, retinopathy, and neuropathy.[7,8] The pathophysiology of diabetic hypomagnesaemia is based on two factors, i.e., the osmotic effect of glycosuria and hyperglycemia per se.[9]

Correspondence: Dr Usama Bin Khalid, Department of Medicine, Pak Emirates Military Hospital Rawalpindi Pakistan
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Being a high-prevalence region for diabetes mellitus, the magnitude of this problem in our region has not been adequately investigated, and very scarce published data are available regarding the comparative serum magnesium levels among diabetic patients with and without microalbuminuria.10 Thus, the diagnostic and prognostic utility of serum magnesium levels in this regard is untapped. Therefore, this study hopes to generate local data by investigating the magnitude of magnesium disturbance in diabetic microalbuminuria and non-microalbuminuria populations so that the patients can be prospectively rationalized and managed accordingly based on the findings of the present study. This study aimed to determine the frequency of hypomagnesemia among type II diabetic patients. Comparison of hypomagnesemia among type II diabetic patients with and without microalbuminuria was also done.

METHODOLOGY

This cross-sectional study was carried out at the Department of Medicine, Pak-Emirates Military Hospital, Rawalpindi, Pakistan, from Nov 20 to Oct 21. Approval by the ethical review committee of Pak Emirates Military Hospital, Rawalpindi, vide letter no. A/28/EC/93 was obtained on 11 March 2020. The WHO calculator was used to determine the sample size, with a 5% margin of error and a 95% confidence interval, using the reference prevalence of diabetes mellitus of 10.8%, which came out to be 149.[11] The approach of non-probability sequential sampling was utilized. All patients gave their written informed consent to participate in the trial, and data were gathered using a pre-made proforma.

Inclusion Criteria: All pre-diagnosed adult patients with diabetes mellitus (type II) aged ≥35 years, presenting to the study setting (with or without microalbuminuria) during the study period were included.

Exclusion Criteria: The patients not consenting to participate in the study, known cases of type 1 diabetes mellitus, chronic liver/lung diseases and malignancy were excluded. Patients on long-term diuretics or magnesium/calcium-based medications, on cancer chemotherapy, with malabsorption syndrome, chronic diarrhea, pregnancy, pre-eclampsia, or eclampsia were also excluded from the sample.

After taking a detailed history and relevant clinical examination, the patients were selected and categorized into two groups: Group-A contained diabetic patients with microalbuminuria, and Group-B contained diabetic patients without microalbuminuria based on spot urine protein-to-creatinine ratio. Thereafter, both groups were observed for serum magnesium status by taking a 2-3 ml venous blood sample in a sterilized disposable vacutainer and sending it to the hospital laboratory for analysis. The other relevant investigations, i.e., fasting or random blood glucose, lipid profile and glycated hemoglobin (HbA1C), urine detailed report, serum urea and creatinine, and electrolytes were also advised. The serum magnesium level was assessed according to the reference range value of 1.7 – 2.4 mg/dL. All patients were also interviewed to exclude known medical disorders that could affect glycemic control and serum magnesium level. Microalbuminuria referred to all instances when the spot urine albumin-to-creatinine ratio ≥ 30 mg/g.

During the whole study period, confidentiality was maintained, and consent was obtained in clearly understandable national or regional (if required) languages. All the maneuvers were performed in accordance with medical ethics, and regarding the financial compensation, all the investigations were free of cost, as patients were fully entitled to this.

The data of all patients were analyzed in the statistical software package for the social sciences (SPSS) version 22. The frequency and percentage (%) were calculated for hypomagnesemia in type 2 diabetic patients with and without microalbuminuria. The frequency and percentage (%) were also calculated for age, gender, duration of diabetes, raised BMI, dyslipidemia, and residency (urban and rural), while the mean ± standard deviation (SD) were calculated for numerical variables like age, serum magnesium, systolic and diastolic blood pressure, HbA1c, body mass index (BMI), dyslipidemia, and duration of disease.

To observe the impact on the results and manage the effect modifiers, stratification was carried out based on age, gender, smoking, dyslipidemia, and place of residence (rural versus urban). Independent samples t-test was employed to determine statistical difference among HbA1c, serum magnesium and other lab parameters between Group-A and Group-B and a *p*-value of ≤0.05 was regarded as statistically significant. Furthermore, Pearson's correlation technique was employed to find an association

between hypomagnesemia and albuminuria, and between serum magnesium and HbA1c.

RESULTS

The study population included 160 patients with diabetes mellitus meeting the criteria. The mean age of the sample stood at 44.19±8.33 years. 95(59.4%) were male, while the remaining 65(40.6%) were female. 106(63.3%) of the respondents hailed from an urban setting, and the remaining 54(36.7%) belonged to a rural background. (Table-I)

Table-I: Demography and general characteristics of study population (n=160)

Variables		Group-A (n=80)	Group-B (n=80)	Overall (n=160)
Age (years) n (%)	35 – 44	49(61.3%)	49(61.3%)	98(61.3%)
	45 – 54	20(25.0%)	20(25.0%)	40(25.0%)
	55 – 64	8(10.0%)	8(10.0%)	16(10.0%)
	65 and above	3(3.8%)	3(3.8%)	6(3.8%)
Gender n (%)	Male	42(52.5%)	53(63.6%)	95(59.4%)
	Female	38(47.5%)	27(39.3%)	65(40.6%)
Residential Status n (%)	Urban	48(60.0%)	58(72.5%)	106(63.3%)
	Rural	32(40.0%)	22(27.5%)	54(36.7%)
Smoking n (%)	Yes	37(46.3%)	36(45.0%)	73(45.6%)
	No	43(53.7%)	44(55.0%)	87(54.4%)
Age (Years)		44.21±8.35	44.18±8.36	44.19±8.33
Systolic Pressure (mmHg)		130.00±10.20	137.00±10.40	133.75±10.97
Diastolic Pressure (mmHg)		82.75±6.25	85.06±7.26	83.91±6.86
BMI		25.41±3.92	24.91±3.67	25.16±3.79
Duration of Disease (years)		5.30±0.80	5.60±1.00	5.40±0.90

BMI = Body Mass Index

Although each patient presented with multiple complaints, the most pressing prime complaint at the time of the visit is shown in the graph (Figure-1). Symptoms of nephropathy were most common among the sample, while weight loss was the least pressing prime complaint. Interestingly enough, symptoms pertaining to retinopathy and skin manifestations such as fungal infections were nearly equally prevalent among the sample (Figure-1).

The fasting and random blood glucose levels (FBS and RBS, respectively) were elevated in nearly all the patients. The lipid profile was, however, somewhat normal. There was a statistically significant difference observed between Group-A and Group-B for Random Plasma Glucose, HDL Cholesterol, LDL Cholesterol, HbA1c, and Serum Magnesium Levels. The results of routine chemistry tests are given in Table-II.

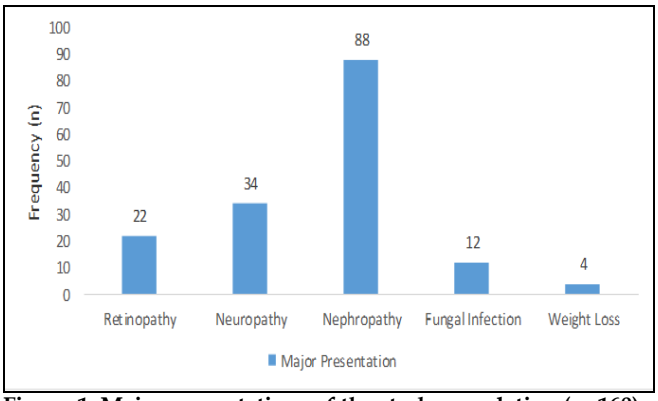


Figure-1: Major presentations of the study population (n=160)

Table-II: Routine Laboratory Investigations of the study population (n=160)

Lab Results	Group-A (n=80)	Group-B (n=80)	*p*-Value*
Fasting Plasma Glucose (mg/dl)	148.35±16.08	147.29±16.49	0.68
Random Plasma Glucose(mg/dl)	261.50±25.39	253.40±24.82	0.04
HDL-Cholesterol (mg/dl)	38.40±5.42	42.96±4.97	<0.001
LDL-Cholesterol (mg/dl)	141.88±12.59	135.49±10.19	<0.001
HbA1c (%)	8.66±1.23	7.43±0.58	<0.001
Serum Magnesium (mg/dl)	1.36±0.24	1.62±0.28	<0.001

**p-value obtained through independent sample t-test, HDL = High Density Lipoprotein, LDL = Low Density Lipoprotein, HbA1c= Glycosylated Hemoglobin*

The mean serum magnesium and glycated hemoglobin (HbA1c) levels were 1.36±0.24 mg/dl and 8.66±1.23% for Group-A and 1.62±0.28 mg/dl and 7.43±0.58 % for Group-B, respectively. (Figure-2) A strong association between hypomagnesemia and albuminuria was found (p<0.001). Moreover, serum magnesium was negatively associated with HbA1c (r=-0.506).

DISCUSSION

In this study, we demonstrated the association of hypomagnesemia with diabetic nephropathy (p<0.001). The mean levels of magnesium in patients with diabetic nephropathy, i.e., patients with albuminuria, were significantly lower (1.36±0.24 mg/dL) than in patients without albuminuria (1.62±0.28 mg/dL). 37% of 100 T2DM patients had

hypomagnesemia. Additionally, individuals with DN had a considerably greater frequency of hypomagnesemia (52%) compared to those without DN (22%).

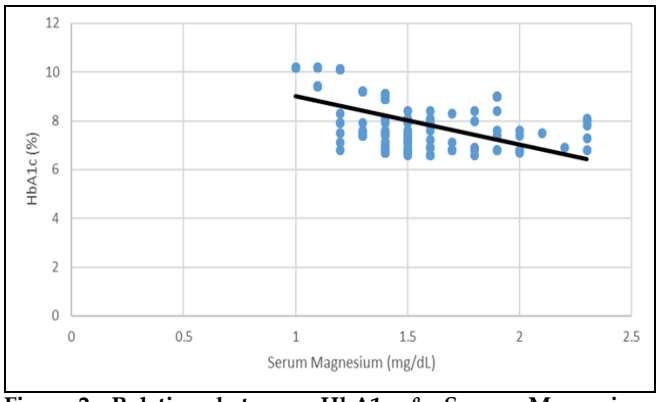


Figure-2: Relation between HbA1c & Serum Magnesium (n=160)

Magnesium (Mg2+) is the second most common divalent cation inside cells and an alkaline earth element. Involved in several critical metabolic activities, including ATP-dependent biochemical reactions, deoxyribonucleic acid (DNA) synthesis, ribonucleic acid (RNA) expression, signaling in muscles and nerves, and blood glucose and blood pressure regulation, it is also the tenth most abundant element by mass in the human body.[12] A deficit of Mg2+ can lead to the development of many problems, such as poor lipid metabolism, insulin resistance (IR), and decreased glucose tolerance, as reported by Kostov *et al*.[13]

Insulin deficit and insulin resistance (IR) coexist in magnesium deficiency, a condition that exacerbates type 2 diabetes (T2DM).[4] The generally acknowledged pathophysiologic theory states that endogenous insulin production fails to meet the high demand associated with insulin resistance (IR) and leads to hyperglycemia.[8] Serum Mg2+ content is negatively correlated with glycated hemoglobin, microalbumin, postprandial blood glucose, and fasting blood glucose (FBG). Bherwani et al., reported that end-stage renal disease (ESRD) is mostly caused by diabetic nephropathy (DN), and 20% of T2DM patients are thought to acquire ESRD at some point in their lives.[14] The pathophysiology of diabetic retinopathy involves several molecular pathways. The development of ESRD from diabetic nephropathy is caused by the emergence of hyperglycemia-driven pathways. Additionally, hyperglycemia is linked to oxidative stress (OS), which causes glomerular sclerosis to accompany proteinuria, thickening of the basement membrane, mesangial growth, a decrease in filtration rate, and nephromegaly[14]

Other findings of our study were also significant; e.g., there was a statistically significant difference between diabetic patients with and without nephropathy with respect to LDL-Cholesterol and HDL-Cholesterol. This can be related to a higher incidence of dyslipidemia and cardiovascular events in patients with diabetes mellitus, especially with diabetic nephropathy. There was no significant difference noted in fasting plasma glucose (p=0.48); however, there was a statistically significant difference found in random plasma glucose (p=0.04) and HbA1c (p<0.001).

The other factors found in the diabetic nephropathy group in our study were smoking and male gender.[3] The effect of smoking was in development and progression of diabetic nephropathy was gauged in a meta-analysis by Su *et al,* where When comparing individuals with diabetic nephropathy to those without the condition, the overall odds ratio (OR) for smoking was 1.70 (95% confidence interval 1.48–1.95).[15] In our study, hypertension was observed, and the systolic and diastolic blood pressure of the study population were 133.75±10.97 mmHg and 83.91±6.86 mmHg, respectively. This finding was substantiated by a study by Wagnew et al., in which the prevalence of hypertension was 41.4% (95% CI 32.2–50.58%) in type-2 diabetes mellitus.[16]

The role of hypomagnesemia in diabetic nephropathy was explored in this study in a Pakistani population. Raazaghi *et al.,* reported that magnesium supplementation can help in overcoming the adverse effects of diabetic nephropathy and other microvascular complications.[17] In this regard, the size of the ulcer and the blood C - reactive protein (CRP) concentration of individuals with diabetic foot ulcers improved after receiving 12-week Mg2+ supplementation, according to a recent research experiment conducted by Ferdoushi *et al.*[18] Thus, magnesium supplementation can be explored as a treatment option for control of diabetic complications.[18]

This study is among the few attempts made at comparing the serum magnesium levels among diabetic patients with and without microalbuminuria in Pakistan. The majority of the numbers obtained are new, and they might potentially form the foundation

for other studies. Furthermore, it finds correlations that could be trustworthy indicators of nephropathy, increasing the likelihood of early detection, diagnosis, and eventually prompt medical assistance.

LIMITATION OF STUDY

This study had several limitations. First, the absence of follow-up precluded the assessment of long-term outcomes. Second, the limited availability of comparable evidence-based literature restricted direct comparison of the findings with those of previous studies and limited their interpretation in the context of the broader population. Finally, the study was conducted at a single center, which may limit the generalizability of the findings. Future multicenter studies involving larger and more demographically diverse populations, with assessment of additional relevant clinical and hematological correlates, are recommended to validate and extend these findings.

CONCLUSION

After careful consideration, it can be concluded that hypomagnesemia is frequently associated with microalbuminuria among diabetic patients. The incidence of hypomagnesemia and microalbuminuria also coincided with higher glycated hemoglobin (HbA1c) levels and poorer glycemic control.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

TH & UBK: Data acquisition, data analysis, critical review, approval of the final version to be published.

AH & SA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

JA & IK: Data acquisition, data analysis, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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