Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Biochemistry

Serum Magnesium Status of Type 2 Diabetic Patients with and without Nephropathy

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DOI: https://doi.org/10.36347/sjams.2024.v12i10.016 | **Received:** 11.09.2024 | **Accepted:** 15.10.2024 | **Published:** 19.10.2024

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Abstract **Original Research Article**

Background: Chronic hyperglycemia induced oxidative stress has been considered as pathogenic factor for diabetes mellitus and diabetic nephropathy. Magnesium (Mg) possess antioxidant properties and is also involved at multiple levels in insulin secretion, binding and activity. Deficiency of Mg increases oxidative stress and contributes in the pathogenesis of diabetes mellitus and diabetic nephropathy. ***Objectives:*** To find out serum Mg status of type 2 diabetic patients with and without nephropathy. ***Methods:*** In this cross-sectional study, a total 162 respondents were selected from outpatient department of Medicine of BIRDEM General Hospital according to inclusion criteria during the period of July 2017 to June 2018. Among them 50 healthy individuals were selected as group I, 58 type 2 diabetic patients without nephropathy as group IIA and 54 type 2 diabetic patients with nephropathy as group IIB. Fasting blood glucose, HbA1c, serum creatinine, spot urine albumin to creatinine ratio (ACR), serum Mg were measured and estimated GFR was calculated by appropriate methods and statistical analysis were done. ***Results:*** It was found that serum Mg was significantly lower in Group IIA (0.77 ± 0.09) and Group IIB (0.69 ± 0.09) than Group I (0.82 ± 0.07). Percentage of hypomagnesaemia in Group I, Group IIA and Group IIB were found 4%, 17.2% and 48.1%, respectively. Furthermore, serum Mg was positively correlated with estimated GFR but negatively correlated with fasting blood glucose, HbA1c, serum creatinine and spot urine ACR in both Group IIA and Group IIB. ***Conclusion:*** The present study concluded that serum Mg level was significantly decreased in type 2 diabetic patients with and without nephropathy than healthy individuals and decline was significantly higher in type 2 diabetic nephropathy patients compared to type 2 diabetic patients without nephropathy.

Keywords: Type 2 diabetes, magnesium, diabetic nephropathy.

INTRODUCTION

Diabetes mellitus (DM) is a global public health problem and is the commonest endocrine disorder across the world [1,2]. It is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both [3]. Around 425 million people were living with diabetes worldwide in 2017 [4]. In Bangladesh, there were 7.1 million people with DM in 2015 and the number will be 13.6 million by 2040 [5]. In 2017, the prevalence of diabetes among adults (20-79 years) was 8.4% in Bangladesh [4]. DM and its complications are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society [6].

Around 90% to 95% are of type 2 diabetes among all types of diabetes [7]. Type 2 DM occurs due to progressive defect in insulin secretion on the background of insulin resistance [8]. Patients with type 2 DM may have complications like cardiovascular disease, nephropathy, retinopathy and polyneuropathy [9]. About 40% of diabetic patients eventually develop nephropathy [10]. In the United Kingdom Prospective Diabetes Study, the prevalence rate of nephropathy in types 2 diabetic patients was reported 30.8% [3]. The prevalence of nephropathy among type 2 diabetic patients in a tertiary care hospital of Bangladesh was found 54.5% [1].

Diabetic nephropathy (DN) is one of the most important micro vascular complications of diabetes and a major cause of end stage renal disease (ESRD). High intracellular glucose concentration has been suggested to be a prerequisite for development of structural and functional changes in the kidney typical of DN [11]. The diabetic kidney is characterized by increased perfusion, which generates increased glomerular filtration and intraglomerular pressure. Pathological changes result in initial micro albuminuria, which progresses to more extensive proteinuria, followed by a decline of glomerular filtration rate (GFR) and ultimately ESRD [12]. Patients with DN are diagnosed based on elevated urinary albumin excretion (UAE) >30 mg/g of creatinine which should be confirmed with additional spot urine tests over the next three to six months and / or reduced estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2 for more than three months [13,14]. DN is not only one of the major causes of morbidity and mortality among patients with diabetes worldwide but also possess a huge economic burden for developing countries like Bangladesh [15].

Oxidative stress has been considered to be a pathogenic factor of diabetic complications including nephropathy [11]. Oxidative stress generated by hyperglycemia, increases ROS production which is followed by cellular dysfunction and damage and ultimately results in diabetic micro and macro vascular complications [16].

Mg is the fourth most abundant cation in human body and plays a key role in many fundamental biological processes, including energy metabolism and DNA synthesis [17]. It is also involved at multiple levels in insulin secretion, binding and activity [18]. Mg deficiency has been shown to cause endothelial cell dysfunction, inflammation and oxidative stress [19]. Mg deficiency and type 2 diabetes have close relationship [20]. In patients with diabetes, insulin resistance or deficiency can promote Mg loss at thick ascending limb of loop of Henle [21]. It has been suggested that Mg deficiency may play prominent role in the pathogenesis of diabetic complication including nephropathy [22].

OBJECTIVE

General Objective

Determine the serum Mg status of type 2 diabetic patients with and without nephropathy

Specific Objectives

1. To measure fasting blood glucose, HbA1c, serum creatinine, spot urine ACR, serum Mg and to calculate estimated GFR in all study subjects.
2. To compare fasting blood glucose, HbA1c, serum creatinine, estimated GFR, spot urine ACR, and serum Mg among type 2 diabetic patients with and without nephropathy and healthy individuals.

METHODOLOGY

Type of study: Cross sectional analytical study

Place of study: Department of Biochemistry and Molecular Biology, BIRDEM Academy, Dhaka.

Period of study: This study was conducted during the period of July 2017 to June 2018.

Sample size: Calculated sample size in each group was 35. But for convenience, minimum 50 sample were taken in each group.

Study population: Type 2 DM patients with and without nephropathy and healthy individuals.

Study sample

A total of 162 subjects aged 30 to 60 years were selected from outpatient department of Medicine of BIRDEM General Hospital for this study. Among them 50 healthy individuals were selected as Group I, 58 type 2 diabetic patients without nephropathy were selected as Group IIA and 54 type 2 diabetic patients with nephropathy were selected as Group IIB.

Selection criteria

Inclusion criteria

Both male and female subjects aged 30 to 60 years were selected in all groups and then included into following groups.

Group I

- Healthy individuals.

Group IIA

- Diagnosed type 2 DM patients without nephropathy.

Group IIB

- Diagnosed type 2 DM patients with nephropathy.

Exclusion criteria

- Patients with acute kidney injury and kidney disease from non-diabetic etiology.
- Patients with chronic diarrhea, malnutrition and malabsorption syndrome.
- Patient with acute and chronic liver disease, cerebrovascular accident and cardiovascular disease such as acute myocardial infarction.
- Patients on renal replacement therapy.
- Patients taking diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blocker, calcium channel blockers, beta blockers, NSAIDS, penicillamine, lithium, antipsychotics, antidepressants, antioxidant vitamins, minerals.

- Patients with acute complications like severe infection, major operation and trauma.
- Pregnant women.
- Smoker.

Sampling technique

- Purposive

Key variables

a) **Demographic variables:** Age, gender, family history of DM and family history of DN of the study subjects.
b) **Anthropometric and clinical variables:** Systolic and diastolic blood pressure.
c) **Laboratory variables:** Fasting blood glucose, HbA1c, serum creatinine, estimated GFR, spot urine ACR and serum Mg.

Research Instrument

- Structured questionnaire was prepared for this purpose, which included all the variables of interest.

Data Collection Technique

According to inclusion criteria, the healthy individuals, diagnosed type 2 DM patients with and without nephropathy who came for routine screening and follow up in outpatient department of Medicine of BIRDEM General Hospital were requested to participate in the study. A structured questionnaire was filled up for each study subject after taking informed written consent. Type 2 diabetic patients were diagnosed by physicians depending on history, clinical features and ADA criteria [7]. Nephropathy was also diagnosed by physicians on the basis of persistent albuminuria (>30 mg/day or ACR >30 mg/g) in at least two occasions within six months period and/ or GFR less than 60 ml/min/1.73m^2 for more than three months [23, 24]. Detail personal, family and medical history of study subjects were collected through history taking and review of diabetic patients clinical and biochemical records from "Diabetic guide book" and included in structured questionnaire.

Statistical Analysis

All statistical analysis was performed with the help of software SPSS (statistical package for social science), 22 versions. Data were described as mean ± SD values or simple percentage as appropriate. Chi-square test was done for comparison of categorical variables. ANOVA test and Independent student's t test were done to compare continuous variables. The statistical significance, direction and strength of linear correlation between two quantitative variables were measured by using Pearson's correlation coefficient test. All statistical tests were considered significant at the level of ≤5%.

RESULTS

This cross sectional analytical study was conducted in the department of Biochemistry and Molecular Biology of BIRDEM Academy from July 2017 to June 2018. A total of 162 study subjects aged 30 to 60 years were selected for this study from outpatient department of Medicine according to inclusion criteria. Among them 50 healthy individuals were selected as group I, 58 type 2 diabetic patients without nephropathy were selected as group IIA and 54 type 2 diabetic patients with nephropathy were selected as group IIB. Fasting blood glucose, HbA1c, serum creatinine, estimated GFR, spot urine ACR and serum magnesium were analyzed by appropriate statistical tests like ANOVA test, Independent student's t test, Chi-square test and Pearson's correlation test. The findings are as presented in the subsequent pages.

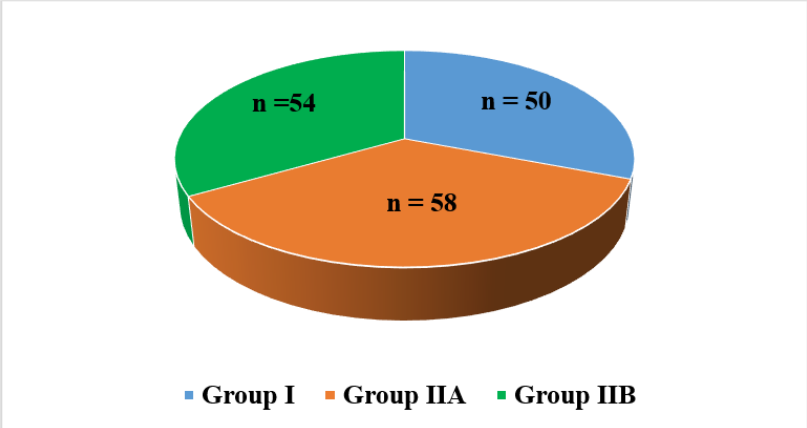

Figure 1: Distribution of study subjects in Group I (healthy individuals), Group IIA (type 2 DM patients without nephropathy) and Group IIB (type 2 DM patients with nephropathy)

Figure 1 shows distribution of study subjects in Group I, Group IIA and Group IIB. In this study, 50 healthy individuals were selected as Group I, 58 type 2 DM patients without nephropathy were selected as Group IIA and 54 type 2 DM patients with nephropathy were selected as Group IIB.

Table I: Frequency distribution of family history of DM and family history of DN in the study subjects (n = 162).

Variables	Frequency	Percentage (%)
Family history of DM Present	101	62.3
Absent	61	37.7
Family history of DN Present	11	6.8
Absent	151	93.2

n = number of study subjects.

Table I shows the frequency distribution of family history of DM and DN of the study subjects. Participants were enquired about their family history of DM and DN. Among them 62.3% and 6.8% had family history of DM and DN, respectively.

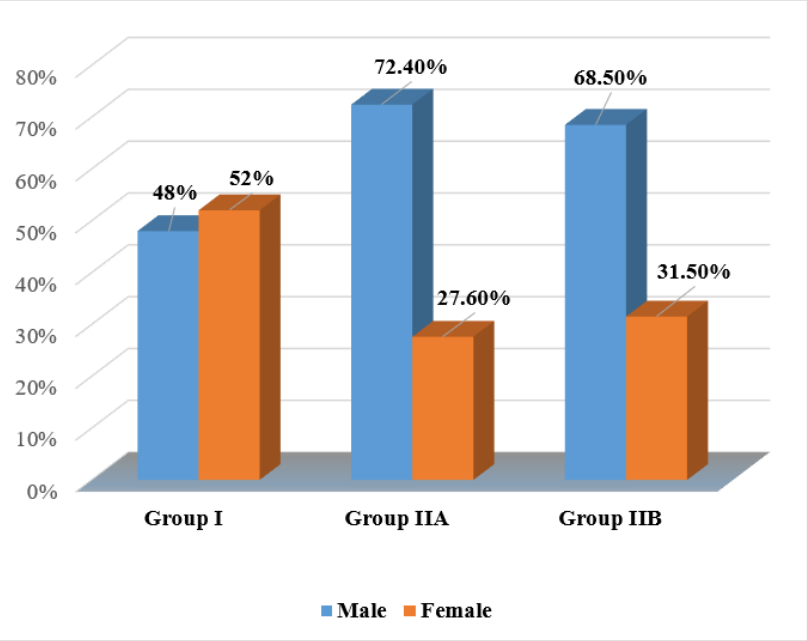

Figure 2: Gender distribution of study subjects of Group I (healthy individuals), Group IIA (type 2 diabetic patients without nephropathy) and Group IIB (type 2 diabetic patients with nephropathy)

Figure 2 shows gender distribution of study subjects of Group I, Group IIA and Group IIB. This study found that in Group I, percentage of male and female participants were 48% and 52%, respectively. Male participants were found more prevalent than female participants in both Group IIA (72.4% vs. 27.6%) and Group IIB (68.5% vs. 31.5%).

Table II: Comparison of variables among Group I (healthy individuals), Group IIA (type 2 DM patients without nephropathy) and Group IIB (type 2 DM patients with nephropathy)

Variables	Group I n = 50	Group IIA n = 58	Group IIB n = 54	p-value
	mean ± SD	mean ± SD	mean ± SD	
Age (years)	44.58 ± 8.94	47.76 ± 8.84	52.28 ± 6.74	<0.001
Systolic BP (mm of Hg)	114.20 ± 7.31	123.79 ± 14.61	129.17 ± 16.93	<0.001
Diastolic BP (mm of Hg)	74.00 ± 6.06	79.66 ± 6.55	80.65 ± 7.53	<0.001

n = number of study subjects.

Data were expressed as mean ± SD. Statistical analysis was done by ANOVA test to compare variables among groups.

*p<0.05, **p<0.0, ***p<0.001

Table II shows comparison of variables among Group I, Group IIA and Group IIB. It was observed that mean ± SD of age (years) at visit of Group I, Group IIA and Group IIB were 44.58 ± 8.94; 47.76 ± 8.84; 52.28 ± 6.74, respectively. Mean age of Group IIB was higher than other groups and their difference was statistically significant (p<0.001). In Group I, Group IIA and Group IIB, mean value of systolic blood pressure (mm of Hg) were 114.20 ± 7.31; 123.79 ± 14.61; 129.17 ± 16.93, respectively and diastolic blood pressure (mm of Hg) were 74.00 ± 6.06; 79.66 ± 6.55; 80.65 ± 7.53, respectively. It was observed that systolic and diastolic

blood pressure were significantly higher (p<0.001) in Group IIB than Group IIA and Group I.

Table III: Comparison of biochemical variables among Group I (healthy individuals), Group IIA (type 2 DM patients without nephropathy) and Group IIB (type 2 DM patients with nephropathy)

Variables	Group I n = 50	Group IIA n = 58	Group IIB n = 54	p-value
	mean ± SD	mean ± SD	mean ± SD	
Fasting blood glucose (mmol/L)	5.02 ± 0.57	9.16 ± 2.90	10.52 ± 4.62	<0.001
HbA1c (%)	4.83 ± 0.47	7.58 ± 1.78	8.94 ± 2.59	<0.001
Serum creatinine (mg/dL)	0.82 ± 0.11	1.04 ± 0.20	1.62 ± 0.48	<0.001
Estimated GFR (ml/min/1.73m^2)	93.88 ± 15.65	76.97 ± 15.78	47.28 ± 12.68	<0.001
Spot urine ACR (mg/g)	6.39 ± 2.75	11.92 ± 8.21	140.19 ± 109.19	<0.001
Serum magnesium (mmol/L)	0.82 ± 0.07	0.77 ± 0.09	0.69 ± 0.09	<0.001

Data were expressed as mean ± SD. Statistical analysis was done by ANOVA test to compare variables among groups. n = number of study subjects.

*p<0.05, **p<0.01, ***p<0.001

Table III shows comparison of biochemical variables among Group I, Group IIA and Group IIB. Mean value of fasting blood glucose (mmol/L) of Group I, Group IIA and Group IIB were found 5.02 ± 0.57; 9.16 ± 2.90; 10.52 ± 4.62, respectively. It was also observed that mean value of fasting blood glucose was significantly higher in Group IIB and Group IIA in comparison with Group I (p<0.001). The study also revealed that mean value of HbA1c (%) was significantly higher in Group IIB and Group IIA than Group I (8.94 ± 2.59; 7.58 ± 1.78; 4.83 ± 0.47; p<0.001). Significantly higher (p<0.001) mean value of serum creatinine (mg/dL) was found in Group IIB (1.62 ± 0.48) than Group I (0.82 ± 0.11) and Group IIA (1.04 ± 0.20). Estimated GFR (ml/min/1.73m^2) was found significantly lower (p<0.001) in Group IIB (47.28 ± 12.68) in comparison with Group I (93.88 ± 15.65) and Group IIA (76.97 ± 15.78). This table also showed that mean value of spot urine ACR (mg/g) was significantly higher (p<0.001) in Group IIB (140.19 ± 109.19) when compared with Group I (6.39 ± 2.75) and Group IIA (11.92 ± 8.21). It was detected that mean value of serum magnesium (mmol/L) of Group I, Group IIA and Group IIB were 0.82 ± 0.07; 0.77 ± 0.09; 0.69 ± 0.09, respectively and the value was significantly lower in Group IIA and Group IIB in comparison with Group I (p<0.001). Furthermore, it was also found that serum Mg level was more decreased in Group IIB than Group IIA.

Table IV: Serum magnesium status in Group I (healthy individuals), Group IIA (type 2 DM patients without nephropathy) and Group IIB (type 2 DM patients with nephropathy)

Serum magnesium (mmol/L)	Hypomagnesaemia <0.70	Within reference range (0.7-1.07)	χ^2	p-value
Group I n (%)	2 (4.0%)	48 (96.0%)		
Group IIA n (%)	10 (17.2%)	48 (82.8%)		
Group IIB n (%)	26 (48.1%)	28 (51.9%)	30.12	<0.001

n = number of study subjects.

Statistical analysis was done by Chi-square test to compare variables among the groups.

*p<0.05, **p<0.01, ***p<0.001

Table IV shows that among participants of Group I, Group IIA and Group IIB, percentage of hypomagnesaemia was 4%, 17.2% and 48.1%, respectively. It was also observed that the percentage of hypomagnesaemia was significantly higher in Group IIB and Group IIA in comparison with Group I (p<0.001).

Table V: Correlation of serum magnesium (mmol/L) with other biochemical variables in Group IIA (type 2 DM patients without nephropathy)

Variables	r	p-value
Estimated GFR (ml/min/1.73m^2)	0.490	<0.001
Fasting blood glucose (mmol/L)	-0.536	<0.001
Serum creatinine (mg/dL)	-0.455	<0.001
Spot urine ACR (mg/g)	-0.650	<0.001

*Pearson's correlation was used for statistical analysis.

*p<0.05, **p <0.01, ***p<0.001

Table V shows correlation of serum magnesium with other biochemical variables in Group IIA. In this study, significant positive correlation of serum magnesium with estimated GFR (r = 0.490; p<0.001) was found in Group IIA. Significant negative correlation of serum magnesium with fasting blood glucose (r = -0.536; p<0.001), serum creatinine (r = -0.455; p<0.001) and spot urine ACR (r = -0.650; p<0.001) were also found in Group IIA.

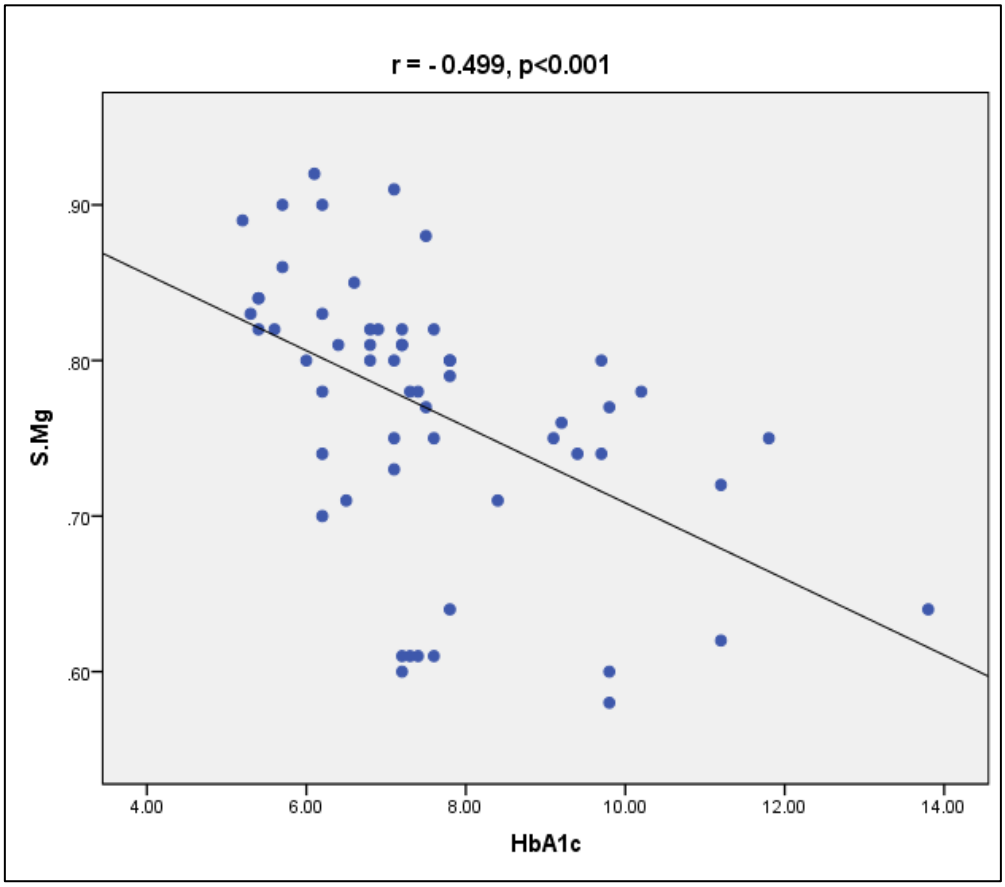

Figure 3: Negative correlation of serum magnesium with glycemic status (HbA1c) in Group IIA (type 2 DM patients without nephropathy)

Figure 3 shows significant negative correlation (r = -0.499, p<0.001) of serum magnesium (mmol/L) with HbA1c (%) in Group IIA.

Table VI: Correlation of serum magnesium (mmol/L) with other biochemical variables in Group IIB (type 2 DM patients with nephropathy)

Variables	r	p-value
Estimated GFR (ml/min/1.73m^2)	0.632	<0.001
Fasting blood glucose (mmol/L)	-0.463	<0.001
Serum creatinine (mg/dL)	-0.429	<0.01
Spot urine ACR (mg/g)	-0.580	<0.001

*Pearson's correlation was used for statistical analysis.
*p<0.05, **p<0.01, ***p<0.001

Table VI shows correlation of serum magnesium with other biochemical variables in Group IIB. In this study, significant positive correlation of serum magnesium with estimated GFR (r = 0.632; p<0.001) was observed in Group IIB. Significant negative correlation of serum magnesium with fasting blood glucose (r = -0.463; p<0.001), serum creatinine (r = -0.429; p<0.01) and spot urine ACR (r = -0.580; p<0.001) were also observed in Group IIB.

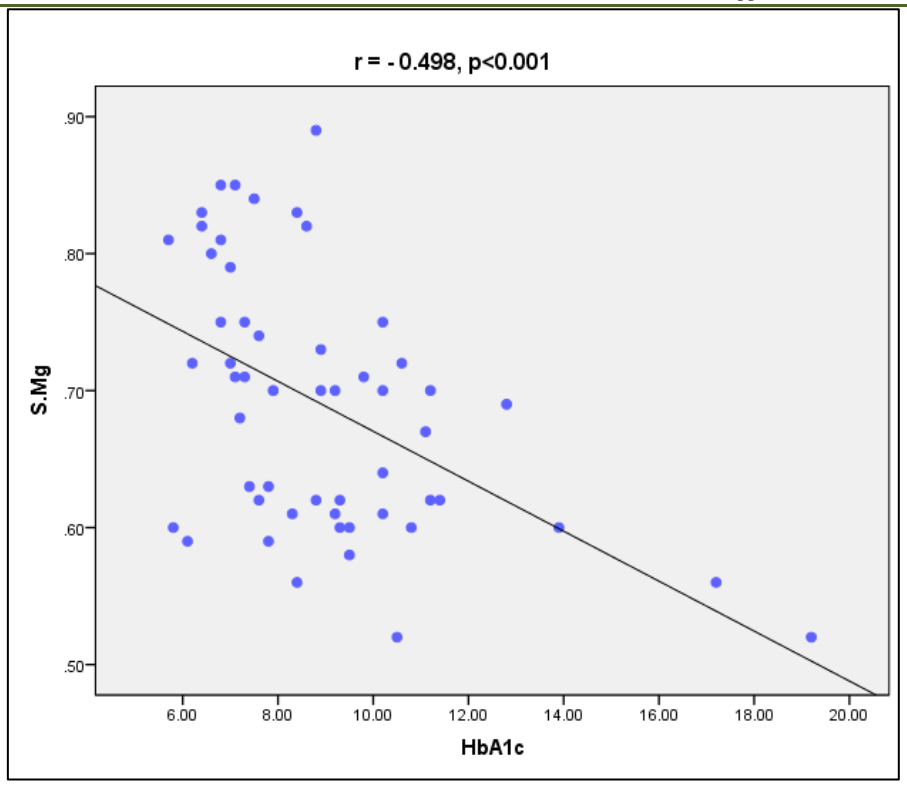

Figure 4: Correlation of serum magnesium with glycemic status (HbA1c) in Group IIB (type 2 DM patients with nephropathy)

Figure 4 shows significant negative correlation (r = -0.498, p<0.001) of serum magnesium (mmol/L) with HbA1c (%) in Group IIB.

DISCUSSION

Type 2 diabetes mellitus and diabetic nephropathy are chronic metabolic disorders associated with oxidative stress. Mg which itself has antioxidant properties, helps in insulin action. Serum Mg has been reported to decrease in type 2 diabetic patients with and without nephropathy.

A cross sectional analytical study was conducted in BIRDEM General Hospital from July 2017 to June 2018 to determine serum Mg level in type 2 diabetic patients with and without nephropathy. A total 162 subjects were selected in this study according to inclusion criteria. Among them 50 healthy individuals were selected as Group I, 58 type 2 DM patients without nephropathy as Group IIA and 54 type 2 DM patients with nephropathy as Group IIB.

In the current study, more male participants were found than female participants in both Group IIA (72.4% vs. 27.6%) and Group IIB (68.5% vs. 31.5%). The mechanism behind could be that men were less insulin sensitive than women due to more visceral and hepatic fat than women [29]. This finding was similar to the findings of other reported studies [30, 31].

In this study mean age of study subjects in Group I, Group IIA and Group IIB were 44.58 ± 8.94, 47.76 ± 8.84 and 52.28 ± 6.74 years, respectively. Mean age in Group IIB was significantly higher than Group I and Group IIA (p<0.001). This finding was consistent with the finding of the study which showed higher mean age among type 2 DM patients with micro albuminuria (56.9 ± 8.6 years) than without micro albuminuria (50 ± 8.0 years) and healthy controls (50.4 ± 10.9 years) [33].

The association between family history of diabetes and risk for the disease has been well documented [35]. In the current study, positive family history of DM was present in 62.10% and 70.40% participants of Group IIA and Group IIB respectively. Similar findings were found in other studies [30, 36].

In the participants of Group I, Group IIA and Group IIB, mean systolic blood pressure were 114.20 ± 7.31, 123.79 ± 14.61 and 129.17 ± 16.93 mm of Hg, respectively and mean diastolic blood pressure were 74.00 ± 6.06, 79.66 ± 6.55 and 80.65 ± 7.53 mm of Hg, respectively. Systolic and diastolic blood pressure were showed significantly higher (p<0.001) in Group IIB than Group I and Group IIA. This finding agreed with previous study [34].

In this study, mean fasting blood glucose in Group IIB, Group IIA and Group I were 10.52 ± 4.62, 9.16 ± 2.90 and 5.02 ± 0.57 mmol/L, respectively. It was also revealed that fasting blood glucose was significantly

higher in Group IIB and Group IIA than Group I ($p<0.001$). In previous study, higher mean fasting blood glucose was found in diabetic nephropathy and diabetic patients than healthy controls (9.07 ± 2.08, 6.02 ± 0.63, 5.09 ± 0.41 mmol/L, respectively) [11].

Mean ± SD value of HbA1c (%) was observed significantly higher ($p<0.001$) in Group IIB (8.94 ± 2.59) and Group IIA (7.58 ± 1.78) in comparison with Group I (4.83 ± 0.47). This finding was in concordance with the study where higher mean HbA1c was found in diabetic nephropathy and diabetic patients than healthy controls (10.92 ± 1.04, 7.37 ± 0.79, 4.95 ± 0.36, respectively) [9].

In the present study, mean value of serum Mg (mmol/L) in Group I, Group IIA and Group IIB were 0.82 ± 0.07, 0.77 ± 0.09, 0.69 ± 0.09, respectively. It was observed that mean value of Mg was significantly lower in Group IIA and Group IIB than Group I ($p<0.001$) and decline was more in Group IIB (0.69 ± 0.09) than Group IIA (0.77 ± 0.09). This finding was in concordance with previous studies [39, 40]. It was also found that the percentage of hypomagnesaemia in Group I, Group IIA and Group IIB were 4%, 17.2% and 48.1%, respectively. Hypomagnesaemia in diabetic patients with and without nephropathy may be due to osmotic diuresis or increased Mg loss at thick ascending limb of loop of Henle as a consequence of insulin resistance or insulin deficiency [41]. Similarly, higher prevalence of hypomagnesaemia was reported in diabetic nephropathy patients (52%) compared to without nephropathy patients (22%) in other study [42]. Another studies also found hypomagnesaemia in type 2 diabetic patients (11.33%, 51.2% and 48%, respectively) [43-45].

Mean ± SD of duration of diabetes was found significantly higher in Group IIB (9.0 ± 4.92 years) than Group IIA (6.90 ± 3.85 years) in the present study. This finding agreed with other study [10].

In Group IIA and Group IIB, significant positive correlation of serum Mg was found with estimated GFR ($r = 0.490$; $p<0.001$ vs. $r = 0.632$; $p<0.001$). Significant negative correlation of serum Mg was also observed with fasting blood glucose ($r = -0.536$; $p<0.001$ vs. $r = -0.463$; $p<0.001$), HbA1c ($r = -0.499$; $p<0.001$ vs. $r = -0.498$; $p<0.001$), serum creatinine ($r = -0.455$; $p<0.001$ vs. $r = -0.429$; $p<0.01$) and spot urine ACR ($r = -0.650$; $p<0.001$ vs. $r = -0.580$; $p<0.001$). This findings agreed with the study where significant negative correlation of serum Mg with fasting blood glucose ($r = -0.738$), HbA1c ($r = -0.569$), serum creatinine ($r = -0.928$) and urine ACR ($r = -0.961$) was reported in type 2 diabetic patients [46]. In previous study, serum Mg was positively correlated with GFR ($r = 0.304$, $p<0.01$) and negatively correlated with serum creatinine ($r = -0.222$, $p<0.05$) and urine ACR ($r = -0.352$, $p<0.001$) in diabetic nephropathy patients [47]. It was reported that serum Mg was negatively correlated with fasting blood glucose ($r = -0.395$) and HbA1c ($r = -0.491$) in diabetic nephropathy patients [48].

CONCLUSION

In this study, significantly lower serum magnesium level was found in both type 2 diabetic patients with and without nephropathy in comparison with healthy individuals. It was also observed that serum magnesium levels was more decreased in type 2 diabetic nephropathy patients than without nephropathy. Significant positive correlation of serum magnesium with estimated GFR and significant negative correlation with fasting blood glucose, HbA1c, serum creatinine and urine ACR were observed in both type 2 diabetic patients with and without nephropathy.

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