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Effect of proton pump inhibitors on Magnesium levels in Type II diabetic patients: a single centre study from Saudi Arabia

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Abstract. – OBJECTIVE: In recent years, increasing evidence suggests an association between low Magnesium levels and type 2 diabetes mellitus. It has also been reported that the use of proton pump inhibitors may induce hypomagnesemia. Although some case reports have described patients with Proton Pump Inhibitor-induced hypomagnesemia, the impact of Proton Pump Inhibitor use on hypomagnesemia has not been fully clarified in comparative studies. The objective of the study was to determine the Magnesium levels in patients with diabetes who are taking proton pump inhibitors and also to correlate the Magnesium levels in diabetic patients who take proton pump inhibitors with those not taking proton pump inhibitors.

PATIENTS AND METHODS: A cross-sectional study was carried out in the study population comprising adult patients attending internal medicine clinics in King Khalid Hospital, Majmaah, KSA. A total of 200 patients who gave informed consent were recruited into the study over one year.

RESULTS: Overall prevalence of hypomagnesemia was observed among 128 patients out of 200 (64%) diabetic patients. Relatively more patients with hypomagnesemia were found in group 2 (without PPI use) (38.5%) compared to group 1 (with PPI use) (25.5%). A statistically significant difference was not observed in group 1 using proton pump inhibitors and group 2 not using proton pump inhibitors (p-value = 0.473).

CONCLUSIONS: Hypomagnesemia is seen in diabetic patients and patients who take proton pump inhibitors. There was no statistically significant difference in Magnesium levels in diabetic patients, irrespective of proton pump inhibitor use.

Key Words:
Hypomagnesemia, Diabetes, Proton pump inhibitors.

Introduction

Magnesium (Mg) is crucial for optimal insulin activity and the proper functioning of many enzymes, including tyrosine kinase, which is vital for glucose metabolism. Inadequate dietary intake of Mg is associated with an increased risk of developing glucose intolerance and type 2 diabetes. Hypomagnesemia is common among patients with type 2 diabetes, which also appears to cause low serum Mg levels. Hypomagnesemia leads to insulin resistance and reduced function of various enzymes, which may result in diabetes. A growing body of evidence suggests that Mg plays a pivotal role in the pathogenesis of diabetes itself[1]. Since hypomagnesemia is linked to poor glycemic control, its insufficiency must be supplemented orally or by increased dietary intake. Dietary supplementation with Mg, besides clinical therapies, might be helpful in the prevention of diabetic complications.

Besides this, bothersome GI symptoms, including gastroesophageal reflux, postprandial fullness, bloating, constipation, and diarrhea, are common in diabetic subjects and are related to abnormal GI motility caused by autonomic neuropathy[2]. Therefore, the use of proton pump inhibitors is commonly encountered in diabetic patients. Recently, it has been reported that hypomagnesemia may also be induced by proton pump inhibitors (PPI). Although many case reports have described patients with PPI-induced hypomagnesemia, the impact of PPI use on hypomagnesemia has not been fully clarified in comparative studies[3].

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Furthermore, low circulating Magnesium levels have been related to elevated blood pressure, atherogenic dyslipidemia, impaired clotting, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease[4,5].

Based on all the above findings, correcting hypomagnesemia may be essential to prevent an additional cardiovascular risk in type 2 diabetes mellitus patients.

Hypomagnesemia has been reported to occur in 13.5-47.7% of non-hospitalized patients with type 2 diabetes compared with 2.5-15% of their counterparts without diabetes. Not only has hypomagnesemia been associated with type 2 diabetes, but also numerous studies have reported an inverse relationship between glycemic control and serum magnesium levels[6].

Although many authors have suggested that diabetes *per se* may induce hypomagnesemia, others have reported that higher magnesium intake may confer a lower risk for type 2 diabetes[7-10]. Not all studies, however, observed a correlation between glycemic control and serum magnesium levels or improvement of diabetic control with Magnesium replacement[11]. The conflicting data may reflect different study designs and populations studied.

Epidemiologic studies[7] have found a high prevalence of hypomagnesemia in subjects with type 2 diabetes, especially those with poor glycemic control. Cross-sectional studies[12] on diabetic patients showed lower serum magnesium concentrations than non-diabetic patients. According to a case-control study on 200 obese subjects, type 2 diabetes was the main factor accounting for the low serum magnesium levels in morbidly obese subjects[13]. Hyperinsulinemia *per se* may also contribute to urinary magnesium depletion[14].

Since serum magnesium levels have been related to high blood pressure and oxidative stress, which are risk factors for diabetes, hypomagnesemia can induce the development of type 2 diabetes by affecting those risk factors. In addition, hypomagnesemia was also associated with poorer glycemic control and nephropathy[14].

A systematic review[16] of 18 case reports of PPI-induced hypomagnesemia found that discontinuation of PPI use resulted in recovery from PPI-induced hypomagnesemia. Although many case reports[12] have described patients with PPI-induced hypomagnesemia, the impact of PPI use on hypomagnesemia has not been fully clarified in comparative studies.

In some studies[17], the association between PPI use and hypomagnesemia was not identified, while in others, PPI use was found to increase the risk of hypomagnesemia[12,18,19].

The discrepancy between these studies may be attributed to various patient characteristics and/or to the underlying conditions.

Hence the present study aims to assess hypomagnesemia in diabetic patients who are taking proton pump inhibitors. The main objective of this study is to determine the magnesium levels in patients with diabetes who are taking proton pump inhibitors and to correlate the magnesium levels in diabetic patients who take proton pump inhibitors with those not taking proton pump inhibitors.

It is expected that this will help the patients improve their magnesium levels and prevent the consequences of hypomagnesemia, including worsening glucose homeostasis.

Patients and Methods

A cross-sectional study was carried out in the study population comprising adult patients attending internal medicine clinics in King Khalid Hospital, Majmaah, KSA. A total of 200 patients who gave informed consent were recruited into the study over one year. Stratified random sampling was implemented with data representing two groups. The first group comprised diabetic patients not taking proton pump inhibitors, and the second group consisted of diabetic patients taking proton pump inhibitors. Children, pregnant ladies, critically ill, and non-diabetic patients were excluded from the study. The sample size was calculated using the formula for descriptive study $[(Z^2 \times P \times q)/d^2]$. The expected prevalence of hypomagnesemia with T2DM (p) = 15%, precision error of estimation (d) = 0.05, and alpha = 0.05, a sample size of 200 cases were taken. Patient data were collected using a questionnaire. Freshly drawn whole blood and serum were used for testing. Glycated hemoglobin and serum magnesium were assessed in all the patients. The chemistry parameters were assessed by SYNCHRON Beckman coulter dxc 600 fully automated clinical chemistry analyzer (Beckman Coulter, Inc., Brea, CA, USA).

Statistical Analysis

The data was entered and analyzed using SPSS 28 (IBM Corp., Armonk, NY, USA).

Table I. Socio-demographic and clinical characteristics of patients (n = 200).

	N	%
Age		
< 40 years	8	4
> 40 years	192	96
Gender		
Female	118	59
Male	82	41
Duration of DM		
< 1 year	12	6
1-5 yrs	34	20
5-10 yrs	52	26
> 10 yrs	96	48
Medication		
Insulin	53	26.5
OHG	168	84
Antacids	1	0.5
Multivitamins	119	59.5
Past illnesses		
Normal	93	46.5
Hypothyroid	38	19
Knee OA	35	17.5
CRF	9	4.5
Osteoporosis	9	4.5
C spondylitis	7	3.5
Low back pain	3	1.5
Neck OA	1	0.5
Back pain	1	0.5
Family history		
No	169	84.5
Yes	31	15.5

Frequencies and percentages are reported for qualitative variables. Pearson Chi-square and Fisher's Exact Tests were applied to observe associations between qualitative variables. A p-value < 0.05 was considered statistically significant. The ethical approval was obtained from Majmaah Research Institutional Ethics Committee of Basic and Health Science Research Center, Al Majmaah, and from Institutional Review Board King Faisal medical city, ethical committee Riyadh, vide IRB log number 18-189E. Informed consent was obtained from all subjects.

Results

In our study, male to female ratio was 0.6:1. In group 1, 32.5% were males, and 67.5% were females. Similarly, in group 2, 33.3% were males, and 66.7% were females. The mean age of patients was 60 and 54 years in groups 1 and 2, respectively. Other demographic and clinical parameters have been summarized in Table I.

The overall prevalence of hypomagnesemia was observed among 128 patients out of 200 (64%) diabetic patients (Table I). Relatively more patients with hypomagnesemia were found in group 2 (without PPI use) (38.5%) compared to group 1 (with PPI use) (25.5%). However, a statistically significant difference was not observed in group 1 using proton pump inhibitors and group 2 not using proton pump inhibitors (p-value = 0.473) (Table II). The only statistically significant parameter observed in the study was gender association (female preponderance) with hypomagnesaemia (p-value = 0.002).

We then determined the possible associations of plasma (Mg) with gender, duration of diabetes, use of various medications (insulin, oral hypoglycemic, antacids, and multivitamins) concurrent and past illnesses. All of which were observed in both groups. Comparisons were made using the Chi-square test. A p-value < 0.05 was considered significant. The results are summarized in Table III.

Discussion

In our study, while evaluating serum magnesium in patients with diabetes not taking proton pump inhibitors (Group 1) as compared with diabetic patients who are taking proton pump inhibitors (Group 2), we found that there was no significant difference between the two groups (p-value = 0.47). It was observed that the magnesium levels in group 2 were slightly low when compared to the magnesium levels of group 1, but

Table II. Association of Hypomagnesemia with PPI use in diabetics.

	Serum Mg level			
Group	Low n (%)	Normal n (%)	Total	p-value
DM with PPI use	51 (25.5)	25 (12.5)	76 (38)	0.473
DM without PPI use	77 (38.5)	47 (23.5)	124 (62)	
Total	128 (64)	72 (36)	200	

Table II. Association of Hypomagnesemia with PPI use in diabetics

	Hypomagnesemia			
	Yes; n (%)	No; n (%)	Total	*p*-value
Gender				0.002*
Female	86 (43)	32 (16)	118	
Male	42 (21)	40 (20)	82	
Duration of DM				0.138
< 1 year	8 (4)	4 (2)	12	
1-5 yrs	19 (9.5)	21 (10)	40	
5-10 yrs	36 (18)	16 (8)	52	
> 10 yrs	65 (32.5)	31 (15.5)	96	
Medication				
Insulin	36 (18)	17 (8.5)	53	0.966
OHG	108 (54)	60 (30)	168	0.679
Antacids	0 (0)	1 (0.5)	1	0.181
Multivitamins	81 (40.5)	38 (19)	119	0.146
Past illnesses				0.317
Normal	58	35	93	
Hypothyroid	22	18	38	
Knee OA	27	8	35	
CRF	5	4	9	
Osteoporosis	5	4	9	
C spondylitis	3	4	7	
Low back pain	3	0	3	
Neck OA	0	1	1	
Back pain	1	0	1	
Family history				0.454
No	110	59	169	
Yes	18	13	31	

the decreased level was not statistically significant. Generally, it is observed that serum magnesium level is low in diabetic patients; these findings were in contrast to numerous studies[6] that reported an inverse relationship between serum magnesium levels and glycemic control. Some authors suggested that diabetes *per se* may induce hypomagnesemia; others have reported that higher magnesium intake may confer a lower risk for type 2 diabetes[7-10]. However, not all studies[11] observed a correlation between glycemic control and serum Magnesium levels or improvement of diabetic control with magnesium replacement. The conflicting data may reflect different study designs and populations studied.

In our study, we also assessed magnesium levels in diabetic patients who were taking proton pump inhibitors and compared it with other diabetic patients who were not taking proton pump inhibitors. It was expected to get a serum magnesium level significantly low in people who have diabetes taking PPI when compared to the diabetic patient not taking PPI. However, it was found that there was a decrease in serum magnesium levels in diabetic patients who were taking proton pump inhibitors. However, the decreased value was not statistically significant compared to those diabetic patients who were not taking PPI. This observation was in accordance with other studies[17].

Although previous case reports[12] have described patients with PPI-induced hypomagnesemia, the impact of PPI use on hypomagnesemia has not been fully clarified in comparative studies[12].

Notably, the assessment of magnesium in diabetic patients who are taking proton pump inhibitors and its correlation with diabetic patients not taking PPI was not assessed in any previous studies. Our observations were in accordance with many studies[12,17-19] that state that hypomagnesemia is observed in diabetic patients and those taking PPI; we found no statistically significant difference between diabetic patients irrespective of taking proton pump inhibitors or not. These findings were in accordance with some studies which showed no association between PPI use and hypomagnesemia[17], while in others, PPI use was found to increase the risk of hypomagnesemia[12,18,19].

This kind of discrepancy between studies could be attributed to different patient characteristics and/or to their underlying clinical conditions. For example, one systematic review study[16] on 18 case reports found that discontinuation of PPI use resulted in recovery from PPI-induced hypomagnesemia.

In our study, most patients were above 40 years (96%), and female predominance comprised 59% of total patients, which was statistically significant (p-value = 0.002). Concerning the duration of diabetes, most patients had diabetes for more than ten years (48%). Furthermore, the medication history showed that 26.5% of patients were taking insulin, whereas most patients (84%) were on oral hypoglycemic drugs, predominantly on metformin (73%).

It was observed that patients were taking different types of insulin preparations, such as Glargine, Lantus [Glargine 100, Sanofi-aventis, (Paris, France)], Mixtard, Novomix, and Novarapid [Aspart, Novonordisk, (Bagsvaerd, Denmark)]. It was found that most of them were taking Aspartate insulin (45%), among them, the patient with hypomagnesemia constituted 41.6%, and those with normal magnesium levels were 25%. When different types of insulin preparation effects were observed in group 1 and group 2, it was observed that there was no statistically significant difference between both groups (p-value = 0.966). These findings contrasted with studies[14] that showed that hyperinsulinemia *per se* may also contribute to urinary magnesium depletion, thereby causing hypomagnesemia in those patients.

In order to rule out the effect of antacids and the use of multivitamins on magnesium levels in both groups, we assessed the use of antacids and multivitamins in patients with diabetes who are taking PPI as well as in diabetic patients not taking PPI; we observed that there was no statistically significant difference in both the groups, A p-value of 0.150 and 0.450 was observed for antacid use and multivitamin use, respectively.

The study results show that clinicians should be alerted to anticipate the occurrence of hypomagnesemia in diabetic patients and in patients who take proton pump inhibitors so that it can be diagnosed promptly. In addition, timely management can be initiated to prevent the complications associated with hypomagnesemia.

Limitations

The limitation of the study was that the sample size was small. Therefore, further research with a larger sample size needs to be conducted, and well-designed prospective cohort studies, which include regular serum magnesium monitoring in diabetic patients and patients using proton pump inhibitors, would provide more conclusive results.

Conclusions

It is concluded from our study that hypomagnesemia is seen in diabetic patients and patients who take proton pump inhibitors. Furthermore, it was found that there was no statistically significant difference in magnesium levels in diabetic patients irrespective of proton pump inhibitor use.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The Ethical approval was obtained from Majmaah Research Institutional Ethics Committee of Basic and Health Science Research Center, Al Majmaah, and from Institutional Review Board King Faisal Medical City, Ethical Committee Riyadh, vide IRB log number 18-189E.

Informed Consent

An informed consent was obtained from all the patients.

Authors' Contribution

M.A. Lateef Junaid: Conception and design, analysis, and interpretation of data, drafted and wrote the manuscript, edited, critically reviewed the manuscript for important intellectual content. A. Faraz: Drafted and wrote the manuscript, analysis, and interpretation of data, edited, critically reviewed the manuscript for important intellectual content. W. Sami: Statistical analysis. M. Vaseem: Conception and design, critically reviewed the manuscript and revised the manuscript for important intellectual content. I.M.A. Salih and H.A. H. Kutbi: Acquisition of data. M.Z. Al Julifi and F.M. Alfhaid: Approval of the final version of the manuscript to be published.

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