The Prevalence of Hypomagnesemia in Hospitalized Type 2 Diabetic Patients Treated with Diuretics and/or Proton Pump Inhibitors

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ABSTRACT

Background: Hypomagnesemia (serum magnesium level < 1.7 mg/dl) occurs more frequently in patients with type 2 diabetes mellitus (T2DM). Serum magnesium levels are not routinely tested in hospitalized patients, including in hospitalized patients with T2DM.

Objectives: To evaluate the prevalence of hypomagnesemia among hospitalized T2DM patients treated with proton pump inhibitors (PPIs) and/or diuretics.

Methods: A total of 263 T2DM patients hospitalized in general departments were included in the study and were further divided into four groups: group 1 (patients not treated with PPIs or diuretics), group 2 (patients treated with PPIs), group 3 (patients treated with diuretics), and group 4 (patients treated with both PPIs and diuretics). Blood and urine samples were taken during the first 24 hours of admission. Electrocardiogram was performed on admission.

Results: Of the 263 T2DM patients, 68 (22.1%) had hypomagnesemia (serum magnesium level < 1.7 mg/dl). Patients in group 2 had the lowest mean serum magnesium level (1.79 mg/dl ± 0.27). Relatively more patients with hypomagnesemia were found in group 2 compared to the other groups, although a statistically significant difference was not observed. Significantly more patients in group 3 and 4 had chronic renal failure. Patients with hypomagnesemia had significantly lower serum calcium levels.

Conclusions: Hospitalized T2DM patients under PPI therapy are at risk for hypomagnesemia and hypocalcemia.

KEY WORDS: diuretics, hypomagnesemia, proton pump inhibitor (PPI), type 2 diabetes mellitus (T2DM)

The relationship between serum levels and total body content is poor since serum magnesium values reflect only 1% of the body’s magnesium content, while 65% is stored in the mineral phase of bone and 34% is found in the cell space. Therefore, even when serum values are within the normal range, the body can be in a severely magnesium depleted state. Consequently, the clinical impact of magnesium deficiency may be largely underestimated [3-5]. Magnesium homeostasis in humans mainly involves the kidneys, the small intestine, and the skeletal system. Gastrointestinal absorption and renal excretion are the most important mechanisms for regulating the magnesium homeostasis [6].

Many patients with magnesium deficiency and hypomagnesemia remain asymptomatic. The clinical manifestations may depend more on the rate of development of magnesium deficiency and/or on the total body deficit rather than the actual serum magnesium concentration [7]. The clinical manifestations of hypomagnesemia may range from nausea, appetite loss, fatigue, general weakness, numbness and muscle cramps to more serious and fatal complications such as seizures, ventricular arrhythmia, coronary artery spasm, and sudden death [1,6].

Hypomagnesemia has been reported to occur more frequently in T2DM patients. Poor dietary intake, autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, and osmotic diuresis may be responsible [8]. Many therapeutic agents cause renal magnesium wasting and subsequent deficiency, including loop and thiazide diuretics, aminoglycosides, cyclosporine, and cisplatin [9]. Long-term proton pump inhibitor (PPI) use has also been associated with hypomagnesemia. This usage may be a result of impaired intestinal magnesium absorption due to disruption of active magnesium transport via TRPM6/7 channels. Often patients with PPI-associated hypomagnesemia develop other electrolyte disturbances, such as hypocalcemia and hypokalemia, which are refractory to calcium and potassium supplements unless hypomagnesemia is corrected [10,11]. The link between PPI use and hypomagnesemic hypoparathyroidism has also been stated by Epstein and co-authors [12] where patients treated by PPI presented with severe hypomagnesemia and hypocalcemia without an appropriate increase in the level of parathyroid hormone.

Several studies have provided convincing evidence in support of the direct effects of magnesium intake on insulin resistance and...
T2DM. Intracellular magnesium deficiency may lead to disorders of tyrosine kinase activity during insulin signaling and glucose-induced insulin secretion, resulting in impaired insulin sensitivity in muscle cells and adipocytes [13]. Oral magnesium supplementation restores serum magnesium levels, improving insulin sensitivity and metabolic control in T2DM patients with decreased serum magnesium levels. [14]. Therefore, it is essential to identify T2DM patients who are at increased risk to develop hypomagnesemia.

In this study, we examined the prevalence of hypomagnesemia in hospitalized T2DM patients receiving PPIs and/or diuretics.

**PATIENTS AND METHODS**

**STUDY DESIGN, SETTNGS, AND PARTICIPANTS**

In this cross-sectional, observational study, T2DM patients receiving PPIs and/or diuretics who had been admitted to internal medicine department at Assaf Harofeh Medical Center from February 2015 to February 2017 were included. All the patients treated with PPI who were included in the study had been on PPI treatment for at least 1 month duration or more. The study population was further categorized into four groups: patients not treated with PPIs or diuretics (group 1), patients under PPI treatment (group 2), patients under diuretics treatment (group 3), and patients treated with both PPIs and diuretics (group 4) [Figure 1].

Inclusion criteria: Patients age 30 years and older who were willing and capable of giving informed consent. Exclusion criteria: Patients not capable or willing to sign informed consent, critically ill patients, pregnant women, unconscious patients, patients younger than 30 years of age, patients taking magnesium supplements, those with repeat hospitalizations, patients on dialysis, and patients who were not able to confirm one month of treatment with PPIs.

Informed consent was obtained from all individual participants included in the study. Patients were asked to confirm taking PPIs and/or thiazide or loop diuretics during the month prior to hospitalization. Blood samples for magnesium, calcium, phosphorous, potassium, sodium, chloride, creatinine, fasting blood glucose, HbA1C, and urine samples for creatinine and magnesium were taken from every patient during the first 24 hours after admission. Demographic and clinical data were collected from the computerized registry of hospitalized patients. An ECG was conducted for each patient and QT and QTc intervals were measured. FeMg was calculated using the following formula:

\[
FeMg = \frac{(Urine\ Mg \times Plasma\ Cr)}{(0.7 \times \text{Plasma}\ Mg) \times \text{UrineCr}} \times 100\%
\]

The eGFR was calculated using the MDRD formula.

**COMPLIANCE WITH ETHICAL STANDARDS**

The study was conducted in compliance with the Declaration of Helsinki.

**ANALYTICAL APPROACH**

Categorical variables were reported as number and percentage. Continuous variables were evaluated for normal distribution using a histogram and Q-Q plot. Normally distributed continuous variables were reported as mean ± standard deviation and non-normally distributed continuous variables were reported as median and interquartile range. Continuous variables were compared between categories using analysis of variants, an independent samples t-test, the Kruskal–Wallis test, or the Mann–Whitney test. Categorical variables were compared using a chi square test or Fisher’s exact test. Univariate and multivariate logistic regression was used to study the association between the group and hypomagnesemia. Age, gender, and variables that were associated with the outcome at a significance level of P < 0.2 were included in the multivariate analysis. We also performed a multivariate analysis that included the group and propensity scores. The propensity score was calculated using multinomial logistic regression and included age, gender, and variables that were associated with the group at a significance level of P < 0.2. All statistical tests were two sided. P < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

**RESULTS**

Data were collected from a total of 307 patients; 44 patients were excluded due to lack of laboratory test results. Among the 263 patients included in the study, the mean ± standard deviation age was 69.6 ± 10.1 years, and 123 ± 47.8% were female. During the study, a single death due to septic shock was recorded.

The 263 T2DM patients included in the study were divided into four groups [Table 1]. Patients in group 1 were significantly
younger than the patients in group 3 and 4 (P = 0.003). The body mass index (BMI) of patients in group 1 and 2 were significantly lower compared to group 3 and 4 (P < 0.001). Regarding chronic illnesses, a significantly lower percentage of patients in group 1 had hypertension, ischemic heart disease, congestive heart failure, atrial fibrillation, and chronic pulmonary disease. A significantly lower percentage of patients in group 2 had chronic renal failure, followed by group 1.

Comparing the four groups according to serum magnesium levels, the T2DM patients in group 2 had the lowest mean serum magnesium level (1.79 ± 0.27, P = 0.003). Group 1 had lower average magnesium levels, but not significantly lowers than groups 3 and 4. Interestingly, the average FeMg of groups 1 and 2 was lower, excluding hypermagnesuria in these groups as the cause for lower magnesium.

The percentage of patients with hypomagnesemia was higher in group 2 (30.9% in group 2 vs. 21.1% in group 1, 14.5% in group 3 and 20% in group 4; P = 0.168). The serum creatinine was significantly higher and eGFR was significantly lower in groups 3 and 4 compared to groups 1 and 2 [Table 2].

There were no patients with hypermagnesemia in groups 1 and 2 (data not shown). Among T2DM patients treated with diuretics, most (82%) were treated with loop diuretics, whereas 14% were treated with thiazide diuretics and 4% were treated with both loop and thiazide diuretics. Among T2DM patients treated with PPI, 76.1% were treated with omeprazole, 7.96% were treated with esomeprazole, 14.15% were treated with lansoprazole, and 1.76% were treated with pantoprazole. Regarding insulin treatment 19.1% of the diabetic patients in group 2 were treated with insulin, compared to 29.5% diabetic patients in group 1, 38.2% diabetics in group 3, and 46.7% diabetics in group 4 (P = 0.012).

Of the 263 T2DM patients, 58 (22.1%) had hypomagnesemia (serum magnesium level < 1.7 mg/dl) [Table 3]. We compared causes of admission among patients with hypomagnesemia to the rest of the patients. Patients with hypomagnesemia were more likely to be admitted due to infectious diseases (32.8% in the hypomagnesemia group vs. 19% in the non-hypomagnesemia group, P = 0.026). However, 52 of the patients (25.4%) with magnesium levels ≥ 1.7 mg/dl were admitted due to cardiovascular diseases. The patients who were admitted with infectious diseases and received antibiotics were mainly treated with cephalosporin, macrolide, and quinolone.
None were treated with aminoglycosides. No patient with hypomagnesemia was admitted due to cerebrovascular accident; however, 21 patients (10.2%) with a serum magnesium level ≥ 1.7 mg/dl were admitted due to cerebrovascular accident (P = 0.006).

As shown in Table 3, there was a statistically significant difference in serum calcium levels in patients with hypomagnesemia compared to patients with magnesium levels ≥ 1.7 mg/dl (P = 0.007). No statistically significant difference was observed regarding serum albumin, creatinine, FeMg, and HbA1C. When we compared magnesium levels by eGFR, 63.8% of the patients with hypomagnesemia had an eGFR ≥ 60 ml/min/1.73 m² and 36.1% had renal failure, and 5.1% of those with renal failure had an eGFR below 30 ml/min/1.73 m². However, among the group with serum magnesium ≥ 1.7 mg/dl, up to 59% of patients had an eGFR above 60 ml/min/1.73 m² and 11.7% of patients had an eGFR below 30 ml/min/1.73 m². No statistically significant difference was observed.

There was no statistically significant difference observed regarding electrocardiogram findings, including QTc intervals between patients with hypomagnesemia and patients with magnesium levels ≥ 1.7 mg/dl. A univariate and multivariate logistic regression was performed, and no significant association was observed between the groups regarding hypomagnesemia after adjusting for age, gender, BMI, congestive heart failure, atrial fibrillation, and chronic kidney disease.

**DISCUSSION**

In this study, we looked at the prevalence of hypomagnesemia among hospitalized patients with T2DM treated with diuretics and/or PPIs. Similar to other studies, we found that a significant portion of patients with T2DM in general wards present with hypomagnesemia (22.1%) [1,15,16]. When we grouped the patients by drug treatment, we found that patients with T2DM treated with PPIs (group 2) had significantly lower mean serum magnesium levels compared to the other groups. The group treated with PPIs also had the highest percentage of patients with hypomagnesemia. Patients treated with PPI and patients not treated with PPI or diuretics (group 1) were significantly younger and had fewer instances of chronic kidney disease. This fact may explain the higher mean serum magnesium levels seen in the other groups. When we compared patients with hypomagnesemia to those with serum magnesium levels ≥ 1.7 mg/dl, we found that the group of patients with hypomagnesemia had significantly lower levels of serum calcium. Patients with hypomagnesemia were admitted mainly due to infectious disease.

Kurstjens and colleagues [1] showed that, among patients with T2DM, only a minor part (< 10%) of hypomagnesemia can be explained by polypharmacy. In contrast, our study suggests that hospitalized patients with T2DM are at risk for hypomagnesemia and hypocalcemia, especially if they are under long-term PPI treatment. PPI-induced hypomagnesemia has been described primarily in long-term users of these drugs. Although the potential underlying mechanism remains unclear, impairment in intestinal magnesium absorption is likely to contribute to hypomagnesemia associated with PPI use [10]. A systemic review and meta-analysis conducted on nine studies, which included a total of 115,455 patients, showed that among patients taking PPIs, the median proportion of patients with hypomagnesemia was 27.1% (range 11.3–55.2%) across all included studies [17,18].

**Table 2. Laboratory indexes by group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>95 (36.1)</td>
<td>68 (25.9)</td>
<td>55 (20.9)</td>
<td>45 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Serum Mg (mg/dl), mean ± SD</td>
<td>1.84 ± 0.25</td>
<td>1.79 ± 0.27</td>
<td>1.95 ± 0.30</td>
<td>1.95 ± 0.35</td>
<td>0.003*</td>
</tr>
<tr>
<td>Hypomagnesemia (serum Mg &lt; 1.7 mg/dl), n (%)</td>
<td>20 (21.1)</td>
<td>21 (30.9)</td>
<td>8 (14.5)</td>
<td>9 (20.0)</td>
<td>0.168</td>
</tr>
<tr>
<td>Serum Cr (mg/dl), median (range)</td>
<td>0.86 (0.68-1.16)</td>
<td>0.86 (0.71-1.12)</td>
<td>1.24 (0.99-1.74)</td>
<td>1.06 (0.89-1.64)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Serum K (mg/dL), mean ± SD</td>
<td>4.28 (0.55)</td>
<td>4.18 (0.50)</td>
<td>4.18 (0.48)</td>
<td>4.33 (0.62)</td>
<td>0.364</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²), mean ± SD</td>
<td>82.18 (32.84)</td>
<td>84.26 (38.67)</td>
<td>57.02 (28.51)</td>
<td>57.85 (29.06)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>FeMg (%), median (range)</td>
<td>4.51 (2.55-7.80)</td>
<td>4.36 (2.53-6.95)</td>
<td>6.01 (3.36-13.14)</td>
<td>7.20 (4.26-13.11)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Serum albumin (g/dl), mean ± SD</td>
<td>3.684 (0.53)</td>
<td>3.70 (0.41)</td>
<td>3.65 (0.64)</td>
<td>3.67 (0.53)</td>
<td>0.952</td>
</tr>
<tr>
<td>HbA1C (%), median (range)</td>
<td>6.60 (5.90-8.20)</td>
<td>6.60 (6.20-8.00)</td>
<td>7.30 (6.37-8.37)</td>
<td>7.20 (6.40-8.00)</td>
<td>0.238</td>
</tr>
</tbody>
</table>

Cr = creatinine, eGFR = estimated glomerular filtration rate, FeMg = fractional excretion of magnesium, HbA1C = hemoglobin A1C, K = potassium, Mg = magnesium, PPI = proton pump inhibitors, SD = standard deviation

Conversion factor for serum Mg in mg/dl to mEq/L, × 0.823
Table 3. Patient characteristics and laboratory indices by serum magnesium levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypomagnesemia n (%)</th>
<th>Magnesium level ≥ 1.7 mg/dl n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years mean ± SD</td>
<td>70.22 ± 10.41</td>
<td>69.48 ± 10.03</td>
<td>0.625</td>
</tr>
<tr>
<td>Gender: male/female, n (%)</td>
<td>30 (51.7)/28 (48.3)</td>
<td>110 (53.7)/95 (46.3)</td>
<td>0.794</td>
</tr>
<tr>
<td>Body mass index, median (range)</td>
<td>28.70 (25.39–32.04)</td>
<td>29.38 (26.00–33.86)</td>
<td>0.163</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>46 (79.3)</td>
<td>167 (81.5)</td>
<td>0.712</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>6 (10.3)</td>
<td>37 (18.0)</td>
<td>0.161</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>10 (17.2)</td>
<td>68 (33.2)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>21 (36.2)</td>
<td>86 (42.0)</td>
<td>0.432</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>6 (10.3)</td>
<td>38 (18.5)</td>
<td>0.140</td>
</tr>
<tr>
<td>Chronic pulmonary diseases, n (%)</td>
<td>11 (19.0)</td>
<td>37 (18.0)</td>
<td>0.873</td>
</tr>
<tr>
<td>Cerebrovascular accident/transient ischemic accident, n no. (%)</td>
<td>6 (10.3)</td>
<td>37 (18.0)</td>
<td>0.873</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>32 (55.2)</td>
<td>144 (71.2)</td>
<td>0.021*</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>2 (3.4)</td>
<td>15 (7.3)</td>
<td>0.378</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl, median (range))</td>
<td>0.94 (0.70–1.24)</td>
<td>0.98 (0.78–1.38)</td>
<td>0.251</td>
</tr>
<tr>
<td>FeMg (%), median (range)</td>
<td>4.88 (2.69–10.56)</td>
<td>5.24 (2.88–8.62)</td>
<td>0.711</td>
</tr>
<tr>
<td>Serum albumin (g/dl), mean ± SD</td>
<td>3.52 ± 0.47</td>
<td>3.72 ± 0.48</td>
<td>0.946</td>
</tr>
<tr>
<td>Serum calcium (mg/dl), mean ± SD</td>
<td>8.68 ± 0.80</td>
<td>8.94 ± 0.55</td>
<td>0.007*</td>
</tr>
<tr>
<td>Serum phosphor (mg/dl), mean ± SD</td>
<td>3.21 ± 0.77</td>
<td>3.37 ± 0.90</td>
<td>0.168</td>
</tr>
<tr>
<td>Serum potassium (mmol/L), mean ± SD</td>
<td>4.08 (0.52)</td>
<td>4.29 (0.54)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

*P < 0.05
SD = standard deviation

Hypomagnesemia has been reported to occur at increased frequency among patients with T2DM compared to their non-diabetic counterparts [13]. Several mechanisms such as osmotic diuresis, hyperinsulinemia, and the common use of diuretics contribute to the development of hypermagnesuria and, subsequently, hypomagnesemia among patients with T2DM. On the contrary, we did not find a significant number of patients with hypomagnesemia among diuretics users, nor did we find increased fractional excretion of magnesium among hypomagnesemic patients.

We found that the prevalence of chronic kidney disease was significantly higher among diuretics users (group 3 and 4). That result might have contributed to the finding of higher serum mean magnesium levels in these groups and the occurrence of hypermagnesemia in some patients. The renal handling of magnesium is highly adaptable, but this ability deteriorates when renal function declines significantly. In moderate chronic kidney disease, there is a compensatory increase in the fractional excretion of magnesium for the loss of glomerular filtration rate in order to maintain normal serum magnesium levels. In more advanced chronic kidney disease (as creatinine clearance falls < 30 ml/min), this compensatory mechanism becomes insufficient, and overt hypermagnesemia develops frequently in patients with creatinine clearances < 10 ml/min. [19].

Hypomagnesemia is known to cause hypocalcemia via peripheral parathyroid hormone (PTH) resistance, inhibition of PTH secretion, and impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [20]. Unsurprisingly, patients with hypomagnesemia had significantly lower mean levels of calcium in our study.

In examining causes of admission according to serum magnesium levels, most patients with hypomagnesemia were admitted due to infectious diseases. It is important to note that none of the patients admitted due to infectious diseases were treated with aminoglycosides in the first 24 hours of admission, and acute gastroenteritis was not included under infectious diseases. Furthermore, pneumonia and urinary tract infections were the most common cause of admission among infectious diseases. We believe that this finding is incidental and not causal, since these diseases by themselves are not known to cause hypomagnesemia, and critically ill patients were excluded from the study.
Most of the patients with magnesium levels ≥ 1.7 mg/dl were admitted due to cardiovascular diseases. Hypomagnesemia is associated with insulin resistance and poor glycemic control. In our study, no statistically significant difference was observed regarding HbA1C levels when comparing patients with hypomagnesemia to patients with serum magnesium levels ≥ 1.7 mg/dl.

No statistically significant difference was observed regarding electrocardiogram findings, including QTc intervals between patients with hypomagnesemia and patients with magnesium levels ≥ 1.7 mg/dl.

LIMITATIONS
The main study limitations include a small sample size and the lack of information about the total duration of PPI use. In addition, medication adherence was assumed to be 100%. Since this was an observational study the groups were different regarding baseline characteristics. During the analysis, we tried to overcome this limitation by performing a multivariate analysis and multivariate analysis adjusted for propensity score.

CONCLUSIONS
Our study suggests that hospitalized patients with T2DM treated with PPI are at risk of hypomagnesemia and hypocalcemia. Health professionals should use more caution in prescribing long-term PPI treatment, particularly in patients with T2DM. When such a patient is hospitalized, attention should be given to the possibility of hypomagnesemia and hypocalcemia.

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References