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The Prevalenceof Hypomagnesemiain Essential Hypertensive Patients

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Abstract: ***Magnesium is the fourth most common cation in the human body, and it plays a critical role in many metabolic processes, including production and use of the energy essential in the maintenance of normal intracellular electrolyte composition. In general, gastrointestinal losses and renal magnesium wasting constitute the major causes of hypomagnesemia . The acquired forms of renal magnesium wasting are largely drug induced. We analyzed serum magnesium levels in ambulatory patients with uncomplicated essential hypertension who are under diuretic or diuretic combination therapy and who are under non-diuretic antihypertensive therapy. We planned to determine hypomagnesemia prevalence in patients on different antihypertensive medications. Serum magnesium levels were determined in 1000 patients attending Antalya Training and Research Hospital, Hypertension Clinic. A total of 456 patients in 2012 and 544 patients in 2013 were enrolled in this study. All patients were on antihypertensive therapy for at least 1 year. Magnesium level below 1.7 mg/dl was considered as hypomagnesemia. The study group included 51.7% male and 48.3% female patients and the mean age was 56.20 ± 17.64 years. Because the proton pump inhibitors may cause hypomagnesemia, patients taking these drugs were also recorded and included in study groups. In both groups, there was statistically no significant difference between the number of the hypertensive agents and the frequency of hypomagnesemia (p>0,05). The chi-squared test found the hypomagnesemia prevalence as 7.1% in the diuretic group, while it was 6.8% .The relationship between the development of hypomagnesemia and use of proton pump inhibitors (PPIs) was also evaluated. 48 patients (9,3%) in diuretic group and 53 patients(10,8) in the non-diuretic group were using PPIs. When the 2 groups were compared in means of hypomagnesemia development, 8 patients in the diuretic receiving group (16.6%) and 4 patients in the non-diuretic receiving group (7.54%) had hypomagnesemia, and the difference was statistically significant (p<0,005). In addition, in our study, the relationship between the number of the antihypertensive drugs and hypomagnesemia presence was evaluated in diuretic and non-diuretic receiving groups, according to the number of the antihypertensive agents the patients were taking. In both groups, there was statistically no significant difference between the number of the hypertensive agents and the frequency of hypomagnesemia (p>0,05). In summary, in ambulatory hypertensive patients which use diuretic and nondiuretic antihypertensive combinations, there was statistically no significant difference in hypomagnesemia frequency. Routine measurement of serum magnesium proved unrewarding in these group of patients. Except in patients receiving high-dose thiazides and loop diuretics, the prevalence of hypomagnesemia may be higher. Serum magnesium determinations might be reserved for selected circumstances, when other factors potentiating magnesium deficiency are present; such as patients with nutritional problems and low dietary intake, gastrointestinal losses, renal losses and PPIs usage. Therefore, in patients with uncomplicated hypertension, if there is no symptom regarded with hypomagnesemia, routine serum magnesium determination seems unnecessary.***

Keywords: Prevalence, Hypomagnesemia, Essential Hypertension, Patients

1. Introduction

Magnesium is the fourth most common cation in the human body, and it plays a critical role in many metabolic processes, including production and use of the energy essential in the maintenance of normal intracellular electrolyte composition. It is predominantly an intracellular cation with less than 1% in the extracellular space (1). Cellular and extracellular magnesium concentrations are carefully regulated by the gastrointestinal (GI) tract, kidney, and bone. In general, gastrointestinal losses and renal magnesium wasting constitute the major causes of hypomagnesemia (2). The acquired forms of renal magnesium wasting are largely drug induced. Renal magnesium wasting has been well documented in a number of patients receiving drugs; virtually all diuretics can increase magnesium excretion modestly.(3). Diuretics are widely used in nephrology practise for hypertension therapy. Nevertheless, serum magnesium levels are measured rather infrequently compared with routine determinations of sodium, potassium, and calcium. Consequently, physicians are less recognizant of the conditions in which magnesium deficiency occurs. Diuretics are often incriminated, however, a number of reports citing diuretics as a major cause of hypomagnesemia include substantial numbers of patients with heart failure, alcoholism, malnutrition, uncontrolled diabetes, and other factors that can contribute to magnesium deficiency (4). Loop diuretics are potent magnesiuric agents, whereas potassium-sparing diuretics conserve magnesium also (5,6). The data regarding thiazide diuretics are inconclusive (7,8). Although they seem to induce, at least acutely, modest urinary magnesium losses are observed (9). Their effects on serum magnesium levels are less clear. Dose may be an important factor. In an early study suggesting thiazide-induced hypomagnesemia, high doses (100 to 150 mg) of hydrochlorothiazide were used, and an inverse relationship between serum magnesium levels and hydrochlorothiazide dose over the entire range of 12.5 to 200 mg was recently reported (10). The issue is important in that magnesium deficiency can result in serious ventricular arrhythmias (11,12). A number of authors advocate routine magnesium determinations to detect what they perceive to be a common problem, namely, diuretic-induced hypomagnesemia (13,14). Given the prevalence of diuretic

use, this policy would be expensive and should be supported by clinical data from appropriate populations. Therefore, we analyzed serum magnesium levels in ambulatory patients with uncomplicated hypertension who are under diuretic or diuretic combination therapy and hypertensive patients who are under non-diuretic antihypertensive therapy. We planned to determine hypomagnesemia prevalence in patients on different antihypertensive medications.

2. Patients and Method

Serum magnesium levels were determined in 1000 patients attending Antalya Training and Research Hospital, Hypertension Clinic. A total of 456 patients in 2012 and 544 patients in 2013 were enrolled in this study. All patients were on antihypertensive therapy for at least 1 year. Magnesium level below 1.7 mg/dl was considered as hypomagnesemia. The study group included 51.7% male and 48.3% female patients and the mean age was 56.20 ± 17.64 years (range: 20 to 86 years). Magnesium analyses were performed using spectrophotometric method. In addition to the magnesium level, serum potassium, urea, creatinin, calcium and uric acid levels were determined. Type of diuretics, other antihypertensive medications, other drugs and diseases were also recorded from the charts. Patients with renal failure, heart failure or cancer and the patients using drugs that cause hypomagnesemia such as chemotherapy agents or aminoglycoside antibiotics were excluded from the study. Because the proton pump inhibitors widely used and may cause hypomagnesemia, patients taking these drugs were also recorded and included in study groups. Patients with diabetes mellitus (without nephropathy) were also included in this study. All patients were divided into two groups: Group 1: Receiving hydrochlorothiazide or diuretic plus ACE / ARB combination or diuretic plus ACE/ARB and calcium canal blockers (CCBs), Group 2: Receiving non-diuretic antihypertensive drugs; ACE or ARB inhibitors, CCBs, beta blockers and alfa adrenergic blockers only or with combinations. In diuretic taking group, the indapamide dose was 1.5 mg/day and thiaside dose was 12.5 mg/day. In addition, the patients that use antihypertensive drugs were classified according to the number of the drugs, as 1,2 or 3 and more antihypertensive drugs.

Data were analyzed with an IBM SPSS Statistics 22 program. The data were evaluated with frequency distribution for categorical variables, and with descriptive statistics (mean value ± ss) for persistent variables (ort. ± ss). Associations between 2 independent categorical variables were evaluated with chi-squared test. For the age variable, Kolmogorov-Smirnov normality test was used and because the normality assumption was achieved, the parametric sample t test was used to evaluate the difference between the 2 independent groups.

3. Results

Table 1, shows the antihypertensive drug use rates and the treatment regimens for both groups. The total number of the patients was 1000, with 513 patients in Group 1 and 487 patients in Group 2. There was no significant difference between the age and sex distribution between the groups. The prevalence of DM was 19% and 17 % respectively in both groups, and the intergroup difference was statistically no significant. The chi-squared test found the hypomagnesemia prevalence as 7.1% in the diuretic group, while it was 6.8% in the non-diuretic taking group ($p = 0.802$). According to this, there is no statistically significant relationship between the use of diuretics with hypomagnesemia. The group of patients using diuretics had significantly lower potassium levels in hipomagnesemic group than the non-diuretic receiving group.No significant difference was observed in the serum BUN, creatinine, calcium, phosporus, sodium and uric acid concentrations between the two groups (receiving diuretics or diuretic ACE/ARB/CCBs combination and those receiving non diuretic antihypertensive therapy) (Table 2).

When the patients with low magnesium levels are evaluated, 37.2% of them were male, and 62.8% were female. The chi-squared test revealed a statistically significant relationship between the magnesium levels and the gender ($p <0.001$). Therefore, the low magnesium values in women are significantly higher than hypertensive male patients. The independent sample t test revealed that there is no statistically significant difference between the age and the magnesium levels ($p> 0.05$). The mean age of patients in the hypomagnesemic group was 58.43 ± 16.74, and 55.84 ± 17.76 in the group with normal magnesium levels; the difference was statistically not significant ($p= 0.119$).

When the relationship between the hypomagnesemia in patients with low levels of magnesium and other parameters was considered, the potassium was low in 4.9% of the hypomagnesemic group, and this rate was 1.0% in the group of patients with normal magnesium levels; the difference was statistically significant ($p =0.026$). There was no statistically significant relationship between the hypomanesemia and BUN, creatinine, sodium, uric acid, calcium and phosphorus measurements ($p>0.05$), (Table 3).

The relationship between the development of hypomagnesemia and use of proton pump inhibitors (PPIs) was also evaluated. 48 patients (9,3%) in diuretic group and 53 patients(10,8) in the non-diuretic group were using PPIs.When the 2 groups were compared in means of hypomagnesemia development, 8 patients in the diuretic receiving group (16.6%) and 4 patients in the non-diuretic receiving group (7.54%) had hypomagnesemia, and the difference was statistically significant ($p<0,005$), (Table 4).

In addition, in our study, the relationship between the number of the antihypertensive drugs and hypomagnesemia presence was evaluated in diuretic and non-diuretic receiving groups, according to the number of the antihypertensive agents the patients were taking. In both groups, there was statistically no significant difference between the number of the hypertensive agents and the frequency of hypomagnesemia($p>0,05$) (Table 5).

4. Discussion

The average daily diet contains 20 to 30 mEq (240 to 360 mg) of elemental magnesium (SCRİER 2). The requirement of magnesium is considered to be about 18 to 33 mEq/day

for young men and 15 to 28 mEq/day for women. This suggests that the average diet is at borderline levels for maintenance of magnesium levels in healthy adults. Magnesium is ubiquitous in our diet and is especially abundant in green vegetables rich in chlorophyll (a chelator of magnesium), as well as in seafood, grains, nuts, and meats (2). Under normal circumstances, the GI tract and kidney closely maintain magnesium balance. Normal serum magnesium concentrations range between 1.5 and 2.3 mEq/L (0.75 to 1.15 mmol/L) in healthy subjects, with a variation between the different laboratories. Serum levels of 1.7 mEq/L usually indicate magnesium deficiency (1,2,3). Only about 1% to 2% of the 21 to 28 g (1,750 to 2,400 mEq) of magnesium present in the adult human body is in the extracellular fluid (ECF) compartment (3). The principal cellular stores of magnesium in the body are bone (67%) and muscle (20%). The status of body magnesium balance and particularly ECF magnesium concentration is largely determined by the renal excretion of magnesium (15). Unlike most cations, the loop of Henle is the major site of magnesium reabsorption. Magnesium concentration in the early distal tubular fluid is only 60% to 70% of the ultrafiltrable magnesium concentration, suggesting that some 50% to 60% of the filtered magnesium is reabsorbed in the loop of Henle, primarily in the thick ascending limb (TAL). In the distal convoluted tubule, fine-tuning of magnesium reabsorption occurs (16).

The first description of symptoms related to hypomagnesemia was in 1960 when Vallee et al. (17) described five patients with hypomagnesemia and symptoms and signs that are now felt to be classic for magnesium deficiency. Magnesium deficiency may be caused by decreased intake or intestinal absorption, increased losses via the GI tract, kidneys, or skin, and rarely, by sequestration in the bone compartment (18). The acquired forms of renal magnesium wasting are largely drug induced. Renal magnesium wasting has been well documented in a number of patients receiving drugs, virtually all diuretics (19). Recently, proton pump inhibitors (PPIs) have been reported to cause hypomagnesemia in some patients. The evidence suggests that it is due to intestinal Mg malabsorption.(20). Loop diuretics inhibit the apical membrane NaK2Cl cotransporter of the TAL and abolish the transepithelial potential difference, thereby inhibiting paracellular Mg reabsorption. (21). Long-term treatment with thiazide diuretics, which inhibit the NaClcotransporter (NCC), also cause renal Mg wasting. Thiazide diuretics causedownregulation of expression of TRPM6, the apical Mg entry channel in the distal convoluted tubule (DCT), which may explain the mechanism of the magnesuria (22). Kroenke et al. in their similar study found no difference in serum magnesium levels between the diuretic users and nondiuretic users, reporting a rate of 10% in the diuretic group. They stated that they found no difference due to the generally low doses of diuretics used as antihypertensive agents, and the use of drugs such as thiazide diuretics which cause hypomagnesemia in higher doses (23). Dose may be an important factor. In an early study (24) suggesting thiazide-induced hypomagnesemia, high doses (100 to 150 mg) of hydrochlorothiazide were used, and an inverse relationship between serum magnesium levels and hydrochlorothiazide dose over the entire range of 12.5 to 200 mg was recently reported (25). However also in our study, hypomagnesemia prevalence was 7.1% in the diuretic group ans 6.8% in the nondiuretic group in the total group of patients, with no significant difference. In our patient group, the diuretic drug was generally in combination with ACE or ARB, with a dosage of 12.5 mg. This suggests that the thiazide diuretics at these dose ranges do not contribute to the hypomagnesemia in hypertensive patients.

It is observed that the only significantly correlated electrolyte with the presence of hypomagnesemia is potassium in the patients that use diuretic combinations in our study. A mild hypokalemia tendency was observed in the diuretic group. While some studies have suggested a frequent association between deficiencies of these two cations (26), others have noted a poor correlation (27). Studies showing a good correlation have often involved hospitalized patients in whom the prevalence of both hypokalemia and hypomagnesemia is much higher than in ambulatory patients and in whom other factors contributing to the depletion of these two cations, such as alcoholism malnutrition, and heart failure, are commonly present. Tissue levels of potassium and magnesium may show a better correlation than serum levels (28,29).

According to our results, the use of PPIs in combination with antihypertensive agents including diuretics increase the frequency of hypomagnesemia. Hypomagnesemia has been described usually in case reports with the chronic use of omeprazole (usually for more than one year) and PPIs [30-31]. The association of PPIs with lower serum magnesium has also been described in population studies. The best data come from a large cohort of 11,490 patients admitted to the intensive care unit at a single center (32). In this study, the relationship between PPI use and magnesium varied by whether patients concurrently used diuretics. The presumed mechanism is impaired absorption of magnesium by intestinal epithelial cells caused by PPI-induced inhibition of transient receptor potential melastatin-6 (TRPM6) and TRPM7 channels [33]. Renal losses are not likely to be involved since urinary magnesium excretion is appropriately low in patients with hypomagnesemia due to PPIs (34).

In March 2011, the United States Food and Drug Administration (FDA) issued a safety warning suggesting that, in patients expected to be on PPIs for long periods of time and in those taking other medications associated with hypomagnesemia as described below (eg, diuretics), providers should measure the serum magnesium levels prior to initiation of PPI therapy and also periodically during the treatment (35).

Magnesium may influence blood pressure by modulating vascular tone and structure through its effects on myriad biochemical reactions that control vascular contraction/dilation, growth/apoptosis, differentiation and inflammation. Magnesium acts as a calcium channel antagonist, it stimulates production of vasodilator prostacyclins and nitric oxide and it alters vascular responses to vasoconstrictor agents.(36) Alterations in some of these systems may contribute to hypomagnesemiaand susceptibility for hypertension or decreased antihypertensive drug response. Magnesium therapy can prevent the

development of resistant hypertension and arrhythmias in hypertensives with diuretic-induced hypomagnesemia. It might also reduce blood pressure at least up to 10/5 mm Hg provided adequate magnesium salts are given for an adequate period of time (37). The prevalence of prehypertension(preHTN) in adult population is 37.5%, and hypomagnesemia is strongly associated with preHTN(38). In according with these results, we evaluated the relationship between the number of the antihypertensive drugs and hypomagnesemia presence. Our results show that, in both diuretic and nondiuretic groups, there was statistically no significant difference between the number of the hypertensive agents and the frequency of hypomagnesemia (p>0,05). It seems that presence of hypomagnecemia doesn't affect drug numbers that needs to control hypertension. But we need more study about this subject.

In summary, in ambulatory hypertensive patients which use diuretic and nondiuretic antihypertensive combinations, there was statistically no significant difference in hypomagnesemia frequency. Routine measurement of serum magnesium proved unrewarding in these group of patients. Except in patients receiving high-dose thiazides and loop diuretics, the prevalence of hypomagnesemia may be higher. Serum magnesium determinations might be reserved for selected circumstances, when other factors potentiating magnesium deficiency are present; such as patients with nutritional problems and low dietary intake, gastrointestinal losses, renal losses and PPIs usage. Therefore, in patients with uncomplicated hypertension, if there is no symptom regarded with hypomagnesemia, routine serum magnesium determination seems unnecessary.

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Tables

Table 1: Anthypertensive regimens in two groups

GROUP 1	**N (513)**	**%**
Indapamide	50	5.0
ACE inh.+Thiazide	197	19.7
ARB inh.+Thiazide	131	13.1
ACEor ARB inh.+Thiazide+CCBs	98	9.8
Other combinations with diuretics	37	3.7
GROUP 2	**N (487)**	
ACE inh.	76	7.6
ARBinh.	48	4.8
CCBs	134	13.4
ACE or ARB inh + CCBs	142	14.2
Beta blockers	67	6.7
Other combinations without diuretics		2
Total	1000	100

Table 2: Comparison ofBiochemical Parameters in Two Groups

	Group 1	**Group 2 p value**
BUN		
	16,35	14,40 NS
CREATININE		
	0,90	0,94 NS
SODIUM		
	139,33	138,22 NS
POTASSIUM		
	4,49	3,52 0,026
CALCIUM		
	9,52	9,61 NS
MAGNESIUM		
	1,95	2,05 NS
URIC ACID		
	5,51	5,23 NS
PHOSPORUS		
	3,43	3,51 NS

NS: Not significant; p value >0,05.

Table 3: The Relationship Between the Magnesium Levels and Other Measurements

			Magnesium		
			Low	Normal	
BUN	Low	%	1,6	1,0	
	Normal	%	98,4	99	
Creatine	Low	%	0,9	0,8	
	Normal	%	99,1	99,2	
Sodium	Low	%	14,0	10,2	
	Normal	%	86,0	89,8	
Potassium	Low	%	3,9	1,0	
	Normal	%	84,5	84,0	
	High	%	13,6	15,0	
Calcium	Low	%	1,7	1,6	
	Normal	%	98,3	98,4	
Uric acid	Low	%	8,5	6,2	
	Normal	%	66,7	69,5	
	High	%	24,8	24,3	
Phosphorus	Low	%	3,9	4,7	4.6
	Normal	%	96,1	95,3	86

Table 4: The Relationship Between the PPI Use and Hypomagnesemia

	Diuretic group		Nondiuretic group		P value
	The number of patients	Hypomg patients	The number of patients	Hypomg patients	
PPI users	48	8	53	4	0.01
Non-PPI users	465	24	434	28	0.32
Total number of patients	513	36	487	33	0.34

Table 5: The Relationship Between the Number of Antihypertensives and Hypomagnesemia

	Diuretic group		Nondiuretic group		P Value
The number of antiHT drugs	The number of patients	Hypomg patients	The number of patients	Hypomg patients	
1	87	5	92	5	NS
2	328	22	283	19	NS
3 and more	98	9	112	9	NS
Total number of patients	513	36	487	33	NS

NS: Not significant; p value >0,05.