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.