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Preoperative Low Serum Magnesium Level is a Significant Predictive Factor for Postoperative Hypomagnesemia in Patients Who Underwent Parathyroidectomy for Primary Hyperparathyroidism

Primer Hiperparatiroidi Cerrahisinde Ameliyat Öncesi Düşük Serum Magnezyum Düzeyi Postoperatif Hipomagnezemi için Önemli Bir Prediktif Faktördür

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ABSTRACT

Aim: Parathyroidectomy causes significant changes in mineral metabolism in patients with primary hyperparathyroidism (PHPT). Hypomagnesemia may be seen after parathyroidectomy with unknown mechanisms. Our study aimed to evaluate the severity of hypomagnesemia and its correlation with clinical and biochemical variables after the surgery.

Materials and Methods: A retrospective study was conducted in the patients with parathyroidectomy for PHPT between January 2017 and December 2020 in a single tertiary hospital. All consecutive patients with preoperative and postoperative magnesium levels (n=80) were included. Patients were divided into two groups according to the postoperative first-day serum magnesium levels: patients whose serum magnesium was <1.9 mg/dL (group HypoMg) and patients whose serum magnesium was ≥1.9 mg/dL (group NorMg). Demographic and clinical parameters and biochemical findings were recorded. The incidence of postoperative hypomagnesemia was the primary outcome.

Results: The mean age was 56.7±12.2 years. The female to male ratio was 3.21. There were 31 (38.8%) and 49 patients (61.2%) in group HypoMg and group NorMg, respectively. The groups were similar considering demographic and clinical parameters (p>0.05). There were no significant differences in the preoperative serum calcium, adjusted calcium, and parathyroid hormone levels between the groups (p>0.05). Preoperative magnesium levels were significantly lower in the HypoMg group (p<0.001). Postoperative serum magnesium levels were positively correlated with preoperative serum magnesium levels (r=0.719, p<0.001).

Conclusion: Postoperative hypomagnesemia may be seen after parathyroidectomy. It was significantly correlated with preoperative hypomagnesemia.

Keywords: Parathyroidectomy, primary hyperparathyroidism, magnesium, magnesium deficiency

ÖZ

Amaç: Paratiroidektomi, primer hiperparatiroidili hastalarda elektrolit metabolizmasında önemli değişikliklere neden olur. Açıklanamayan nedenlerle paratiroidektomi sonrası hipomagnezemi görülebilir. Çalışmamızda ameliyat sonrası hipomagnezeminin şiddetini, klinik ve biyokimyasal parametreler ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Ocak 2017-Aralık 2020 tarihleri arasında hiperparatiroidizm nedeniyle paratiroidektomi ameliyatı yapılan hastalar retrospektif olarak değerlendirildi. Çalışmaya preoperatif ve postoperatif magnezyum düzeylerine ulaşılabilinen 80 hasta dahil edildi. Hastalar ameliyat sonrası birinci gün serum magnezyum düzeylerine göre iki gruba ayrıldı. Gruplar, serum magnezyum düzeyi <1,9 mg/dL olan (grup HypoMg) ve ≥1,9 mg/dL olan (grup NorMg) olarak belirlendi. Demografik, klinik parametreler ve biyokimyasal bulgular kaydedildi. Postoperatif hipomagnezemi ise birincil veri olarak değerlendirildi.

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Bulgular: Ortalama yaş 56,7±12,2 yıl idi. Kadın/erkek oranı 3,21 idi. Grup HypoMg'de 31 (%38,8) ve grup NorMg'de 49 (%61,2) hasta vardı. Gruplar demografik ve klinik parametreler açısından benzerdi (p>0,005). Gruplar arasında preoperatif serum kalsiyum, düzeltilmiş kalsiyum ve paratiroid hormon düzeyleri açısından anlamlı fark yoktu (p>0,05). Preoperatif magnezyum düzeyi ise HypoMg grubunda anlamlı olarak düşüktü (p<0,001). Postoperatif serum magnezyum değeri ile preoperatif değer arasında pozitif korelasyon vardı (r=0,719, p<0,001).

Sonuç: Paratiroid cerrahisi sonrası serum magnezyum eksikliği görülebilir. Bu klinik durum, özellikle preoperatif hipomagnezemi ile anlamlı derecede koreledir.

Anahtar Kelimeler: Paratiroidektomi, primer hiperparatiroidizm, magnezyum, magnezyum eksikliği

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disease. It occurs most commonly due to one or more autonomously functioning parathyroid adenomas. Parathyroid hyperplasia and rarely parathyroid carcinoma are other underlying pathologies for PHPT[1-3]. Hypercalcemia and high or inappropriately normal parathyroid hormone (PTH) levels are the major diagnostic criteria for the disease. Parathyroidectomy is regarded as the only opportunity for a definitive cure for PHPT[2]. The rapid decline in serum PTH and normalization or lowering of serum calcium following parathyroidectomy cause significant metabolic changes in the bone and mineral metabolism[2].

As the second most abundant intracellular cation and the fourth most abundant cation of the body, the metabolism of magnesium is directly related to that of calcium[2,4]. It is generally known that there is a positive correlation between calcium and magnesium levels[5]. Considering the possible pathophysiological mechanisms between magnesium, calcium, and PTH, it has been reported that magnesium levels regulate PTH secretion and induces an end-organ resistance to PTH[6-8]. Previous studies have shown that postoperative hypomagnesemia is linked to the onset of clinically relevant hypocalcemia following thyroidectomy[5,7-9]. In several case reports, it has also been mentioned that severe hypomagnesemia could be seen following parathyroidectomy for PHPT[10-12]. It seems very difficult to prove the exact mechanisms between serum magnesium and calcium levels in these patients[4,12].

Although there is no current guideline reporting serum magnesium measurements before and after parathyroidectomy, there may be a close relationship between postoperative serum levels of magnesium and calcium in PHPT patients after the surgery[2]. So, the influence of parathyroidectomy on serum magnesium levels in PHPT patients remains controversial. We hypothesized that there might be some degree of correlation between serum magnesium, calcium, and PTH levels in PHPT patients following parathyroidectomy.

This study aimed to investigate the possible relationships between preoperative and postoperative serum magnesium levels and parathyroidectomy.

MATERIALS AND METHODS

Study

A retrospective study of the patients who underwent parathyroidectomy for PHPT was conducted between January 2017 and December 2020 in a single tertiary hospital. The Institutional Review Board of Bağcılar Training and Research Hospital approved the study (protocol no: 2021.01.1.05.005, date: 15.01.2021). All procedures in this study were in agreement with the Declaration of Helsinki. We applied the institutional guidelines during data collection to ensure patient privacy and confidentiality. Written consent could not be taken from the patients due to the retrospective design of the study and unanimity of data.

Patients

All consecutive patients with parathyroidectomy for PHPT were recruited using the hospital information system. Diagnostic criteria for PHPT were as follows: albumin-corrected serum calcium >10.2 mg/dL and increased or inappropriately normal plasma PTH[1]. Patients with asymptomatic PHPT and simultaneous thyroidectomy were also included. The medical records of a total of 91 patients were analyzed. The patients without the measurements of preoperative and postoperative 1st-day serum magnesium levels (n=11) were excluded. Familial PHPT and lack of medical data were regarded as the other exclusion criteria. So, 80 patients were finally evaluated in the study.

The type of surgery was determined as minimally invasive, one-sided, and two-sided parathyroidectomy at the Endocrine Surgery Board based on the preoperative imaging findings. The surgical procedures were performed by the consultant surgeons of our endocrine surgery unit.

Patients were divided into two groups according to the postoperative 1st-day serum magnesium levels: patients whose serum magnesium was <1.9 mg/dL (group HypoMg) and patients whose serum magnesium was ≤1.9 mg/dL (group NorMg).

Variables

Demographic and clinical variables were collected using the medical records of the patients. Age, sex, history of osteoporosis, and medication use before or at the time of surgery (diuretics, proton pump inhibitors, bisphosphonates), operative details, and postoperative pathological diagnosis adenoma or double adenoma were recorded. Laboratory investigations included serum calcium and magnesium, serum adjusted calcium, PTH, and estimated glomerular filtration rate (eGFR) both preoperatively and on the postoperative first day. An intact PTH assay (Abbott Architect®, Illinois, USA) was used to measure the concentration of PTH (range 12-88 pg/mL). The EPI-CKD formula was used to calculate eGFR[1]. Patients were grouped based on the serum and plasma levels of calcium, adjusted calcium, and PTH as normal or high.

Statistical Analysis

The incidence of postoperative hypomagnesemia in the study group was the primary outcome. Postoperative hypomagnesemia with demographic, clinical, and laboratory parameters and the correlation of biochemical parameters with postoperative hypomagnesemia were the secondary outcomes.

Statistical analysis was performed using a statistical package (IBM, Statistical Package for the Social Sciences software, 21.0, Chicago, IL, USA). Descriptive statistics were given as mean±standard deviation and median with interquartile range (1-3) of 25% to 75% for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The Kolmogorov-Smirnov test checked the normality of the numerical variables. In comparing two independent groups, the Independent Samples t-test was used where numerical variables had a normal distribution. In comparing the variables before and after the surgery, the paired t-test and Wilcoxon signed rank test were used. For variables without normal distribution, the Mann-Whitney U test was applied. To compare the differences between categorical variables, the Pearson chi-square and Fisher Freeman Halton tests were used in 2x2 tables. The Spearman and Pearson correlation coefficients depending on the type of distribution were calculated to analyze the relationships between numerical variables. Statistical significance was defined as $p<0.05$.

RESULTS

The mean age of all patients was 56.7±12.2 years. There were 19 (23.8%) male and 61 female patients (76.3%). There were 31 (38.8%) and 49 patients (61.2%) in group HypoMg and group NorMg. The groups were similar considering age and sex distribution (Table 1).

There were no significant associations between the postoperative hypomagnesemia and the incidence of osteoporosis and history of medications (diuretics, proton pump inhibitors, and bisphosphonates) between the groups ($p>0.05$).

The different types of parathyroidectomy showed almost equal distribution. Thyroidectomy was performed in 23 patients (28.8%). The types of parathyroidectomy and the incidence of coexisting thyroidectomy revealed no significant differences between the groups (Table 1).

In Table 2, the results of the preoperative biochemical investigations are given. The groups were similar regarding preoperative serum calcium, adjusted calcium, and PTH levels. The preoperative serum levels of magnesium were 1.76±0.26 mg/dL in the HypoMg group and 2.13±0.26 mg/dL in the NorMg group. The difference was statistically significant

Table 1. Demographic and clinical characteristics of the study groups

			Groups		p
		Overall (n=80)	HypoMg (n=31)	NorMg (n=49)	
Age (year)		56.7±12.2	58.9±10.6	55.3±13.0	0.200
Sex	Male	19 (23.8)	9 (29.0)	10 (20.4)	0.268
	Female	61 (76.3)	22 (71.0)	39 (79.6)	
Osteoporosis		24 (30.0)	7 (22.6)	17 (34.7)	0.184
Diuretic use		6 (7.5)	2 (6.5)	4 (8.2)	0.571
PPI		10 (12.5)	7 (22.6)	3 (6.1)	0.036
Biphosphonates		9 (11.3)	4 (12.9)	5 (10.2)	0.488
Surgery	Minimal invasive	28 (35)	9 (29.0)	19 (38.8)	0.542
	One-sided	28 (35)	13 (41.9)	15 (30.6)	
	Two-sided	24 (30)	9 (29.0)	15 (30.6)	
Thyroidectomy		23 (28.8)	10 (32.3)	13 (26.5)	0.380
Pathology	Adenoma	75 (93.8)	30 (96.8)	45 (91.8)	0.644
	Double adenoma	5 (6.3)	1 (3.2)	4 (8.2)	

(p<0.001). The incidence of the patients with low preoperative serum magnesium was significantly higher in the HypoMg group (p<0.001).

Considering the postoperative biochemical investigations, there were no significant differences in postoperative serum calcium, adjusted calcium, and PTH levels (Table 3). In 11 patients (13.75%), we detected low adjusted serum calcium levels. Postoperative magnesium levels were 1.7±0.2 mg/dL and 2.1±0.1 mg/dL in the HypoMg and NorMg groups (p<0.001).

Preoperative serum adjusted calcium, PTH, and magnesium levels reduced significantly after parathyroidectomy (p<0.0001, p<0.001, and p=0.009, respectively) (Table 4). The percentage of the reduction in serum magnesium levels in patients with osteoporosis [-2.7% (-6.1-2.1)] was not significantly different from the changes in patients without osteoporosis [-5.1 (-8.6-1.9)] (p=0.159).

Postoperative serum magnesium levels were positively correlated with preoperative serum magnesium levels (r=0.719, p<0.001) (Figure 1). Other parameters showed no significant correlations (Table 5).

DISCUSSION

This retrospective study showed that postoperative hypomagnesemia was significantly associated with preoperative hypomagnesemia. We found a significant positive correlation between preoperative and postoperative magnesium levels. We could not find any demographic, clinical, and laboratory variables predicting postoperative hypomagnesemia except

Table 2. Preoperative laboratory findings of the study groups

			Groups		p
		Overall (n=80)	HypoMg (n=31)	NorMg (n=49)	
Preop Ca		11.6 (11.1-12.3)	11.7 (11.0-12.6)	11.4 (11.1-12.0)	0.567
Adj. preop Ca		11.4 (10.8-11.9)	11.5 (10.8-12.5)	11.4 (10.8-11.7)	0.219
Preop Ca groups	Normal	6 (7.5)	3 (9.7)	3 (6.1)	0.429
	High	74 (92.5)	28 (90.3)	46 (93.9)	
Adj. preop Ca groups	Normal	8 (10)	2 (9.7)	6 (12.2)	0.512
	High	72 (90)	28 (90.3)	42 (87.8)	
Preop PTH		167.2 (130-326.8)	159.6 (122.4-300)	208.4 (145-366.3)	0.336
Preop PTH groups	Normal	3 (3.8)	2 (6.5)	1 (2.0)	0.332
	High	77 (96.3)	29 (93.5)	48 (98.0)	
Preop Mg		2.0±0.32	1.76±0.26	2.13±0.26	<0.001
Preop Mg groups	Low	31 (38.8)	26 (83.9)	5 (10.2)	<0.001
	Normal	49 (61.3)	5 (16.1)	44 (89.8)	
Preop eGFR		98.5 (88.0-106.8)	85.0 (97.0-104.0)	99.0 (89.0-111.0)	0.311

eGFR: Estimated glomerular filtration rate, Mg: Magnesium, PTH: Parathyroid hormone

Table 3. Postoperative laboratory findings of the study groups

			Groups		p
		Overall (n=80)	HypoMg (n=31)	NorMg (n=49)	
Postop Ca		9.0±0.9	9.1±0.8	9.5±0.7	0.596
Adj. postop Ca		9.3±0.8	9.5±0.7	9.2±0.9	0.127
Postop Ca groups	Low	28 (35)	11 (35.5)	17 (34.7)	0.726
	Normal/high	52 (65)	20 (64.5)	32 (65.3)	
Adj. postop Ca groups	Low	11 (13.75)	5 (16.1)	6 (12.2)	0.654
	Normal/high	69 (86.25)	26 (83.9)	43 (87.7)	
Postop PTH		26.6 (12.7-57.9)	25.6 (11.6-53.9)	32.7 (12.9-58.9)	0.632
Postop PTH groups	Normal	65 (81.3)	25 (80.6)	40 (81.6)	1.0
	High	15 (18.7)	6 (19.4)	9 (18.4)	
Postop Mg		1.9±0.3	1.7±0.2	2.1±0.1	<0.001
Postop eGFR		97 (88-106)	97 (89-100)	97 (84-109)	0.448

eGFR: Estimated glomerular filtration rate, Mg: Magnesium, PTH: Parathyroid hormone

for low preoperative serum magnesium levels. The absence of any correlation between calcium, PTH, and magnesium levels in patients who underwent parathyroidectomy was another striking finding in this study.

Several pathophysiological mechanisms are proposed to develop hypomagnesemia, including impaired intestinal absorption, increased gastrointestinal losses, or disturbances in renal magnesium handling[2,4]. Bowel preparation, blood transfusions, administration of catecholamines, and extracellular volume expansion are regarded as the other contributing mechanisms for hypomagnesemia[2]. We thought these contributing factors, except for a rapid decline in PTH and normalization or lowering of serum calcium levels after parathyroid surgery, are unlikely. So, postoperative hypomagnesemia might be directly related to postoperative PTH and calcium metabolism.

A highly significant negative correlation between serum calcium and magnesium levels in patients with PHPT was reported in a limited number of older studies[13,14]. Nevertheless, the association of serum magnesium, serum calcium, and PTH has been analyzed in patients with secondary hyperparathyroidism[4,6,15,16]. Fang et al.[4] studied the effect of PTH on serum magnesium levels in hemodialysis patients with secondary hyperparathyroidism. They found that hypermagnesemia was seen in 44% of the patients preoperatively, and there were significant decreases in serum magnesium levels immediately after the surgery. The severity was minimal at the first day, and gradually restored from the third day. Similar changes have been reported in patients with PHPT after parathyroidectomy[14,16]. They concluded that PTH might influence magnesium metabolism. Although magnesium is essential for PTH synthesis and release, it has also been mentioned that PTH increases gastrointestinal absorption and bone resorption of magnesium, leading to an increase in serum levels of magnesium[4]. In this study, we did not find significant correlations between calcium, PTH, and magnesium. So, we have difficulty showing a possible association between hypomagnesemia and a rapid decrease in PTH levels after parathyroidectomy, which necessitates prospective large-scale studies.

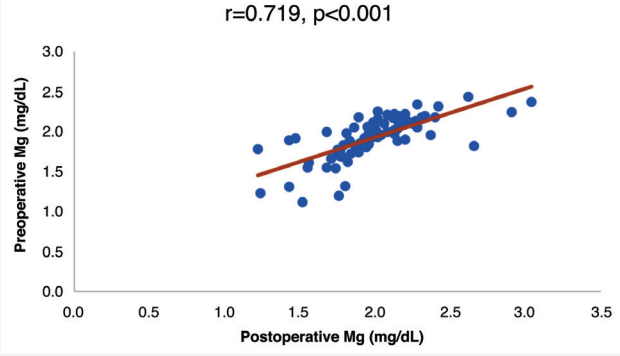

Figure 1. Correlation of preoperative and postoperative magnesium levels in the study group

Novodvorsky et al.[2] reported that a combination of hungry bone syndrome and hypoparathyroidism was the leading cause of early postoperative hypomagnesemia following parathyroidectomy. They found a rate of 7.1% for postoperative hypocalcemia in their parathyroidectomy series. There might be a shift of calcium and magnesium into the bones in these patients, which is the pathophysiological mechanism of the hungry bone syndrome[2]. In our study, low postoperative levels of adjusted calcium were seen in 13.75% of the cases without any clinical symptoms and signs of hypocalcemia. Contrary to Novodvorsky et al.[2] study, we could not detect a significant difference in the postoperative serum calcium levels depending on the postoperative magnesium levels.

Previous studies have commented that postoperative hypomagnesemia is associated with generalized bone disease[8,11,14]. King and Stanbury[14] reported that significant decreases in serum magnesium levels after parathyroidectomy were common. Besides, it was shown that it was sustained only in those with bone diseases and associated with prolonged postoperative hypocalcemia. Due to the retrospective design, we did not evaluate bone diseases in the study group. Investigation of severe bone diseases in PHPT patients may help to understand the pathophysiology of hypomagnesemia.

Study Limitations

Retrospective design and lack of postoperative follow-up period were the major limitations of this study. We

Table 4. Comparison of preoperative and postoperative levels of the laboratory variables

		95% CI		p
Postop vs. preop	Mean±SD	Lower	Upper	
Serum Ca	-2.83±1.33	-3.12	-2.53	<0.001
Adjusted Ca	-2.43±1.37	-2.73	-2.13	<0.001
PTH	-408.2±686.4	-561.0	-255.5	<0.001
Mg	-0.67±0.23	-0.12	-0.18	0.009
eGFR	0.15±13.6	-0.90	3.2	0.921

eGFR: Estimated glomerular filtration rate, Mg: Magnesium, PTH: Parathyroid hormone, SD: Standard deviation, CI: Confidence interval

Table 5. Correlation of postoperative serum magnesium levels

		Postop Mg
Age	r	-0.175
	p	0.123
Preop Ca	r	-0.870
	p	0.445
Adj. preop Ca	r	-0.132
	p	0.244
Preop PTH	r	0.023
	p	0.842
Preop Mg	r	0.719
	p	<0.001
Preop eGFR	r	0.097
	p	0.393
Postop Ca	r	-0.075
	p	0.508
Adj. postop Ca	r	-0.198
	p	0.078
Postop PTH	r	-0.054
	p	0.632
Postop eGFR	r	0.078
	p	0.497

eGFR: Estimated glomerular filtration rate, Mg: Magnesium, PTH: Parathyroid hormone

analyzed a single magnesium measurement taken on the first postoperative day. So, we could not contribute to trends in the postoperative magnesium levels. Due to the absence of preoperative or postoperative serum magnesium levels in some of our excluded cases, a selection bias might occur. We did not investigate these laboratory changes with clinical signs and symptoms of hypocalcemia and hypomagnesemia. Investigation of the clinical presentation of hypomagnesemia in these patients may help to increase the reliability of our results.

CONCLUSION

Hypomagnesemia may be seen after parathyroidectomy. It was significantly correlated with preoperative low magnesium levels. Prospective studies are needed to investigate the clinical importance of hypomagnesemia and its association with PTH and calcium metabolism.

Ethics

Ethics Committee Approval: The Institutional Review Board of Bağcılar Training and Research Hospital approved the study (protocol no: 2021.01.1.05.005, date: 15.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.M., N.A.H., Design: S.M., N.A.H., Data Collection or Processing: S.M., N.A.H., Analysis or Interpretation: S.M., Literature Search: S.M., N.A.H., Writing: S.M., N.A.H.

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