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Hungry Bone Syndrome in Patients with End-Stage Renal Disease Receiving Hemodialysis

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Abstract

Objective: *Hyperparathyroidism develops in the majority of patients with end-stage renal disease receiving hemodialysis. Parathyroidectomy can be performed in cases who cannot be managed with medical therapy and a portion of the patients develop hungry bone syndrome (HBS) in the postoperative period. In this study, we investigated the factors that influence the development of HBS and the hospitalization times in hemodialysis patients who underwent parathyroidectomy.*

Method: *This study included 49 patients. Demographic, clinical and laboratory parameters of these patients were retrospectively evaluated.*

Results: *Patients' median age was 46 years (22-62). The parathyroid gland that showed hyperplasia the most frequently was the left inferior 79.6% (n=39), followed by the right inferior 77.6% (n=38) gland. Rate of four-gland hyperplasia was 32.7% (n=16). Of the 49 operated patients, 34 (69.4%) developed HBS. In patients with postoperative PTH <500 pg/ml, calcium < 7mg/dl during the first 24 hours after surgery and calcium infusion > 4 ampules during the first 24 hours, hospitalization times were prolonged and the need for parenteral calcium infusion was elevated.*

Conclusion: *The need for parenteral calcium replacement during the first 24 hours, postoperative PTH and calcium levels during the first 24 hours were determined to be factors indicating the severity of HBS in the postoperative period.*

Keywords: *Hungry bone syndrome, Hemodialysis, Chronic renal failure, Hyperparathyroidism, Calcium*

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Introduction

Calcium and phosphate homeostasis is regulated by the parathyroid hormone (PTH) and calcitriol. PTH is secreted via the activation of the calcium-sensing receptors on the parathyroid gland due to hypocalcemia [1]. Generally, parathormone receptors are found in the bone tissue and kidneys [2]. Secondary hyperparathyroidism involves the biochemical abnormalities of the mineral disorders of the bone and occurs in the majority of patients with end-stage renal disease receiving hemodialysis [3]. Chronic hyperphosphatemia, hypocalcemia, 1,25-dihydroxyvitamin D are the primary factors that stimulate PTH synthesis and parathyroid cell proliferation [4]. In cases that cannot be managed with diet, phosphate binders and calcitriol therapy, an indication for parathyroidectomy arises [5]. Hungry bone syndrome (HBS) was first described by Albright and Reifenstein in 1950 when long-term hypocalcemia and hypophosphatemia occurred in a patient with hyperparathyroidism following parathyroidectomy [6]. HBS develops in patients who undergo parathyroidectomy due to primary, secondary or tertiary hyperparathyroidism [7]. It is believed that the sudden decline in the serum PTH concentration after parathyroidectomy alters the balance between bone formation and absorption, supports bone formation through a substantial increase in the skeletal calcium uptake, which results in severe hypocalcemia. Although this is a transient phenomenon that resolves with calcium and active vitamin D supplementation, patients with HBS may develop severe hypocalcemia with life-threatening complications, i.e. cardiac arrhythmia, tetany and laryngeal stridor. Previous studies have reported the incidence of HBS to vary between 28% and 88% in patients with end-stage renal disease receiving hemodialysis who underwent parathyroidectomy due to the diagnostic criteria of HBS [8]. A large parathyroid adenoma size, age>60 years, high pre-parathyroidectomy PTH, alkaline phosphatase (ALP) and calcium levels constitute risk factors for HBS [7]. In patients with HBS, which is characterized by rapid, deep and long-term hypocalcemia, the total serum calcium concentration is usually below 8.4 mg/dl and hypocalcemia for more than four days postoperatively is encountered [9]. Hospitalization times are generally associated with the severity of hypocalcemia [10]. Very few studies have been conducted on HBS in patients with end-stage renal disease receiving hemodialysis. Determining the risk factors for HBS preoperatively is very important for early diagnosis, treatment and hospitalization times. The present study aims to determine the incidence of HBS in patients with end-stage renal disease receiving hemodialysis, to investigate the risk factors and the factors that influence the hospitalization times.

Materials and Methods

This study included 49 patients with end-stage renal disease receiving hemodialysis who underwent parathyroidectomy due to tertiary hyperparathyroidism, which is a complication of this disease, and were followed up in the nephrology clinic for HBS in Yuzuncu Yil University, Medical Faculty Hospital between 2006-2020. Clinical and laboratory findings of the patients were retrospectively reviewed through the hospital automation system and archived files. Materials to be sent to the hospital laboratory are received and sent according to standard protocols. Clinical (age, gender, time with chronic renal failure (CRF), time on dialysis, parathyroid gland(s) with hyperplasia and their number, treatments received, hospitalization time) and laboratory **[**ALP, calcium, phosphate, PTH **(**PTH blood sample was taken between 08:00 and 10:00 a.m., measured preoperative and within 24 hours postoperatively, regardless of calcium level**)**, platelet count**]** findings were evaluated with respect to their relationship with the patients' hospitalization times and the treatments they received. Patients on peritoneal dialysis, patients diagnosed with CRF not receiving dialysis, patients with nephrotic or nephritic syndrome, patients who received a kidney transplant and patients with inadequate data were not included in the study. Our study was approved by the Yuzuncu Yil University Medical Faculty Ethics Committee (date/reference number: 11.12. 2020/2020/10-11).

Statistical Analysis: SPSS 18.0 program package was used in the statistical analysis of the data. Descriptive statistics were used to evaluate patient characteristics and the frequency of parameters, the Mann-Whitney U test was used for the analysis of non-normally distributed or non-parametric variables. T-test, chi-square test, Fisher's exact and Mann-Whitney U tests were used for univariate analysis. A confidence interval of 95% and a p-significance level <0.05 were adopted. For the analysis of hospitalization times and influencing factors, the Kaplan-Meier method (log-rank) and Cox regression analysis were used.

Result

Our study included a total of 49 end-stage renal disease patients receiving hemodialysis who underwent parathyroidectomy for tertiary hyperparathyroidism, comprising 23 (46.9%) females and 26 (53.1%) males. The patients' median age was 46 years (22-62), median time with CRF was 10 (3-13) years and median time on dialysis was 8 (1-13) years. The most common CRF etiology was found to be hypertension 27% (n=13). The parathyroid gland that showed hyperplasia the most frequently was the left inferior 79.6% (n=39), followed by the right inferior 77.6% (n=38) gland.

The rate of four-gland hyperplasia was 32.7% (n=16). Of the 49 operated patients, 34 (69.4%) developed HBS. The patients' mean time of hospitalization for parenteral treatment was 8.6 days (1-42), mean total parenteral calcium requirement during the first seven days of hospitalization was 54.7 (95% CI; 46-63.4) ampules (each ampule containing 225 mg calcium gluconate monohydrate + 572 mg calcium levulinate dihydrate). Intravenous calcium replacement was performed in symptomatic patients, and the target calcium level was accepted as at least 7.5 mg/dL. Other findings are summarized in Table 1. Mean laboratory results obtained preoperatively and on the first postoperative day (Table 2) are, respectively: PTH (pg/ml): 2038 (95% CI; 1927-2310), 416 (95% CI; 254-602), ($p<0.001$), calcium (mg/dl): 9.9 (95% CI; 9.5-10.1), 7.9 (95% CI; 7.3-8.2), ($p<0.001$), phosphate (mg/dl): 5.3 (95% CI; 4.5-5.9), 4.3 (95% CI; 3.9-4.7), ($p<0.001$), platelet (x 103/microL): 214 (95% CI; 190-239), 194 (95% CI; 176-215), ($p=0.012$). When compared with regard to HBS occurrence, there was a significant relationship between HBS and postoperative PTH levels ($p=0.04$). Other laboratory (pre- and postoperative ALP and platelet count) and clinical (time on dialysis, time with CRF, gender, age) parameters did not show a significant relationship with HBS. While 34 (69.4%) patients showed need for parenteral calcium replacement on postoperative day 1, the need for parenteral calcium replacement persisted in only 3 (6.1%) patients on the 21st day (Figure 1, Table 3). When the factors influencing the hospitalization time were evaluated; postoperative PTH <500 pg/ml, calcium level< 7mg/dl during the first 24 hours after surgery and calcium infusion > 4 ampules during the first 24 hours were associated with prolonged hospitalization times and an elevated need for parenteral calcium infusion (Table 4). Again, when considered in terms of the duration of hospitalization requiring parenteral calcium infusion; gender, time with CRF, time on dialysis, number of hyperplastic glands, preoperative laboratory results (calcium, phosphate, PTH, ALP, platelet count) and postoperative platelet count and phosphate levels were not found to be statistically significant. However, it was found in the univariate analysis that the calcium level during the first 24 hours and PTH levels on the first day postoperatively, as well as the parenteral calcium requirement on the first day, had borderline statistical significance in predicting the hospitalization time, and in multivariate analysis that the calcium level during the first 24 hours and PTH levels on the first day postoperatively were statistically significant predictors of hospitalization time (Table 5).

Table 1. *Basal characteristics of all patients*

	N=49 (%)
Age yr (median, range)	**46(22-62)**
Gender	
Male	**26(53.1)**
Female	**23(46.9)**
Etiyology	
HT	**13(27)**
DM	**3(6)**
Nephrolithiasis	**3(6)**
PCKD	**2(4)**
others	**28(57)**
Gland localization	
Superior	
Right	**24(49)**
Left	**26(46.9)**
İnferior	
Right	**38(77.6)**
Left	**39(79.6)**
Hyperplasic gland count	
1	**13(26.5)**
2	**10(20.4)**
3	**10(20.4)**
4	**16(32.7)**
Duration of dialysis yr (median, range)	**8(1-13)**
Duration of CRF yr (median, range)	**10(3-13)**

CRF: Chronic renal failure, **HT:** Hypertension, **DM:** Diabetes mellitus, **PCKD:** polycystic kidney disease

Table 2. *Comparison of preoperative and postoperative first day laboratory values*

	Level (mean, std dev.)	**P value**
Calcium mg/dl		**<0.001**
Preoperative	9.9(0.9)	
Postoperative	7.9(1.4)	
Phosphorus mg/dl		**<0.001**
Preoperative	5.3(1.6)	
Postoperative	4.3(1.3)	
parathyroid hormone pg/ml		**<0.001**
Preoperative	2038(707)	
Postoperative	416(503)	
Platelet x 10^3/microL		**0.012**
Preoperative	214(79)	
Postoperative	194(62)	

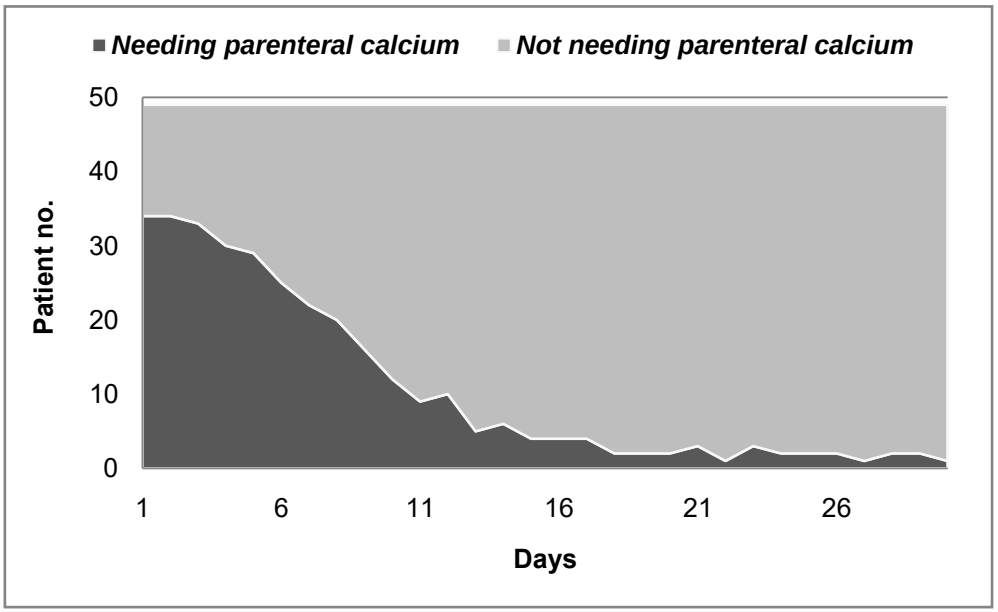

Figure 1: The proportion of patients requiring intravenous calcium replacement by day in patients with hungry bone syndrome

Table 3. Postoperative calcium phosphorus levels and the need per patient daily parenteral calcium replacement with hungry bone syndrome

	Patient requiring calcium replacement (n)	Ca mg/dl	P mg/dl	Ca x P	Daily mean calcium replacement per patient (ampoule*)
1st day	34	7.9(5.7-12.7)	4.2(2.2-6.2)	29(15-80)	6(2-12)
2nd day	34	7.2(4.8-9.9)	3.2(2.3-7.0)	23(11-61)	8(6-14)
3rd day	33	7.4(4.9-10.1)	3.6(2.2-7.5)	27(12-70)	8(4-12)
4th day	30	7.7(4.6-9.5)	3.1(1.9-7.9)	23(11-75)	7(4-12)
5th day	29	7.8(4.6-9.4)	3.0(1.7-6.4)	24(10-37)	6(2-12)
14th day	6	8.0(6.3-9.0)	5.0(3.4-5.4)	45(22-51)	5(3-8)
21st day	3	9.4(8.4-10.7)	3.0(2.5-4.1)	21(28-44)	5(2-8)

Ca: Calcium, **P:** Phosphorus,
*Each ampoule contained 225 mg calcium gluconate monohydrate + 572 mg calcium levulinate dihydrate.

Table 4. *Factors affecting the length of stay in the hospital*

	Length of stay in the hospital (day) (mean, 95% CI)	**Log-rank P**
All patients	8.6(6.1-11.0)	
Postoperative PTH (pg/ml)		**0.030**
≥ 500	4.9(2.4-7.3)	
< 5 00	10.6(7.3-13.9)	
Calcium level in the first 24 hours (mg/dl)		**0.036**
≥ 7	6.8(4.6-9.0)	
< 7	12.3(6.7-17.8)	
Calcium requirement for the first 24 hours (ampoule*)		**0.038**
≤ 4 ampoule	5.6(2.9-8.2)	
> 4 ampoule	11(7.4-14.7)	

PTH: parathyroid hormone,
*Each ampoule contained 225 mg calcium gluconate monohydrate + 572 mg calcium levulinate dihydrate.

Table 5. *Effects of parameters on length of stay in hospital requiring parenteral calcium replacement*

	Univariate analysis		**Multivariate analysis**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Gender	0.76(0.43-1.36)	0.36		
Duration of CRF	0.98(0.87-1.11)	0.84		
Duration of dialysis	1.12(0.93-1.34)	0.21		
Hyperplasic gland count	0.91(0.71-1.16)	0.45		
Preoperative				
Calcium	0.99(0.73-1.33)	0.95		
Phosphorus	1.04(0.85-1.28)	0.64		
parathyroid hormone	1(0.99-1.0)	0.27		
Platelet	1(0.99-1.0)	0.59		
Alkaline Phosphatase	1(0.99-1.0)	0.33		
Postoperatif				
Calcium	0.53(0.28-0.9)	**0.05**	0.39(0.18-0.84)	**0.016**
Phosphorus	1.16(0.92-1.46)	0.19		
parathyroid hormone	0.52(0.27-0.9)	**0.05**	0.32(0.15-0.68)	**0.003**
Platelet	0.9(0.9-1.0)	0.49		
Day 1 IV. calcium replacement	0.56(0.31-1.0)	**0.05**	0.66(0.35-1.23)	0.19

CRF: Chronic renal failure, **IV:** intravenous

Discussion

HBS is encountered frequently in parathyroidectomies performed due to secondary hyperparathyroidism, which is a complication associated with end-stage renal disease [5,6]. This study included 49 patients receiving hemodialysis who were followed up in our clinic due to end-stage renal failure and developed tertiary hyperparathyroidism. These cases had undergone parathyroidectomy due to non-response to medical treatment. They had been followed up in our clinic due to the risk of hypocalcemia. Of the cases, 34 (69.4%) were found to have developed HBS that would require parenteral calcium infusion. Although there exists no exact definition for HBS in the literature, it was described in a study that included 198 cases as a serum calcium level below 8.5 mg/dl and a phosphate level below 3.0 mg/dl during the first three postoperative days [10]. In another study, 148 end-stage renal disease patients were evaluated and the rate of HBS in CRF was reported as 20% [11]. In our study, the rate of HBS was 69.4% among CRF hemodialysis patients, which was higher compared with the rates reported in the literature. We reasoned that this situation could be linked to the fact that our clinic admitted patients who were at higher risk for HBS. In HBS, hypocalcemia can present with benign conditions such as fatigue, headache, paresthesia, while it can sometimes become manifest with the symptoms of arrhythmia, laryngeal stridor, tetany, convulsion and heart failure [12]. In one patient, a scapula fracture occurred due to convulsions during hemodialysis. Postoperative HBS is encountered more frequently in individuals with certain risk factors. Advanced age, large parathyroid gland size, high ALP levels, high blood urea nitrogen, presence of advanced bone disease can be listed among the clinical and laboratory risk factors for HBS. Meanwhile, hospitalization times of the patients are reported to be linked to the severity of hypocalcemia [10]. Conditions such as advanced age, reduced renal 1α-hydroxylase activity, low-calcium diet, which are risk factors for HBS [10], are associated with a negative calcium balance and bone disease [13]. In our study, age, gender, time on dialysis and time with CRF were not associated with the patients' postoperative hospitalization times and parenteral calcium replacement needs. In a study by Jofre and colleagues, multinodular hyperplasia was found in 79.5% of the glands and nodular hyperplasia was found in the remaining 20.5% [11]. Hyperplasia of multiple glands is encountered more commonly in CRF-related tertiary hyperparathyroidism [14]. In our study, hyperplasia was encountered the most frequently in the left inferior parathyroid gland 79.6% (n=39), and the least frequently in the left superior parathyroid gland 46.9%. Thirty-six (73.5%) patients had modular hyperplasia, 13 (26.5%) patients had nodular hyperplasia and 16 (32.7%) had

four-gland hyperplasia. However, the number of hyperplastic parathyroid glands was not correlated with the duration of postoperative hypocalcemia. Preoperative serum ALP levels reflect the bone turnover, osteoclast activity and the degree of osteoporosis. Preoperative ALP levels may provide information as to the severity and duration of hypocalcemia, which can develop after a successful parathyroidectomy [15]. In our study, preoperative ALP, calcium, phosphate, PTH and platelet levels were not found to be associated with the hospitalization time (Table 5). Although the hypocalcemia duration is variable, it can approach 3 months in some patients [16]. In our study, the mean duration of hypocalcemia that required hospitalization was 8.6 (1-42) days. However, postoperative calcium level< 7mg/dl during the first 24 hours, PTH <500 pg/ml during the first 24 hours and calcium infusion > 4 ampules during the first 24 hours predicted a long hospitalization time requiring parenteral calcium replacement (Table 4). As expected, the comparison of the preoperative and postoperative values in our study showed a statistically significant decline in PTH, calcium, phosphate levels. Furthermore, a significant decrease was also determined in the postoperative platelet count when compared with the preoperative levels (p=0.012). There is no data in the literature that clearly reveals the relationship between hypocalcemia, hypoparathyroidism and thrombocytopenia. We reasoned that this situation could be linked to the decrease in the levels of calcium, which is a coagulation factor.

The limitations of our study included the small number of patients and the single-center study.

Conclusion:

Since bone turnover and calcium phosphate homeostasis are multifactorial conditions, they are difficult to explain by a single parameter. The severity and duration of hypocalcemia varies across patients. According to the results of our study, the need for parenteral calcium replacement during the first 24 hours, postoperative PTH and calcium levels during the first 24 hours can be listed as factors indicating the severity of HBS in the postoperative period. However, it should be remembered that postoperative hypocalcemia is a serious condition that can even result in bone fractures.

References

1. Filopanti F, Corbetta S, Barbieri AM, and Spada A, ‑Pharmacology of the calcium sensing receptor,‖ Clinical Cases in Mineral and Bone Metabolism, 2013; 10(3): 162– 165.
2. Dunlay R. and Hruska K. PTH receptor coupling to phospholipase C is an alternate pathway of signal transduction in bone and kidney, The American Journal of Physiology—Renal Fluid and Electrolyte Physiology, 1990; 258(2): F223–F231.
3. Jofre R, Lopez Gomez JM, Menarguez J, et al. Parathyroidectomy: whom and when? Kidney Int

Suppl. 2003;63:S97–S100.

4. Jamal SA, Miller PD. Secondary and tertiary hyperparathyroidism. J Clin Densitom. 2013;16(1):64–68.
5. Assadi F. Hypophosphatemia: An evidencebased problem-solving approach to clinical cases. Iran J Kidney Dis 2010;4:195-201.
6. Albright F, Reifenstein EC. The parathyroid glands and metabolic bone disease, Ulster Medical Journal, 1950; 19 (1):130–131.
7. Farese S. The hungry bone syndrome: An update. Ther Umsch 2007;64:277-80.
8. Kritmetapak K, Kongpetch S, Chotmongkol W, Raruenrom Y, Sangkhamanon S and Pongchaiyakul C. Incidence of and risk factors for post-parathyroidectomy hungry bone syndrome in patients with secondary hyperparathyroidism. RENAL FAILURE 2020;42(1): 1118–1126
9. Jain N, Reilly RF. Hungry bone syndrome. Curr Opin Nephrol Hypertens. 2017;26(4):250–255.
10. Brasier AR, Nussbaum SR. ‒Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery,‖ The American Journal of Medicine, 1988; 84(4): 654–660.
11. Jofré R, López Gómez JM, Menárguez J. et al. Parathyroidectomy: whom and when? Kidney Int Suppl 2003; S97.
12. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *European Journal of Endocrinology/European Federation of Endocrine Societies*. 2013;168(3):R45–R53.
13. Heath DA, Van't Hoff W, Barnes AD and Gray JG. Value of 1-α-hydroxy vitamin D3 in treatment of primary hyperparathyroidism before parathyroidectomy. BMJ 1979;1: 450–452.
14. Kebebew E, Duh QY, Clark OH. Tertiary hyperparathyroidism: histologic patterns of disease and results of parathyroidectomy. Arch Surg 2004; 139:974.
15. Vercauteren M, Boeckx E and Adriaensen H. Parathyroidectomy and postoperative hypocalcemia: a retrospective study. Acta Anaesthesiologica Belgica 1988;39: 59–63.
16. Benz RL, Schleifer CR, Teehan BP, et al. Successful treatment of postparathyroidectomy hypocalcemia using continuous ambulatory intraperitoneal calcium (CAIC) therapy. Perit Dial Int 1989; 9:285.