CORRELATION OF SERUM PARATHORMONE WITH HYPERTENSION IN CHRONIC RENAL FAILURE PATIENTS UNDERGOING HEMODIALYSIS.

Hemodiyaliz Tedavisi Gören Kronik Böbrek Yetmezliği Hastalarında Serum Paratiroid Hormonunun Hipertansiyon ile İlişkisi

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Abstract

Purpose: *To consider the effect of serum parathormone on severity of hypertension in end-stage renal failure patients undergoing hemodialysis treatment.*

Patients and Methods: *A cross-sectional study was performed on patients with end-stage renal disease undergoing maintenance hemodialysis treatment. Serum calcium, phosphorus, alkalene phosphatase, serum albumin and intact PTH levels were measured. Stratification of hypertensive patients was performed from stage one to three. A stage of zero means the absence of hypertension. Stages of hypertension were measured before treatment and at the beginning of the first hemodialysis treatment.*

Results: *The total number of patients was 73 (F=28 M=45), including 58 non-diabetic (F=22 M=36) and 15 diabetic hemodialysis patients (F=6 M=9). The mean age of patients was 46.5±16 years. The mean period of time that patients had spent on hemodialysis was 21.5±23.5 months. Serum iPTH of total patients was 309±349 pg/ml and serum alkaline phosphatase of total patients was 413±348 IU/L. There was a significant positive correlation between the stages of hypertension and serum iPTH levels (r=0.200; p=0.045). There was no significant correlation between the stages of hypertension and serum alkalene phosphatase levels (r=0.135; p=0.128). A significant positive correlation between stages of hypertension with Ca x P products of patients (r = 0.231; p=0.027) was also seen.*

Conclusion: *The relationship between serum iPTH and severity of hypertension in this group requires further research on nontraditional causes of hypertension in hemodialysis patients. Hypertension and secondary hyperparathyroidism both interact in the process of accelerated atherosclerosis in hemodialysis patients. This combination may aggravate the rapid progressive athrosclerosis process.*

Key Words: *Hemodialysis; Hyperparathyroidism, Secondary; Hypertension; Parathyroid Hormone.*

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Özet

Amaç: *Hemodiyaliz tedavisi alan son dönem renal yetmezlikli hastalatda hipertansiyonun şiddeti üzerine serum parathormonunun etkisi araştırıldı.*

Hastalar ve Metod: *Hemodiyaliz tedavisi gören son dönem renal yetmezlikteki hastalarda kesitsel bir çalışma yapıldı. Serum kalsiyum, fosfor, alkalen fosfataz, albumin ve parathormon (iPTH) seviyeleri ölçüldü. Hipertansif hastalar "1" ile "3" arasında devrelendirildi. Hipertansiyonu olmayan hastalar devre "0" olarak kabul edildi. Hipertansiyon devreleri tedaviden önce ve ilk hemodiyaliz tedavisinin başlangıcında ölçüldü.*

Bulgular: *Çalışmaya 15'i diyabetik (9'u erkek), 58'i diyabetik olmayan (45'i erkek) toplam 73 hasta alındı. Hastaların ortalama yaşı 46.5±16 yıldı. Hastaların tedavi gördükleri hemodiyaliz süresi ortalama 21.5±23.5 aydı. Çalışmaya alınan tüm hastaların ortalama serum iPTH düzeyi 309±349 pg/ml ve serum alkalen fosfotaz düzeyi 413±348 IU/L olarak bulundu. Hipertansiyonun devresi ile serum iPTH düzeyi arasında anlamlı bir pozitif ilişki bulundu. (r=0.200; p=0.045). Hipertansiyonun devresi ile serum alkalen fosfataz düzeyi arasında anlamlı bir ilişki yoktu (r=0.135; p=0.128). Hipertansiyonun devresi ile hastaların Ca ve P düzeylerinin çarpımı arasında da anlamlı bir ilişki gözlendi (r = 0.231; p=0.027).*

Sonuç: *Deney grubumuzda hipertansiyonun şiddeti ve serum iPTH arasında ilişkinin varlığı hemodiyalizdeki hastalarda hipertansiyonun geleneksel olmayan nedenleri üzerine ileri çalışmaları gerektirmektedir. Hipertansiyon ve sekonder hiperparatiroidizm hemodiyalizdeki hastalarda hızlanmış ateroskleroz süreci ile etkileşmektedir. Bu kombinasyon hızlı ilerleyici aterosklerotik süreci ağırlaştırıyor olabilir.*

Anahtar Kelimeler: *Hemodiyaliz; ikincil hiperparatiroidizm; hipertansiyon; Paratiroid hormonu*

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Introduction:

The pathogenesis of hypertension in haemodialyzed uraemic patients is multifactorial: sodium and water retention as a result of the impaired excretory capacity of the kidneys, excessively increased activity of the renin-angiotensin-aldosterone system and sympathetic nervous system, increased levels of the vascular constrictor endothelin-1, cumulation of endogenous inhibitors of NO synthesis, and reduced formation of vasodepressor factors (1-2). The prevalence of hypertension in patients with chronic renal insufficiency is high, in the stage of renal insufficiency this rate is 60% and in conservatively terminal renal failure it is as high as 90%. After the initiation of dialysis treatment it declines temporarily, although it is higher during chronic haemodialysis (50-80%) (3). Hypertension is one of the main risk factors for cardiovascular morbidity and mortality in the general population. Hypertension is more prevalent in patients on dialysis than in the non-uraemic population (4) and may be a major cause of mortality, although epidemiological studies are controversial in this regard (5). As other factors in the development of hypertension are raised intracellular calcium associated with hyperparathyroidism (1), and both hypertension and secondary hyperparathyroidism are common features of the uremic syndrome, it has been suggested that secondary hyperparathyroidism causes hypertension in end-stage renal disease (6). However whether hyperparathyroidism causes the hypertension is questionable and the nature of the mechanism is unknown.

Parathormone (PTH) functions to maintain Ca^{++} levels in the blood. PTH is stimulated by low Ca^{++} levels in the blood and leads to Vitamin D activation, increased Ca^{++} absorption in the gut, increased bone reabsorption, increased Ca^{++} reabsorption in the kidney and increased PO_4^- excretion in the urine. The net result of PTH activity is an increase in the blood Ca^{++} levels without an increase in PO_4^-. Hypertension could be caused by an increase in the total peripheral resistance or an increase in blood volume. PTH can cause hypertension by increasing either of these two factors (7). It has been shown that when administered acutely, PTH causes a hypotensive response as a result to arterial smooth musle relaxation (8). In patients exposed to chronically elevated PTH levels, however, it has exactly the opposite effect and leads to sustained hypertension (9). A more recent study provides evidence that there is a permitting role for PTH in the genesis of hypertension of patients with primary or secondary (renal) hyperparathyroidism (10). However clinically not enough is known about the effects of serum parathormone on hypertension in patients under regular hemodialysis, therefore we aimed to consider the effect of serum parathormone on the severity of hypertension in end-stage renal failure patients under hemodialysis treatment.

Patients and Methods:

This study is cross-sectional and was carried out on patients with end-stage renal disease, undergoing maintenance hemodialysis treatment. Factors serving as exclusion criteria were cigarette smoking and body mass index (BMI) more than 25. According to the severity of the secondary hyperparathyroidism of each patient, they were treated with oral active vitamin D3 (Rocaltrol) and with calcium carbonate capsules in various doses. The serum calcium (Ca), phosphorus (P), alkalin phosphatase (ALP) and albumin levels of the patients were measured with standard kits, and intact PTH (iPTH) levels by RIA with DSL-8000 kits, USA. For stratification of hypertensive patients, according to the 6th and 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, we evaluated hypertensive patients from stage one to three (11-12) (stage zero equals an absence of hypertension). Stages of the hypertension of HD patients were considered prior to treatment and at the start of first hemodialysis treatment.

For statistical analyses descriptive data are expressed as Mean±SD and as frequency distributions. Comparison between the two groups were performed by Student's T test. For correlation analysis, we used Spearman`s rho and partial correlation test after

adjustment for age, duration of hemodialysis treatment and also serum albumin. All statistical analysis were performed using the SPSS software (version 11.00). Statistical significance was inferred at a p value< 0.05.

Results:
The total number of patients were 73 (F=28, M=45), including 58 nondiabetic (F=22 M=36) and 15 diabetic hemodialysis patients (F=6, M=9). Tables 1 and 2 show the mean±SD of age, the length of time the patients had been on hemodialysis and the results of laboratory tests. Table 3 shows the frequency distribution of stages of hypertension.

The mean age (±SD) of subjects was 46.5±16 years. The mean length of the time patients had been on hemodialysis were 21.5±23.5 months. The mean serum iPTH of all patients was 309±349 pg/ml. The iPTH levels of the diabetic group and nondiabetic group were 234±265 pg/ml and 329±368 pg/ml, respectively. Serum alkaline phosphatase level of all patients was 413±348 IU/L. Serum alkaline phosphatase levels of diabetic group and nondiabetic group were 295±179 IU/L and 443±375 IU/L, respectively. Stage two hypertension was observed in 40% of all patients and stage three hypertension was found in 19% of all patients.

There were no significant differences of age, duration of hemodialysis treatment, serum ALP and serum iPTH between diabetic and nondiabetic hemodialysis (HD) patients. A significant difference in CaxP products between diabetic and non diabetic group was found (46±19 versus 61±24 respectively, p=0.037). A significant positive correlation between serum iPTH and serum ALP(r=0.302, p=0.005) was observed. There was a significant positive correlation between stages of hypertension and serum iPTH(r=0.200, p=0.045). There was no significant correlation between stages of hypertension and serum ALP (r=0.135, p=0.128). A significant positive correlation between stages of hypertension and Ca x P products of patient(r=0.231 p=0.027) was also observed.

Discussion:
In this study the principal finding was a positive correlation between serum iPTH levels and stages of hypertention. In a cross-sectional study, in a random sample of 612 hemodialysis patients from 10 dialysis centers, serum PTH and calcium levels were examined. The results of the study indicated that 25% of patients had serum PTH levels within the normal range, 25% of patients had higher PTH level than normal (but less than three times normal), and 50% had PTH levels higher than three times normal values. It was also found that diabetic patients had lower PTH levels than those of nondiabetic patients. The result of this study has clearly demonstrated that hyperparathyroidism is highly prevalent in hemodialysis population. (13). Owda et al. evaluated 122 patients who had been receiving maintenance hemodialysis for at least 12 months in two dialysis centers in mid Michigan. Seventy-eight percent of their patients had iPTH above 200 pg/mL (mean value: 481 pg/mL), 19% had iPTH within the accepted normal range (mean value: 155 pg/mL), while 3% had levels below 100 pg/mL (mean 53 pg/mL). Phosphate, calcium, calcium phosphate product, age and duration of hemodialysis treatment are important factors correlating with elevated iPTH. There was no significant difference in iPTH between diabetic and nondiabetic patients with mean iPTH of 403 pg/mL and 407 pg/mL, respectively (14). To assess whether parathyroidectomy (PTx) affects blood pressure, Pizzarelli et al. studied 22 hemodialysis patients and found that blood pressure was lower in uremic patients who underwent PTx than uremic patients not submitted to PTx (15). The mean duration of hemodialysis treatment was 8.2±0.9 years in that study. The data of 45 patients with secondary hyperparathyroidism in dialysis who had undergone PTx were retrospectively collected from 8 different dialysis units by Coen et al. to evaluate the long-term results of PTx on parathyroid function and blood pressure. It was found that 20 of the 45 patients with preoperative hypertension experienced a statistically and clinically significant decrease in blood pressure levels (16). In contrast to these results, it has also

been reported that PTx fails to correct hypertension in hemodialysis patients with secondary hyperparathyroidism (6). In this study, blood pressure values obtained during a different period (before PTx, one month after PTx, and following period-mean 16 months-) were compared in 19 hemodialysis patients. In 12 of those 19 patients, neither a clinically nor a statistically significant change has found in systolic or diastolic blood pressure.

In the present study there is a relationship between serum iPTH levels (but not serum ALP) and the severity of hypertension in our patiens. Since secondary hyperparathyroidism in addition to hypertension are two factors involved in accelerated atherosclerosis in hemodialysis patients and the resultant increased mortality, further clinical studies into this important aspect of the care of patients with end-stage renal disease is needed.

Table 1: Mean±SD, Minimum and Maximum of age and duration of hemodialysis treatment.

		Age (years)	D.H.T* (months)
total patients	Mean±SD	51±16	21.5±23.5
	Min	15	1
	Max	78	112
diabetic group	Mean±SD	58±16	22±23
	Min	27	1
	Max	78	72
non-diabetic group	Mean±SD	49±15.6	21±24
	Min	15	1
	Max	78	112

*Duration of Hemodialysis Treatment

Table 2: Mean ±SD , Minimum and Maximum of laboratory data in hemodialysis patients.

		iPTH* (Pg/ml)	ALP (IU/l)	CaxP (products)	Albumin (g/dl)
total patients	Mean±SD	309±349	413±348	58±24	4±0.75
	Min	10	100	18	2
	Max	2235	2438	135	6.8
diabetic group	Mean±SD	234±265	295±179	46±19	3.6±0.7
	Min	10	120	18	2
	Max	900	734	74	4.6
non-diabetic group	Mean±SD	329±368	443±375	61±24	4.2±0.7
	Min	20	100	25	2.5
	Max	2235	2438	135	6.8

*Intact PTH

Table 3 : Frequency distribution of stages of hypertension in hemodialysis patients.

Stages of hypertension	Total patients		DM group*		Non-DM group	
	Number	Per cent	Number	Per cent	Number	Per cent
0	7	9.6	0	0	7	12.1
1	7	9.6	1	6.7	6	10.3
2	40	54.8	10	66.7	30	51.7
3	19	26	4	26.7	15	25.9

*DM=Diabetes Mellitus.

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