Association between secondary hyperparathyroidism and coronary artery disease in patients on regular hemodialysis

Düzenli hemodiyalize giren hastalarda sekonder hiperparatiroidili ile koroner arter hastalığının ilişkisi

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Abstract

Objective: To understand the association between parathormone excess due to secondary hyperparathyroidism/hyperphosphatemia and coronary artery disease in hemodialysis (HD) patients.

Methods: This cross-sectional study was carried out on 36 stable patients undergoing maintenance HD. Blood samples were collected after overnight fasting for serum calcium, phosphorus, and intact serum parathormone (iPTH). The presence of cardiac chest pain was confirmed through the complaint of heart burn or epigastric pain, of retrosternal discomfort and chest compression which was confirmed by symmetrical depressed T wavea observed in the 12-lead ECG performed at that time and also by observing the relief of the pain after taking sublingual trinitroglycerine.

Results: The mean age of the patients was 46.5±17 years. The length of time patients had been on hemodialysis was 32±36 months (median: 19 months). Cardiac chest pain was detected in 21% of the patients. Mean level of serum intact PTH was 434±455 pg/mL (median: 309 pg/mL). A significant relationship was found between patients with and without cardiac chest pain in duration of hemodialysis (r=0.009), number of hemodialysis sessions (r=0.029) and serum phosphorus levels (r=0.013) There was also a significant relationship between male hemodialysis patients with and without cardiac chest pain in serum iPTH levels (r=0.026).

Özet

Amaç: Sekonder hiperparatiroidi/hiperfosfatemi ve koroner arter hastalığı olan hemodiyaliz olgularında parathormon değerlerinin yüksekliğini anlamak.

Metod: Bu kesitsel çalışma hemodiyaliz alan 36 stabil hasta üzerinde yapıldı. Bir gecelik açlık sonrası serum kalsiyum, fosfor ve intakt parathormon (iPTH) çalışıldı, aynı zamanda 12 derivasyonlu elektrokardiyografide T dalgasında simetrik negatiflik gösterilmiş göğüs ağrısı, retro sternal huzursuzluk, göğüs sıkışması ve epigastrik ağrı veya yanma şikayeti olan olguların sublingual trinitrogliserin verildikten sonra ağrılarının hafiflediği gözlendi.

Sonuçlar: Olguların yaş ortalaması 46,5±17 yıl idi. Olguların hemodiyalize girme süreleri 32±36 ay (ortalama: 19 ay idi). Göğüs ağrısı %21 olguda tespit edildi. Serum iPTH 434, 455 pg/mL idi. (ortalama 309 pg/mL). Göğüs ağrısı olan veya olmayan olgularda hemodiyaliz süresi (r=0.009), hemodiyaliz seansları sayıları (r=0.029) ve serum fosfor düzeyleri (r=0.013) arasında anlamlı fark saptandı. Aynı zamanda göğüs ağrısı olan veya olmayan erkek hemodiyaliz alan olgularda serum iPTH düzeylerinde anlamlı fark saptandı (r=0.026).

Tartışma: Bizim bulgularımız koroner arter hastalığı olan hemodiyalizli olgularda serum fosfor düzeylerinin daha iyi kontrol altına alınmasının önemi ve parathormon değerlerinin yüksekliğinin önlenmesini desteklemektedir.

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Conclusion: Our data support the importance of better control of serum phosphorus levels and also of treatment of parathormone excess in promoting prevention of coronary artery disease in hemodialysis patients.

Keywords: secondary hyperparathyroidism, hyperphosphatemia, hemodialysis, coronary artery disease

Anahtar sözcükler: sekonder hiperparatiroidizm, hiperfosfatemi, hemodiyaliz, koroner arter hastalığı

Introduction

Cardiovascular diseases are frequently encountered in patients with end-stage renal failure. Cardiovascular disease is the most common cause of death in patients with end-stage renal disease (ESRD) and accounts for most of the morbidity in this group of patients[1-3]. Dialysis patients are also subject to atherosclerosis and consequent ischemic heart disease, but myocardial dysfunction and overt heart failure also are highly prevalent[1-6].

Secondary hyperparathyroidism (SHPTH) is common in patients with chronic kidney disease (CKD) and is characterized by elevated serum parathyroid hormone (PTH) levels[7-11], parathyroid hyperplasia and an imbalance in calcium and phosphorus metabolism[12-18].

PTH is a major uremic toxin, and may be responsible for long-term consequences that include renal osteodystrophy, severe vascular calcifications, alterations in cardiovascular structure and function, immune dysfunction, and anemia[19-22]. These adverse effects may contribute to an increased risk of cardiovascular morbidity and mortality among end-stage kidney failure patients[21-23]. Recent studies have also shown that hyperphosphatemia is associated with cardiovascular disease and thus, increased mortality and morbidity[24-25].

In spite of dramatic advances in our understanding of the pathogenesis, pathophysiology and sequels of SHPTH, research is still required to better understand the role of parathormone excess and hyperphosphatemia in hemodialysis (HD) patients. We therefore decided to study the association CAD with SHPTH in a group of HD patients.

Methods

This cross-sectional study was carried out on patients with ESRD undergoing maintenance HD. The total number of patients included in the study was 36 (F=15 M=21), consisting of 25 nondiabetic and 11 diabetic hemodialysis patients.

Blood samples were collected after overnight fasting for serum calcium, phosphorus, and intact serum parathormone (iPTH). According to the severity of anemia and hyperphosphatemia, patients were given intravenous (i.v.) iron, sucrose, calcium carbonate and 1,25 $(OH)_2$ VitD3 in varying doses after each dialysis session.All patients were also given folic acid, 3 mg daily; L-carnitine, 750 mg daily; B-complex tablets, and 2000 units of i.v. Eprex [recombinant human erythropoietin (rHuEPO)] after each dialysis session routinely. All of the study patients were hypertensive, which was controlled with amlodipine and/or atenolol in varying doses. Exclusion criteria were presence of active gastric pain confirmed by history and pericardial effusion on echocardiography. Blood samples were collected after overnight fasting for complete blood count (CBC) and determination of levels of serum calcium (Ca), phosphorus (P), albumin (Alb), using standard methods. Intact serum parathormone (iPTH) was measured by the RIA method using DSL-8000 kits from the USA (normal range of values is 10-65 pg/mL). Complaints of heart burn or epigastric pain, of retrostrenal discomfort and chest compression were taken as symptoms of cardiac chest pain, confirmed by presence of symmetrical depressed T waves in a 12-lead ECG by means of a 12-channel and also by observing relief of the pain after taking sublingual trinitroglycerine (TNG). For measurement of adequacy of HD, urea reduction rate (URR) was calculated from pre- and post-blood urea nitrogen (BUN) data[26].

Body mass index (BMI) was calculated using the standard formula [post-dialysis weight in kilograms/height in meters squared (kg/m^2)]. Duration and frequency of HD

Tablo 1: Demographic, clinical and biochemical findings of the patients

N=36	Minimum	Maximum	Mean+SD	Median	Range
Age (years)	16	80	17±46	43	64
DH (months)	2	156	36±32	19	154
Number of dialysis	36	1584	393±294	156	1548

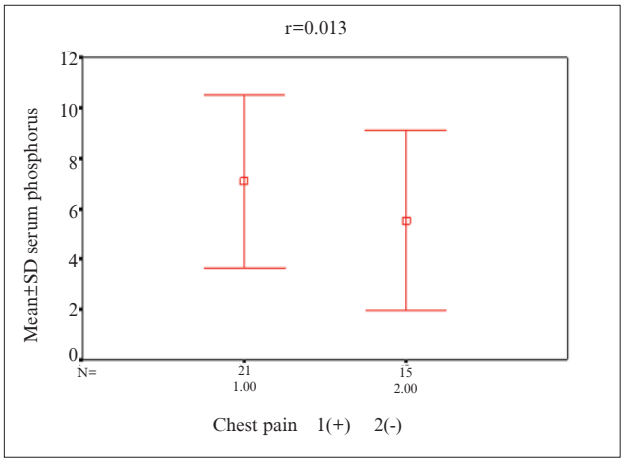

Fig 1. Relationship between serum phosphorus and cardiac chest pain (r=0.013)

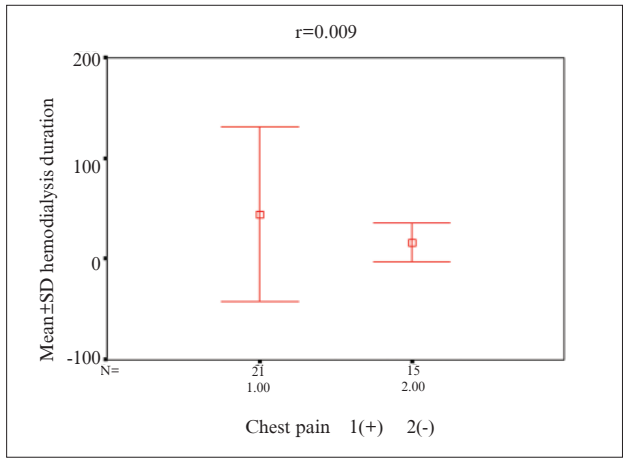

Fig 2. Relationship between hemodialysis duration and cardiac chest pain (r=0.009)

treatment were calculated from the patients' records. The duration of each HD session was 4 hours.

For statistical analysis, descriptive data are expressed as mean ± SD, median values, and frequency distributions. Comparison between groups was performed by using the T test.

All statistical analyses were performed using the SPSS (version 11.5.00). Statistical signi-ficance was set at p value < 0.05.

Results

Table 1 shows the demographic, clinical and biochemical data on the patients..

Mean age was 46.5±17 years. The mean length of time the patients had been on hemodialysis was 32±36 months (median:19 months). About 21% of patients had chest pain.

Mean±SD value for serum iPTH level was 434±455 pg/mL(median=309 pg/mL).

Significant differences in hemodialysis duration (r=0.009; Figure 1), number of hemodialysis sessions (r=0.029; Figure 2) and serum phosphate levels (r=0.013; Figure 3) were found between patients with and without cardiac chest pain.

While the differences in iPTH levels between patients with and without cardiac chest pain were weak (r=0.079) in the total group and in female hemodialysis patients (r=0.70).

We found a significant difference in iPTH levels (r=0.026; Figure 4) between male hemodialysis patients with and without cardiac chest pain.

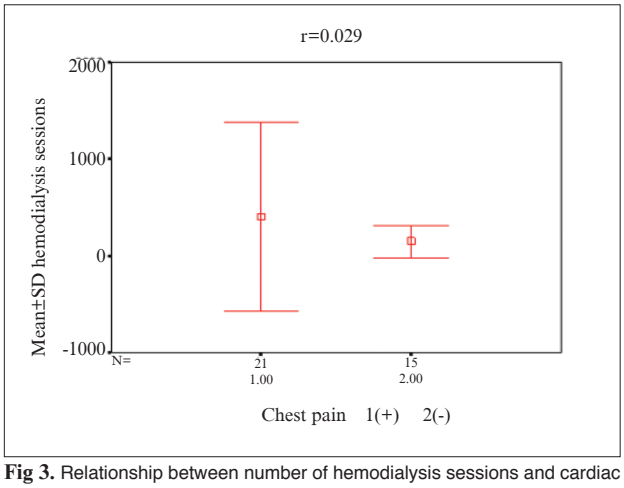

Fig 3. Relationship between number of hemodialysis sessions and cardiac chest pain (r= 0.029)

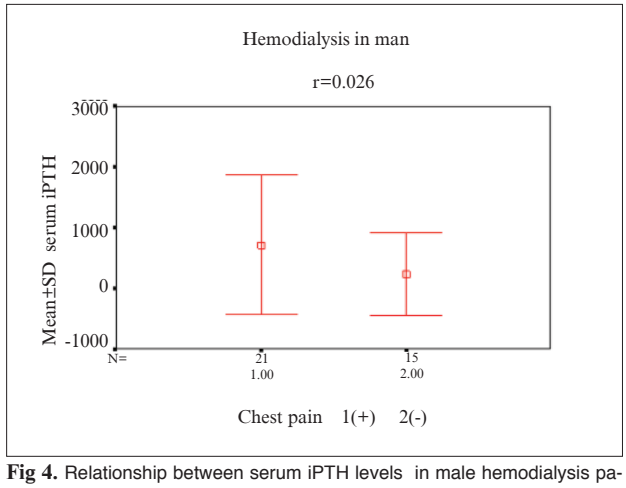

Fig 4. Relationship between serum iPTH levels in male hemodialysis patients with and without cardiac chest pain (r= 0.026)

Discussion

In this study we found significant differences with regard to hemodialysis duration, number of hemodialysis sessions, serum phosphorus between hemodialysis patients who had evidence of cardiac chest pain and those who were free of chest pain. A significant relationship between serum parathormone levels and chest pain was found only in male patients. Cardiovascular mortality and morbidity is 10-20 times higher in dialysis patients as compared with the general population[1-6]. This increased risk is linked to elevated levels of serum phosphorus[17,20-21]. Ganesh et al showed that levels of serum phosphorus higher than 6.5 mg/dL were associated with a 41% increase in risk of death from coronary artery disease compared with levels of 2.5-6.5 mg/dL. An elevated Ca x P product has also been associated with increased mortality; a 34% increase in risk has been observed in patients with Ca x P product levels greater than 5.8 71.9 mg2/dL2, compared with levels of 43.0-52.1 mg2/dL2[27].

The increase in mortality associated with high phosphorus and Ca x P product levels probably results, at least in part, from the increased risk of soft-tissue calcifications. Clearly, the effective management of phosphorus levels is an essential factor in reducing cardiovascular mortality in this patient population. In a prospective study of 15 patients by Park et al, it was reported that PTH-suppressive calcitriol therapy led to a regression in myocardial hypertrophy in dialysis patients[28]. It was also found that SHPTH might be a contributing factor in congestive heart failure[29]. Adverse effect of excess PTH on cardiac function was shown in our previous study[22] and also by other authors[30-35]. A substantial amount of evidence now exists that suggests a role for excess PTH and the changes in ion regulation induced by PTH in the pathogenesis of uremic cardiomyopathy[15,22,35-40]. A direct effect of PTH on myocardial contractility has not been demonstrated in human adult myocytes, but the cellular influx of calcium induced by PTH has been shown to increase contractility in animal cells. Indeed, myocardial and vascular cells are a target for PTH via specific receptors on their membranes. Experimental studies have shown that PTH produces positive inotropic and chronotropic effects on isolated cardiomyocytes, which occur in association with increased intracellular calcium and cAMP activity[15,22,35,41-44]. There is growing evidence for a role for PTH in the development of left ventricular hypertrophy. Parathormone indirectly reduces myocardial contractility, but, in the terms of left ventricular (LV) structural changes, existing evidence suggests that PTH may play a role in the development of cardiac interstitial fibrosis via the permissive activation of cardiac fibroblasts[15,22,42-44]. Cardiac fibrosis is known to be associated with uremia and may contribute to diminished LV compliance and consequently diastolic dysfunction in these patients[15,22,44-46].

Conclusions

Our data is in agreement with the findings of previous investigators and showed the importance of better control of phosphorus levels as well as of excess PTH in promoting prevention of coronary artery disease in patients with renal disease.

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