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Association of Secondary Hyperparathyroidism with Coronary Artery Disease in Patients on Regular Hemodialysis

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Abstract
Objective: To understand the association of parathormone excess due to secondary hyperparathyroidism and hyperphosphatemia with coronary artery disease, a study was designed on a group of stable hemodialysis (HD) patients. *Methods*: This cross-sectional study was carried out on 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, retrosternal discomfort and chest compression was confirmed by symmetrical depressed T wave at that time on a 12-lead ECG by means of a 12-channel and also reliving the pain after taking sublingual Trinitroglycerine pearls (TNG). *Results*: A sample of 36 stable HD patients was investigated. The mean age of patients was 46.5±17 years. The length of the time patients have been on hemodialysis were 32± 36 months (Median = 19 months). About 21% of patients had chest pain. Mean±SD of intact PTH of patients was 434±455 pg/ml (Median = 309 pg/ml). In this study, there was a significant difference of hemodialysis duration ($p = 0.009$), hemodialysis amount ($p = 0.029$) and also serum phosphorus ($p = 0.013$) between patients with and without cardiac chest pain. There was also a significant difference of iPTH ($p = 0.026$) between male hemodialysis patients with and without cardiac chest pain. *Conclusion*: Our data supported the importance of better control of serum phosphorus and also treatment of parathormone excess as the responsible factors promoting the coronary artery disease in hemodialysis patients.

Keywords: Secondary hyperparathyroidism; Hyperphosphatemia; Hemodialysis; Coronary artery disease.

Introduction

Patients with end-stage renal failure commonly have different cardiovascular diseases and 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 too [1-6].

Secondary hyperparathyroidism (SHPTH) is common in patients with chronic kidney disease (CKD) and is characterized by excessive 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 [21-25].

It was found that hyperphosphatemia is associated with cardiovascular disease and, thus, increased mortality and morbidity [24].

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. In this regard, we decided to study the association coronary artery disease with secondary hyperparathyroidism in this group of patients.

Material and Method

This cross-sectional study was carried out on patients with ESRD undergoing maintenance HD. Study was conducted between January 2009 to April 2009. According to the severity of anemia and hyperphosphatemia, patients were given intravenous (i.v.) iron sucrose, calcium carbonate and 1,25-dihydroxyvitamin D3 in varying doses after each dialysis session. All patients were also given folic acid 3 mg daily, L-carnitine, 750 mg daily, B-complex tabletsand also 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 (2 to 4mg/daily) and/or atenolol(50 to 100/d) 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 levels of serum Calcium (Ca), phosphorus (P), Albumin (Alb). CBC were measured by cell counter Cismex K-1000. Calcium, Alb and P were measured by calorimetric method through auto analyzer BT 3800. 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). The presence of cardiac chest pain was confirmed through the complaint of heart burn or epigastric pain, retrostrenal discomfort and chest compression which confirmed by symmetrical depressed T wave at that time by performing a 12-lead ECG by means of a 12-channel and also reliving the pain after taking sublingual 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/square height in meters, kg/m^2). Duration and frequency of HD 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 ± standard deviations (SD), median values, and confidence interval of mean. The distribution of the variables of interest was not normal, so the Mann-Whitney test was used for analysis. All statistical analyses were performed using the SPSS (version 11.5.00). Statistical significance was set at p value < 0.05.

Results

The total patients were 36 (42% were female) consisting of 25 non diabetic hemodialysis patients and 11 diabetic hemodialysis patients.

Table 1 shows patients' data.

Table 1. Data of the investigated patients (n=36)

Variable	Min	Max	Mean ± SD	Median	Range	95% CI of Mean
Age (year)	16	80	46.6 ± 17.1	43	64	(40.8 – 52.4)
DH (month)[1]	2	156	32.3 ± 36.1	19	154	(20.1 – 44.5)
Amount (number of dialysis)	36	1584	294.4 ± 393.1	156	1548	(161.4 – 427.4)
BMI[2]	16	34	21.8 ± 4.4	23	18	(20.3 – 23.3)
URR (%)[3]	39	76	58.9 ± 9	58	37	(55.9 – 61.9)
Calcium (mg/ dL)	5	10	7.7 ± .9	8	5	(7.4 – 8)
Phosphorus (mg/ dL)	3	10	6.4 ± 1.9	6	7	(5.8 – 7.1)
CA×P (mg²/dL2)	21	80	51.2 ± 15.2	50	59	(46 – 56.3)
iPTH* (Pg/mL)	16	1980	434.6 ± 455.1	309	1980	(280.6 – 588.6)
Albumin (g/dL)	2	5	3.8 ± .5	4	2	(3.7 – 4)
Hemoglobin (g/dL)	5	13	9 ± 2.1	9	8	(8.3 – 9.7)
Hematocrit %	14	40	28.2 ± 6.3	30	26	(26 – 30.3)
Alkaline phosphatase (IU/L)	176	5487	628.2 ± 891.9	628	5312	(326.4 – 930)

[1]duration of hemodialysis, [2]Body mass index,[3] Urea reduction rate,*Intact PTH

The mean age of patients was 46.6±17 years. The length of the time patients have been on hemodialysis were 32±36 months (Median=19 months). About 21% of patients had chest pain.

Mean±SD of iPTH of patients was 434±455 pg/ml (Median=309 pg/ml),(95% of CI for iPTH=280.6 – 588.6).Also a significant difference of hemodialysis duration (p = 0.009; Figure 1), hemodialysis amount (sessions)(p = 0.029; Figure 2) and also serum phosphorus (p = 0.013; Figure 3) between patients with and without cardiac chest pain were found.

Using the Mann-Whitney test a significant difference of hemodialysis duration (p = 0.042; Figure 1) as well as of serum phosphorus levels (p = 0.013; Figure 2) between patients with and without cardiac chest pain were found.

The Skewness of hemodialysis amount was very high and using the Mann Whiney test the hemodialysis amount was not significance between two group (p = 0.17).

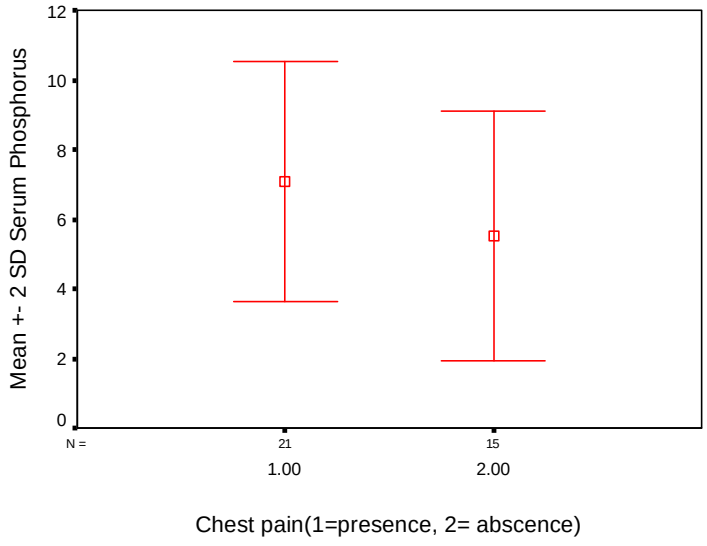

Figure 1. Significant difference of serum phosphorus between patients with and without cardiac chest pain

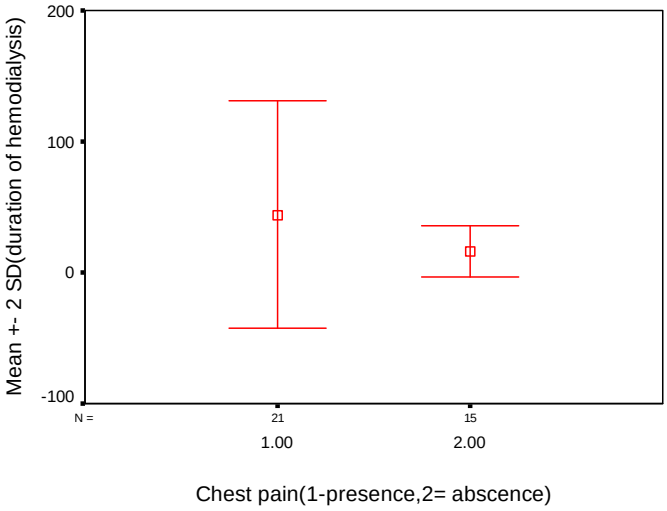

Figure 2. Significant difference of hemodialysis duration between patients with and without cardiac chest pain (p=0.009)

There was a weak differences of iPTH between patients with and without cardiac chest pain (p = 0.079), however we found a significant difference of iPTH (p=0.026; Figure 3) between male hemodialysis patients with and without cardiac chest pain, but there was not significant difference of iPTH (p = 0.70) between female hemodialysis patients with and without cardiac chest pain.

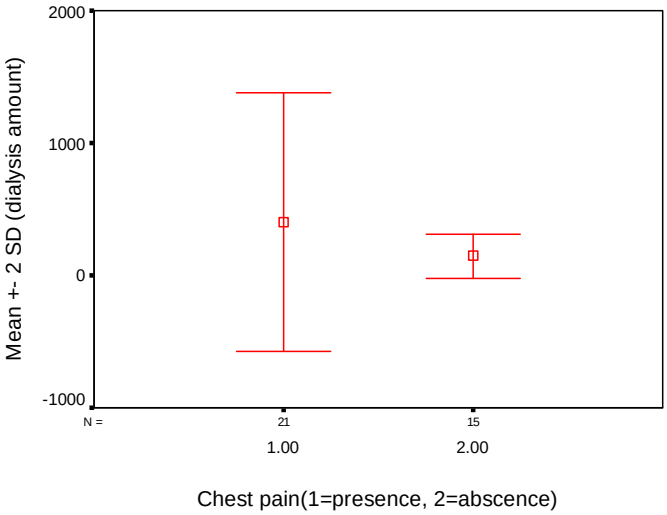

Figure 3. Significant difference of iPTH between male hemodialysis patients with and without cardiac chest pain

Discussion

In this study we found a significant difference of hemodialysis duration (Figure 2), serum phosphorus and parathormone of male hemodialysis patients (Figure 3) with and without cardiac chest pain. Cardiovascular mortality and morbidity is 10-20 times higher in dialysis patients, 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 P > 6.5 mg/d were associated with a 41% increase in risk of death from coronary artery disease compared with levels of 2.5-6.5 mg/dL

[27]. They found, elevated Ca×P product has also been associated with increased mortality; a 34% increase in risk has been observed in patients with Ca×P product levels of > 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×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. Park et al., in a prospective study of 15 patients, found 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 by other authors too [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 [15]. 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, evidences 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].

Conclusion

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

Ethical Issues

This study was approved by the ethical committee of Shahrekord University of Medical Sciences.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

AB carried defined the aim of research and the design of experiment and carried out the experiments. SB and MM participated in the design of the study and performed statistical analysis. HN coordinates and helped to draft the manuscript. All authors read and approved the final manuscript.

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