Association of secondary hyperparathyroidism with malnutrition and inflammation in maintenance hemodialysis patients

Running title: **secondary hyperparathyroidism and malnutrition in hemodialysis**

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ABSTRACT: This study conducted to found out the association of high PTH levels with various indices of malnutrition and inflammation in hemodialysis (HD) patients. Intact serurm PTH (iPTH) and serum C-reactive protein (CRP), serum calcium (Ca), phosphorus (P), Alkaline Phosphatase (ALP), serum cholesterol (chol) and serum triglyceride (TG) were measured. Total patients were 36 (f=15 m=21). The mean patient's age was 44(±17) years. The value of serum iPTH of all HD patients was 434+455 pg/mL, the value of serum iPTH of diabetic and non-diabctic dialysis patients were 201±277 and 537±483 pg/mL, respectively. In this study we found a significant positive correlation of serum iPTH with serum CRP, a significant inverse correlation of serum iPTH with BMI and a significant positive correlation of serum ALP with Logarithm of CRP. Also a significant positive correlation of serum phosphorus with serum CRP and a significant inverse correlation of serum phosphorus with BMI were found. When patients with iPTH below than 200 pg/mL were deleted, the correlation of iPTH with CRP became positive (r=0.42, p =0.085) and when patients with iPTH more than 500pg/mL were deleted, this correlation was found to be negative (r=-0.42, p:0.047), which means that a low iPTH value is an index of malnutrition while higher value is associated with inflammation. Further attention needs to better control of hyperphosphatemia and maintaining the iPTH levels l.5 times of normal to avoid the sides effects of secondary hyperparathyroidism.

[Rafiean-Kopaei, M, Baradaran, Aand Nasri H. **Association of secondary hyperparathyroidism with malnutrition and inflammation in maintenance hemodialysis patients**. Life Sci J 2012;9(3):1871-1878] (ISSN:1097-8135). http://www.lifesciencesite.com. 272

Keywords: secondary hyperparathyrcdisim, End stage, renal failure, nutritional status

Introduction

Among potential candidates for the high rate of hospitalization and mortality in maintenance hemodialysis (HD) patients, both protein-energy malnutrition (PEM) and inflammation continue to be at the top of the list (1-7). Epidemiological studies repeatedly and consistently have shown a strong association between clinical outcome and measures of both malnutrition (4-14), and inflammation in dialysis patients (9-17). Moreover, many investigators have observed that these two conditions tend to occur concurrently and coexist in individuals with end-stage renal disease (ESRD), and many factors that engender one of these conditions also lead to the other (18-22). Therefore, the terms malnutrition-inflammation complex syndrome (MICS), or malnutrition, inflammation, and atherosclerosis syndrome have been proposed to indicate the combination of these two conditions in these patients (23-27). The MICS increasingly has become the main focus of attention of outcome research concerning maintenance dialysis patients (25-34). Indeed malnutrition is present to some extent in approximately 40% of chronic renal failure (CRF) patients on maintenance HD (28-38). Several markers of malnutrition such as low body mass index and low serum albumin have been associated with high morbidity and mortality rates in this group of patients (38-42). Malnutrition in these patients is considered to be due to anorexia with low food intake (30-34), to the loss of nutrients and catabolism during the dialysis procedure, intercurrent illnesses (30-43), metabolic acidosis (40-44), glucose intolerance, increased cytokine levels, and other hormonal derangements (40-47). Among these last disturbances, high parathyroid hormone (PTH) level, frequently observed in CRF patients may be

implicated in the nutritional abnormalities found in these patients (48-56). In fact, it has been observed that patients with primary hyperparathyroidism may show evidence of weight loss, weakness and muscle atrophy and negative nitrogen balance (57-63). In this regard few studies have analyzed the association of high PTH levels with body mass index as a marker of nutritional status and serum C reactive protein as a marker of inflammation to better found the association of high PTH levels with malnutrition-inflammation complex syndrome (MICS) (58-66). We therefore sought to study this adverse effect of secondary hyperparathyroidism (sHPTH) in a group of maintenance hemodialysis patients (MHPs) consisting of non-diabetic and diabetic patients.

Patients and methods

Patients

This cross-sectional study was conducted on patients with end-stage renal disease (ESRD), who were undergoing maintenance HD treatment. The etiologies of renal failure were different, containing mainly diabetic nephropathy, hypertension, various glomerular diseases, autosomal dominant poly cystic kidney disease (ADPKD) and also urinary tract infections (64-70). According to the severity of hyperparathyroidism, each patient being treated for sHPTH was given oral active vitamin D3 (Rocaltrol), calcium carbonate, and Rena-Gel capsules at various doses. According to the severity of anemia, patients were under IV iron therapy with Iron sucrose (venofer) at various doses after each dialysis session, all patients were under treatments of 6mg folic acid daily, 500mg L-Carnit hyperparathyroidism in daily, oral Vitamin B complex tablet daily and also 2000U W Eprex (recombinant human erythropoietin (rHuEPO) unique for each patient after each dialysis session routinely (71-73). Exclusion criteria were active or chronic infection. The study was done in the hemodialysis section of Shahrekord University of Medical Sciences in Shahrekord of Iran.

Laboratory methods

After an overnight fast, blood samples were obtained. Intact serum PTH (iPTH) was measured by the radioimmunoassay (RIA) method using DSL-8000 of USA (normal range of values is 10-65 pg/mL). Also peripheral venous blood samples were collected for biochemical analysis including serum predialysis creatinine (Creat), post and predialysis blood urea nitrogen (BUN), albumin (Alb) as well as serum C-reactive protein (CRP), serum calcium (Ca), phosphorus (P), Alkaline Phosphatase (ALP), serum cholesterol (Chol) and serum triglyceride (TG) were measured using standard kits. Body mass index (BMI) calculated using the standard formula (post dialyzed weight in kilograms/height in square meters ; kg/m^2). For the efficacy of hemodialysis the urea reduction rate (URR) was calculated from pre- and post-blood urea nitrogen (BUN) data (74). Duration and the amount of sessions of HD were calculated from the patients' records, The duration of each hemodialysis session was 4 hours. Statistical analysis: Results are expressed as the mean±SD and median values. Comparison between the groups was done using Student's t-test. Statistical correlations were assessed using partial correlation test. Statistical analysis was performed on total hemodialysis, females, males, diabetics and non diabetic populations separately. For some correlations the logarithm of some data were used too. All statistical analyses were performed rising SPSS (version 1 1.5.00). Statistical significance was determined at a $p<0.05$.

Results

Total patients were 36 (F: 15, M: 21), consisting of 25 (F: 1l , M:14) non-diabetic HD patients and 11 (F:4, M:7) diabetic HD patients. Table 1, 2 and 3 show the Mean ±SD, minimum and maximum and median of age, duration and sessions of HD and also laboratory results of all patients. The value of serum iPTH of total HD patients was 4J4±455 (median: 309) pg/mL, the value of serum iPTH of diabetic and non-diabetic HD patients were 201+277 (median:41) and 537+483(median:340)pg/mL respectively. In total HD patients a near significant positive correlation of serum iPTH with serum CRP (r=0.33, p=0.081) (adjusted for Ca, P, URR, DM, age, duration and sessions of dialysis) was seen, a significant inverse correlation of serum iPTH with BMI (r=-0.46, p=0.038) (adjusted for dialysis sessions) were seen. In total patients a near significant positive correlation of serum ALP with Logarithm of CRP (r=0.32, p=0.069) (adjusted for age, duration and sessions of dialysis) was found. In this group also a significant positive correlation of serum phosphorus with serum CRP (r=0.31, p=0.065) (adjusted for age duration & sessions of dialysis) and a significant inverse correlation of serum phosphorus with BMI (r=-0.31, p=0.042) (adjusted for dialysis sessions) were found too. Moreover in all patients a significant positive correlation of serum TG with BMI (r=0.43 p=0.012) (adjusted for age, duration and sessions of dialysis for correlations) was existed too. In all patients a significant inverse correlation of serum albumin with logarithm of CRP (r=-0.33, p=0.038) (adjusted for age, dialysis sessions and duration, serum Ca and P) was seen. In male HD patients there was a near significant positive correlation of serum albumin with BMI (r=0.99, p=0.063).

Table 1: Data of all HD patients

N=36	Minimum	Maximum	Mean±SD	Median
Age in years	16	80	44±16.5	43
DH+ months	2	156	30±36	17.5
Dialysis dose (cessions)	18	1584	285±396	144
URR%	39	75	53.5±9.8	57.5
Ca (mg/dL)	5	10	6.4±1.9	7.9
P (mg/dL)	3	10	6.4±1.9	6.2
ALP (IU/L)	175	5487	628±891	433
Alb g/dL	2.4	4.8	3.8±0.5	3.96
CRP (mg/dL)	3	40	8.7±6.7	8
iPHT pg/mL	16	1980	434±455	309
Chol (mg/dL)	59	211	117±38	115
TG (mg/dL)	29	461	130±96	95
BMI kg/m^2	16	34	22±4.4	21.5

Table 2: Data of non diabetic patients.

n=25	Minimum	Maximum	Mean±SD	Median
Age (years)	16	80	44±16.5	43
DH* (months)	2	156	40±40.8	22
Dialysis dose cessions	36	1584	370±452	156
URR%	60	76	61±7.5	60
Ca (mg/dL)	6	15	7.8±0.75	8
P (mg/dL)	4	10	606±1.8	6.5
ALP (IU/L)	190	5478	760±1044	478
Alb (g/dL)	2.4	4.7	3.8±0.5	4
CRP (mg/dL)	2	20	7.4±3.8	6
iPHT pg/ml	22	1980	537±483	340
Chol (mg/dL)	59	171	110±33	120
TG (mg/dL)	61	461	129±85	99
BMI(kg/m^2)	16	33	21±4.6	19

* Duration of hemodialysis

Table 3: Data of diabetic HD patients.

n=11	Minimum	Maximum	Mean±SD	Median
Age (years)	27	75	53±15.8	55
DH (months)	6	24	14.5±6	12
Dialysis (dose cessions)	54	216	123±54	108
URR%	39	75	53.5±9.85	54
Ca (mg/dL)	5	10	7.4±1.3	7.5
P (mg/dL)	3	10	5.9±2	6
ALP (IU/L)	175	584	327±148	295
Alb (g/dL)	3	4.8	3.8±0.5	3.9
CRP (mg/L)	4	40	12±10	10
iPHT (pg/mL)	16	840	201±277	41
Chol (mg/dL)	60	211	133±49	111
TG (mg/dL)	29	456	130±120	88
BMI (kg/m^2)	20	34	23.3±4	23

Discussion

In this study we found a near significant positive correlation of serum iPTH with serum CRP, a significant inverse correlation of serum iPTH with BMI and a near significant positive correlation of serum ALP with Logarithm of CRP. Also a significant positive correlation of serum phosphorus with serum CRP and also a significant inverse correlation of serum phosphorus with BMI were found. A significant inverse correlation of serum cholesterol with serum

phosphorus was seen. We also found a significant inverse correlation of serum albumin with logarithm of CRP. Moreover a significant positive correlation of serum albumin with BMI was observed, too. Serum albumin, cholesterol and also BMI are indexes of nutritional status in HD patients while serum CRP could show the inflammation status (5,9, 18-24). PTH has long been considered a uremic toxin, with many deleterious cellular and metabolic effects (52-58). It increases bone turn over and induces neuropathy, myopathy, cardiac hypertrophy, hyperlipidemia, carbohydrate intolerance, and immune dysfunction (52-63). Although specific studies are lacking, such conditions could influence the nutritional status of uremic patients with sHPTH (75-81). Garber demonstrated in vitro that high PTH levels enhanced muscle proteolysis and increased the release of alanine and glutamine. This effect, however, was observed only in normal rats (82). In a study conducted by Yasunaga et al. on Thirty-four patients under dialysis therapy received a parathyroidectomy (PTx) for secondary hyperparathyroidism found that PTx had beneficial effects on hurmoral immunological markers (83). They concluded that this effect is probably due to the remarkable PTH reduction and partly improver nutritional state after PTx (83). The nutritional and biochemical parameters of 15 chronic HD patients with severe sHPTH who had undergone total PTX with a forearm implant, were retrospectively studied by Khajehdehi et al. at 1, 3, 6, and 12 months pre- and post-PTx. They found that in 53% of the patients, the weight gain was more than 5% above the baseline (84). Avram et al. studied prospectively the relationship between the enrollment serum iPTH and all cause mortality in 345 HD and 277 peritoneal dialysis patients for 14 years and found that lower than expected levels of PTH in uremic patients are associated with increased mortality (85). Moreover, Guh et a136 recently reported similar findings that low levels of serum PTH at entry and lower time-dependent PTH levels predict mortality in HD patients(85). Avram et a1., hypothesized that inadequate protein intake, phosphorus intake or both result in impaired development of the expected sHPTH and in the excess mortality risk inherent with malnutrition(85), however, to date epidemiologic studies have shown a positive association between a high serum phosphorus and poor outcome among ESRD patients (49). In MHD patients, associations between demographic, clinical and laboratory values and mortality, including cardiovascular death, are significantly different and, in some cases, in the opposite direction of those derived from the general population, a phenomenon, termed reverse epidemiology (12, 42, 45, 47). Hence, the association between serum PTH and nutritional status may be bidirectional. Similar reverse epidemiologic observations have been made for serum creatinine and cholesterol in our previous study too (86). These studies show that, in MHD patients, the relation between the measure and outcome is counterintuitive. The cause of the unanticipated relation between lower serum PTH and increased mortality might be explained by the malnutrition-inflammation syndrome. Low intakes of calcium phosphorus, protein and 1ow serum phosphorus (which may all be associated with malnutrition or an inflammatory state or both), may account for this relation. Reduced intakes of these substances might lead to lower serum PTH concentrations and, directly or as a result of associated diseases, might induce higher mortality. While a 1.5 time of PTH level is necessary for bone activity in dialysis patients, the values more than this amount have deleterious effects as mentioned. While serum CRP is a marker of inflammation (14,42), we showed its positive correlations with serum iPTH as well as its negative correlation with BMI. Whilest the BMI is a marker of nutritional status(86,87). More over positive associations of high serum phosphorus and ALP as the markers of uncontrolled secondary hyperparathyroidism in MHPs with CRP and also negative correlation of high serum phosphorus with BMI further support the association of poorly controlled SHPTH with MCS in dialysis patients. In this regard when we deleted patients with iPTH below than 200 pg/mL, we found that the correlation of iPTH with CRP was positive (r=0.42, p=0.085) and when we deleted patients with iPTH mare than 500pg/mL, we found that this correlation was negative (r=-0.42, p=0.04), means that a low iPTH is an index of malnutrition while higher values is associated with inflammation. Thus further attention needs to control of hyperphosphatemia and maintaining the iPTH levels 1.5 times of normal to avoid the sides effects of secondary hyperparathyroidism.

Conflict of interest

The author declared no competing interests.

Acknowledgments

We would like to thank staffs of hemodialysis section. This work was supported by Research deputy of Shahrekord University of Medical Sciences, Shahrekord, Iran.

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10/27/22012