

Strong Inverse Association of Serum Parathormone with Plasma HCO₃ in Female Hemodialysis Patients

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Abstract: Secondary hyperparathyroidism (SHPTH) is a common complication of chronic kidney disease and is characterized by elevated levels of serum parathyroid hormone (PTH) and abnormalities in bone and mineral metabolism. This serious disorder could be aggravated by metabolic acidosis which is a common consequence of advanced chronic renal failure and in maintenance dialysis patients. To investigate factors influencing the intensity of secondary hyperparathyroidism (SHPTH) in patients on chronic maintenance haemodialysis we tested the association of relative acidosis of hemodialysis patients with parathyroid gland activity. This is a cross-sectional study that was conducted on patients undergoing maintenance hemodialysis treatment with acetate basis dialysate and polysulfone membrane. Serum calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP) and intact serum PTH (iPTH) and plasma HCO₃ were measured. A significant positive correlation of plasma HCO₃ with duration and dosage of hemodialysis were found. In all patients a significant inverse correlation of logarithm of serum iPTH with plasma HCO₃ was seen while this association was very significant in female hemodialysis patients. A strong inverse association between plasma HCO₃ and serum PTH in female gender may show the more aggressive form of SHPTH in this group.

Key words: Hemodialysis, acidosis, secondary hyperparathyroidism, parathormone, end-stage renal failure

Introduction

The renal elimination of nonvolatile acids, mainly formed by oxidation of sulfuric amino acids, is about 70 mmol/day. In hemodialysis (HD) patients who cannot eliminate an excess of H⁺ via the kidneys (Bergstrom, 1995). In maintenance dialysis patients, severe metabolic acidosis is associated with an increased relative risk for death (Movilli *et al.*, 2001). Metabolic acidosis contributes to renal osteodystrophy and together with hyperphosphatemia, hypocalcemia and altered vitamin D metabolism may result in increased levels of intact parathyroid hormone (iPTH) and metastatic calcifications (Mehrotra *et al.*, 2003). Secondary hyperparathyroidism (SHPTH) is a common complication of chronic kidney disease (CKD) that can lead to clinically significant bone disease. Additional consequences of secondary HPT, such as soft-tissue and vascular calcification, cardiovascular disease, and calcific uremic arteriopathy, may contribute to the increased risk of cardiovascular morbidity and mortality among CKD patients (Moe and Drüeke, 2003; Nasri *et al.*, 2004; Nasri and Baradaran, 2004). Correction of acidosis in hemodialysis patients increases the sensitivity of the parathyroid glands to calcium (Graham *et al.*, 1997). Apart of deleterious effects of metabolic acidosis on SHPTH and bone, it is associated with many adverse effects: negative nitrogen

balance, increased protein decomposition, anorexia, fatigue, impaired function of the cardiovascular system, impaired function of the gastrointestinal system, hormonal disturbances, insulin resistance, hyperkalemia, altered gluconeogenesis and triglyceride metabolism, increased progression of chronic renal failure, and growth retardation in children (Kovacic *et al.*, 2003). Little attention has been given to this aspect of hemodialysis patients and much less is known about the effects of acidosis on the parathyroid glands in chronic hemodialysis, therefore the purpose of this study was to study the association of relative acidosis of hemodialysis patients with parathyroid gland activity. We also aimed to test this associations in female and male groups and also sought to analysis these association between diabetic and non diabetics separately.

Materials and Methods

This is a cross-sectional study which was conducted on patients with end-stage renal disease (ESRD), undergoing maintenance hemodialysis (HD) treatment with acetate basis dialysate and polysulfone membrane. According to the severity of the secondary hyperparathyroidism, each patient was under treatment for SHPTH with oral active vitamin D3 (Rocaltrol), calcium carbonate and Rena-Gel capsules at various dosages. 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 post and predialysis blood urea nitrogen (BUN), serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), serum and magnesium (Mg). Plasma HCO_3 and blood PH was measured by arterial blood gas. For the efficacy of hemodialysis the urea reduction rate (URR) was calculated from pre- and post-blood urea nitrogen (BUN) data (Boag, 2002). Duration and dosage of hemodialysis treatment were calculated from patients records. The duration of each hemodialysis session was four hours. For statistical analysis descriptive data are expressed as Mean \pm SD. Comparison between groups were considered using T test. For correlations, partial correlation test was used. For correlations, the logarithm of some data was used. All statistical analysis were performed using the SPSS (version 11.5.00). Statistical significance was inferred at a p value < 0.05.

Results

The total patients were 60 (F=21 M=39), consisting of 44 non diabetic hemodialysis patients (F=15 M=29), and 16 diabetic hemodialysis patients (F=6 M=10). Table 1 shows the Mean \pm SD of age, the length of the time patients had been on hemodialysis, dialysis dosage and the result of laboratory tests. Mean \pm SD of age of total patients were 46 \pm 18 years. The length of the time patients had been on hemodialysis were 25 \pm 30, median (13.5) months. Serum iPTH of total patients were 357 \pm 395 pg/ml, (median=223). Mean \pm SD of iPTH of diabetic group and nondiabetic group were 199 \pm 246 (median=44.5) pg/ml, median and 414 \pm 424 (median=271) pg/ml respectively. Mean \pm SD of iPTH of female and male group were 921 \pm 294pg/ml and 390 \pm 442 pg/ml respectively. Plasma HCO_3 (pHCO₃) of total patients were 20 \pm 2.3 mEq/L. Mean \pm SD of pHCO₃ of diabetic group and nondiabetic group were 20.3 \pm 1.5 mEq/L and 19.8 \pm 2.50 mEq/L respectively. Mean \pm SD of plasma HCO_3 of female and male group were 20 \pm 2.5 mEq/L and 20 \pm 2.2 mEq/L respectively. In this study no significant differences of age, duration of hemodialysis treatment, dialysis dosage, and dialysis adequacy by URR and also serum iPTH, Ca, P, ALP, pHCO₃ and serum Mg between males and females were found (p N.S.). No significant differences of pHCO₃ between diabetics and nondiabetic hemodialysis patients was found, also no significant differences of pHCO₃ between males and females of hemodialysis patients were found (p N.S.). In this study a significant positive correlation of plasma HCO_3 with duration (r = 0.27 p = 0.039) and dosage of hemodialysis (p = 0.35 p =0.006) were seen (adjusted for age). No significant positive correlation of pHCO₃ with serum Ca, P, ALP and also with dialysis

adequacy by URR in total patients were found (p N.S.). In total patients a significant inverse correlation of pHCO₃ with logarithm of serum iPTH when adjusted for dialysis doses (sessions)was seen (r = - 0.29 p = 0.023; Fig. 1). This association was very significant (and also inverse) in female hemodialysis group (r = -0.66 p = 0.001) (adjusted for age), while this association was not significant in male group when adjusted for age, duration and dosage of dialysis ,more over in non diabetics the correlation of logarithm of serum iPTH with pHCO₃ was near significant (r = -0.27 p = 0.070) (adjusted for duration of hemodialysis).This association in diabetic group was not significant.

Discussion

Important findings of this study were a significant positive correlation of plasma HCO_3 with duration and dosage of hemodialysis. In all patients a significant inverse correlation of plasma HCO_3 with serum iPTH, while this association was very significant (and inverse) in female hemodialysis patients. In a study conducted by Lin *et al.* (2002) on 120 maintenance hemodialysis patients showed 17% frequency of metabolic acidosis. In another study on 70 stable patients receiving high-efficiency hemodialysis for at least 4 months underobservation over a 1-year period, Sepandj found, twenty patients (28%) had a mean predialysis serum bicarbonate of less than 21 mEq/L (Sepandj *et al.*, 1996). In a large study on 7,000 hemodialysis patients from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States, Bommer *et al.* (2004) showed that the average of midweek predialysis serum bicarbonate level was 21.9 mEq/L (Bommer *et al.*, 2004). The mean \pm SD of HCO_3 of our patients were 20 \pm 2.3 which is near the result of previous study. Relative metabolic acidosis contributes to renal osteodystrophy and together with hyperphosphatemia, hypocalcemia and altered vitamin D metabolism may result in increased levels of intact parathyroid hormone and metastatic calcifications (Movilli *et al.*, 2001). Studies concerning the effects of plasma HCO_3 on serum PTH showed interesting results. In the study of Lu on 18 hemodialysis patients after continuous bicarbonate infusion, plasma PH, bicarbonate, total CO₂, sodium, serum total calcium and 1,25(OH)₂ vitamin D₃ levels increased significantly while serum concentrations of iPTH, alkaline phosphatase and albumin showed significant decreases. The plasma ionized calcium, potassium, serum magnesium and inorganic phosphorus levels showed no significant difference before and after bicarbonate infusion. They concluded that rapid correction of metabolic acidosis attenuates circulating PTH activity in chronic renal failure and may underline the importance of maintaining normal acid-base homeostasis particularly in the presence of secondary hyperparathyroidism (Lu *et al.*, 1994). Previous studies in ESRD have shown that

Nasri and Baradaran: Secondary hyperparathyroidism

Table 1: Mean±SD, Minimum and Maximum of age, duration and dose hemodialysis and also laboratory results of total, non-diabetic and diabetic hemodialyzed patients

Total patients n=60		Minimum	Maximum	Mean±SD	Median
Age	years	11	80	46 ±18	44
DH*	months	2	156	25±30	13.5
Dialysis					
dose	sessions	18	1584	219±321	106
URR	%	39	76	57.4±9	57
HCO ₃	mEq/L	14	25	20±2.3	20
iPTH	Pg/ml	10	1980	357±395	223
Ca	mg/dl	5.00	10.00	7.7±0.9	8
P	mg/dl	2.00	14.00	6.5±2	7
Alp	IU/L	135	5487	538±746	347
Mg	mg/dl	1.600	3.500	2.42±0.41	2.35
Non diabetics n=44					
Age	years	11	80	42.9±18	40
DH*	months	2	156	29.8±35	16
Dialysis					
dose	sessions	18	1584	258±367	107
URR	%	47	76	59.3±8	58.5
HCO ₃	mEq/L	14	25	19.8±2.50	20
iPTH	Pg/ml	10	1980	414±424	271
Ca	mg/dl	6	10	7.8±0.9	8
P	mg/dl	2	14	6.6±2.2	7
Alp	IU/L	139	5487	623±854	390
Mg	mg/dl	1.6	3.3	2.45±0.4	2.4
Diabetics n=16					
Age	years	27	79	54±16.7	55
DH*	months	6	24	13±6	12
Dialysis					
dose	sessions	54	216	114±52	95
URR	%	39	75	52.3±9.5	53.5
HCO ₃	mEq/L	18	25	20.3±1.5	20
iPTH	Pg/ml	16	860	199±246	44.5
Ca	mg/dl	5	10	7.5±1	7.5
P	mg/dl	3	10	6.2±2	6
Alp	IU/L	135	584	306±138	297
Mg	mg/dl	2	3.5	2.36±0.43	2.2

*Duration of hemodialysis

correction of acidosis with either oral bicarbonate supplementation or increases in dialysate bicarbonate led to relative reductions in PTH and improvements in bone histology (Lefebvre *et al.*, 1989; Movilli *et al.*, 2001). The mechanism of the bicarbonate-PTH association is unknown, though direct effects on PTH secretion, and increased sensitivity of the parathyroid gland to calcium (Bichara *et al.*, 1990) and an indirect effect due to acidosis-related hypercalciuria been proposed (Graham *et al.*, 1997). In our study no significant association between dialysis efficiency (by URR) with plasma HCO₃ was noted in an agreement with our study, no significant association between dialysis efficiency (by KT/V) with plasma HCO₃ in the study of Chauveau *et al.* (2000) was found too. Important finding of the present study was the significant and inverse correlation of serum HCO₃ with

serum iPTH in female hemodialysis patients, while in total patients this association was near significant and in male HD group no correlation was found. Is it possible that hemodialysis females are more susceptible to be involved by secondary hyperparathyroidism specially in the background of acidosis? In the other words is gender a major determinant of secondary hyperparathyroidism in uremic patients? In contrast to our data, Trovato *et al.* (1998) in a study on seventy patients on long-term bicarbonate dialysis, (34 male and 36 post-menopausal female) assessed serum iPTH at three months intervals and found serum iPTH was significantly higher in women vs men. In a study conducted by Almaden on forty-six parathyroid glands from 19 hemodialysis patients who underwent for gland parathyroidectomy showed, female

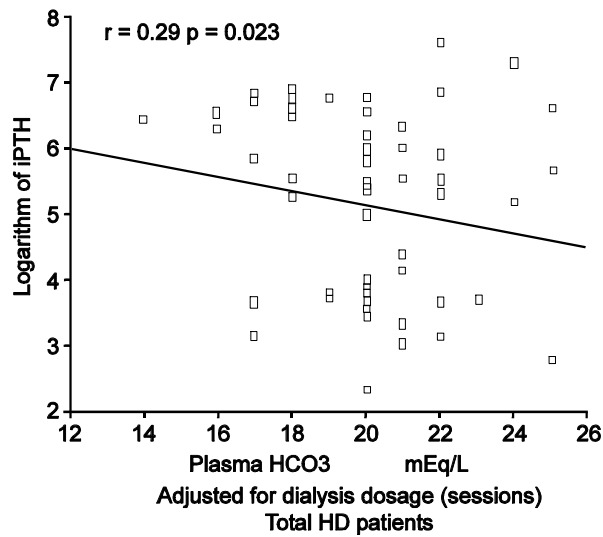


Fig. 1: Significant inverse correlation of plasma HCO₃⁻ with logarithm of serum iPTH

gender favor parathyroid cell proliferation and could reduce the inhibition of parathyroid function by calcitriol (Almaden *et al.*, 2003). Moreover Lomonte *et al.* (2005) on hemodialysis patients performed parathyroidectomy found that female gender is associated with more aggressive histological SHPTH patterns and suggest that female gender predisposes to monoclonal proliferation of parathyroid glands in chronic uremia. Olafur *et al.* (1998) studied 52 new hemodialysis patients with mild secondary hyperparathyroidism (PTH, 110-670 pg/mL) treated with a standardized regimen of calcium supplements and could show that, PTH suppression was less in women than in men, although there were statistically significant differences between the genders with respect to the primary disease and dialysis dose in that study. In this regard, females had more diabetes, and the dialysis dose, KT/V, was higher in women. In addition, women showed slightly fewer increases in calcium concentration over the 4 weeks than men. After controlling for these factors in a multivariable regression the effect of gender remained significant. Olafur *et al.* (1998) concluded that gender seems to be an independent predictor of changes in PTH over time. Gupta *et al.* (2000) and De Boer *et al.* (2002) were also noted the higher PTH has been associated with African American race, female gender, younger age, and lack of diabetes mellitus. The effect of gender on parathyroid activity may be regulated by sex steroids, since estrogen receptors are present in parathyroid cells and estrogens increase PTH mRNA levels (Prince, 1994). Even though estradiol levels are normal in the majority of women on dialysis amenorrhea or anovulatory periods are common, and long periods of unopposed estrogen exposure may lead to stimulation of the parathyroid gland (Zingraff *et al.*, 1982; Lim *et al.*, 1980). In a recent study, hyperparathyroid bone disease

was more frequently seen in uremic women than men (68.5% versus 51%,) (Gerakis *et al.*, 1996) However, in the general population, men and women have similar PTH levels (Bell *et al.*, 1985). Also other investigators noted a sexual difference in bone metabolism in dialysis patients (Luisetto and Bertoli, 1994), and in the general population, there are gender differences in bone metabolism as well as in propensity to develop parathyroid abnormalities (Harrell *et al.*, 1996). As mentioned in the above studies, possible mechanism for this gender effect concluded the effects of estrogens and progestins on the secretion of PTH (Naveh-Many *et al.*, 1992; Cosman *et al.*, 1994) or modulation of the PTH response to various stimuli by these hormones. An interesting aspect of our study was the strong association between female gender and PTH response to pHCO₃. Our own results confirm previous mentioned data and we could conclude a novel finding: female gender is associated with more aggressive form of SHPTH. In fact in any event this interesting relationship needs further investigation and confirmation in larger studies.

Aknowlegments

We would like to thanking from research deputy of our university, specially from Dr, Yussefi PHD to provid facilities to do this research.

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Nasri and Baradaran: Secondary hyperparathyroidism

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