Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

SECONDARY HYPERPARATHYROIDISM IN ALL THE STAGES OF CHRONIC KIDNEY DISEASE IN SOUTHERN INDIAN POPULATION

MALAWADI BN*, SUMA MN*, PRASHANT V*, AKILA P*, ANJALIDEVI BS*, MANJUNATH S **

***Department of Biochemistry and **Nephrology, Jagadguru Sri Shivarathreeshwara Medical College and Hospital, JSS university, SS Nagar, Mysore-570015, Karnataka, India., Department of Biochemistry, Belgaum Institute of Medical Sciences, Belgaum 590001, Karnataka, India.**

Email: drbhimrao@rediffmail.com

Received: 14 Feb 2014 Revised and Accepted: 29 Feb 2014

ABSTRACT

Objectives: 1.To estimate serum intact parathormone(iPTH) and other biochemical parameters (calcium, inorganic phosphate, urea and creatinine) in chronic renal failure and healthy volunteers. 2. To compare and find out correlation between serum intact parathormone and biochemical parameters in the study group.

Methods: For the study of 5 stages of chronic renal failure(CRF) totally 150 patients(30 patients in each stage of CRF and 30 healthy controls) in the age group of 20-60 years were taken. Serum intact parathormone was estimated by chemilumino-metric assay and other biochemical parameters were estimated using standard methods. Creatinine clearance was calculated by using Cockcroft and Gault equation.

Results: The serum iPTH (331.68 ± 204.99 pg/ml) was significantly higher in more advanced renal failure(CRF stage 5) which confirms the relationship between severity of hyperparathyroidism and the degree of renal impairment. The increased levels of serum iPTH (156.94 ± 44.26 pg/ml for CRF stage 2) were present even in early renal failure and it was related to low serum calcium level (8.46 ± 1.21 mg/dl for CRF stage 2) and progressive rise of serum inorganic phosphate from early to advanced renal failure. Therefore serum iPTH is negatively correlated with creatinine clearance($r = -0.718$, $p<0.001$) and serum total calcium($r = -0.454$, $p<0.001$). However, the serum iPTH is positively correlated with inorganic phosphate($r = +0.621$, $p<0.001$), urea($r = +0.526$, $p<0.001$) and creatinine. ($r = +0.656$, $p<0.001$).

Conclusion: The estimation of serum iPTH and other biochemical parameters can help to diagnose the secondary hyperparathyroidism in the early stage of CRF which inturn has advantage to manage the patients of CRF accordingly to prevent the future complications.

Keywords: Chronic renal failure, Hyperparathyroidism, Parathormone

INTRODUCTION

Chronic kidney disease (CKD) is a debilitating condition responsible for high morbidity and mortality throughout the world [1]. Diabetic and hypertensive nephropathy are the leading underlying etiologies of both CKD and end stage renal disease (ESRD) [2]. Chronic renal failure (CRF) produces a number of abnormalities of calcium and phosphorus metabolism. Secondary hyperparathyroidism develops early in the course of chronic renal insufficiency, even at the glomerular filtration rate (GFR) of 50-80mL/min/1.73m^2.

It is generally thought to result from hypocalcaemia as a result of phosphate retention and deficient vitamin D synthesis. In response to an increase in serum phosphorus concentration, production of vitamin D is decreased and secretion of parathyroid hormone (PTH) is increased, which in turn increases urinary excretion of serum phosphorus to maintain normal serum calcium and phosphorus level. Therefore, PTH is an important factor in the regulation of calcium and phosphorus metabolism. The key target organs of parathormone action are the kidneys and skeleton [3].

The intact PTH peptide (MW ~ 9425 k.daltons) consists of 84 amino acids that are sequenced and designated according to reactivity. The N-terminal or amino terminal 1-34 region of the intact PTH molecule is biologically active. The middle and carboxy terminal 35-84 region of the iPTH molecule is biologically inactive but possesses immunological reactivity[4, 5].

In South India, data regarding PTH in relation to different biochemical parameters in adults with respect to various stages of CRF are very few. Therefore this study was conducted to estimate iPTH levels in adults with CRF in their different stages of presentation as well as in healthy controls to find out its correlation with different biochemical parameters.

MATERIAL AND METHODS

a) Selection and staging of subjects

This cross-sectional study was carried out in the department of Biochemistry in collaboration with department of Nephrology, JSS medical college and hospital, JSS university, Mysore during September 2006 to September 2008. This study was approved by the institutional ethical committee before commencing. 150 well diagnosed patients of CRF (30 patients in each stage) and 30 age and sex matched healthy controls in the age group of 20 to 60 years were included. Stages of CRF was based on creatinine clearance and calculated by using Cock-croft and Gault formula:

$$\text{Creatinine clearance (ml/min/1.73m}^2\text{)} = \frac{[140 - \text{Age (years)}] \times [\text{Weight (kgs)}]}{72 \times \text{Serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for females})$$

b) Exclusion criteria

Patients with acute renal failure, primary hyperparathyroidism, patients undergoing thyroid and parathyroid surgeries and secondary hyperparathyroidism other than the causes of CRF were excluded from the study.

c) Sample collection

Aseptically 5ml of venous blood was drawn from antecubital vein in a plain vacutainer with due consent from the patients and controls. Immediately it was transported to the laboratory in a ice-container and serum was used for estimation of various parameters.

d) Laboratory methods

Serum intact parathormone (iPTH) was estimated by direct chemilumino-metric assay (two site sandwich immuno assay) by

using Bayers Automated Chemiluminescence System (ACS:180), serum total calcium by Arsenazo-III method, serum inorganic phosphate by ammonium molybdate method, blood urea by urease method and serum creatinine by Jaffe's method.

e) Statistical analysis

All statistical analysis and significance of difference between groups were determined by independent samples 't' test. Chi-square test (contingency table analysis) and descriptive statistics were also used. Correlation coefficients were calculated using Pearson's product moment correlation. All these statistical methods were performed through SPSS (statistical package for social sciences) for windows version 2007.

RESULTS

The CRF cases were divided into five stages based on their creatinine clearance values [6]: (a) Kidney damage with normal or increased GFR, clearance: >90mL/min/1.73m^2 (n=30). (b) Mildly decreased GFR, clearance: 60-89 mL/min/1.73m^2 (n=30). (c) Moderately decreased GFR, clearance: 30-59 mL/min/1.73m^2 (n=30). (d) Severely reduced GFR, clearance: 15-29 mL/min/1.73m^2 (n=30). (e) Kidney failure (ESRD), clearance <15 mL/min/1.73m^2 (n=30) and age and sex matched healthy controls (n=30).

The mean±SD values of GFR (i.e. calculated by creatinine clearance), iPTH, serum total calcium, inorganic phosphate, urea and creatinine are listed in Table 1.

Table 1: Shows mean ± SD values of GFR and other biochemical parameters in various stages of CRF with healthy controls

Stages	GFR (ml/min/1.73m^2)	iPTH (pg/ml)	Calcium (mg/dl)	Phosphate (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Control (n=30)	120.45 ± 6.25	36.93 ± 16.03	9.53 ± 0.79	3.53 ± 0.67	29.29 ± 5.29	1.09 ± 0.18
Stage 1 (n=30)	96.64 ± 5.27	46.50 ± 1.15	8.85 ± 1.15	4.36 ± 0.46	71.00 ± 23.22	1.80 ± 0.30
Stage 2 (n=30)	73.45 ± 8.81	156.94 ± 44.26	8.46 ± 1.21	6.22 ± 1.03	123.86 ± 52.99	4.28 ± 2.83
Stage 3 (n=30)	44.76 ± 9.09	205.95 ± 87.15	7.78 ± 2.20	6.43 ± 1.09	124.77 ± 40.95	5.01 ± 2.74
Stage 4 (n=30)	21.17 ± 3.71	273.83 ± 124.41	7.26 ± 1.63	6.76 ± 1.36	160.60 ± 56.06	5.86 ± 25.53
Stage 5 (n=30)	8.49 ± 2.41	331.68 ± 204.99	7.250 ± 0.60	6.96 ± 1.22	169.63 ± 19.32	10.58 ± 2.67

Note: SD = Standard deviation; GFR= Glomerular Filtration Rate; CRF = Chronic Renal Failure; iPTH= Intact Parathormone; n=number of subjects in each stage

This table shows that GFR values go on decreasing as the stage of CRF progresses and this decrement was statistically significant in various stages of CRF when compared to healthy controls (p<0.001) (Table 2).

The iPTH values go on increasing as the stage of CRF advances and these increased values of iPTH are statistically significant except for the stage 4 versus stage 5 because of calcium supplementation in these patients during dialysis therapy.

Table 2: Shows the 'p' values for various biochemical parameters between various stages of CRF and age and sex matched healthy controls

STAGES	GFR (ml/min/ 1.73m^2)	iPTH (pg/ml)	Calcium (mg/dl)	Phosphate (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Control Vs Stage1	<0.001	<0.05	<0.05	<0.001	<0.001	<0.001
Control Vs Stages 2,3,4,5	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage 1 Vs Stage 2	<0.001	<0.001	NS	<0.001	<0.001	<0.001
Stage 1 Vs Stage 3	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage 1 Vs Stage 4	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage 1 Vs Stage 5	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage 2 Vs Stage 3	<0.001	<0.01	NS	NS	NS	NS
Stage 2 Vs Stage 4	<0.001	<0.001	<0.01	NS	<0.05	<0.05
Stage 2 Vs Stage 5	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage 3 Vs Stage 4	<0.001	<0.05	NS	NS	<0.01	NS
Stage 3 Vs Stage 5	<0.001	<0.01	NS	NS	<0.001	<0.001
Stage 4 Vs Stage 5	<0.001	NS	NS	NS	NS	<0.001

Note: NS = Not significant; GFR=Glomerular filtration rate; iPTH=Intact parathormone. 'p' value <0.05 was taken as statistically significant for all the parameters.

The 'p' value for control versus stage1 and stage 3 versus stage 4 was < 0.05. For stage 3 versus stage 5 'p' value was < 0.01. The 'p' values in all other groups were compared was < 0.001. The decrement of serum total calcium with the advancement of CRF stages was statistically significant except wherever calcium was supplemented during the dialysis therapy.

The corrected formula of serum calcium with serum albumin level was not used in this study. The mean±SD values of serum inorganic phosphate, urea and creatinine go on increasing as CRF stage advances when compared to controls. This increase is statistically significant (p < 0.001) in all the stages.

The serum iPTH level is negatively correlated with creatinine clearance (r = -0.718, p<0.001) and serum total calcium (r = -0.454, p<0.001) (Figure 1).

However it is positively correlated with inorganic phosphate (r = +0.621, p<0.001) (Figure 2), urea (r = +0.526, p<0.001) and creatinine (r = +0.656, p<0.001).

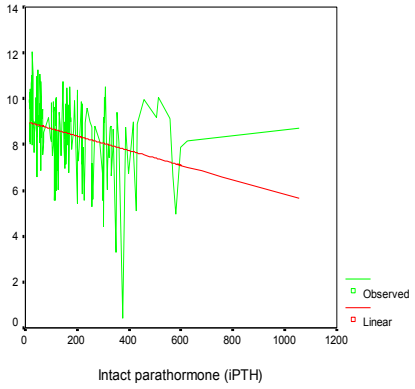

Fig. 1: Relationship between iPTH and serum total calcium in various stages of CRF and controls

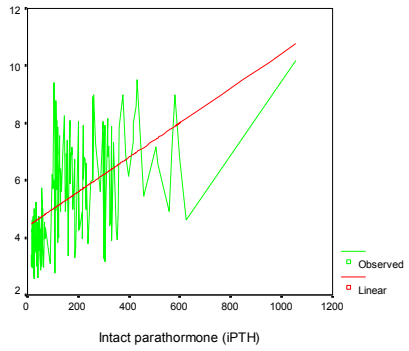

Fig. 2: Relationship between iPTH and serum inorganic phospate in various stages of CRF and controls

DISCUSSION

The present study has been undertaken to assess the iPTH in adults with CRF and to correlate the levels with GFR and other biochemical parameters like serum total calcium, inorganic phosphate, urea and creatinine. It is observed that serum concentration of mean iPTH was significantly increased progressively as the stage of CRF advances when compared to age and sex matched healthy controls with normal kidney function. Except stage 1, in all the stages iPTH was significantly increased and none of them had iPTH within normal range (14-72 pg/ml). The iPTH starts rising in early stage of CRF only (stage 2).

Secondary hyperparathyroidism is a well known complication of ESRD. Among several forms of renal osteodystrophy, the predominant effect of secondary hyperparathyroidism on bone is termed as osteitis fibrosa cystica (OFC), a condition associated with high bone turnover, pain and increased risk of fractures [7]. Disordered mineral metabolism is implicated in pathogenesis of musculoskeletal and vascular complications that afflict patients with advanced chronic kidney disease. Several studies showed a compelling association between abnormalities in serum phosphate, calcium, calcium x phosphate (Ca x P) product, and parathyroid hormone (PTH) levels and all cause mortality and cardiovascular events [8].

The pathophysiology of bone disease due to secondary hyperparathyroidism is related to abnormal mineral metabolism as follows: a) Decreased GFR leads to reduced inorganic phosphate (PO_4^{3-}) excretion and consequent PO_4^{3-} retention. b) Retained PO_4^{3-} has a direct stimulatory effect on PTH synthesis and on cellular mass of the parathyroid glands. c) Retained PO_4^{3-}—also indirectly causes excessive production and secretion of PTH through lowering of ionized Ca^{2+} and by suppression of calcitriol (1,25-dihydroxycholecalciferol) production. d) Reduced calcitriol production in CKD results both from decreased synthesis due to reduced kidney mass and from hyperphosphatemia.

Low calcitriol levels, in turn, lead to hyperparathyroidism via both direct and indirect mechanisms. Calcitriol is known to have a direct suppressive effect on PTH transcription (i.e., a genomic effect), and therefore reduced calcitriol in CRD causes elevated levels of PTH. In addition, reduced calcitriol leads to impaired Ca^{2+} absorption from the gastrointestinal tract, thereby leading to hypocalcemia, which then increases PTH secretion and production. Taken together, hyperphosphatemia, hypocalcemia and reduced calcitriol synthesis all promote the production of PTH and the proliferation of parathyroid cells, resulting in secondary hyperparathyroidism. High PTH levels stimulate osteoblasts and result in high bone turnover, which leads to osteitis fibrosa cystica[2].

The GFR value goes on decreasing as the kidney damage increases. Our findings regarding iPTH and GFR are comparable with the previous studies done by Rahman MH et. al., who have correlated the serum parathormone level with biochemical parameters in chronic renal failure in children [3]. Ian H. de Boer et. al., have also observed reduced GFR and increased iPTH levels as the stage of CRF advances. In their study they have demonstrated the severity of secondary hyperparathyroidism in chronic renal insufficiency [7]. The level of serum iPTH was higher in more advanced renal failure thus confirming the relationship between severity of hyperparathyroidism and the degree of renal impairment [3]. Sanchari Datta et. al., have demonstrated the correlation of anaemia and secondary hyperparathyroidism with left ventricular hypertrophy (LVH) in chronic kidney disease patients. Our values of iPTH and GFR can be compared with this study [9].

In the present study the total serum calcium goes on decreasing as the kidney failure advances. Our findings are supported by the previous study done by Rahman MH et. al., where they have correlated the iPTH with biochemical parameters in CRF [3]. The levels of inorganic phosphate, urea and creatinine had increased progressively as the CRF stage advances. The phosphate levels were normal in few cases, which was due to calcium supplementation. It was originally proposed that hypocalcemia triggers hyperparathyroidism in early renal failure [3]. In our study, the increased levels of mean serum iPTH were present even in early renal failure and it was related to low mean serum calcium level and progressive rise of serum inorganic phosphate from early to advanced renal failure. Nasri et. al., have concluded that there is a positive correlation of serum phosphate, Ca x P product and iPTH with conjunctival and corneal calcification and no significant correlation with serum calcium implying that there is a central role for phosphorus in calcium-phosphorus deposition in soft tissues like cornea and conjunctiva, underscoring further attention to phosphorus control in hemodialysis patients [10]. The significantly increased urea and creatinine levels were in conformity with the results obtained by Dirican et.al., who also observed that these values were increased when compared to controls [11].

CONCLUSION

The results of our study indicate that the serum iPTH levels were higher even in early renal failure and the higher values are directly related to the degree of renal failure. Therefore the serum iPTH was negatively correlated with GFR and calcium levels. However iPTH was positively correlated with the levels of inorganic phosphate, urea and creatinine. It is concluded that the estimation of serum iPTH and other biochemical parameters helps for the diagnosis of secondary hyperparathyroidism in the early stage of CRF and to manage the future complications of chronic renal failure.

REFERENCES

1. Sanjay KA, Suresh CD, Mohammed I, Sreebhusan R, Ravinder S, Ravinder MP. Prevalence of chronic renal failure in adults in Delhi, India.
2. NDT 2005; 20(8):1638-42.
3. Karl S, Jacob G, Barry MB. Chronic renal failure. In: Kasper, Braunwald, Fauci, Hauser, Longo, Jameson, editors, Harrison's Principles of Internal Medicine.
4. 16th edition: New York: McGraw-Hill; 2005:1653-63.
5. Rahman MH, Hosain MM, Sultana S, Jamal CY, Karim MA. Correlation of Serum parathormone level with biochemical parameters in chronic renal failure. Indian Pediatrics 2005; 42:250-54.
6. Itani O, Tsang RC. Bone disease. In: Kaplan LA, Pesce AJ, editors, Clinical Chemistry; Theory, analysis and correlation. 3rd edition: St. Louis: Mosby CV; 1996:534-36.
7. Endres DB, Rude RK. Mineral and Bone Metabolism. In: Burtis CA, Ashwood, ER,editors, Tietz textbook of clinical chemistry. 4th edition; Philadelphia: WB Saunders 2006:1891-1965.
8. Michael PD, Christopher PP, David JN, Edmund L. Kidney Disease. In: Carl AB, Edward RA, David EB, editors, Tietz textbook of clinical chemistry and molecular diagnostics, 4th edition: Philadelphia. WB Saunders 2006; 1671-1745.
9. Ian H, Inina Gorodetskaya, Belinda Young, Chi-yuan, Glenn MC. The severity of secondary hyperpatathyeoidism in chronic renal insufficiency is GFR dependent, race dependent and associated with cardiovascular disease.
10. J Am Soc Nephrol 2002; 13: 2762- 69.
11. Ron W, Francesca T, Hocine T, Philip GZ, Dana CM. Impact of the Kidney Disease outcomes Quality Initiative (KDOQI) clinical

practice guidelines for bone metabolism and disease in a large dialysis network.

12. AJKD 2007;49:257-66.
13. Sanchari Datta et. al., Correlation of anaemia, secondary hypreparathyoidism with left ventricular hypertrophy in CKD patients. JAPI 2006; 54: 699-703.
14. Nasir. H. et. al., Relationship of conjunctival and corneal clarification with secondary hyperparathyroidism in hemodialysis patients. IJMS 21003; 28(2) : 86-89.
15. Dirican M, Akca R, Sarandol E, Dilek K. Serum paraoxonase activity in uremic pre-dialysis and hemodialysis patients. J Nephrol 2004; 17 : 813-18.