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

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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/1.73m².

It is generally thought to result from hypocaemia 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 PTH 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:

\[ \text{Cockcroft and Gault formula:} \]

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...

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: >90 mL/min/1.73m² (n=30). (b) Mildly decreased GFR, clearance: 60-89 mL/min/1.73m² (n=30). (c) Moderately decreased GFR, clearance: 30-59 mL/min/1.73m² (n=30). (d) Severely reduced GFR, clearance: 15-29 mL/min/1.73m² (n=30). (e) Kidney failure (ESRD), clearance <15 mL/min/1.73m² (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. 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 1: Shows mean ± SD values of GFR and other biochemical parameters in various stages of CRF with healthy controls

<table>
<thead>
<tr>
<th>STAGES</th>
<th>GFR (ml/min/1.73m²)</th>
<th>iPTH (pg/ml)</th>
<th>Calcium (mg/dl)</th>
<th>Phosphate (mg/dl)</th>
<th>Urea (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=30)</td>
<td>120.45 ± 6.25</td>
<td>36.93 ± 16.03</td>
<td>9.53 ± 0.79</td>
<td>3.53 ± 0.67</td>
<td>29.29 ± 5.29</td>
<td>1.09 ± 0.18</td>
</tr>
<tr>
<td>Stage 1 (n=30)</td>
<td>96.64 ± 5.27</td>
<td>46.50 ± 1.15</td>
<td>8.85 ± 1.15</td>
<td>4.36 ± 0.46</td>
<td>71.00 ± 23.22</td>
<td>1.80 ± 0.30</td>
</tr>
<tr>
<td>Stage 2 (n=30)</td>
<td>73.45 ± 8.81</td>
<td>156.94 ± 44.26</td>
<td>8.46 ± 1.21</td>
<td>6.22 ± 1.03</td>
<td>123.86 ± 52.99</td>
<td>4.28 ± 2.83</td>
</tr>
<tr>
<td>Stage 3 (n=30)</td>
<td>44.76 ± 9.09</td>
<td>205.95 ± 87.15</td>
<td>7.78 ± 2.20</td>
<td>6.43 ± 1.09</td>
<td>124.77 ± 40.95</td>
<td>5.01 ± 2.74</td>
</tr>
<tr>
<td>Stage 4 (n=30)</td>
<td>21.17 ± 3.71</td>
<td>273.83 ± 124.41</td>
<td>7.26 ± 1.63</td>
<td>6.76 ± 1.36</td>
<td>160.60 ± 56.06</td>
<td>5.86 ± 25.53</td>
</tr>
<tr>
<td>Stage 5 (n=30)</td>
<td>8.49 ± 2.41</td>
<td>331.68 ± 204.99</td>
<td>7.250 ± 0.60</td>
<td>6.96 ± 1.22</td>
<td>169.63 ± 19.93</td>
<td>10.58 ± 2.67</td>
</tr>
</tbody>
</table>

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 with compared to healthy controls (p<0.001) (Table 2).

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

<table>
<thead>
<tr>
<th>STAGES</th>
<th>GFR (ml/min/1.73m²)</th>
<th>iPTH (pg/ml)</th>
<th>Calcium (mg/dl)</th>
<th>Phosphate (mg/dl)</th>
<th>Urea (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Vs Stage 1</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Control Vs Stage 2,3,4,5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1 Vs Stage 2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1 Vs Stage 3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1 Vs Stage 4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1 Vs Stage 5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 2 Vs Stage 3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 2 Vs Stage 4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 2 Vs Stage 5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 3 Vs Stage 4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 3 Vs Stage 5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 4 Vs Stage 5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 stage 1 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 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).

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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
Serum inorganic phosphate (IP7H), a condition associated with bone disease due to secondary 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 IP7H 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.

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