Biochemical and Clinical Variables of Normal Parathyroid and Hyperparathyroid Diabetic Chronic Kidney Disease Patients

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Abstract

Background: In chronic kidney disease (CKD) intact parathyroid hormone (iPTH) level is often increased before clinical hyperphosphatemia occurs. Despite its importance very few studies evaluated parathyroid status in CKD. Objective: The study was undertaken to estimate level of parathormone in diabetic CKD patients at a tertiary level hospital and assessing its relationship with different parameters like hemoglobin, calcium etc. and comparing biochemical and clinical variables between normal parathyroid and hyperparathyroid groups. Materials and Methods: It was a hospital based cross-sectional study involving purposively selected chronic kidney disease patients attending nephrology and endocrinology outdoor and indoor services of BIRDEM hospital, Dhaka, Bangladesh. Study was conducted during the period of April to October 2010. All the subjects were divided into two groups based on serum parathormone level and different parameters were compared between groups. Results: The mean duration of chronic kidney disease was significantly higher in hyperparathyroid group than that in the normal group (<0.001). Retinopathy and hypertension were more common in hyperparathyroid group than that in patients with normal serum parathormone (p<0.001 and p=0.012). Neuropathy was solely present in hyperparathyroid group (p<0.001). Mean fasting blood glucose, serum creatinine and serum phosphate were significantly higher in the hyperparathyroid group compared to normal group (p<0.001 in all cases) while the mean serum calcium and haemoglobin were lower in hyperparathyroid group than those in the normal group (p<0.001 in both cases). Serum creatinine and serum parathormone bear a significantly linear relationship (r=0.986, p<0.001), while serum parathormone and serum calcium bear a significantly negative relationship (r=-0.892 and p<0.001). Conclusion: Earlier intervention on the basis of iPTH in addition to other biochemical parameters of chronic kidney disease is recommended.

Key words: Chronic kidney disease; Secondary hyperparathyroidism; Intact PTH; Active vitamin D3

Introduction

Patients with chronic kidney disease (CKD) have major disturbances in their homeostasis of calcium and phosphate with associated changes in vitamin D metabolism and parathyroid hormone (PTH) secretion.¹

In vitro, using bovine parathyroid cells in primary culture, 1,25(OH)2D3 decreased PTH mRNA levels.²

In vivo studies confirmed the physiologic relevance of

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these in vitro studies. Identifying patients at risk and evaluating for secondary hyperparathyroidism (SHPT) is imperative because early intervention may slow or arrest the progression of both bone and cardiac disease.

Parathyroid hormone (PTH), a polypeptide of 84 amino acids is involved in calcium and phosphate balance and homeostasis of bone and referred to as the intact hormone (iPTH) which is measured to assess bone metabolism and disease though smaller fragments of this molecule may have unique actions in the body. Intact PTH is predominantly cleared in liver and kidney.

Calcitriol or active vitamin D3 (1,25(OH)2D3) molecule is the active form that binds to the vitamin D receptor (VDR). Vitamin D3 also decreases PTH indirectly by stimulating VDRs in the gut, thereby increasing calcium absorption and serum calcium. With declining kidney function renal 1α-hydroxylase activity responsible for the final hydroxylation reaction in calcitriol synthesis decreases. Deficient active vitamin D3 levels increase PTH concentrations. However, unlike 1,25(OH)2D3, the regulatory actions of serum Ca2+ and phosphate are at the post-transcriptional level. Parathyroid glands recognize the changes in serum Ca2+ concentration by a cell membrane G-protein-coupled receptor, the calcium receptor (CaR), helping to limit tonic release by parathyroid cells. In vitro studies have shown a direct effect of phosphate on the parathyroid to regulate PTH secretion by a mechanism involving inhibition of cytosolic phospholipase A2 (cPLA2).

As the glomerular filtration rate (GFR) declines to <60 mL/min/1.73 m², the remaining nephrons compensate by hyperexcreting the daily phosphate load to maintain normal serum phosphate concentrations. This can continue until the GFR declines to <25–40 mL/min/1.73 m². With progressive CKD, insufficient excretion of phosphate load leads to hyperphosphatemia.

Calcium and phosphate have a high binding affinity for each other. Increased serum concentration of one or both ions increases the risk for an ionic bond forming an insoluble complex that may lead to extra-skeletal calcification and potentially calciphylaxis or cardiac disease. The precipitation may decrease serum calcium concentrations, further stimulating PTH secretion. PTH production and secretion may be stimulated by hypocalcemia, hyperphosphatemia, and vitamin D deficiency. SIPT produces an imbalance of these osteoclastic and osteoblastic activities leading to enhanced bone breakdown that eventuates in renal osteodystrophy.

Extraskeletal calcification (primarily cardiovascular calcification) has been documented in patients with CKD, and is directly correlated to an increase in cardiovascular morbidity and mortality. Research has shown that the primary cause of death in patients with ESRD is cardiovascular disease. A study of patients on hemodialysis found that even when stratified for variables such as sex, race, and presence of diabetes, dialysis patients still had a cardiovascular mortality rate nearly 30 times greater than the general population.

Coexistent diabetes, hypertension, hyperlipidemia, and anemia play a role in these findings. Cardiovascular calcification has also been identified as a contributing factor associated with hyperphosphatemia, increased calcium phosphate product (Ca x P), hypercalcemia, vitamin D therapy, and increased doses of calcium-containing phosphate binders and calcium supplements.

The balance of calcium, phosphate, vitamin D, and iPTH is complex and interrelated. Patients must adhere to dietary restrictions, dialysis therapies, and complicated medication regimens. These factors create barriers to achieving and maintaining control of SHPT.

In fact, one study on nearly 200 chronic hemodialysis outpatients revealed that <10% of patients could be simultaneously maintained within the target ranges of the above parameters.

The ultimate goals of treating SHPT are to normalize mineral metabolism, prevent bone disease and extraskeletal manifestations. Until recently, it was thought that hyperphosphatemia was the earliest sign of SHPT and bone metabolism disorders. In fact, the iPTH level is often increased before clinical hyperphosphatemia occurs. For this reason, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KQODI) guidelines recommend that all patients with a GFR <60 mL/min/1.73 m² should undergo evaluation of serum calcium, phosphate, and iPTH levels. Additionally, if the iPTH concentration exceeds the CKD stage-specific target, the 25(OH)D level should be assessed and treated. Hopefully, earlier identification and assessment of SHPT will improve bone and mineral metabolism in CKD and reduce its associated complications.
Despite its importance very few studies evaluated parathyroid status in CKD, and this justifies a new study to be conducted at tertiary level hospital in Bangladesh.

**Materials and Methods**

This cross-sectional study was conducted in Nephrology and Endocrinology units of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital in Dhaka, Bangladesh during the period of April to October 2010 involving a population of purposively selected 100 established chronic kidney disease patients with serum creatinine more than 1.5 mg/dL on three or more occasions over six months. Very sick non-amulant ESRD patients with acute exacerbation of renal failure, altered consciousness, congestive cardiac failure, chronic liver disease and stroke were excluded. All selected patients were divided into two groups based on parathyroid hormone level. Different parameters were compared between two groups. Subjects with serum parathormone >53 pg/ml were considered hyperparathyroid.

**Sampling technique**

One hundred subjects were selected purposively from both indoor and outdoor following inclusion and exclusion criteria. After taking consent, interview of the study subjects was taken in the indoor and outdoor units of Nephrology department of BIRDEM Hospital. The purpose, procedure, risks and benefits of the study were adequately explained to each and every patient prior to data collection. Data were collected by using following tools.

**Questionnaire**

Detailed history was taken by a set of questionnaire containing the structured and semi-structured questions according to the objectives and variables of the study. Pretesting was done and it was finalized based on response from patients. Questions regarding age, sex, education, monthly income, family history, dietary habit, patient’s drug history, general examination, systemic examination and investigation were included.

**Laboratory investigations**

- All the laboratory investigations were reviewed with a special emphasis on hemoglobin, serum creatinine, urine biochemical and microbiological examination, serum electrolytes, calcium, phosphate and blood glucose. Liver function tests including serum bilirubin, SGOT, SGPT and alkaline phosphatase, chest radiography were reviewed to exclude comorbidities.
  - With all aseptic precautions 5 mL venous blood was drawn and sent to laboratory for serum calcium and serum PTH.
  - Intact PTH (iPTH) level was detected by two-site chemiluminescent enzyme-labeled immunometric assay.

**Data management and analysis**

All interviewed questions were rechecked for its completeness, correctness and internal consistency to exclude missing or inconsistent data. The statistical analysis of the data was carried out by using software program SPSS version 15.0 and Excel. Data were checked, coded and edited properly before analysis. Both univariate and bivariate analyses were done. For analyzing data some descriptive statistics like mean, median, mode, SD and percentages were used. In order to find out association between dependent and independent variables, Chi square tests at 5% significance level were done.

**Quality control and quality assurance**

In order to ensure utmost quality, interview was done with the help of duty doctors and assistant registrars who worked in the outdoor and indoor of the nephrology department of BIRDEM Hospital. Everyday filled-in questionnaire sheets were checked to exclude any gross mistake. Data were checked and edited to ensure correctness. Laboratory investigation quality was ensured.

**Ethical consideration**

All ethical issues were considered as per Bangladesh Medical Research Council (BMRC). Ethical clearance was taken from the Ethical Review Committee of BIRDEM before the study was launched. Verbal consent was taken from all respondents before conducting the interview. Consent form was read before the respondent and the interview was taken after receiving consent. Rights to refuse and withdraw from the study at any time were accepted. The information gathered from the respondent was kept confidential. There was no conflict of interest.
Results
A total of 100 chronic kidney disease patients with diabetes mellitus were included in the study for estimation of serum parathormone level and to observe the demographic and anthropometric characteristics and the presence of co-morbidities associated with hyperparathyroidism.

Demographic characteristics of study population
Of 100 people participating in the study 24% were 55 years of age or older, 22% were 45–49 years old, 17% were 50–54 years old, 16% were 35–39 years old, 13% were 30–34 years old, 8% were 40–44 years old. Of sample population 59% were male, 41% were female.

Table I demonstrates that 30% of the CKD patients with normal serum parathormone level were less than 40 years, another 30% were of 40–50 years and 40% were > 50 years old. In the hyperparathyroid group, 26.7% were below 40 years, 30% were of 40–50 years and 43.3% were > 50 years old. The mean ages of normal and hyperparathyroid groups were 44.9 ± 9.2 years and 47.3 ± 10.1 years respectively (p=0.237) (Table I).

Table I: Age distribution of the study subjects

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Normal (n = 40)</th>
<th>Hyperparathyroid (n = 60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>12 (30.0)</td>
<td>16 (26.7)</td>
<td></td>
</tr>
<tr>
<td>40–50</td>
<td>12 (30.0)</td>
<td>18 (30.0)</td>
<td>0.237</td>
</tr>
<tr>
<td>&gt;50</td>
<td>16 (40.0)</td>
<td>26 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.9 ± 9.2</td>
<td>47.3 ± 10.1</td>
<td></td>
</tr>
</tbody>
</table>

Figures in the parenthesis denote corresponding %; χ² test was employed to analyse the data.

Sex distribution
Over two-thirds (67.5%) of the patients with normal parathormone level were male and the rest (32.5%) were female. In the hyperparathyroid group male and female patients were almost equal (53.3% vs. 46.7%).

Body mass index (BMI)
Table II shows the body mass index of the participants. Majority of the patients in the normal and hyperparathyroid groups (92.5% and 85%) were overweight and obese. Three of 40 patients (7.5%) with normal parathormone level and 9 of 60 patients (15%) with raised parathormone were of normal weight (Table II).

Table II: Comparison of BMI between two groups

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 40)</td>
<td>Hyperparathyroid (n = 60)</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>3 (7.5)</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>(normal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25 (overweight and obese)</td>
<td>37 (92.5)</td>
<td>51 (85.0)</td>
</tr>
</tbody>
</table>

Figures in the parenthesis denote corresponding %; χ² test was employed to analyse the data.

Duration of CKD
In the study 42.5% of patients in normal group and 20% in hyperparathyroid group had been suffering from chronic kidney disease for less than 3 years, while majority (80%) of the patients in hyperparathyroid group had been suffering from the disease for 3 or more than 3 years. The mean duration of CKD was significantly higher in hyperparathyroid group than that in the normal group (4.4 ± 2.0 vs. 2.4 ± 1.1 years, p<0.001) and the minimum and maximum duration were one and eight years respectively.

Presence of co-morbidities
Table III demonstrates that retinopathy and hypertension were frequently common in hyperparathyroid group than that in patients with normal serum parathormone (53.3% vs. 7.5%, p<0.001 and 70% vs. 55%, p=0.012). Neuropathy was solely present in hyperparathyroid group (p<0.001).

Table III: Comparison of presence of co-morbidities between groups

<table>
<thead>
<tr>
<th>Presence of co-morbidities</th>
<th>Groups</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 40)</td>
<td>Hyperparathyroid (n = 60)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>3 (7.5)</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>00</td>
<td>33 (55.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (55.0)</td>
<td>42 (70.0)</td>
</tr>
</tbody>
</table>

Figures in the parenthesis denote corresponding %; χ² test was employed to analyse the data.

Dialysis done
Of the total 100 chronic kidney disease patients, majority (84%) did not have dialysis in the past. All hyperparathyroid patients were undergoing dialysis.
Biochemical parameters
Table IV shows the comparison of certain biochemical parameters between patients with normal serum parathormone and raised parathormone.

Table IV: Comparison of biochemical parameters between groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal (n = 40)</th>
<th>Hyperparathyroid (n = 60)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>7.0 ± 0.3</td>
<td>7.9 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.1 ± 0.3</td>
<td>4.0 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>8.7 ± 0.2</td>
<td>8.0 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>4.0 ± 0.2</td>
<td>4.3 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.4 ± 0.6</td>
<td>10.6 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Student t test was employed to analyse the data.

Correlation of parathormone level with age and duration of CKD
Fig 1 and Fig 2 show the influence of age and duration of CKD on parathormone level. With the increase of age and duration of CKD, parathormone level also increases significantly (r=0.488, p<0.001 and r=0.789, p<0.001 respectively).

Fig 1. Correlation between age and parathormone level

Fig 2. Correlation between duration of CKD and parathormone level

Correlation of parathormone level with serum creatinine and calcium
Fig 3 and Fig 4 show the correlation between serum creatinine and parathormone and between serum parathormone and calcium. Serum creatinine and serum parathormone bear a significantly linear relationship (r=0.986, p<0.001), while serum parathormone and serum calcium bear a significantly negative relationship. (r=−0.892, p<0.001).

Fig 3. Correlation between serum creatinine and parathormone level

Fig 4. Correlation between serum parathormone and serum calcium

Frequencies of different stages of CKD
Staging of CKD was done using Cockcroft-Gault equation with GFR presumed to be approximating calculated creatinine clearance. There was no stage 1 CKD patient. There were 13% CKD stage 2 patients, 37% stage 3, 28% stage 4, and 22% stage 5 patients.
Serum calcium and PTH in different CKD stages

Table V shows serum calcium and PTH levels in different stages of CKD.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean calcium (mg/dL)</th>
<th>p value</th>
<th>Mean PTH (pg/mL)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8.8 ± 0.2</td>
<td></td>
<td>32 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8.5 ± 0.2</td>
<td>&lt;0.001</td>
<td>55 ± 4</td>
<td>&lt;0.015</td>
</tr>
<tr>
<td>4</td>
<td>8.2 ± 0.3</td>
<td></td>
<td>170 ± 5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7.8 ± 0.2</td>
<td></td>
<td>165 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

F test (ANOVA) was employed to analyse the data.

Discussion

Diabetic nephropathy is one of the microvascular complications of diabetes mellitus which is a leading cause of chronic kidney disease. Secondary hyperparathyroidism is a consequence and a probable marker of severity of chronic kidney disease. A few comparable studies have been conducted on chronic kidney disease and secondary hyperparathyroidism in different perspectives. Different aspects of those studies can be compared with the present study.

In the current study 60 out of 100 patients were hyperparathyroid, so prevalence of hyperparathyroidism was found to be 60%. One study carried out in St Luke’s medical centre, Philippines comparing clinical and laboratory profile of type 2 diabetic patients with CKD on haemodialysis during the period 2000–2009 showed that 41 patients had secondary hyperparathyroidism and 101 had normal parathormone level.

In the current study the mean ages of normal and hyperparathyroid groups were 44.9 ± 9.2 years and 47.3 ± 10.1 years respectively (p=0.237). One study showed that the mean age was 64 ± 11 years for the hyperparathyroid patients and 63.1 ± 12 years for the patients with normal parathormone level. Both the studies showed slightly higher mean age for the patients with secondary hyperparathyroidism. This may reflect deterioration of renal function with age.

Over two-thirds (67.5%) of the patients with normal parathormone level were male and the rest (32.5%) were female in the current study. In the hyperparathyroid group male and female patients were almost equal (53.3% vs. 46.7%). This might well have reflected slight male preponderance in the study sample.

Body mass index of the participants shows that majority of the patients in the normal and hyperparathyroid groups (92.5% and 85%) were overweight and obese. Three of 40 patients with normal parathormone (7.5%) level and 9 of 60 patients with raised parathormone (15%) were of normal weight (p=0.258). It did not reflect any significant difference between the two groups though one of the previous studies in Iceland pointed to higher body mass index in the hyperparathyroid group. Correlation between body mass index and parathormone level was also found insignificant in one study in Philippines (r=-0.113 p=0.21).

Retinopathy and hypertension were frequently common in hyperparathyroid group than that in patients with normal serum parathormone (53.3% vs. 7.5%, p<0.001 and 70% vs. 55%, p=0.012). Neuropathy was solely present in hyperthyroid group (p<0.001). This might represent progression of common microvascular pathophysiology of diabetes mellitus.

In the present study the mean fasting blood glucose, serum creatinine and serum phosphate were significantly higher in the hyperparathyroid group compared to normal group (7.9 ± 0.8 vs. 7.0 ± 0.3 mmol/L, p<0.001; 4.0 ± 1.1 vs. 2.1 ± 0.3 mg/dL, p<0.001 and 4.3 ± 0.2 vs. 4.0 ± 0.2 mg/dL, p<0.001 respectively) while the mean serum calcium and haemoglobin were lower in hyperparathyroid group than those in the normal group (8.0 ± 0.5 vs. 8.7 ± 0.2 mg/dL, p<0.001 and 10.6 ± 1.3 vs. 12.4 ± 0.6 gm/dL, p<0.001 respectively). In the study in St. Luke’s medical centre serum creatinine was higher in hyperparathyroid patients than in patients with normal parathyroid level (8.2 ± 2.6 vs. 7.42 ± 3.9 mg/dL).

The current study shows that with the increase of age and duration of CKD parathormone level also increases significantly (r=0.488, p<0.001 and r=0.789 and p<0.001 respectively). These correlations were consistent with another study and may reflect the effects of age related decline in renal function and more prolonged presence of pathophysiologic insult on kidney.
Serum creatinine and serum parathormone bear a significantly linear relationship ($r=0.986$, $p<0.001$), while serum parathormone and serum calcium bear a significantly negative relationship ($r=0.892$ and $p<0.001$). Another study showed similar result for the relationship between serum creatinine and parathormone but insignificant findings for the relationship between serum calcium and parathyroid hormone.

In the current study rising of serum PTH above normal level was associated with falling creatinine clearance or GFR. This is probably due to the fact that impaired excretory function of kidneys is associated with impaired synthesis of active vitamin D and impaired regulation of serum calcium.

Secondary hyperparathyroidism is not uncommon in diabetic patients with CKD. In older group of people with CKD secondary hyperparathyroidism is more prevalent. Patients with longer duration of CKD are more likely to have secondary hyperparathyroidism. Diabetic patients with secondary hyperparathyroidism are more likely to suffer from retinopathy, hypertension and neuropathy. They are more likely to have higher fasting blood sugar, higher serum creatinine, lower serum calcium and lower haemoglobin. The present study shows that with the progression of CKD stages serum calcium decreases and serum PTH increases. Increasing PTH above normal level in the current study was associated with decreasing creatinine clearance or GFR.

From the current study, it is also evident that serum iPTH level should be measured in all patients with CKD along with other parameters like serum calcium and phosphate. Early detection of secondary hyperparathyroidism gives a chance of early pharmacological and nonpharmacological intervention to suppress parathyroid glands keeping the biochemical parameters within normal range, and thus preventing related complications and comorbidities. Further prospective study with larger sample size should be conducted in future to confirm the findings of this study.

References


