Role of iPTH in Diagnosis of Disorders of Bone Mineral Metabolism in CKD Patients

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ABSTRACT

Objective: The objective of this study is a) Evaluate relationship of PTH levels to mineral metabolism in CKD, b) To provide a description of mineral metabolism parameters in CKD patients of MGM Medical College & Hospital, Aurangabad.

Methods: A total of 100 patients were classified in stages 1-5 as per National Kidney Foundation Criteria were included. The following clinical and biochemical data were recorded: age, sex, weight, serum creatinine, serum calcium, serum phosphate, serum alkaline phosphatase (ALP), serum parathyroid hormone (PTH), GFR and Ca×PO₄ product.

Results: From the study it was observed that PTH was the one to be deranged since the initial stages of CKD and calcium & phosphate were deranged in later stages. Also the study showed a negative correlation between serum calcium and serum PTH which was statistically significant (r= -0.271) & (p=0.004) and a positive correlation between serum ALP and serum PTH (p=0.002). Hypocalcaemia was seen in all stages specially stage 5 and was statistically significant (p=0.046). It was also seen that iPTH level increases as the GFR falls below 30ml/min which is statistically significant (p=0.001).

Conclusion: Bone Mineral Metabolism is altered in all stages of CKD. The first parameter to be altered is PTH. With the availability of iPTH it is easy to keep a follow up of the patients since the early stages and reduce the bone mineral disorders that tend to occur in CKD patients.

Key Words: iPTH, CKD, Bone Mineral Metabolism.

INTRODUCTION

Secondary hyperparathyroidism is one of the most popular and important abnormalities of mineral metabolism in patients with chronic kidney disease (CKD). Renal osteodystrophy (ROD) is an alteration of bone morphology that occurs in pts with CKD. Bone biopsy has always been the method for diagnosis of ROD. It is invasive and an expensive procedure which might not be acceptable to all the patients. On the other hand the newer non invasive diagnostic techniques of serum evaluation of markers of bone turnover have made it easy to evaluate the mineral disorders.

Measurement of intact parathyroid hormone (iPTH) has long been considered the principle biochemical marker for diagnosing ROD. Also CKD is described
as an accelerated aging process affecting regulation of hormones that are important in many body functions. [5] Prevention of bone disease in CKD needs proper evaluation of mineral metabolism.

ROD provides an opportunity to review various other matters like relation between relation of calcium and Phosphorus in plasma and bone mineral disorders and control of parathyroid activity and secretion. The Spectrum of ROD includes: [6]
- Osteitis Fibrosa - High bone turnover (due to SPTH)
- Osteomalacia – Low bone turnover, not always due to aluminum toxicity.
- Adynamic bone disease – Low bone turnover, in children rickets may be associated
- Osteosclerosis –Less frequent

Chronic Kidney Disease- Mineral Bone Disorder (CKH-MBD) is the term used to determine the pathological changes that occur in the vascular system in association with CKD. These changes can be diagnosed if a patient has evidence of one or more of the following:
- Abnormalities of calcium, phosphorus, pTH or Vit D metabolism.
- Vascular and/or tissue calcification.
- Abnormalities of bone turnover, metabolism, volume, linear growth or strength.

Kidney disease Improving Global Outcome (KDIGO)- CD –MBD guidelines have recommended monitoring of serum calcium, phosphorus, PTH and alkaline phosphatase activity in CKD stage 3. [7]

We have studied abnormalities of calcium, phosphorus, PTH and ALP in CKD patients to evaluated CKD – MBD.

MATERIALS AND METHODS
This was a prospective study in which 100 patients diagnosed to have Chronic Kidney Disease according to National Kidney Foundation and fulfilled the inclusion and exclusion criteria were taken. The following clinical and biochemical data were recorded: age, sex, Presence of diabetes, serum creatinine, serum calcium, serum phosphate, serum iPTH, serum alkaline phosphatase, Ca x P product. GFR was calculated by Cockcroft Gault formula.

iPTH concentrations were measured by a solid phase, two site chemiluminescent enzyme labelled immunometric assay. (Immulite ® 1000) (Normal Range – 90-300 pg/dl). Serum calcium was measured by modification of calcium o cresolphthalein reaction (Dimension ®) (Normal Range – 7.5-9.5 mg/dl). Serum phosphorus was measured by modification of classical phosphomolybdate method (Dimension ®) (Normal Range – 3. 5-10 mg/dl).

Our inclusion criteria was patients having kidney damage > 3 months with or without decreased GFR manifest either as: a) Pathological abnormalities or b) Markers of kidney damage, including biochemical and imaging abnormalities.

Our EXCLUSION CRITERIA were patients with primary hyperparathyroidism, neoplastic disorders of parathyroid or elsewhere or Osteoporosis under treatment with biphosphates or calcitonin.

Statistical Analysis:
To determine the differences between means in CKD groups we used a one way analysis of variance ANOVA test using the SPSS package.

RESULTS
Table No. 1 gives the clinical details of 100 patients and comparisons of parameters among the CKD stages. A lot of difference can be seen in the variables such as Sr. Calcium, Sr. Phosphorus, Sr. iPTH, Sr. Alkaline phosphatase between the study groups.
Figure No. 1 shows the intergroup comparison using the ANOVA test.

It was seen in our study that Sr. Calcium levels decrease from stage 1 of CKD to Stage 5. Sr. Phosphorus on the other hand showed the opposite trend and was seen high in patients of CKD stage 5. Sr. iPTH levels were seen to have a rising trend from stage 1 to stage 5 as well. Sr. Alkaline Phosphatase (ALP) also showed a rising trend when it came to comparison between stage 1 to stage 5. CaxP product also was on the same lines of having an increasing trend with increase in the CKD stage.

**Table No. 1: Characteristics of Study population:**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CKD Stage (1-3)</th>
<th>CKD Stage (4)</th>
<th>CKD Stage (5)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>42.43</td>
<td>48.21</td>
<td>49.34</td>
<td>0.000</td>
</tr>
<tr>
<td>Lab Data:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr. Calcium (mg/dl)</td>
<td>6.91±1.88</td>
<td>8.10±1.12</td>
<td>7.54±1.17</td>
<td>0.0064</td>
</tr>
<tr>
<td>Sr. Phosphorus (mg/dl)</td>
<td>4.97±1.72</td>
<td>5.34±1.98</td>
<td>6.77±2.94</td>
<td>0.0187</td>
</tr>
<tr>
<td>Sr. iPTH (pg/dl)</td>
<td>222.4±141</td>
<td>282.6±164</td>
<td>363.9±225</td>
<td>0.0346</td>
</tr>
<tr>
<td>Product CaxP (mg/dl²)</td>
<td>32.68±8.61</td>
<td>42.05±12.86</td>
<td>51.31±24.98</td>
<td>0.0240</td>
</tr>
<tr>
<td>Sr. Alkaline Phosphatase (/)</td>
<td>119.57±38.88</td>
<td>137±45.59</td>
<td>165.9±86.57</td>
<td>0.0030</td>
</tr>
</tbody>
</table>
When it came to comparing the variable with iPTH, Calcium showed a negative correlation with iPTH ($r^2=-0.267$, $p<0.05$), phosphorus and ALP had a positive correlation with iPTH and the values were $r^2=0.109$ & $r^2=0.058$ ($p<0.05$) respectively.

**DISCUSSION**

This study provides a description about the bone mineral metabolism parameters in the different CKD Stages. It shows the alteration of many parameters in the different study. Sr. Calcium and Phosphorus abnormalities start in stage 2 of CKD which may be the cause of hyperparathyroidism and alteration in other parameters also.

The development of hyperparathyroidism is a complex pathophysiology and causes a lot of doubts. The early parameter to rise is Parathyroid and helps in the monitoring of the disease, the study helps to support this hypothesis and proving the usefulness of the measuring of iPTH as a parameter to diagnose bone mineral metabolism abnormalities early and hence initiate treatment.

In our study 100 patients were evaluated in this study 71% patients being male & 29% females and M:F ratio was 12:5. Study done by L. Carver et al. [8] showed the no of males were more, i.e, 61% in their study, also Shankar et al. [9] showed a male preponderance of 68%. The mean age in our study was 48 yrs whereas 47 and 42 in studies done by Shankar et al [9] & Agrawal et al [10] respectively.

Calcium is the major regulator of PTH secretion; persistent hypocalcaemia is a powerful stimulus for the development of hyperparathyroidism. [6] The mean serum calcium level in our study was 7.90+0.95 mg/dl for all stages of CKD. It was observed that a decreasing trend in serum calcium levels as CKD stages progressed from stage 1-5 as was seen in other studies by Agrawal et al, [10] B. Ghosh et al [11] and L. Carver et al. [8] Hypocalcemia was seen in 44% and was in comparison with the study of Agarwal et al [10] (49.6%).

Serum phosphate levels also contribute to PTH stimulation but they act in the same stages since they don’t begin to rise till stage 5 due to decreased tubular excretion. [8] Also there is resistance to calcitriol in parathyroid gland and favors development of hyperparathyroidism and induces resistance to actions of PTH. [6] The mean serum phosphorus level in our study was 6.21+2.69 mg/dl for all stages of CKD. It was observed that a increasing trend in serum phosphorus levels as CKD stages progressed from stage 1-5. The same findings were seen when compared with the other studies carried out by Agrawal et al. [10] B. Ghosh et al [11] and L. Carver et al. [8] Hyperphosphatemia were seen in 59% patients and was in comparison with that of B. Ghosh et al [11] (70.27%).

The levels of iPTH in the serum have been shown to correlate with the histologic abnormality present in bone, elevated iPTH levels are elevated are characteristic of patients with ostetes fibrosa and low levels are seen with low turnover syndromes. [6] The mean serum PTH level in our study was 328.46+ 126.33 pg/ml for all stages of CKD. It was observed that mean PTH level in stage 5 and is >300pg/ml. Hyperparathyroidism was seen in 44% and was in comparison with that of Agrawal et al (39.4%). [10]

Serum Calcium x Phosphorus (Ca x P ) product is also increased in secondary hyperparathyroidism [8] The mean serum Ca x P product in our study was 48.93+/ 20.61 mg/dl² for all stages of CKD. It was observed that a increasing trend in serum Ca x P product levels as CKD stages progressed from stage 1-5. Even the study done by Craver et al [8] proposes the same findings.
The present study shows a negative correlation between serum calcium and serum PTH which was statistically significant \( (r=-0.271) \) \( (p=0.004) \) and there was a positive correlation between serum ALP and serum PTH \( (p=0.002) \). B Gosh et al \[11\] also showed a negative correlation between serum calcium and serum PTH which was statistically significant \( (r=-1.176) \) \( (p=0.008) \). There was a positive correlation between serum ALP and serum PTH \( (p<0.001) \).

Studies have also shown that Ca & P levels reduces cardiovascular disease which also adds to the morbidity and mortality rates seen in patients of CKD. Hence its optimization is out most important.

**CONCLUSION**

Parathyroid hormone is the first to be altered in CKD patients. Bone mineral metabolism alteration is a known complication of CKD patients and with the ready availability of iPTH in most of the laboratories its use can help in early detection and prevention of mortality and morbidity caused by the mineral disturbances.

**REFERENCES**

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