Levels of Serum 1,25(OH)₂D in Patients with Pre-Dialysis Chronic Renal Failure

SHIGERU YUMITA¹, MASASHI SUZUKI², TAKASHI AKIBA³, TADAOKI AKIZAWA⁴, YOSHIKI SEINO⁵ and KIYOSHI KUROKAWA⁶

¹Department of Nephroendocrinology, Kojinkai Central Hospital, Sendai 983, ²Kidney Center, Shinrakuen Hospital, Niigata 951, ³The Second Department of Internal Medicine, Tokyo Medical and Dental University School of Medicine, Tokyo 113, ⁴Department of Nephrology, Fujigaoka Hospital, Showa University School of Medicine, Yokohama 227, ⁵Department of Pediatrics, Okayama University Medical School, Okayama 700, and ⁶Department of Internal Medicine, School of Medicine, Tokai University, Isehara 259-11

YUMITA, S., SUZUKI, M., AKIBA, T., AKIZAWA, T., SEINO, Y. and KUROKAWA, K. Levels of Serum 1,25(OH)₂D in Patients with Pre-Dialysis Chronic Renal Failure. Tohoku J. Exp. Med., 1996, 180 (1), 45-56 —— One hundred and ninety-five outpatients in pre-dialysis period served as subjects. The mean age of subjects was 58.0 ± 11.2 (range: 29-82) years. The subjects were divided into 8 groups according to their serum creatinine (Cr) levels (Cr ≤ 1.0, 1.0 < Cr ≤ 2.0, 2.0 < Cr ≤ 3.0, 3.0 < Cr ≤ 4.0, 4.0 < Cr ≤ 5.0, 5.0 < Cr ≤ 6.0, 6.0 < Cr ≤ 8.0, and Cr > 8.0 mg/100 ml). The levels of 1,25-dihydroxyvitamin D (1,25(OH)₂D) decreased in accordance with the progression of chronic renal failure (CRF). Even in subjects with 1.0 < Cr ≤ 2.0 mg/100 ml, the levels of 1,25(OH)₂D were significantly lower than those in subjects with Cr ≤ 1.0 mg/100 ml. The levels of calcium adjusted by serum albumin levels (adjusted Ca) were relatively maintained within the normal range until Cr > 8.0 mg/100 ml. The levels of inorganic phosphate (IP) were significantly lower in subjects with 1.0 < Cr ≤ 2.0 mg/100 ml, but significantly higher in subjects with Cr > 4.0 mg/100 ml than in those subjects with Cr ≤ 1.0 mg/100 ml. The levels of immunoreactive high-sensitive parathyroid hormone (i-HS-PTH) were greatly increased and the levels of intact PTH were significantly increased even in subjects with 1.0 < Cr ≤ 2.0 mg/100 ml, in association with a decrease in levels of 1,25(OH)₂D, suggesting that a decline in 1,25(OH)₂D production due to a decrease in renal mass contributes to the acceleration of secondary hyperparathyroidism. When the levels of adjusted Ca, intact PTH and 1,25(OH)₂D of subjects with hypophosphatemia (IP < 2.8 mg/100 ml), normophosphatemia

Received for publication, February 1, 1996; revision accepted for publication July 10, 1996.

Address for reprints: Dr. Shigeru Yumita, Department of Nephroendocrinology, Kojinkai Central Hospital, 2-1-6 Tsutsujigaoka, Miyagino-ku, Sendai 983, Japan.

45
and hyperphosphatemia (IP > 4.4 mg/100 ml) were compared, there were not any significant differences in the levels of adjusted Ca among these subjects in each group. But, the levels of 1,25(OH)₂D in subjects with hypophosphatemia were significantly higher than those with normophosphatemia in groups with Cr≤2.0 mg/100 ml, and those with hyperphosphatemia were significantly lower than those with normophosphatemia in groups with 3.0<Cr≤4.0, 5.0<Cr≤6.0 and Cr>8.0 mg/100 ml. These results suggest that increased secretion of PTH might compensate the decreased production of 1,25(OH)₂D₃ by lowering phosphate in the early phase of CRF, and phosphate retention inhibits the activity of 1α-hydroxylase and contributes to the decrease in 1,25(OH)₂D₃ in the advanced stage of CRF. Monitoring of 1,25(OH)₂D is considered to be vitally important for diagnosing the 1,25(OH)₂D₃ deficiency in CRF. —— 1,25(OH)₂D; chronic renal failure; secondary hyperparathyroidism

The loss of functional renal mass causes decreased production of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) in patients with chronic renal failure (CRF). The development and progression of renal osteodystrophy (ROD) involves the combined effects of metabolic acidosis, hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, and decreased receptor density for 1,25(OH)₂D₃ in association with reduced circulating levels of this hormone (Portale et al. 1982; Korkor 1987; Brown et al. 1989).

This study has been conducted to determine the relationship between residual renal function and the serum levels of 1,25(OH)₂D in the patients with predialysis chronic renal failure.

SUBJECTS AND METHODS

One hundred and ninety-five outpatients in pre-dialysis periods from six institutions (Department of Nephroendocrinology, Kojinkai Central Hospital; Kidney Center, Shinrakuen Hospital; The Second Department of Internal Medicine, Tokyo Medical and Dental University School of Medicine; Department of Nephrology, Fujigaoka Hospital, Showa University School of Medicine; Department of Pediatrics, Okayama University Medical School; and Department of Internal Medicine, School of Medicine, Tokai University served as subjects. The mean age of the subjects was 58.0 ± 11.2 (range: 29–82) years. None of the subjects was administered 1α-hydroxylated vitamin D preparations, immunosuppressants nor steroids. The subjects were divided into 8 groups according to their serum creatinine (Cr) levels (Cr≤1.0 (control group), 1.0<Cr≤2.0, 2.0<Cr≤3.0, 3.0<Cr≤4.0, 4.0<Cr≤5.0, 5.0<Cr≤6.0, 6.0<Cr≤8.0, and Cr>8.0 mg/100 ml) (Table 1). Fasting blood samples were drawn for measuring blood biochemicals and hormones. The serum calcium (Ca) level was adjusted by serum albumin level (adjusted Ca = Ca−albumin + 4.0) (Payne et al. 1973); immunoreactive high-sensitive parathyroid hormone (HS-PTH) and intact PTH were measured by means of radioimmunoassay using antibodies against the mid-portion of the molecule (Martin et al. 1980) and immunoradiometric assay for the intact
[1-84]-hormone (Nussbaum et al. 1987) using commercial kits obtained from YAMASA Corporation (Tokyo) and Nichols Institute Diagnostics (San Guan Capistrano, CA, USA), respectively; and 1,25(OH)₂D was determined by means of a radioreceptor assay using a 1,25(OH)₂D receptor prepared from bovine mammary gland, after purification of the serum sample with a simple column (Watanabe et al. 1994). The range of 1,25(OH)₂D in normal subjects is 20–60 pg/ml (Seino et al. 1993).

Statistics

Data are expressed as mean±s.d. Student’s t-test was used to compare differences between the group with Cr≤1.0 mg/100 ml and the other groups. Differences were considered significant at p<0.05.

RESULTS

The biochemical data for the subjects is summarized in Table 1. The levels of adjusted Ca in groups with Cr>3.0 mg/100 ml were significantly lower than those in the group with Cr≤1.0 mg/100 ml (p<0.05). The mean value of adjusted Ca was lower than the normal range (8.4–10.2 mg/100 ml) in the group with Cr>8.0 mg/100 ml. The levels of inorganic phosphate (IP) were significantly

<table>
<thead>
<tr>
<th>Cr (mg/100 ml)</th>
<th>n</th>
<th>Adjusted Ca (mg/100 ml)</th>
<th>IP (mg/100 ml)</th>
<th>1,25(OH)₂D (pg/ml)</th>
<th>Intact PTH (pg/ml)</th>
<th>HS-PTH (ng/ml)</th>
<th>ALP (IU/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.0</td>
<td>61</td>
<td>9.2±0.50</td>
<td>3.4±0.58</td>
<td>46.0±13.7</td>
<td>21.8±15.3</td>
<td>0.39±0.17</td>
<td>187±64.9</td>
</tr>
<tr>
<td>1.0–2.0</td>
<td>49</td>
<td>9.3±0.46</td>
<td>3.1±0.60*</td>
<td>31.7±12.2*</td>
<td>29.6±13.2*</td>
<td>0.76±0.41**</td>
<td>178±108</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>28</td>
<td>9.2±0.39</td>
<td>3.6±0.97</td>
<td>24.4±9.1*</td>
<td>38.5±37.8*</td>
<td>1.80±1.31**</td>
<td>204±88.4</td>
</tr>
<tr>
<td>3.0–4.0</td>
<td>15</td>
<td>9.1±0.35</td>
<td>3.7±0.73*</td>
<td>19.7±9.5**</td>
<td>47.3±23.5*</td>
<td>1.96±0.74**</td>
<td>193±101</td>
</tr>
<tr>
<td>4.0–5.0</td>
<td>9</td>
<td>8.9±0.64</td>
<td>4.3±0.81*</td>
<td>13.7±8.7**</td>
<td>140.1±95.5**</td>
<td>4.80±1.81**</td>
<td>190±38.0</td>
</tr>
<tr>
<td>5.0–6.0</td>
<td>8</td>
<td>9.0±0.69</td>
<td>4.9±0.95**</td>
<td>10.0±7.3**</td>
<td>151.6±50.7**</td>
<td>6.39±2.08**</td>
<td>288±139</td>
</tr>
<tr>
<td>6.0–8.0</td>
<td>11</td>
<td>8.8±0.55*</td>
<td>5.3±1.28**</td>
<td>8.7±5.4**</td>
<td>162.2±79.7**</td>
<td>7.45±4.55**</td>
<td>206±68.4</td>
</tr>
<tr>
<td>8.0–</td>
<td>14</td>
<td>8.2±1.22**</td>
<td>6.2±1.56**</td>
<td>6.7±4.7**</td>
<td>239.3±114.9**</td>
<td>15.0±11.3**</td>
<td>267±163</td>
</tr>
</tbody>
</table>

The subjects were divided into 8 groups relative to creatinine (Cr) levels. Data represent mean±s.d. Calcium was adjusted by albumin (adjusted Ca). IP represents inorganic phosphate. 1, 25-dihydroxyvitamin D (1,25(OH)₂D) was determined by means of RRA using a 1,25(OH)₂D receptor prepared from bovine mammary gland, after purification of the serum sample with a simple column. Intact PTH was determined by means of IRMA. HS-PTH represents immunoreactive high-sensitive parathyroid hormone measured by means of RIA using antibodies against the mid-portion of the molecule. ALP represents serum alkaline phosphatase activity.

*significantly different from control group (Cr≤1.0 mg/100 ml) (p<0.05).
**significantly different from control group and greater/lower than upper/lower normal limit.
lower in the group with $1.0 < \text{Cr} \leq 2.0 \text{ mg/100 ml}$ ($p < 0.05$) and significantly higher in groups with $\text{Cr} > 3.0 \text{ mg/100 ml}$ ($p < 0.05$) than those in the group with $\text{Cr} \leq 1.0 \text{ mg/100 ml}$. The mean value of IP was more than the normal range (2.8-4.4 mg/100 ml) in groups with $\text{Cr} > 5.0 \text{ mg/100 ml}$. The levels of 1,25(OH)$_2$D were significantly lower in groups with $\text{Cr} > 1.0 \text{ mg/100 ml}$ ($p < 0.001$) than those in the group with $\text{Cr} \leq 1.0 \text{ mg/100 ml}$. The levels of HS-PTH were greatly higher in groups with $\text{Cr} > 1.0 \text{ mg/100 ml}$ than those in the group with $\text{Cr} \leq 1.0 \text{ mg/100 ml}$ ($p < 0.001$). The levels of intact PTH were also significantly higher in groups with $\text{Cr} > 1.0 \text{ mg/100 ml}$ than those in the group with $\text{Cr} \leq 1.0 \text{ mg/100 ml}$ ($p < 0.01$), and the mean value of intact PTH in group with $\text{Cr} > 4.0 \text{ mg/100 ml}$ was more than the upper normal limit (60 pg/ml). There were no significant differences in alkaline phosphatase activity between the group with $\text{Cr} \leq 1.0 \text{ mg/100 ml}$ and the other groups.

The relationship of $1/\text{Cr}$ to 1,25(OH)$_2$D is shown in Fig. 1. The levels of 1,25(OH)$_2$D decreased in accordance with reduction of $1/\text{Cr}$. Once $1/\text{Cr}$ was less than 0.33 ($\text{Cr} > 3.0 \text{ mg/100 ml}$), the mean value of 1,25(OH)$_2$D was less than 20 pg/ml, the lower normal limit. When $1/\text{Cr}$ was less than 0.15 ($\text{Cr} > 6.7 \text{ mg/100 ml}$), the levels of 1,25(OH)$_2$D in 95% of the subjects were less than 20 pg/ml.

The relationship of $1/\text{Cr}$ to adjusted Ca and IP is shown in Fig. 2A. The mean value of adjusted Ca was maintained within the normal range until $1/\text{Cr}$ was less than 0.125 ($\text{Cr} > 8.0 \text{ mg/100 ml}$). There was a slight but significant decrease in levels of IP in subjects with $1.0 < 1/\text{Cr} \leq 0.5$ ($1.0 < \text{Cr} \leq 2.0 \text{ mg/100 ml}$), but once $1/\text{Cr}$ was less than 0.25 ($\text{Cr} > 4.0 \text{ mg/100 ml}$), the mean level of IP was

![Fig. 1. Relationship of $1/\text{Cr}$ to 1,25(OH)$_2$D.](image-url)

The level of 1,25(OH)$_2$D decreased in accordance with reduction of $1/\text{Cr}$. The mean value of 1,25(OH)$_2$D was less than 20 pg/ml, the lower normal limit, when $1/\text{Cr}$ was less than 0.33, and the levels of 1,25(OH)$_2$D in 95% of the subjects was less than 20 pg/ml when $1/\text{Cr}$ was less than 0.15.

The bold line represents the course of the mean level, and dotted lines represent the range of mean ± 2s.d. of 1,25(OH)$_2$D in the subjects.
Fig. 2A. Relationship of 1/Cr to adjusted Ca and IP.
Mean value of Ca adjusted by serum albumin levels (adjusted Ca) in the subjects was relatively maintained within the normal range (8.4–10.2 mg/100 ml) near the end stage of chronic renal failure (CRF). There was a slight but significant decrease in the levels of inorganic phosphate (IP) in subjects with 1.0 > 1/Cr ≥ 0.5, but, once 1/Cr was less than 0.25, the mean level of IP was more than the upper normal limit (4.4 mg/100 ml). The open circle represents the level of adjusted Ca and closed circle represents the level of inorganic phosphate (IP).

Fig. 2B. Relationship of 1, 25(OH)₂D to adjusted Ca and IP.
There was not a significant relationship between adjusted Ca and 1, 25(OH)₂D. Subjects with lower levels of 1, 25(OH)₂D showed higher IP levels than subjects with normal levels of 1, 25(OH)₂D. The open circle represents the level of adjusted Ca and closed circle represents the level of inorganic phosphate (IP).
more than the upper normal limit (4.4 mg/100 ml). Thus, hyperphosphatemia appeared earlier than hypocalcemia. The relationship of 1,25(OH)₂D to adjusted Ca and IP is shown in Fig. 2B. There was not a significant relationship between adjusted Ca and 1,25(OH)₂D, but subjects with lower levels of 1,25(OH)₂D showed higher levels of IP than subjects with normal levels of 1,25(OH)₂D.

When the levels of adjusted Ca, intact PTH and 1,25(OH)₂D of subjects with hypophosphatemia (IP < 2.8 mg/100 ml), normophosphatemia and hyperphosphatemia (IP > 4.4 mg/100 ml) were compared in each group, there were not any significant differences in the levels of adjusted Ca among these subjects in each group (Table 2). But, the levels of 1,25(OH)₂D in subjects with hypophosphatemia were significantly higher than those with normophosphatemia in groups with Cr ≤ 2.0 mg/100 ml, and those with hyperphosphatemia were significantly lower than those with normophosphatemia in groups with 3.0 < Cr ≤ 4.0, 5.0 < Cr ≤ 6.0 and Cr > 8.0 mg/100 ml (Fig. 3).

The relationship of 1/Cr to HS-PTH is shown in Fig. 4A. HS-PTH greatly increased in accordance with the reduction of 1/Cr. Even in patients with mild renal insufficiency, 1.0 < Cr ≤ 2.0 mg/100 ml, the mean level of HS-PTH was

![Graph](image)

Fig. 3. Relationship of Cr to 1, 25(OH)₂D regarding to IP level.
The levels of 1, 25(OH)₂D in subjects with hypophosphatemia (IP < 2.8 mg/100 ml), normophosphatemia (2.8 ≤ IP ≤ 4.4 mg/100 ml) and hyperphosphatemia (IP > 4.4 mg/100 ml) were compared in each group. The levels of 1, 25(OH)₂D in subjects with hypophosphatemia were significantly higher than those with normophosphatemia in groups with Cr ≤ 2.0 mg/100 ml, conversely, the levels of 1, 25(OH)₂D in subjects with hyperphosphatemia were significantly lower than those with normophosphatemia in groups with 3.0 < Cr ≤ 4.0, 5.0 < Cr ≤ 6.0 and Cr > 8.0 mg/100 ml.
The hatched, open and closed columns represent the levels of 1, 25(OH)₂D in subjects with hypophosphatemia, normophosphatemia and hyperphosphatemia, respectively.

*p < 0.05 vs. the levels of 1, 25(OH)₂D in subjects with normophosphatemia.
Fig. 4A. Relationship of $1/Cr$ to HS-PTH.
The levels of HS-PTH in the subjects greatly increased in accordance with reduction of $1/Cr$. Even in subjects with mild renal insufficiency, $1.0 > 1/Cr \geq 0.5$, the mean level of HS-PTH was significantly higher than that in subjects with $1/Cr \geq 1.0$ ($p < 0.001$).

Fig. 4B. Relationship of $1/Cr$ to intact PTH.
The levels of intact PTH in the subjects increased as $1/Cr$ decreased. When $1/Cr$ was less than 0.25, the mean level of intact PTH was more than the upper normal limit (65 pg/ml).

significantly higher than that in subjects with $Cr \leq 1.0$ mg/100 ml. The relationship of $1/Cr$ to intact PTH is shown in Fig. 4B. Intact PTH was also increased in accordance with the reduction of $1/Cr$, and when $1/Cr < 0.25$, the mean value of intact PTH was more than the upper normal limit (65 pg/ml). The levels of intact PTH in subjects with hyperphosphatemia were significantly higher than those with normophosphatemia in groups with $4.0 < Cr \leq 5.0$ and $Cr > 8.0$ mg/100 ml (Table 2).
Table 2. The levels of adjusted Ca, intact PTH and 1,25(OH)$_2$D in subjects with hypophosphatemia, normophosphatemia and hyperphosphatemia

<table>
<thead>
<tr>
<th>Level of creatinine (mg/100 ml)</th>
<th>-1.0</th>
<th>1.0-2.0</th>
<th>2.0</th>
<th>3.0</th>
<th>3.0-4.0</th>
<th>4.0-5.0</th>
<th>5.0-6.0</th>
<th>6.0-8.0</th>
<th>8.0-</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>14</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Ca (mg/100 ml)</td>
<td>9.3±0.56</td>
<td>9.3±0.44</td>
<td>9.2±0.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>26±8.7</td>
<td>31±13.4</td>
<td>27±11.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25(OH)$_2$D (pg/ml)</td>
<td>64.9±15.6*</td>
<td>43.9±6.7*</td>
<td>32.1±8.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>31</td>
<td>17</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Normophosphatemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Ca (mg/100 ml)</td>
<td>9.3±0.50</td>
<td>9.3±0.47</td>
<td>9.2±0.40</td>
<td>9.1±0.39</td>
<td>9.2±0.47</td>
<td>8.7±1.04</td>
<td>8.8±0.45</td>
<td>8.2±1.41</td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>26±16.1</td>
<td>31±13.3</td>
<td>42±24.4</td>
<td>43±25.4</td>
<td>92±56.6</td>
<td>121±48.5</td>
<td>150±28.3</td>
<td>130±28.3</td>
<td></td>
</tr>
<tr>
<td>1,25(OH)$_2$D (pg/ml)</td>
<td>43.9±13.0</td>
<td>31.9±8.0</td>
<td>24.0±8.5</td>
<td>22.8±7.4</td>
<td>18.0±4.2</td>
<td>16.4±2.7</td>
<td>11.1±3.6</td>
<td>10.4±3.8</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Ca (mg/100 ml)</td>
<td>9.0±0.38</td>
<td>9.0±0.35</td>
<td>9.1±0.37</td>
<td>9.1±0.15</td>
<td>8.6±0.75</td>
<td>9.2±0.43</td>
<td>8.9±0.62</td>
<td>8.3±1.26</td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>21±7.1</td>
<td>19±14.1</td>
<td>85±82.1</td>
<td>57±19.7</td>
<td>227±95.0*</td>
<td>170±46.9</td>
<td>224±58.9</td>
<td>288±78.7*</td>
<td></td>
</tr>
<tr>
<td>1,25(OH)$_2$D (pg/ml)</td>
<td>45.4±7.6</td>
<td>29.0±2.8</td>
<td>17.7±3.9</td>
<td>7.1±5.3*</td>
<td>10.9±9.8</td>
<td>7.3±3.9*</td>
<td>7.9±5.9</td>
<td>4.9±2.5*</td>
<td></td>
</tr>
</tbody>
</table>

The levels of adjusted Ca, intact PTH and 1,25(OH)$_2$D in subjects with hypophosphatemia (IP < 2.8 mg/100 ml). Normophosphatemia (2.8 ≤ IP ≤ 4.4 mg/100 ml) and hyperphosphatemia (IP > 4.4 mg/100 ml) were compared with each other.

*p < 0.05 vs. the levels of intact PTH or 1,25(OH)$_2$D in subjects with normophosphatemia.
DISCUSSION

Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D). The enzyme 25(OH)D-1α-hydroxylase, found in the mitochondria of proximal convoluted tubular cells, is a mixed-function oxidase that catalyzes a second hydroxylation to form the active compound 1,25(OH)_2D (Kawashima and Kurokawa 1986). In chronic renal failure (CRF), there is an early occurrence of secondary hyperparathyroidism (Reiss et al. 1968) which has been attributed to phosphate retention according to the well-known "trade-off" hypothesis (Bricker et al. 1969). Recently, this view has been subjected to criticism, and on the basis of reports of relatively early reduction in 1,25(OH)_2D_3 serum levels in CRF (Portale et al. 1982), it has been postulated that decreased production of this hormone is the major event leading to secondary hyperparathyroidism (Wilson et al. 1985; Szado et al. 1989). The current view is that loss of renal endocrine capacity to produce 1,25(OH)_2D_3 most likely precedes the loss of phosphate excretory capability and initiates the hypersecretion of PTH. Early in the course of progressive renal failure, the remaining nephrons may demonstrate an adaptive increase in phosphate excretion in order to prevent hyperphosphatemia at the expense of reduced 1,25(OH)_2D synthesis and PTH hypersecretion. In the present study, the levels of IP in group with 1.0 < Cr ≤ 2.0 mg/100 ml were significantly lower and the levels of intact PTH in this group were significantly higher than those in subjects with Cr ≤ 1.0 mg/100 ml, and there was not a significant difference in the levels of adjusted Ca between these two groups. Moreover, the levels of 1,25(OH)_2D in subjects with hypophosphatemia were significantly higher than those with normophosphatemia in group with 1.0 < Cr ≤ 2.0 mg/100 ml. These findings support the speculation that the increased secretion of PTH compensates the decreased production of 1,25(OH)_2D_3 by lowering phosphate in the early phase of CRF.

When the relationship of IP to 1,25(OH)_2D was examined, the levels of 1,25(OH)_2D in subjects with hyperphosphatemia were significantly lower than those with normophosphatemia in groups with 3.0 < Cr ≤ 4.0, 5.0 < Cr ≤ 6.0 and Cr > 8.0 mg/100 ml. These results suggest that phosphate retention inhibits the activity of 1α-hydroxylase and contributes to the decrease in 1,25(OH)_2D_3. As phosphate restriction prevented the development of secondary hyperparathyroidism in chronically azotemic dogs (Slatopolsky et al. 1971), earlier restriction of dietary phosphate, and the use of Ca-containing phosphate binders may be useful in preventing and delaying secondary hyperparathyroidism. In fact, phosphate restriction in children with moderate chronic renal insufficiency increased the serum concentration of 1,25(OH)_2D as PTH levels fell (Portale et al. 1984), and low-phosphorus low-protein diets decreased serum phosphorus and PTH while ionized Ca, 1,25(OH)_2D and GFR did not vary in patients with advanced CRF and mild secondary hyperparathyroidism (Combe and Aparicio 1994). These
reports strongly suggest the importance of phosphate restriction in patients with CRF.

In the present study, the levels of adjusted Ca were unexpectedly maintained within a normal range near the end stage of CRF. However, the levels of intact PTH in groups with Cr > 1.0 mg/100 ml were significantly higher than in group with Cr ≤ 1.0 mg/100 ml, and were more than the upper normal limit in groups with Cr > 4.0 mg/100 ml. And the levels of 1,25(OH)₂D were significantly lower in groups with Cr > 1.0 mg/100 ml than in group with Cr ≤ 1.0 mg/100 ml. 1,25(OH)₂D₃ directly inhibits PTH secretion and acts to reduce prepro-PTH gene transcription, reducing the synthesis and release of PTH (Silver et al. 1985, 1986). This effect is compromised in the parathyroid gland cells of patients with CRF because these cells have a reduced number of receptors for 1,25(OH)₂D₃ (Korkor 1987; Brown et al. 1989). 1,25(OH)₂D₃ deficiency results in an upward shift of the set point for calcium-stimulated PTH release so that higher serum calcium levels are required to achieve a reduction in PTH levels (Felsenfeld and Llach 1993). This leads us to speculate that the decrease in the generation of 1,25(OH)₂D due to the decrease in the renal mass contributes to the acceleration of secondary hyperparathyroidism. Recently, Slatopolsky et al. (1995) reported that high phosphate stimulates the PTH secretion in tissue culture independently of ionized Ca, and phosphate restriction prevents growth of parathyroid gland and secondary hyperparathyroidism independently of ionized Ca and 1,25(OH)₂D. In the present study, the levels of intact PTH in subjects with hyperphosphatemia were significantly higher than those with normophosphatemia in the group with 4.0 < Cr ≤ 5.0 mg/100 ml, although there were not significant differences in the level of adjusted Ca nor 1,25(OH)₂D in this group, suggesting that hyperphosphatemia might stimulate the secretion of PTH. And, the levels of intact PTH were significantly higher and the levels of 1,25(OH)₂D were significantly lower in subjects with hyperphosphatemia than those with normophosphatemia in the group with Cr > 8.0 mg/100 ml, although there was not a significant difference in the levels of adjusted Ca in this group. These results suggest two possibilities; the first, hyperphosphatemia directly stimulated the secretion of PTH but PTH failed to increase the production of 1,25(OH)₂D₃ due to hyperphosphatemia, and the second, hyperphosphatemia indirectly stimulated the secretion of PTH through the modification of the set point for calcium-stimulated PTH release caused by decreased production of 1,25(OH)₂D₃ due to hyperphosphatemia itself.

Supplements of 1α-hydroxylated vitamin D preparations should be considered to normalize these disturbances of calcium metabolism in patients with CRF. Supplements of these drugs potentiate to cause hypercalciuria, which may accelerate the deterioration of kidney function (Christiansen et al. 1978), this requires careful clinical observation of not only serum Ca but also urinary excretion of Ca.
References


