CLINICAL STUDY

Skeletal responsiveness to parathyroid hormone in pseudohypoparathyroidism

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Abstract

Background: Although there have been some case reports suggesting that bone in patients with pseudohypoparathyroidism (PHP) might respond to parathyroid hormone (PTH), no information is available as to whether serum PTH concentration is related to bone metabolic markers or to bone mineral density (BMD) in PHP.

Objective: To address these relationships, by comparing intact serum PTH, bone metabolic markers and BMD in patients with PHP with those in patients with idiopathic hypoparathyroidism (IHP) and postoperative hypoparathyroidism (OHP).

Methods: Intact serum PTH, bone metabolic markers (osteocalcin, tartrate-resistant acid phosphatase, pyridinoline, deoxypyridinoline) and BMD by dual-energy X-ray absorptiometry or single-photon absorptiometry were measured in patients with PHP Ia (n = 2) and PHP Ib (n = 8). The results were compared with those in patients with IHP (n = 5) and OHP (n = 14).

Results: All bone metabolic markers measured were present in significantly greater amounts in patients with PHP Ib than in those with IHP+OHP. The Z score (standard deviation of average BMD at each age) of the BMD of femoral neck was significantly lower in patients with PHP Ib than in those with IHP+OHP. The Z scores of BMD of lumbar spine and radius were also lower in patients with PHP Ib than in those with IHP+OHP, but the difference was not significant. Moreover, the intact serum PTH concentrations were significantly and positively related to bone metabolic marker levels in all patients, and the intact serum PTH concentrations were significantly and negatively related to BMD of lumbar spine in PHP patients.

Conclusions: These results suggest that PTH stimulates bone turnover in PHP Ib patients, resulting in a relatively lower BMD in PHP Ib patients than in IHP+OHP patients. The present study indicates that bones of most cases of PHP could respond to PTH.

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Introduction

Pseudohypoparathyroidism (PHP) is a heterogeneous disease complex characterized by resistance of the proximal kidney tubule to the action of parathyroid hormone (PTH) with or without typical features of Albright’s hereditary osteodystrophy (AHO) such as short stature, round face, brachydactyly, mental retardation and ectopic calcification (1). Biochemical characteristics are hypocalcemia, hyperphosphatemia, increased immunoreactive PTH and a subnormal phosphaturic response to exogenous PTH associated with a blunted (PHP type I) or normal increase (PHP type II) in cyclic AMP (cAMP) excretion. Hypocalcemia despite increased circulating PTH and subnormal calcemic response to prolonged intramuscular PTH administration suggests the existence of skeletal resistance in addition to renal resistance in PHP (2). This was believed to result from the same abnormality in cAMP generation occurring in bone tissue. In contrast, radiographic and histological findings (3–8), in addition to diminished bone density (9) and increased serum alkaline phosphatase activity (10), have provided evidence of excessive PTH action on bone in at least some patients with PHP. Furthermore, Murray et al. (11) and Ish-Shalom et al. (12) demonstrated that bone cells from patients with PHP showed a normal cAMP response to PTH. Although these findings suggest that bones in some patients with PHP could respond to PTH, no information is available on whether serum PTH level is related to bone metabolic markers or to bone mineral density (BMD) in patients with PHP. In this study, we demonstrated that PTH could stimulate bone turnover in PHP patients, resulting in a relatively lower BMD in patients with PHP than in patients with idiopathic and postoperative hypoparathyroidism.
Table 1 Characteristics of patients with hypoparathyroidism.

<table>
<thead>
<tr>
<th>Group</th>
<th>PHP Ia</th>
<th>PHP Ib</th>
<th>IHP</th>
<th>OHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5±6.1</td>
<td>43.3±6.1</td>
<td>50.2±5.6</td>
<td>49.9±4.6</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1:1</td>
<td>4:4</td>
<td>3:2</td>
<td>2:12</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>8.9</td>
<td>9.1±0.1</td>
<td>8.9±0.1</td>
<td>9.0±0.1</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>3.6</td>
<td>4.2±0.1</td>
<td>4.0±0.1</td>
<td>4.0±0.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Serum intact PTH (pg/ml)</td>
<td>22.5</td>
<td>95±31.9*</td>
<td>2.2±1.4</td>
<td>3.9±1.2</td>
</tr>
<tr>
<td>Serum 25(OH)D3 (ng/l)</td>
<td>10.7</td>
<td>19.5±2.7</td>
<td>21.6±3.5</td>
<td>14.9±3.2</td>
</tr>
<tr>
<td>Serum 1,25(OH)2D3 (ng/l)</td>
<td>23.1</td>
<td>15.3±4.8†</td>
<td>47.9±17.4</td>
<td>ND</td>
</tr>
<tr>
<td>Vitamin D therapy 1α(OH)D3 (μg/day)</td>
<td>1.25</td>
<td>2.06±0.14†</td>
<td>2.80±0.25</td>
<td>1.80±0.10</td>
</tr>
</tbody>
</table>

Data are expressed as means ± S.E.M.  
ND, not determined.  
*P < 0.05 compared with IHP+OHP; †P < 0.05 compared with IHP.

Table 2 Renal responses to rapid infusion of PTH1-34 and erythrocyte membrane Gsα activity in PHP patients.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>AHO</th>
<th>Ellsworth–Howard test</th>
<th>Gsα activity (% of standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>∆Urinary cAMP (μmol/h)</td>
<td>∆Urinary Pi (mmol/2 h)</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>(+)</td>
<td>0.03</td>
<td>0.63</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>(+)</td>
<td>0.21</td>
<td>1.06</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>(+)</td>
<td>0.02</td>
<td>0.37</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>M</td>
<td>(-)</td>
<td>0.23</td>
<td>0.48</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>F</td>
<td>(-)</td>
<td>0.41</td>
<td>0.73</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>(-)</td>
<td>0.33</td>
<td>0.91</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>(-)</td>
<td>0.80</td>
<td>0.06</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>M</td>
<td>(-)</td>
<td>0.35</td>
<td>0.19</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>M</td>
<td>(-)</td>
<td>0.29</td>
<td>0.41</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>F</td>
<td>(-)</td>
<td>0.01</td>
<td>0.34</td>
</tr>
<tr>
<td>Normal range</td>
<td></td>
<td></td>
<td></td>
<td>&gt;1</td>
<td>&gt;1.13</td>
</tr>
</tbody>
</table>

Pi, inorganic phosphate.

Study participants and methods

Patients

This study was carried out in a total of 29 patients. Five of these patients (two women and three men; age 50.2±5.6 years) had idiopathic hypoparathyroidism (IHP), 14 (12 women and two men; age 49.9±4.6 years) had postoperative hypoparathyroidism (OHP; serum intact PTH < 15 ng/l), two (one woman and one man; mean age 47.5 years) had PHP Ia, and eight (four women and four men; age 43.3±6.1 years) had PHP Ib. The clinical data and therapy during the study are shown in Table 1. The diagnosis of PHP was based on clinical symptoms, hypocalcemia, hyperphosphatemia, serum concentrations of intact PTH, and increases in urinary phosphate and cyclic AMP in response to exogenous PTH (13) (Table 2). Two of the ten patients with PHP had Albright’s hereditary osteodystrophy (AHO) and were diagnosed as PHP type Ia. Gsα activity of the erythrocyte plasma membranes was 40% of the control value in one of the two PHP type Ia patients, and 58% in the other (Table 2). The other eight PHP patients without AHO were diagnosed as PHP type Ib. Gsα activity of the erythrocyte plasma membranes was normal in all PHP type Ib patients (Table 2).

All patients had been receiving active vitamin D3 treatment for more than 3 years to maintain normal serum concentrations of calcium and phosphorus. Each patient was receiving an unrestricted diet as an outpatient. Supplementary oral calcium, phosphate-binding antacids, or thiazide diuretics were not prescribed for any of the patients studied. This study was approved by the Institution Review Board of Kobe University School of Medicine. Informed consent was obtained from all patients.

Measurement of erythrocyte membrane Gsα activity

We measured Gsα activity in the erythrocyte membrane by assessing the ability of cholera toxin to catalyze 125I-ADP ribosylation of the 42 000 dalton α subunit of Gs. Human erythrocyte ghosts were prepared by the method of Ikeda et al. (14), with a
slight modification. The ghosts were recovered in a final volume of 3 ml at 2–3 mg of protein/ml. Cholera toxin (250 µg/ml) and islet-activating protein (50 µg/ml) were preincubated for 15 min at 37 ºC. Twenty microliters ghost, 20 µl preincubated Cholera toxin or islet-activating protein and 60 µl reaction mixture were activated for 10 min at 30 ºC. The reaction mixture contained 5 mmol/l HEPES, 0.5 mmol/l EDTA-Na, 1 mmol/l ATP, 10 mmol/l thymidine, 100 mmol/l potassium phosphate buffer (pH 8.0), 4 mmol/l GTP, 100 µmol/l [32P]NAD, 5mmol/l MgCl2, and 1mmol/l dithiothreitol. Incubations were terminated by dilution with 2.5 ml ice-cold 5 mmol/l Tris–HCl (pH 7.5) and centrifuged at 27 000 g for 15 min. The pellets were dissolved in Laemmli’s sample buffer (15), and applied to a 12% SDS-polyacrylamide gel. The gels were dried and autoradiographed with a Kodak X-Omat film using an intensifying screen at −80 ºC.

**Bone mineral density (BMD)**

BMD was measured at the lumbar spine (L2–4) and femoral neck by dual energy X-ray absorptiometry (Hologic QDR, Hologic, MA, USA) and at the one-third distal site of the radius by single photon absorptiometry (Bone Mineral Analyzer 278 O, Norland, WI, USA). The coefficients of variation (precision) of measurements of lumbar spine, femoral neck, and radius by our methods were 0.9, 1.7 and 1.9% respectively. The Z score is the deviation (in standard deviations) from the normal age- and sex-matched mean.

**Biochemical measurement**

Serum concentrations of calcium, phosphorus and creatinine were assayed by standard methods at the central laboratory of Kobe University Hospital. Serum intact PTH (i-PTH) concentration was measured by immunoradiometric assay (Allegro Intact PTH-RIA kit, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) (16). Serum osteocalcin (OC) was assayed by an IRMA using tracer anti-OC1–49 antibody and solid-phase anti-OC30–49 antibody with synthetic human OC1–49 as a standard (17). Epitope mapping revealed that anti-OC12–33 antibody recognizes OC22–28, and anti-OC30–49 antibody recognizes OC38–43. A recent study demonstrated that the 1–43 and 20–43 fragments of OC consist of approximately 30 and 15% respectively, and that intact OC consists of 36% of circulating bone-derived OC (18). In addition, because these fragments do not appear to originate from bone resorption and can be generated during the processing of blood samples (18), this assay is expected to measure the major portions of bone-derived OC reflecting the bone formation process. The intra- and interassay variations of this assay are 4.6 and 6.3% respectively and the sensitivity is 0.1 mg/l. Urinary total pyridinoline (Pyr) and total deoxypyridinoline (D-Pyr) were quantified by HPLC using a fluorescence detector, as reported previously (19). In brief, after urine samples were hydrolysed with HCl, they were ultrafiltrated and applied to C18 cellulose columns. The samples were eluted from the cellulose columns with distilled water, and pyridinium cross-links were separated by reversed-phase HPLC and detected by fluorometry. The intra- and interassay variations for total Pyr were 3.5 and 9.1% respectively, and those for total D-Pyr were 7.5% and 10.1% respectively. The sensitivity of the assays is 1.66 mmol/l for both Pyr and D-Pyr. Serum tartrate-resistant acid phosphatase (TRAP) activity was determined by measuring the absorbance of 2,6-dichloro-4-acetylphenol at 340 nm. 2,6-Dichloro-4-nitrophenol-phosphate was used as the substrate. For measurement of serum 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], vitamin D metabolites were extracted from 1-ml serum samples. The extract was applied to a Bond Elut C18/OH cartridge (Varian, MA, USA), and 1,25(OH)2D3 was eluted by isopropanol/hexan (1:1). The samples were evaporated and resuspended and 1,25(OH)2D3 concentration was measured with a radioreceptor assay kit (1,25VD Kit-Med, Japan Mediphysics Co, Nishinomiya, Japan), which uses purified calf thymus vitamin D receptor that preferentially recognizes 1,25(OH)2D3 (20). The sensitivity of the assay is 16 pmol/l. The intra- and interassay variations were 8.5 and 15.0% respectively. Serum 25(OH)D3 was assayed by means of a rat serum binding protein system (21, 22).

**Statistical analysis**

Data are expressed as mean ± S.E.M. Statistical significance was determined using Student’s t-test. P values <0.05 were considered significant. The regression analysis was performed using the statistical computer program Statview (Abacus Concepts, Inc., Berkeley, CA, USA). Simple regression analysis was used to assess the linear relationship between the study parameters, and then Pearson’s correlation coefficients were calculated.

**Results**

Table 1 shows background data of the PHP Ia, PHP Ib, IHP and OHP patients. All patients were being treated with active vitamin D3 to maintain normal serum concentrations of calcium and phosphorus because they presented hypocalcemia and hyperphosphatemia when untreated. There was no significant difference in the average age between PHP Ib and IHP+OHP patients. Serum concentrations of i-PTH in PHP Ib patients were significantly greater than those in IHP+OHP patients. The doses of 1α(OH)D3 were significantly lower in patients with PHP Ib than those in patients with IHP (Table 1). There was no significant difference in serum concentrations of 25(OH)D3 between PHP Ib and IHP+OHP patients (Table 1).
Concentrations of all bone metabolic markers (OC, TRAP, Pyr, D-Pyr) were significantly greater in patients with PHP Ib than in those with IHP+OHP (Table 3). The BMD Z score of the femoral neck was significantly lower in patients with PHP Ib than in those with IHP+OHP (Table 3). The BMD Z score of the femoral neck was significantly lower in patients with PHP Ib than in those with IHP+OHP, although the difference was not significant. This study also demonstrates that the concentrations of all bone metabolic markers (OC, TRAP, Pyr, D-Pyr) were significantly greater in patients with PHP Ib than in those with IHP+OHP. Moreover, the intact serum PTH concentrations were significantly and negatively related to bone metabolic marker levels. In contrast, the intact PTH concentrations were significantly and negatively related to BMD values of the lumbar spine in PHP patients. These results suggest that PTH stimulates bone turnover in PHP Ib patients, resulting in a lower BMD in PHP Ib patients than in IHP+OHP patients.

Subperiosteal bone resorption is the most characteristic radiographic feature of hyperparathyroidism, and cortical bones are usually affected. In this study, BMD of the mid-radius was not remarkably different between PHP Ib and IHP+OHP patients. In addition, no significant relationship was observed between the intact PTH concentrations and BMD values at the mid-radius. These results are incompatible with the concept that the decrease in BMD of cortical bones is prominent in the hyperparathyroid state. A 6% increase in radial BMD at the peripheral cortical bone sites was observed in patients with senile osteoporosis treated with 1α-hydroxyvitamin D₃ for 5 years (23). It is possible that long-term treatment with active Vitamin D₃ might affect BMD of the mid-radius in PHP Ib patients.

The doses of 1α(OH)D₃ and serum concentrations of 1,25(OH)₂D₃ that are necessary to maintain the normal concentrations of serum calcium were significantly lower in PHP Ib patients than in IHP patients. The doses of 1α(OH)D₃ were negatively related to OC and D-Pyr concentrations in PHP patients, although the correlation was not significant (Fig. 3).

**Table 3** Comparison of bone metabolic markers between PHP, and idiopathic (IHP) and postoperative (OHP) hypoparathyroidism.

<table>
<thead>
<tr>
<th>Marker</th>
<th>PHP la (n = 2)</th>
<th>PHP Ib (n = 8)</th>
<th>IHP and OHP (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC (ng/ml)</td>
<td>7.75</td>
<td>6.34±1.32*</td>
<td>2.67±0.29</td>
</tr>
<tr>
<td>TRAP (IU/l)</td>
<td>4.05</td>
<td>5.61±0.40**</td>
<td>4.35±0.25</td>
</tr>
<tr>
<td>Pyr (pmol/µmol creatinine)</td>
<td>49.05</td>
<td>33.30±5.7*</td>
<td>25.00±1.40</td>
</tr>
<tr>
<td>D-Pyr (pmol/µmol creatinine)</td>
<td>6.35</td>
<td>6.10±0.80*</td>
<td>4.20±0.29</td>
</tr>
</tbody>
</table>

Data are expressed as means ± S.E.M. *P < 0.05, **P < 0.01 compared with IHP and OHP.

**Table 4** Comparison of bone mineral density between PHP, and idiopathic (IHP) and postoperative (OHP) hypoparathyroidism.

<table>
<thead>
<tr>
<th>BMD (Z score)</th>
<th>PHP la (n = 2)</th>
<th>PHP Ib (n = 8)</th>
<th>IHP and OHP (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>3.34</td>
<td>1.04±0.56</td>
<td>2.00±0.35</td>
</tr>
<tr>
<td>Radius</td>
<td>–0.42</td>
<td>0.72±0.60</td>
<td>1.14±0.26</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.13</td>
<td>0.68±0.33*</td>
<td>2.07±0.56</td>
</tr>
</tbody>
</table>

Data are expressed as means ± S.E.M. *P < 0.05 compared with IHP and OHP.

Discussion

This study demonstrates that the BMD Z score of the femoral neck was significantly lower in patients with PHP Ib than in those with IHP+OHP. BMD Z scores of the lumbar spine and mid-radius were also lower in patients with PHP Ib than in those with IHP+OHP, although the difference was not significant. This study also demonstrates that the concentrations of all bone metabolic markers (OC, TRAP, Pyr, D-Pyr) were significantly greater in patients with PHP Ib than in those with IHP+OHP. Moreover, the intact serum PTH concentrations were positively related to bone metabolic marker levels. In contrast, the intact PTH concentrations were significantly and negatively related to BMD values of the lumbar spine in PHP patients. These results suggest that PTH stimulates bone turnover in PHP Ib patients, resulting in a lower BMD in PHP Ib patients than in IHP+OHP patients.
Patients with PHP type Ib do not have dysmorphic features, and Gs activity is normal. Bone resorption is often increased in these patients (27). In contrast, patients with PHP type Ia have AHO and decreased Gs activity. Relatively few studies have reported an increase in bone resorption in patients with PHP type Ia (6, 12). Mice homozygous for the loss of the PTHrP gene have multiple anomalies in the development of cartilage and bone (28). In addition, mice (29) and humans (30) that are homozygous for inactivation of the gene encoding the PTH/PTHrP receptor exhibit multiple, severe skeletal defects characterized by an advanced endochondral maturation. These anomalies in cartilage and bone resemble the anomalies observed in AHO, suggesting that responsiveness of bone and cartilage to PTH might be poor in PHP type Ia. In this study, there were only two patients with PHP type Ia. We were not able to clarify the relationship between PHP type Ia and the responsiveness of bone to PTH.

Individuals with PHP type Ib who have increased concentrations of PTH often manifest skeletal lesions similar to those in patients with hyperparathyroidism (4). These observations suggested that at least one intracellular signaling pathway coupled to the PTH receptor in bone may be intact in patients with PHP type Ib. The present study suggests that bones in most cases of PHP type Ib respond to PTH. However, there were two patients in whom the responsiveness of bone

Figure 1 Relationship between PTH and bone metabolic marker concentrations in hypoparathyroidism. Creat, creatinine. ■, PHP Ia; ●, PHP Ib; ○, OHP; □, IHP.

Figure 2 Relationship between PTH and BMD values in hypoparathyroidism. F-Neck, femoral neck. ■, PHP Ia; ●, PHP Ib; ○, OHP; □, IHP.

Figure 3 Relationship between dose of vitamin D replacement and bone metabolic marker concentrations in pseudohypoparathyroidism. Creat, creatinine.
to PTH was low, suggesting a heterogeneity in PTH/PTHrP receptor expression. In PHP type Ib, the specific resistance of target tissues to PTH and normal activity of Gsα appeared to be due to a decreased expression or function of the PTH/PTHrP receptor. Fibroblasts from some PHP type Ib patients accumulate less cAMP in response to PTH (31) and contain decreased levels of mRNA encoding the PTH/PTHrP receptor (32). However, several lines of evidence suggest that the primary defect in PHP type Ib is not in the gene encoding the PTH/PTHrP receptor: molecular studies failed to disclose mutations in the coding exons (33) or promoter regions (34) of the PTH/PTHrP receptor gene or its mRNA (35). In contrast, mice (29) and humans (30) that are homozygous for inactivation of the gene encoding the PTH/PTHrP receptor exhibit multiple, severe skeletal defects characterized by an advanced endochondral maturation. Conversely, the constitutive activation of the PTH/PTHrP receptor has been demonstrated to be responsible for Jansen’s chondrodysplasia, a disease characterized by delayed endochondral bone formation (36, 37). These findings indicate the importance of signaling through the PTH/PTHrP receptor in fetal skeletal development. They are also compatible with the failure to find any abnormality on the PTH/PTHrP receptor gene in PHP type Ib patients, who do not show signs of AHO. It has recently been reported that the gene responsible for PHP type Ib is paternally imprinted in the same mode as PHP type Ia and maps to chromosome 20q13.3 near the GNAS1 gene (38). Preliminary data from Gsα gene-ablated mice suggest that offspring that inherit the mutant allele from a female show substantially decreased concentrations of the Gsα protein in the renal cortex and in adipocytes, but not in the renal medulla or in several other tissues (39, 40). These mice also develop hypocalcemia and secondary hyperparathyroidism (39, 40). These results indicate that the ablation of one Gsα allele combined with paternal imprinting, can lead to changes in mineral ion homeostasis that are similar to those observed in PHP type Ia or PHP type Ib. Although it is not known whether Gsα and the PHP-Ib gene are close enough to allow the sharing of regulatory elements or even coding nucleotide sequences as is observed with other imprinted genes (41–45), our study raises the possibility that the expression of the PHP-Ib gene is tissue-specific – that is to say, it is likely that the PHP Ib gene is expressed in the kidney, which has the effect of conferring resistance to PTH, whereas it would not be expressed in other tissues, including bone, in PHP type Ib.

It has been reported that plasma PTH bioactivity in patients with PHP type I was greater in the metatarsal bone than in the renal bioassay (46). Further, it was reported that no such differences were found in normal individuals or patients with primary hyperparathyroidism (46). Bradbeer et al. (46) suggested that PHP may be caused by a circulating inhibitor of PTH action that is less effective on the skeleton. This supports our hypothesis that bone is able to respond to circulating PTH in patients with PHP type I.

In conclusion, bones of most patients with PHP Ib could respond to endogenous PTH. This responsiveness of bone to PTH, together with the calcium reabsorption by PTH in the distal convoluted tubule under supplementation with active vitamin D₃, would explain why the dose of vitamin D₃ needed to maintain normal concentrations of serum calcium is lower in PHP Ib than in IHP and OHP.

Acknowledgements

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