Significance of time-course changes of serum bone markers after parathyroidectomy in patients with uraemic hyperparathyroidism

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Abstract

Background. The increase of bone mineral density in cortical bone after parathyroidectomy is smaller than that in cancellous bone. Changes of serum bone markers reflect those of bone metabolism both in cortical and cancellous bone after parathyroidectomy. The present study was undertaken to investigate changes of histomorphometric parameters of cortical and cancellous bone together and their correlation with those of serum bone markers.

Methods. Iliac bone biopsy was performed before and 1 week after parathyroidectomy in Group I \( (n=13) \), and before and 4 and 12 weeks after in Group II \( (n=11) \). Moreover, changes of histomorphometric parameters of the endocortical, intracortical and periosteal surfaces as well as in cancellous bone were monitored. Serum levels of intact parathyroid hormone and bone markers were measured simultaneously.

Results. In cancellous bone, osteoclast surface (Oc.S/BS) decreased to 0% within 4 weeks after parathyroidectomy, while osteoblast surface (Ob.S/BS) transiently increased at 1 week, followed by a reduction at 4 weeks to levels below the pre-surgical level. In cortical bone, Oc.S/BS was not reduced to 0%, while a significant and temporary increase of Ob.S/BS was observed only on the endocortical and intracortical surfaces at 4 weeks, but not at 1 week. Serum bone resorption markers did not completely disappear and significant and sustained increases of bone formation markers were observed until 4 weeks after parathyroidectomy.

Conclusions. Changes of bone formation markers lagged behind those of histomorphometric parameters in cancellous bone because changes of cortical bone were observed later and were incomplete compared with those of cancellous bone.

Keywords: endocortical surface; intracortical surface; parathyroidectomy; periosteal surface; secondary hyperparathyroidism; serum bone markers

Introduction

Because bone resorption is most prominent at the endocortical surface in patients with primary osteoporosis as well as in those with uraemic hyperparathyroidism, reduction of bone mineral density (BMD) in cortical bone is also marked [1–3]. In addition, the intracortical surfaces are eroded by osteoclasts and intracortical spaces are progressively enlarged. Many of the large marrow spaces that develop in the inner cortex originate from resorption cavities on the endocortical surface. Thus, the marrow cavities in cancellous bone communicate with the intracortical surface because bone resorption is more prominent at the endocortical surface than elsewhere. The intracortical surfaces also communicate with each other, leading to the conversion of cortical bone into a cancellous-like structure along with expansion of the marrow cavity. These changes are the main causes of cortical thinning and the reduction of cortical BMD in patients with primary osteoporosis [1–3]. Even more rapid cortical thinning occurs in patients with uraemic hyperparathyroidism [1], and intracortical spaces are often seen at the outer and inner cortex in these patients. Because cortical bone loss is the net
result of endocortical and intracortical bone loss combined with a small amount of periosteal bone gain in patients with primary osteoporosis [4], it would also seem important to observe the periosteal surface in patients with uraemic secondary hyperparathyroidism. The degree of bone resorption differs among the four bone surfaces (endocortical surface, intracortical surface, periosteal surface in cortical bone and the cancellous surface in cancellous bone) [1–3].

Parathyroidectomy [5,6] or cinacalcet is recommended for patients who do not respond to other conservative therapies for uraemic secondary hyperparathyroidism or for those with increasing soft tissue calcification or calciphylaxis, resulting from an increased calcium (Ca) × phosphorus (P) product [7]. Parathyroidectomy drastically improved hyperparathyroidism bone disease of cancellous bone from the viewpoint of its histology in patients with uraemic hyperparathyroidism [5,6], although no data have been reported on the effect of parathyroidectomy on cortical bone of those patients. The increase of BMD is greater in cancellous bone than in cortical bone [8]. The degree of bone resorption differs among the three envelopes, i.e., the endocortical surface, intracortical surface and periosteal surface in patients with uraemic hyperparathyroidism [1–3,9]. However, the time-course change of high bone turnover status improvement on each envelope after parathyroidectomy has not been investigated as yet by bone histomorphometric analysis. In addition, cortical bone constitutes approximately 75% of systemic bone mass in the normal population, and bone fractures generally initiate in cortical bone [1]. In addition, a selective increase of cortical bone metabolism induced by parathyroid hormones (PTH) excess has been reported [1,3]. Therefore, the impact of parathyroidectomy on cortical bone histology in these patients deserves to be investigated.

Since, serum bone markers are hypothesized to represent the sum of bone metabolism including cortical and cancellous bone, it is important to investigate the correlation of time-course changes of serum bone markers with those of histomorphometrical parameters either in cortical or cancellous bone after parathyroidectomy in patients with uraemic secondary hyperparathyroidism.

The background scenario prompted us to investigate the changes of histomorphometrical parameters in cortical and cancellous bone from the iliac crest after parathyroidectomy in patients with uraemic hyperparathyroidism and to compare them with those of serum bone markers.

Subjects and methods

Patients

Twenty-four patients on chronic haemodialysis (HD), who decided to undergo parathyroidectomy because of failure of conservative therapy with calcitriol or maxi-calcitriol and/or increasing extraosseous calcification resulting from a persistent elevation of serum Ca × P product, underwent serial iliac bone biopsies before and at several time points after parathyroidectomy. Informed consent was obtained from each patient prior to each iliac bone biopsy after we explained the procedure, discomfort, possible risks and outcome. This study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Towa Hospital and its affiliated hospitals.

The underlying kidney disease was chronic glomerulonephritis in 16 patients, polycystic kidney disease in two, and unknown in six patients. None of the patients had liver dysfunction or diabetes mellitus. Transiliac bone biopsy was done before parathyroidectomy and at the indicated times afterwards. All the patients had a fibrosis volume (Fb.V/TV) >0.5% in cancellous bone, indicating the presence of osteitis fibrosa or mixed uraemic osteodystrophy [10,11]. In addition, the patients were excluded from this study if the serum level of intact parathyroid hormone (iPTH) (Allegro intact PTH; Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) [12] was over 30 pg/ml at 1 week postoperatively because our objective was to observe the changes of cortical bone in patients with markedly suppressed resorption of cancellous bone after parathyroidectomy [5,6]. As a result, two of the 14 patients reported in our previous study were excluded [5]. Another patient was enrolled for this study, so 13 patients (Group I) underwent iliac bone biopsy before and 1 week after parathyroidectomy. In addition, one of the nine patients reported elsewhere was excluded [6] and the three additional patients were enrolled in this study, so that 11 patients (Group II) underwent bone biopsy before and 4 weeks after surgery (six of these Group II patients also underwent the third biopsy at 12 weeks postoperatively). The subjects were allocated at random into two groups. In Group I, the mean age and duration of HD were 56.1 ± 6.9 years (range 43–64) and 18.7 ± 6.5 years (range 6–27), respectively, whereas the respective values were 57.0 ± 10.9 years (range 37–71) and 11.4 ± 6.8 years (range 1–25) in Group II. There were 13 (nine male, four post-menopausal female) patients in Group I and 11 (six male, five post-menopausal female) patients in Group II, respectively.

Parathyroidectomy

After total parathyroidectomy was performed, 150 mg of diffuse hyperplastic parathyroid tissue was divided into small pieces measuring approximately 1 mm in diameter, and immediately autotransplanted into the subcutaneous fat of the abdominal wall [5,6] to avoid progressive soft tissue calcification secondary to prolonged hypoparathyroidism [7]. Alfacalcidol (Chugai, Tokyo, Japan) was administered orally after parathyroidectomy at doses of 2.0 μg/day or <2.0 μg/day to avoid severe impairment of bone mineralization caused by hypophosphataemia and/or hypocalcaemia [5,6]. Ca gluconate and/or Ca carbonate were also administered to avoid the drop of serum Ca level below 7.0 mg/dl. The mean dose of elemental Ca administered during the first week after parathyroidectomy was 8.5 ± 5.2 g (range 1.5–19.5) in Group I and 10.8 ± 7.5 g (range 2.3–23.2) in Group II.
performed at a point distant from the site of the first biopsy. To exclude the effect of the first biopsy, the third biopsy was obtained from the left side again; however, to perform parathyroidectomy, while the second specimen was taken from the right iliac crest (Figure 1). In six patients, the third specimen was taken from the left iliac crest just prior to parathyroidectomy. All these parameters were measured before and 1, 4 and 12 weeks after parathyroidectomy. Although histomorphometric data of the only thicker cortex were shown separately in the recent study [16,17], the data in these papers were the average for the thicker and thinner cortex [2,9]. Because impacts of parathyroidectomy on bone remodelling were significantly different between the thicker cortex and the thinner cortex (data not shown), the histomorphometric data of the only thicker cortex were shown to avoid the complexity in the present study. In addition, the histomorphometric data of the thicker cortex and the thinner cortex were shown separately in the recent study [16,17]. Bone histomorphometry was performed separately for cancellous bone, endocortical surface, intracortical surface and periosteal surface (Figure 1). The changes of serum bone metabolism parameters after parathyroidectomy were assessed in relation to each histomorphometric parameter for cancellous bone, endocortical surface, intracortical surface and periosteal surface. The normal values of the histological indices for the cancellous, endocortical and intracortical surfaces were based on values obtained from 66 post-menopausal Caucasian women aged 65.2 ± 6.0 years, as reported by Han et al. [2]. Normal values for the periosteal surface were taken from the report of Balena et al. [9]. Although there were more male patients than female patients in both Group I and II in our study, the normal values of the post-menopausal Caucasian women were adopted. Increased bone remodelling due to oestrogen deficiency may lead to an increase in the values of bone formation parameters including osteoid-related parameters and bone formation rate (BFR/BS). Although statistical analyses could not be performed, QS/BS (20.6 ± 11.2%) and BFR/BS (0.015 ± 0.010 mm³/mm²/year) of the post-menopausal Caucasian women reported by Han et al. [2] seemed greater than those of the male subjects reported by Clarke et al. [18]. According to the report of the latter, the distribution of the OS/BS and BFR/BS values, respectively, in the male subjects according to the age was as follows: between 50 and 59 years, 10.4 ± 2.6% and 0.007 ± 0.002 mm³/mm²/year; between 60 and 69 years, 14.2 ± 2.3% and 0.011 ± 0.004 mm³/mm²/year; between

**Serum bone metabolism markers**

Serum iPTH was measured by an immunoradiometric assay (IRMA) [12], while tartrate-resistant acid phosphatase (TRAP) was measured by colorimetry with nitrophenyl phosphate as the substrate [6]. In addition, deoxypyridinoline (DPD) was measured by high-performance liquid chromatography (HPLC) [13], total alkaline phosphatase (total ALP) was measured by colorimetry using nitrophenyl phosphate as the substrate, carboxy-terminal propeptide of type I procollagen (PICP) was measured by radioimmunoassay (RIA) (PICP ORION; ORION Diagnostica, Espoo, Finland) [14], and intact osteocalcin (OC) [1–49] was measured by IRMA (IRMA MITSUBISHI; Mitsubishi Kagaku, Tokyo, Japan) [15]. Serum Ca and P as well as these serum bone markers were measured before and 1, 4 and 12 weeks after parathyroidectomy. All these parameters were measured before and 1 week after parathyroidectomy in Group I and before and 4 weeks after in Group II. Six of Group II patients who underwent the third bone biopsy, were additionally evaluated at 12 weeks.

**Bone histomorphometry**

Since bone volumetric density and histomorphometric parameters do not differ significantly between the left and right iliac crests [5], we performed serial bone biopsy from each iliac crest in turn. In all patients, the first bone biopsy specimen was taken from the left iliac crest just prior to parathyroidectomy, while the second specimen was taken from the right iliac crest (Figure 1). In six patients, the third biopsy was obtained from the left side again; however, to exclude the effect of the first biopsy, the third biopsy was performed at a point distant from the site of the first biopsy. Therefore, bone-remodelling features, such as callus formation seen during the fracture healing process, were not observed in the third bone biopsy specimens in our study. The core diameter of each bone specimen was 8 mm. The biopsy specimens were fixed in ethanol, stained by the Villanueva method, and embedded in methylmethacrylate without decalcification. A single experienced investigator (Akemi Ito) examined all the biopsy specimens [16] and determined the following histomorphometric parameters for cancellous bone and for the endocortical, intracortical and periosteal surfaces of cortical bone [1,2,5,6,9]: osteoclast surface (Oc.S/BS), eroded surface (ES/BS), fibrosis volume (Fb.V/TV for cancellous bone or Fb.V/BS for the three surfaces of cortical bone), osteoblast surface (Ob.S/BS), osteoid surface (OS/BS) and osteoid thickness (O.Th). Discrimination between cortical and cancellous bone was decided according to the texture of mineralized bone revealed by polarized light microscopy, with concentric rings of osteon indicating cortical bone and a flowing pattern indicating cancellous bone. Intracortical surface was defined as interconnecting and eroded marrow cavities located inside cortical bone. As we performed transiliac bone biopsy, samples of both cortices (thicker and thinner cortex) were obtained, and the thicker one was measured for histomorphometric analyses in this study. Although histomorphometric indices of transiliac bone biopsy specimens were shown in the quoted papers, the data in these papers were the average for the thicker and thinner cortex [2,9]. Because impacts of parathyroidectomy on bone remodelling were significantly different between the thicker cortex and the thinner cortex (data not shown), the histomorphometric data of the only thicker cortex were shown to avoid the complexity in the present study. In addition, the histomorphometric data of the thicker cortex and the thinner cortex were shown separately in the recent study [16,17]. Bone histomorphometry was performed separately for cancellous bone, endocortical surface, intracortical surface and periosteal surface (Figure 1). The changes of serum bone metabolism parameters after parathyroidectomy were assessed in relation to each histomorphometric parameter for cancellous bone, endocortical surface, intracortical surface and periosteal surface. The normal values of the histological indices for the cancellous, endocortical and intracortical surfaces were based on values obtained from 66 post-menopausal Caucasian women aged 65.2 ± 6.0 years, as reported by Han et al. [2]. Normal values for the periosteal surface were taken from the report of Balena et al. [9]. Although there were more male patients than female patients in both Group I and II in our study, the normal values of the post-menopausal Caucasian women were adopted. Increased bone remodelling due to oestrogen deficiency may lead to an increase in the values of bone formation parameters including osteoid-related parameters and bone formation rate (BFR/BS). Although statistical analyses could not be performed, QS/BS (20.6 ± 11.2%) and BFR/BS (0.015 ± 0.010 mm³/mm²/year) of the post-menopausal Caucasian women reported by Han et al. [2] seemed greater than those of the male subjects reported by Clarke et al. [18]. According to the report of the latter, the distribution of the OS/BS and BFR/BS values, respectively, in the male subjects according to the age was as follows: between 50 and 59 years, 10.4 ± 2.6% and 0.007 ± 0.002 mm³/mm²/year; between 60 and 69 years, 14.2 ± 2.3% and 0.011 ± 0.004 mm³/mm²/year; between

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**Fig. 1.** Cancellous and cortical bone at 1 week after parathyroidectomy (PTX). Osteoclast surface (Oc.S/BS) decreased to 0% and osteoblast surface (Ob.S/BS) significantly increased in cancellous bone at 1 week after PTX, but Oc.S/BS did not decrease to 0% on the endocortical, intracortical and periosteal surfaces in cortical bone. In addition, Ob.S/BS did not increase in cortical bone at 1 week after PTX. Oc, osteoclast; Ob, osteoblast; Fb, fibrous tissue.
Table 1. Differences in serum bone metabolism parameters between before and 1 week after parathyroidectomy (PTX) in Group I (n = 13), between before and 4 weeks after surgery in Group II (n = 11), and between 4 weeks and 12 weeks after surgery in Group II (n = 11)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I Before/1 week after PTX</th>
<th>Group II Before/4 weeks after PTX</th>
<th>Group II 12 weeks after PTX</th>
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</thead>
<tbody>
<tr>
<td>iPTH (pg/ml)</td>
<td>1282.1 ± 799.1/1469.7 ± 478.9</td>
<td>151.1 ± 21.0/15.1 ± 21.0</td>
<td>15.1 ± 21.0/15.1 ± 21.0</td>
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<tr>
<td>TRAP (U/l)</td>
<td>20.8 ± 9.2/15.2 ± 9.7</td>
<td>7.3 ± 3.7/7.3 ± 3.7</td>
<td>7.3 ± 3.7/7.3 ± 3.7</td>
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<tr>
<td>DPD (pmol/ml)</td>
<td>43.1 ± 44.5/384.7 ± 272.2</td>
<td>8.8 ± 3.1/8.8 ± 3.1</td>
<td>8.8 ± 3.1/8.8 ± 3.1</td>
</tr>
<tr>
<td>PICP (ng/ml)</td>
<td>244.7 ± 85.9/384.7 ± 272.2</td>
<td>384.7 ± 272.2/384.7 ± 272.2</td>
<td>1132.6 ± 551.0/1132.6 ± 551.0</td>
</tr>
<tr>
<td>Total ALP (U/l)</td>
<td>536.1 ± 454.0/483.4 ± 478.6</td>
<td>239.1 ± 171.9/239.1 ± 171.9</td>
<td>339.1 ± 171.9/339.1 ± 171.9</td>
</tr>
<tr>
<td>OC[1–49] (ng/ml)</td>
<td>410.9 ± 339.5/280.2 ± 103.4</td>
<td>132.6 ± 551.0/132.6 ± 551.0</td>
<td>239.1 ± 171.9/239.1 ± 171.9</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>9.9 ± 1.0/9.5 ± 0.8</td>
<td>10.8 ± 2.1/10.8 ± 2.1</td>
<td>10.8 ± 2.1/10.8 ± 2.1</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>6.5 ± 2.0/5.1 ± 1.4</td>
<td>3.2 ± 1.9/3.2 ± 1.9</td>
<td>3.2 ± 1.9/3.2 ± 1.9</td>
</tr>
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</table>

Data are represented as mean ± SD. P-values are based on Wilcoxon signed rank test. Serum iPTH, TRAP, DPD and P levels decreased significantly at 1 and 4 weeks after PTX. Serum iPTH, TRAP, and P levels increased again at 12 weeks after PTX. Although serum PICP and total ALP levels increased at 1 and 4 weeks after PTX, they significantly decreased at 12 weeks after PTX. iPTH, intact parathyroid hormone; TRAP, tartrate-resistant acid phosphatase; DPD, deoxypyridinoline; PICP, carboxy-terminal propeptide of type 1 procollagen; total ALP, total alkaline phosphatase; OC[1–49], intact osteocalcin; Ca, calcium; P, phosphorus. Data are presented as mean ± SD and were analysed by Wilcoxon signed rank test.

Statistical analysis

Differences of serum bone markers were assessed by comparison between before and 1 week after parathyroidectomy (n = 13) in Group I, or between before and 4 weeks after (n = 11), as well as between 4 and 12 weeks after (n = 11) in Group II (Table 1). Likewise, the differences in histomorphometric parameters were assessed between before and 1 week after surgery (n = 13) in Group I (Table 2), between before and 4 weeks after (n = 11) in Group II (Table 3), or between 4 and 12 weeks after (n = 6) in Group II (Table 4) for endocortical surface, intracortical surface, periosteal surface and cancellous bone by Wilcoxon signed rank test. In addition, statistical differences were assessed by Student’s t-test in the study of Ca supplementation. All results are expressed as the mean ± SD and a P-value <0.05 was considered to indicate statistical significance.

Results

Serum bone metabolism parameters

Group I (n = 13). Serum levels of iPTH, TRAP and DPD all decreased after parathyroidectomy. Although total ALP and PICP levels increased significantly, that of OC [1–49] decreased. Ca level did not change postoperatively probably due to vitamin D and Ca supplementation, but P-level was decreased at 1 week after parathyroidectomy (Table 1, Figure 2).

Group II (n = 11). Serum iPTH decreased at 4 weeks after surgery, along with a significant decrease of...
Table 2. Differences in static histomorphometric parameters of iliac bone between before and 1 week after parathyroidectomy (PTX) in Group I

<table>
<thead>
<tr>
<th></th>
<th>Oc.S/BS (%)</th>
<th>ES/BS (%)</th>
<th>Fb.V/BS (mcm²/mcm)</th>
<th>Ob.S/BS (%)</th>
<th>OS/BS (%)</th>
<th>O.Th (mcm)</th>
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<tr>
<td><strong>Endo</strong></td>
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<tr>
<td>Before/1 week after PTX</td>
<td>5.3 ± 2.5/0.5 ± 0.7</td>
<td>27.0 ± 8.9/11.6 ± 10.0</td>
<td>21.0 ± 23.0/12.0 ± 16.8</td>
<td>27.2 ± 12.7/37.5 ± 21.6</td>
<td>55.6 ± 18.2/64.0 ± 23.8</td>
<td>10.4 ± 3.2/12.5 ± 5.6</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.003</td>
<td>0.002</td>
<td>0.314</td>
<td>0.064</td>
<td>0.039</td>
<td>0.087</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.4 ± 1.7</td>
<td>9.6 ± 5.2</td>
<td>6.0 ± 7.1</td>
<td>24.4 ± 14.4</td>
<td>(−)</td>
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<td><strong>Intra</strong></td>
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<tr>
<td>Before/1 week after PTX</td>
<td>4.7 ± 3.4/1.3 ± 1.3</td>
<td>29.0 ± 12.6/15.5 ± 8.1</td>
<td>15.5 ± 17.6/8.8 ± 8.9</td>
<td>18.0 ± 10.8/27.4 ± 21.7</td>
<td>39.0 ± 15.7/51.0 ± 28.2</td>
<td>10.2 ± 3.0/9.7 ± 3.3</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.004</td>
<td>0.028</td>
<td>0.308</td>
<td>0.152</td>
<td>0.345</td>
<td>0.701</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0 ± 0.8</td>
<td>6.3 ± 4.8</td>
<td>5.9 ± 3.4</td>
<td>18.7 ± 7.9</td>
<td>(−)</td>
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<td><strong>Peri</strong></td>
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<tr>
<td>Before/1 week after PTX</td>
<td>3.7 ± 2.9/0.1 ± 0.5</td>
<td>24.4 ± 10.0/11.4 ± 9.9</td>
<td>6.1 ± 8.0/5.0 ± 9.1</td>
<td>18.7 ± 16.7/36.1 ± 19.9</td>
<td>51.7 ± 20.1/73.3 ± 23.9</td>
<td>13.4 ± 3.5/17.6 ± 6.0</td>
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<tr>
<td><em>P</em></td>
<td>0.003</td>
<td>0.011</td>
<td>0.124</td>
<td>0.002</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0 ± 0.8</td>
<td>7.7 ± 3.3</td>
<td>6.0 ± 4.0</td>
<td>20.6 ± 11.2</td>
<td>(−)</td>
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</tbody>
</table>

Data are represented as mean ± SD. *P*-values are based on Wilcoxon signed rank test.

Oc.S/BS decreased significantly on the endocortical surface, but did not decrease to zero. Oc.S/BS was still above the normal value after PTX on the intracortical and periosteal surfaces. Fb.V/BS and Fb.V/TV did not decrease significantly in cortical and cancellous bone after PTX. Ob.S/BS significantly increased in cancellous bone, but not on the three surfaces in cortical bone.

Oc.S/BS, osteoclast surface; ES/BS, eroded surface; Fb.V/TV, fibrosis volume for cancellous bone; Fb.V/BS, fibrosis volume for the three surfaces in cortical bone; Ob.S/BS, osteoblast surface; OS/BS, osteoid surface; O.Th, osteoid thickness; Endo, endocortical surface; Intra, intracortical surface; Peri, periosteal surface.
Table 3. Differences of static histomorphometric parameters of iliac bone between before and 4 weeks after parathyroidectomy (PTX) in Group II

<table>
<thead>
<tr>
<th>Surface</th>
<th>Oc.S/BS (%)</th>
<th>ES/BS (%)</th>
<th>Fb.V/BS (mcm²/mcm)</th>
<th>Ob.S/BS (%)</th>
<th>OS/BS (%)</th>
<th>O.Th (mcm)</th>
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<tbody>
<tr>
<td><strong>Endo</strong></td>
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<tr>
<td>Before/4 weeks after PTX</td>
<td>5.1±3.9/0.1±0.3</td>
<td>24.8±14.5/5.7±6.1</td>
<td>8.0±11.3/0.6±1.4</td>
<td>28.4±14.6/44.4±23.8</td>
<td>49.6±24.2/82.6±13.5</td>
<td>11.4±6.2/15.5±7.0</td>
</tr>
<tr>
<td>P</td>
<td>0.004</td>
<td>0.008</td>
<td>0.007</td>
<td>0.041</td>
<td>0.004</td>
<td>0.006</td>
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<tr>
<td><strong>Intra</strong></td>
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<td></td>
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</tr>
<tr>
<td>Before/4 weeks after PTX</td>
<td>4.5±4.4/0.6±1.4</td>
<td>27.8±16.9/8.3±7.8</td>
<td>12.1±12.4/3.1±4.5</td>
<td>22.7±12.8/36.2±20.9</td>
<td>37.3±17.0/63.4±25.1</td>
<td>10.7±5.9/16.2±7.1</td>
</tr>
<tr>
<td>P</td>
<td>0.026</td>
<td>0.013</td>
<td>0.028</td>
<td>0.021</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Peri</strong></td>
<td></td>
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</tr>
<tr>
<td>Before/4 weeks after PTX</td>
<td>1.3±1.4/0.3±0.6</td>
<td>14.5±14.0/12.8±15.4</td>
<td>2.0±3.9/0.1±0.2</td>
<td>9.6±9.7/7.6±8.9</td>
<td>52.4±24.2/56.6±31.3</td>
<td>10.3±2.9/12.0±3.1</td>
</tr>
<tr>
<td>P</td>
<td>0.058</td>
<td>0.386</td>
<td>0.144</td>
<td>0.139</td>
<td>0.859</td>
<td>0.109</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0±0.8</td>
<td>6.3±4.8</td>
<td>0</td>
<td>5.9±3.4</td>
<td>18.7±7.9</td>
<td>(−)</td>
</tr>
<tr>
<td><strong>Cancellous bone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before/4 weeks after PTX</td>
<td>4.6±3.8/0</td>
<td>29.2±11.0/3.4±2.9</td>
<td>6.9±4.8/0.7±1.6</td>
<td>21.7±9.0/12.1±13.7</td>
<td>55.6±18.0/81.7±17.6</td>
<td>15.6±8.4/21.1±10.3</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>0.004</td>
<td>0.004</td>
<td>0.026</td>
<td>0.009</td>
<td>0.006</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0±0.8</td>
<td>7.7±3.3</td>
<td>0</td>
<td>6.0±4.0</td>
<td>20.6±11.2</td>
<td>(−)</td>
</tr>
</tbody>
</table>

Data are represented as mean±SD. P-values are based on Wilcoxon signed rank test.

Oc.S/BS significantly decreased on the endocortical and intracortical surfaces, but it did not decrease to 0%. Oc.S/BS decreased to 0% in cancellous bone. Ob.S/BS decreased in cancellous bone, but it increased on the endocortical and intracortical surfaces at 4 weeks after PTX. OS/BS and O.Th increased on the endocortical and intracortical surfaces as well as in cancellous bone. Bone formation parameters including Ob.S/BS, OS/BS and O.Th did not change on the peristeal surface. Oc.S/BS, osteoclast surface; ES/BS, eroded surface; Fb.V/Tv, fibrosis volume for cancellous bone; Fb.V/BS, fibrosis volume for the three surfaces in cortical bone; Ob.S/BS, osteoblast surface; OS/BS, osteoid surface; O.Th, osteoid thickness; Endo, endocortical surface; Intra, intracortical surface; Peri, peristeal surface.
Table 4. Differences of static histomorphometric parameters of iliac bone between 4 weeks and 12 weeks after parathyroidectomy (PTX) in Group II ($n = 6$)

<table>
<thead>
<tr>
<th></th>
<th>Oc.S/BS (%)</th>
<th>ES/BS (%)</th>
<th>Fb.V/BS (mcm$^2$/mcm)</th>
<th>Ob.S/BS (%)</th>
<th>OS/BS (%)</th>
<th>O.Th (mcm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4 weeks/12 weeks after PTX</td>
<td>0.0/0.2 ± 0.5</td>
<td>9.8 ± 5.4/4.2 ± 6.3</td>
<td>0.9 ± 2.3/0.2 ± 0.5</td>
<td>33.4 ± 16.2/7.2 ± 1.8</td>
<td>74.7 ± 13.8/72.8 ± 15.1</td>
<td>11.3 ± 3.6/12.3 ± 2.3</td>
</tr>
<tr>
<td>$P$</td>
<td>0.363</td>
<td>0.046</td>
<td>0.493</td>
<td>0.046</td>
<td>0.753</td>
<td>0.249</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.4 ± 1.7</td>
<td>9.6 ± 5.2</td>
<td>0</td>
<td>6.9 ± 7.1</td>
<td>24.4 ± 14.4</td>
<td>(--)</td>
</tr>
<tr>
<td><strong>Intra</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4 weeks/12 weeks after PTX</td>
<td>1.4 ± 2.2/0.5 ± 0.3</td>
<td>12.5 ± 7.6/6.4 ± 3.6</td>
<td>1.9 ± 3.1/0</td>
<td>33.3 ± 20.9/11.8 ± 8.1</td>
<td>56.7 ± 27.1/65.8 ± 13.3</td>
<td>11.8 ± 4.4/18.0 ± 8.9</td>
</tr>
<tr>
<td>$P$</td>
<td>0.249</td>
<td>0.345</td>
<td>0.285</td>
<td>0.075</td>
<td>0.345</td>
<td>0.046</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0 ± 0.8</td>
<td>6.3 ± 4.8</td>
<td>0</td>
<td>5.9 ± 3.4</td>
<td>18.7 ± 7.9</td>
<td>(--)</td>
</tr>
<tr>
<td><strong>Peri</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks/12 weeks after PTX</td>
<td>0/1.2 ± 2.4</td>
<td>11.2 ± 18.3/9.3 ± 18.5</td>
<td>0.1 ± 0.3/0</td>
<td>10.0 ± 10.0/0</td>
<td>61.9 ± 34.1/63.8 ± 31.1</td>
<td>11.8 ± 2.7/12.4 ± 3.3</td>
</tr>
<tr>
<td>$P$</td>
<td>0.295</td>
<td>0.345</td>
<td>0.363</td>
<td>0.08</td>
<td>0.917</td>
<td>0.834</td>
</tr>
<tr>
<td>Normal values</td>
<td>0.11 ± 0.04</td>
<td>11.2 ± 1.29</td>
<td>0</td>
<td>2.34 ± 0.36</td>
<td>23.5 ± 1.96</td>
<td>6.83 ± 0.36</td>
</tr>
<tr>
<td><strong>Cancellous bone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks/12 weeks after PTX</td>
<td>0/0</td>
<td>4.2 ± 3.5/2.0 ± 1.6</td>
<td>0.8 ± 2.0/0</td>
<td>5.4 ± 2.4/0.7 ± 0.3</td>
<td>72.2 ± 19.2/79.3 ± 20.7</td>
<td>19.1 ± 8.1/19.8 ± 11.7</td>
</tr>
<tr>
<td>$P$</td>
<td>(--)</td>
<td>0.249</td>
<td>0.352</td>
<td>0.046</td>
<td>0.463</td>
<td>0.917</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.0 ± 0.8</td>
<td>7.7 ± 3.3</td>
<td>0</td>
<td>6.0 ± 4.0</td>
<td>20.6 ± 11.2</td>
<td>(--)</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SD. Statistical analysis was not performed because of the small number of the patients.

Although Oc.S/BS did not decrease to 0% on the three surfaces in cortical bone at 12 weeks after PTX, it was 0% in cancellous bone at 4 and 12 weeks after PTX. The mean of Ob.S/BS decreased in cancellous and cortical bone at 12 weeks after PTX. Oc.S/BS, osteoclast surface; ES/BS, eroded surface; Fb.V/TV, fibrosis volume for cancellous bone; Fb.V/BS, fibrosis volume for the three surfaces in cortical bone; Ob.S/BS, osteoblast surface; OS/BS, osteoid surface; O.Th, osteoid thickness; Endo, endocortical surface; Intra, intracortical surface; Peri, periosteal surface.
Fig. 2. Changes of serum bone metabolism parameters after PTX. Serum parameters were measured before and 1 week after PTX in Group I (●), as well as before and 4 and 12 weeks after surgery in Group II (○). Changes of serum intact parathyroid hormone (iPTH) (Figure 2A), tartrate-resistant acid phosphatase (TRAP) (Figure 2B), deoxypyridinoline (DPD) (Figure 2C), carboxy-terminal propeptide of type I procollagen (PICP) (Figure 2D), total alkaline phosphatase (total ALP) (Figure 2E), and intact osteocalcin (OC[1–49]) (Figure 2F) levels after PTX in Group I and II were indicated, respectively. Serum iPTH, TRAP and DPD decreased at 1 and 4 weeks after PTX, while iPTH and TRAP levels were significantly higher at 12 weeks than those at 4 weeks. Serum PICP and total ALP levels increased at 1 and 4 weeks after PTX, while serum PICP, total ALP and OC[1–49] decreased significantly at 12 weeks after PTX.
TRAP and DPD. Subsequently, iPTH increased again at 12 weeks, along with a concordant increase of TRAP. Although PICP and total ALP increased at 4 weeks postoperatively, these markers decreased again by 12 weeks. OC [1–49] did not change at 4 and decreased at 12 weeks. Although P-level decreased significantly at 4 weeks, it increased again (like PTH) at 12 weeks after parathyroidectomy (Table 1, Figure 2).

**Bone histomorphometry**

**Group I (Before vs 1 week after parathyroidectomy; n = 13).** Endocortical surface. Oc.S/BS showed a significant decrease, but osteoclasts were still detected in four out of 13 patients (Table 2, Figure 3C). Bone formation parameters, except for OS/BS, did not change after parathyroidectomy (Table 2, Figure 3D).

Intracortical surface. Oc.S/BS was significantly decreased, although osteoclasts were still observed in eight out of 13 patients (Table 2, Figures 1 and 3E). None of the formation parameters showed any changes (Table 2, Figure 3F).

Periosteal surface. Static parameters were unchanged at 1 week after surgery (Table 2, Figures 3G and H).

Cancellous bone. Oc.S/BS decreased to 0% in all except one patient and no osteoclasts were seen in the 12 patients, although Fb.V/TV did not change significantly (Table 2, Figure 3A). Ob.S/BS increased from 18.7 ± 16.7 to 36.1 ± 19.9% (P = 0.002), and both OS/BS and O.Th also increased (Table 2, Figures 1 and 3B).

**Group II: (Before vs 4 weeks after parathyroidectomy; n = 11).** Endocortical surface. Oc.S/BS, ES/BS and Fb.V/BS all showed a significant decrease at 4 weeks postoperatively, and osteoclasts were observed only in two of the 11 patients (Table 3, Figure 4C). Ob.S/BS increased from 28.4 ± 14.6 to 44.4 ± 23.8% (P = 0.041) (Table 3, Figure 4D). In addition, both OS/BS and O.Th significantly increased at 4 weeks after compared with before surgery (Table 3).

Intracortical surface. Oc.S/BS, ES/BS, and Fb.V/BS significantly decreased at 4 weeks after parathyroidectomy, but osteoclasts were still observed in two out of 11 patients (Table 3, Figure 4E). Ob.S/BS, OS/BS and O.Th significantly increased at 4 weeks (Table 3, Figure 4F).

Periosteal surface. Oc.S/BS, ES/BS and Fb.V/BS did not decrease at 4 weeks, and osteoclasts were still observed in two out of 11 patients (Table 3, Figure 4G), while Ob.S/BS, OS/BS and O.Th showed no changes (Table 3, Figure 4H).

Cancellous bone. Oc.S/BS decreased to 0% at 4 weeks postoperatively (Table 3, Figure 4A) and ES/BS and Fb.V/TV were significantly decreased. Although Ob.S/BS transiently increased at 1 week in Group I, it was again below the preoperative level at 4 weeks after parathyroidectomy (before vs 4 weeks after parathyroidectomy = 21.7 ± 9.0 vs 12.1 ± 13.7% (P = 0.026) (Table 3, Figure 4B). Both OS/BS and O.Th increased at 4 weeks after surgery.

**Group II: (Four weeks vs 12 weeks after parathyroidectomy; n = 6).** Oc.S/BS of the three surfaces of cortical bone increased at 12 weeks in some patients. After 12 weeks, Ob.S/BS decreased on the endocortical surface (P = 0.046) and in cancellous bone (P = 0.046) in all six patients (Table 4, Figures 4B and D). OS/BS and O.Th did not increase again at 12 weeks.

The relationships of serum PTH and Oc.S/BS before parathyroidectomy with the dose of Ca supplementation after surgery

The dose of Ca supplementation during the first week after surgery in Group A was smaller than that in Group B (6.4 ± 4.6 vs 12.6 ± 6.4 g/week, P = 0.02). In addition, serum iPTH before parathyroidectomy was lower in Group C than in Group D (988.8 ± 319.7 vs 1559.8 ± 822.5 pg/ml, P = 0.04). Oc.S/BS of Group C was smaller than that of Group D before parathyroidectomy (2.8 ± 2.9 vs 5.4 ± 3.3%, P = 0.05).

**Discussion**

Although bone resorption ceased abruptly in cancellous bone after parathyroidectomy, osteoclasts were still observed in cortical bone. At 1 week postoperatively, the mean values of Oc.S/BS for the intracortical and periosteal surfaces were still above the mean of normal values reported by Han et al. [2] and Balena et al. [9] in spite of the extremely low iPTH levels. Since the patients received alfalcacidol at doses of 2.0 µg/day or below 2.0 µg/day after parathyroidectomy, depending on their serum Ca level [5,6], it was assumed that the plasma 1,25-(OH)2D3 level would increase to nearly the upper limit of the normal range [5], suppressing bone resorption and not increasing it [19]. Despite low iPTH levels, high doses of Ca administration, and maintenance of 1,25-(OH)2D3 within the normal range, bone resorption was not completely suppressed in cortical bone [19,20]. Moreover, although Oc.S/BS was 0% in cancellous bone in all six patients and the differences of Oc.S/BS between the three surfaces of cortical bone and cancellous bone were not significant at 12 weeks (P-value of the difference between the endocortical surface and cancellous bone was 0.363, that of the difference between the intracortical surface and cancellous bone was 0.07, and that of the difference between the periosteal surface and cancellous bone was 0.295, n = 6), Oc.S/BS surprisingly increased on the three surfaces in cortical bone in some patients at 12 weeks. In particular, P-value of the difference between the intracortical surface and cancellous bone was 0.07. It is probably because the number of the
Fig. 3. Changes of Oc.S/BS and Ob.S/BS for the four surfaces (endocortical surface, intracortical surface of the intracortical resorption spaces, periosteal surface in cortical bone and cancellous surface in cancellous bone) at 1 week after PTX in Group I. (Changes of Oc.S/BS in cancellous bone (Figure 3A), Ob.S/BS in cancellous bone (Figure 3B), Oc.S/BS on the endocortical surface (Figure 3C), Ob.S/BS on the endocortical surface (Figure 3D), Oc.S/BS on the intracortical surface (Figure 3E), Ob.S/BS on the intracortical surface (Figure 3F), Oc.S/BS on the periosteal surface (Figure 3G), and Ob.S/BS on the periosteal surface (Figure 3H) were indicated, respectively.) Oc.S/BS decreased significantly at 1 week after PTX, except on the periosteal surface. Ob.S/BS significantly increased in only cancellous bone after PTX.
Fig. 4. Changes of Oc.S/BS and Ob.S/BS for the four surfaces at 4 and 12 weeks after PTX in Group II. (Changes of Oc.S/BS in cancellous bone (Figure 4A), Ob.S/BS in cancellous bone (Figure 4B), Oc.S/BS on the endocortical surface (Figure 4C), Ob.S/BS on the endocortical surface (Figure 4D), Oc.S/BS on the intracortical surface (Figure 4E), Ob.S/BS on the intracortical surface (Figure 4F), Oc.S/BS on the periosteal surface (Figure 4G), and Ob.S/BS on the periosteal surface (Figure 4H) were indicated, respectively.) Oc.S/BS decreased on all surfaces at 4 weeks after PTX, except on the periosteal surface. Although Ob.S/BS increased transiently at 1 week after PTX in Group I (Figure 3B), it significantly decreased in cancellous bone at 4 weeks. And it also decreased at 12 weeks after PTX in all patients. Ob.S/BS significantly increased on the endocortical and intracortical surface at 4 weeks after PTX. And then it also decreased on the endocortical surface in all patients at 12 weeks after PTX.
patients is too small and that may be clinically significant. Therefore, it may be too difficult to suppress bone resorption completely in cortical bone within 12 weeks after parathyroidectomy.

Oc.S/BS abruptly decreased to essentially zero at 1 week and until 12 weeks after parathyroidectomy in cancellous bone, and serum iPTH was extremely suppressed during 1 to 4 weeks (Table 1). However, serum TRAP and DPD decreased progressively during the first 4 weeks after parathyroidectomy, which is concomitant with the progressive decline in the Oc.S/BS on the two surfaces except for the periosteal surface in cortical bone. Therefore, it is apparent that changes of serum resorption parameters lag behind those of histomorphometric parameters, and it is possible that the slower rate of reduction of serum TRAP and DPD might also reflect both the production of TRAP and DPD by other tissues other than bone tissue and the slower reduction of Oc.S/BS in cortical bone.

In addition, concordant with a significant increase of serum iPTH from week 4 to week 12, TRAP also increased along with a simultaneous re-increase of Oc.S/BS on the endocortical and periosteal surfaces in some patients (Figures 2B,4C and G).

Ob.S/BS increased significantly and maximally at 1 week after parathyroidectomy and then decreased in cancellous bone, whereas Ob.S/BS of the endocortical and intracortical surfaces, but not of the periosteal surface, showed a progressive increase up to 4 weeks. In particular, a 37% increase in Ob.S/BS of the endocortical surface ($P=0.064$) at 1 week in only 13 patients, could express a clinically (but not statistically) significant increase in bone formation. Since Ob.S/BS decreased to a value below the pre-surgical level in cancellous bone until 4 weeks after surgery, the sustained increase of the serum levels of total ALP and PICP could be explained by the sustained increase of Ob.S/BS of the endocortical and intracortical surfaces (Table 3, Figures 4D and F). Alternative explanation is that the enhanced expression of transforming growth factor-$\beta$ (TGF-$\beta$) by osteoblasts and in osteoid seams at 1 week after parathyroidectomy, which was demonstrated in another study by positive immunohistochemical staining of the osteoid seams for TGF-$\beta$, might have suppressed the production of osteocalcin (Table 1, Figure 2F) [5].

As a result of the assessment of the difference between Group A and Group B or between Group C and Group D, it was found that large doses of Ca supplementation were needed after parathyroidectomy in patients with more severe hyperparathyroidism. It is because Ca is released from bone to blood due to osteoclastic bone resorption before parathyroidectomy, but the release of Ca is sustained after surgery, resulting in the more severe decline of serum Ca levels in patients with severe secondary hyperparathyroidism [5].

Osteoclast surface in cancellous bone is transformed to osteoblast surface after parathyroidectomy [5] and the cement line between old mineralized bone and newly formed mineralized bone are irregular (scalloped) lines and because osteoclasts are detected on the lines before surgery. The total cancellous surface is much longer than the three surfaces in cortical bone [1,2], namely, bone surface per bone volume (BS/BV) in cancellous bone is 4 times longer than in cortical bone in healthy young women. Thus, the absolute number of osteoclasts per bone volume should be much larger in cancellous bone before surgery. These results indicate the magnitude of the increase of Ob.S/BS which was estimated to be greater in cancellous bone than in cortical bone. No significant increase of Ob.S/BS on the periosteal surface could be detected in this study. The incomplete and delayed suppression of bone resorption after parathyroidectomy should lead to an incomplete and tardier increase of Ob.S/BS in cortical bone. The only variable that measures changes in bone formation is Ob.S/BS. In fact, Ob.S/BS increased at 1 week in cancellous bone and at 4 weeks at the endocortical and intracortical surfaces. And Ob.S/BS significantly decreased again at 12 weeks (Table 4, Figures 4B and D), indicating that bone formation increased transiently after parathyroidectomy. OS/BS and O.Th are useless in this respect: an increase in osteoid tissue can express either increased bone formation, or reduced mineralization. But according to tetracycline labelling performed at 4 weeks after parathyroidectomy in some patients, there were many vague or diffuse labellings seen in the patients, indicating that bone formation rate was decreased after parathyroidectomy [11]. The increased remodelling of cortical bone accounts for the delayed apoptosis of osteoclasts, leading to greater bone loss [16]. The retention of bone resorption in cortical bone may be responsible for the smaller increase of BMD in cortical bone after parathyroidectomy [8].

It is important that lack of periosteal bone gain could also contribute to a smaller gain of BMD in cortical bone. Cortical thickness is the result of the net effects of both the endocortical and periosteal bone turnover. The present study showed that renal hyperparathyroidism destroyed endocortical bone, and that parathyroidectomy reduced endocortical bone loss and increased bone formation. Nothing much happened at the periosteal surface after operation, and changes after operation were marginal. Thus, parathyroidectomy should improve cortical thinning, mainly by increasing the endocortical and intracortical bone although the degree of the gain of BMD may be smaller in cortical bone than in cancellous bone. Because low BMD is often associated with increased odds of bone fracture, continued attention should be paid to the uraemic patients soon after parathyroidectomy.

Changes of bone markers reflected net changes of metabolism in cortical and cancellous bone metabolism. Even parathyroidectomy could not completely stop bone resorption, and only a transient increase of bone formation on the endocortical and intracortical surfaces was observed, suggesting
that cortical bone loss associated with uraemic
hyperparathyroidism cannot be completely compen-
sated. Therefore, treatment of secondary hyperpara-
thyroidism should be provided at the stage of
the disease before the greater cortical bone loss.

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Conflict of interest statement. None declared.

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