Clinical Study

Serum Bone Resorption Markers after Parathyroidectomy for Renal Hyperparathyroidism: Correlation Analyses for the Cross-Linked N-telopeptide of Collagen I and Tartrate-Resistant Acid Phosphatase

Kuo-Chin Hung,1 Chung-Yu Huang,2 Chuan-Chieh Liu,1 Chih-Jen Wu,3 Shao-Yuan Chen,1 Pauling Chu,4 Chia-Chao Wu,4 Lan Lo,1 Liang-Kuang Diang,4 and Kuo-Cheng Lu1

1 Department of Medicine, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, No. 510, Zhongzheng Road, Xinzhuang District, New Taipei City 24205, Taiwan
2 Department of Medicine, Show-Chwan Memorial Hospital and Department of Nursing, Meiho University, 542, Sec. 1 Chung-shan Road, Changhua 50008, Taiwan
3 Division of Nephrology, Mackay Memorial Hospital and Department of Pharmacology, Taipei Medical University, No. 252, Wu-Hsing Street, Taipei City 11031, Taiwan
4 Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Chenggong Road, Neihu District, Taipei City 11490, Taiwan

Correspondence should be addressed to Kuo-Cheng Lu, kuochenglu@gmail.com

Received 11 May 2012; Accepted 5 June 2012

Academic Editors: K. D. Burns and K. Furuichi

Copyright © 2012 Kuo-Chin Hung et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Patients on long-term dialysis may develop secondary hyperparathyroidism (SHPT) with increased serum concentrations of bone resorption markers such as the cross-linked N-telopeptide of type I collagen (NTX) and type-5b tartrate-resistant acid phosphatase (TRAP). When SHPT proves refractory to treatment, parathyroidectomy (PTX) may be needed. Renal patients on maintenance HD who received PTX for refractory SHPT (n = 23) or who did not develop refractory SHPT (control subjects; n = 25) were followed prospectively for 4 weeks. Serum intact parathyroid hormone (iPTH), NTX, TRAP, and bone alkaline phosphatase (BAP) concentrations were measured serially and correlation analyses were performed. iPTH values decreased rapidly and dramatically. BAP values increased progressively with peak increases observed at 2 weeks after surgery. NTX and TRAP values decreased concurrently and progressively through 4 weeks following PTX. A significant correlation between TRAP and NTX values was observed before PTX but not at 4 weeks after PTX. Additionally, the fractional changes in serum TRAP were larger than those in serum NTX at all times examined after PTX. Serum iPTH, TRAP, and NTX values declined rapidly following PTX for SHPT. Serum TRAP values declined to greater degrees than serum NTX values throughout the 4-week period following PTX.

1. Introduction

Secondary hyperparathyroidism (SHPT), a common complication of chronic renal disease and of end-stage renal disease under dialysis, results from vitamin D deficiency, impaired mineral metabolism, and decreased serum erythropoietin values [1–3]. Serum parathyroid hormone (PTH) concentrations are elevated such that bone demineralization and bone turnover are enhanced, a condition characterized by the predominance of bone resorption over bone formation [4, 5]. Patients with SHPT are therefore typically treated with vitamin D analogues or calcimimetics. When SHPT is resistant to such treatments, parathyroidectomy (PTX) is indicated; substantial increases in bone mineral density are observed following this surgery [6, 7].

Bone remodeling normally begins with the creation of resorption pits by osteoclasts, followed by osteoclast apoptosis, osteoblast formation, and mineralization [8, 9]. However,
this form of remodeling is not observed in patients who have undergone PTX. The pathophysiology of the “hungry bone syndrome” observed after PTX is similar to the bone marrow ablation model used to investigate osteogenic capacity [10, 11]. Accordingly, PTX induces an initial rapid and prominent activation of bone synthetic activity, followed by a suppression of osteoclast activity which persists for at least one year [12].

Several enzymes and type I collagen fragments released during bone formation or resorption have recently been proposed as markers of bone remodeling. Type-5b tartrate-resistant acid phosphatase (TRAP) is an osteoclast-specific enzyme released during the process of bone resorption, and serum concentrations of the enzyme have been found to correlate directly with the number of osteoclasts in bone biopsies. TRAP is therefore proposed to serve as a marker of bone resorption in renal disease [13]. The cross-linked N-telopeptide of type I collagen (NTX), another marker of osteoclastic bone resorption, is measurable in urine or serum [14]. Although renal disease precludes urinary measurements of NTX for hemodialysis (HD) patients, measurement of serum NTX should serve as a valid marker of the bone resorption state for such patients [15].

Persistent suppression of osteoclast function is well-established to follow PTX. However, the relative dispositions of TRAP and NTX and their relationships to other markers of bone resorption have not been established following the surgery. The following study was undertaken to determine serum concentrations of iPTH, NTX, and TRAP at various times following PTX. The main objective was to ascertain whether the post-surgical concentrations of TRAP and NTX are interrelated.

2. Methods

2.1. Patients. A total of 48 patients receiving long-term hemodialysis therapy were enrolled in this study, which included 23 subjects with refractory SHPT and 25 subjects who did not develop refractory SHPT (control subjects). Informed consent was secured from all subjects. Patients deemed eligible were between 32 and 72 years of age. Control subjects had serum iPTH values <300 pg/mL; gender and age distributions for the control group were similar to those of the study group. Patients with refractory SHPT were known to have end-stage renal disease of at least 3 months duration and were receiving maintenance HD three times weekly. None of the patients in this study exhibited signs of malnutrition and all had serum aluminum values below 1.0 µmol/L. The study was approved by the Institutional Review Board of the Cardinal Tien and Tri-Service General Hospitals (Taipei, Taiwan).

PTX was considered necessary when (a) optimal medical and dietary treatments for hyperparathyroidism were unsuccessful, (b) high serum iPTH values persisted, and (c) drug-resistant hyperphosphatemia, hypercalcemia, severe osteopathy, vascular calcification, and calciphylaxis were observed. Exclusion criteria included the presence of adynamic bone disease, recent infection, chronic obstructive pulmonary disease, malignant disease, chronic alcoholism, gastrointestinal disease, coronary artery disease, or use of mineralocorticoids, immunosuppressants, or anabolic agents [16, 17]. Patients who had received a renal transplant were also excluded.

The known causes of renal failure were diabetic nephropathy (n = 6), hypertensive nephrosclerosis (n = 2), chronic glomerulonephritis (n = 8), polycystic kidney disease (n = 1), and analgesic nephropathy (n = 1). Five subjects had renal failure of unknown cause. No subject had received an aluminum-containing phosphate binder for at least one year prior to surgery.

2.2. Parathyroidectomy (PTX). After performance of total PTX, resected parathyroid tissue was divided into pieces of approximately 1 mm in diameter, and a single piece (100 mg of tissue) was auto-transplanted into the subcutaneous fat of one forearm. Following PTX and transplantation of parathyroid tissue, serum iPTH values were <100 pg/mL and serum calcium values were maintained at approximately 8 to 9 mg/dL. If iPTH subsequently rose to values >100 pg/mL, serum calcium was maintained at approximately 9 to 10 mg/dL by administration of low-dose active vitamin D and calcium salts to prevent recurrent HPT. When iPTH values fell below 70 pg/mL, the vitamin D treatment was interrupted to avoid adynamic bone disease [18].

No supplementation with vitamin D was provided to any patient for at least one month preceding surgery. Postoperatively, all subjects received oral calcitriol (1,25(OH)2 vitamin D3, 2.0 µg/d) [19]. Otherwise, intravenous calcium gluconate was administered postoperatively as needed. Some patients received oral calcium supplements at established daily doses. No cases of permanent hypoparathyroidism were observed.

2.3. Biochemical Parameters and Serum Bone Resorption Markers. To obtain baseline values, fasting (10 h) blood samples were collected between 8:00 and 9:00 AM preoperatively on the day of PTX (D0). Post-PTX blood samples were collected at 24 and 72 h (D2 and D4, resp.) and at 1, 2, and 4 weeks (W1, W2 and W4, resp.) after the surgery. To harvest serum, blood samples were subjected to centrifugation for 30 min. Serum was obtained within 1 h and stored at −30°C until use for measurements of iPTH, calcium, phosphate, and other bone metabolism parameters.

Serum iPTH concentrations were measured using a two-site immunoradiometric assay (Nichols Institute diagnostics, San Juan Capistrano, CA, USA) which detects the biologically intact 84-amino-acid chain of PTH. Total calcium (TCa), serum phosphate (Pi), alkaline phosphatase, and albumin were determined with an AU5000 automated chemistry analyzer (Olympus, Tokyo, Japan). Serum aluminum was measured by atomic absorption spectrometry in a graphite oven. Serum NTX concentrations were measured using an ELISA kit (OSTEOMARK; Mochida pharmaceutical Co., Tokyo, Japan); this marker is measured spectrophotometrically and its concentration is determined from a standard calibration curve. Normal NTX values ranged between 6.2 and 19.0 nM bone collagen equivalents/L (BCE/L) for premenopausal women and between 5.4 and 24.2 nM BCE/L for men. Serum TRAP activity was assayed in multi-well plates in the presence of monoclonal antibody
The relationship between parameters was linear. Spearman's simple regression analysis was used to ascertain whether (ANCOVA) test after adjusting for age and sex. Univariate groups were evaluated using the analysis of covariance as the means ± SD, and categorical values are expressed in percentages. The Shapiro-Wilk test was employed to assess the normality of sample distribution. Differences between groups were evaluated using the analysis of covariance (ANCOVA) test after adjusting for age and sex. Univariate simple regression analysis was used to ascertain whether the relationship between parameters was linear. Spearman's correlation coefficients were calculated assuming nonnormal distribution. A P value of <0.05 was considered statistically significant. All statistical tests were performed with the statistical package for social sciences (SPSS, version 17.0) for Windows (SPSS Inc, Chicago, IL, USA).

### 3. Results

#### 3.1. Characteristics of the Study Subjects.

General characteristics, clinical variables, and biochemical parameters of the control and study groups are shown in Table 1. Compared to the control group, patients with SHPT had higher baseline (pre-PTX, D0) values for iPTH, NTX, TRAP, BAP, TCa, and Pi. At 4 weeks following PTX for subjects with SHPT (W4), serum iPTH, NTX, TRAP, and Pi values decreased significantly. Table 1 also presents the fractional changes (FC, %) in serum bone marker concentrations between D0 and W4.

#### 3.2. Serum Biochemical Parameter Changes before and after Parathyroidectomy.

Figure 1 presents serum values for NTX, iPTH, TRAP, and BAP for the study group at D0, D2, D4, W1, W2, W3, and W4. iPTH declined sharply after PTX, with minimum values observed at D2 (D0: 1293.3 ± 591.9 pg/mL; W2: 65.2 ± 44.5 pg/mL; P < 0.001; panel (a)). NTX values declined rapidly during the first week post-PTX but more slowly during subsequent weeks (D0: 1227.3 ± 559.5 nM BCE/L; W4: 152.6 ± 56.1 nM BCE/L; P < 0.001; panel (b)). TRAP values also declined rapidly during the first week post-PTX but more slowly during subsequent weeks (D0: 5.27 ± 2.81 U/L; W4: 2.81 ± 0.61 U/L; P < 0.001; panel (c)).

### Table 1: Clinical variables and biochemical parameters for the control group and for the parathyroidectomy (PTX) group before and 4 weeks after the surgery.

|                         | PTX (n = 23) | Control (n = 25) |
|-------------------------|--------------|-----------------|
| Age, y                  | 49.3 ± 10.8  | 49.6 ± 11.4     |
| Gender (M/F)            | 11/12        | 12/13           |
| HD duration             | 70.1 ± 21.9 months | 68.7 ± 19.3 months |
| 1,25(OH)2 vitamin D3    | 2.0 µg/day   | (—)            |
| iPTH, pg/mL             | 1293.3 ± 591.9              | 189.4 ± 75.2              |
| NTX, (nM BCE/L)         | 1227.3 ± 458.8              | 784.1 ± 325.6              |
| TRAP, U/L               | 8.87 ± 5.27              | 2.19 ± 0.67              |
| BAP, U/L                | 158.6 ± 71.2              | 27.4 ± 9.1              |
| TCa, mg/dL              | 10.89 ± 0.86              | 9.6 ± 0.6              |
| Pi, mg/dL               | 6.10 ± 0.48               | 5.0 ± 0.6              |
| Albumin, g/dL           | 3.91 ± 0.36               | 3.96 ± 0.36              |
| FC, %                   | −96.92 ± 1.90              | 1.58 ± 16.22             |
| iPTH                    | −44.43 ± 11.02             | 3.40 ± 8.33              |
| NTX                     | −61.76 ± 13.84             | −2.23 ± 3.08             |
| TRAP                    | −0.75 ± 17.04             | −1.87 ± 1.84             |
| BAP                     |                           |                          |

*p < 0.05, *p < 0.01, compared with control group at D0; *p < 0.05, *p < 0.01, compared with PTX group at D0; *p < 0.05, *p < 0.01, compared with PTX group at W4. Abbreviations: BCE, bone collagen equivalents; BAP, bone alkaline phosphatase; D0, Day 0, before performance of PTX; HD, hemodialysis; W4, 4 weeks after the surgery. Table 1 also presents the fractional changes (FC, %) in marker value between D0 and W4.
through W2 (D0: 158.6 ± 71.2 versus W2: 216.7 ± 74.9 U/L; \( P < 0.001 \); panel (c)). Thereafter, BAP values decreased reaching baseline values at W4 (152.6 ± 53.6 U/L, \( P < 0.001 \) compared with W2; panel (c)).

3.3. Correlation Analyses. To examine potential relationships between NTX and other parameters, measurements obtained at various times were pooled and statistical analysis was performed (Table 2). NTX values correlated significantly with those for iPTH, TRAP, BAP, TCa, and Pi (\( r = 0.450, P < 0.001; r = 0.690, P < 0.001; r = 0.448, P < 0.001; r = -0.161, P = 0.042; \) and \( r = 0.197, P = 0.012, \) resp.).

We calculated univariate Spearman’s correlation coefficients to determine the relationships between serum NTX and iPTH, BAP, and TRAP levels at different times after PTX (Table 3).

Figure 2 presents correlations between serum NTX values and those for other bone biomarkers before (D0) and at 4 weeks after PTX (W4). Before PTX, iPTH concentrations were significantly correlated with NTX concentrations (\( r = 0.742, P < 0.001 \); panel (a)). This finding is consistent with the presence of high iPTH values due to increased osteoclast

| Parameter | \( r \) | \( P \) |
|-----------|--------|--------|
| iPTH      | 0.450  | <0.001 |
| TRAP      | 0.690  | <0.001 |
| BAP       | 0.448  | <0.001 |
| Ca        | -0.161 | 0.042  |
| Pi        | 0.197  | 0.012  |

iPTH, intact parathyroid hormone; TRAP, tartrate-resistant acid phosphatase 5b; BAP, bone alkaline phosphatase; TCa, total calcium; Pi, inorganic phosphate. Spearman’s correlation coefficients were calculated assuming a nonnormal distribution.
activity as reflected by elevated NTX values. However, this correlation was lost at 4 weeks after PTX ($P = 0.276$). TRAP and NTX values (panel (b)) were also found to correlate significantly before ($r = 0.874$, $P < 0.001$), but not 4 weeks after ($r = 0.293$, $P = 0.174$), PTX. Correlations between NTX and BAP are presented in panel (c). Since BAP concentrations were observed to peak at W2, this time was chosen for analysis. BAP and NTX were significantly correlated both before and 2 weeks after PTX ($r = 0.701$, $P < 0.001$ versus $r = 0.777$, $P < 0.001$, resp.).

The fractional changes (FC, %) in serum NTX and TRAP concentrations were calculated as a function of time following PTX (Figure 3). FC values for NTX were significantly lower than those for TRAP at all times examined. FC values for NTX versus TRAP were: D2 ($−8.94 ± 5.58\%$ versus $−24.60 ± 9.06\%$, $P < 0.001$), D4 ($−20.74 ± 6.84\%$ versus $−36.30 ± 11.93\%$, $P < 0.001$), at W1 ($−34.42 ± 9.22\%$ versus $−52.89 ± 16.00\%$, $P < 0.001$), W2 ($−38.04 ± 9.26\%$ versus $−57.55 ± 15.78\%$, $P < 0.001$), W3 ($−41.68 ± 10.34\%$ versus $−60.21 ± 14.45\%$, $P < 0.001$), and W4 ($−44.43 ± 11.02\%$ versus $−61.76 ± 13.84\%$, $P < 0.001$).

4. Discussion

The present study is the first to examine a variety of serum markers of bone resorption with respect to their disposition and interrelationships following PTX for SHPT. iPTH concentrations were found to decrease profoundly within...
Table 3: The relationships between serum NTX and iPTH, TRAP, and BAP levels at different times after parathyroidectomy (PTX).

|          | NTX D0        | NTX D2        | NTX D4        | NTX W1        | NTX W2        | NTX W3        | NTX W4        |
|----------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| iPTH D0  | \( r = 0.742, \) \( P < 0.001 \) |               |               |               |               |               |               |
| iPTH D2  | \( r = 0.236, \) \( P = 0.279 \) |               |               |               |               |               |               |
| iPTH D4  |               | \( r = 0.307, \) \( P = 0.155 \) |               |               |               |               |               |
| iPTH W1  |               |               | \( r = 0.370, \) \( P = 0.082 \) |               |               |               |               |
| iPTH W2  |               |               |               | \( r = 0.314, \) \( P = 0.145 \) |               |               |               |
| iPTH W3  |               |               |               |               | \( r = 0.290, \) \( P = 0.179 \) |               |               |
| iPTH W4  |               |               |               |               |               | \( r = 0.237, \) \( P = 0.276 \) |               |
| TRAP D0  | \( r = 0.874, \) \( P < 0.001 \) |               |               |               |               |               |               |
| TRAP D2  |               | \( r = 0.887, \) \( P < 0.001 \) |               |               |               |               |               |
| TRAP D4  |               |               | \( r = 0.700, \) \( P < 0.001 \) |               |               |               |               |
| TRAP W1  |               |               |               | \( r = 0.647, \) \( P < 0.001 \) |               |               |               |
| TRAP W2  |               |               |               |               | \( r = 0.451, \) \( P = 0.031 \) |               |               |
| TRAP W3  |               |               |               |               |               | \( r = 0.412, \) \( P = 0.051 \) |               |
| TRAP W4  |               |               |               |               |               |               | \( r = 0.293, \) \( P = 0.174 \) |
| BAP D0   | \( r = 0.701, \) \( P < 0.001 \) |               |               |               |               |               |               |
| BAP D2   |               | \( r = 0.643, \) \( P < 0.001 \) |               |               |               |               |               |
| BAP D4   |               |               | \( r = 0.704, \) \( P < 0.001 \) |               |               |               |               |
| BAP W1   |               |               |               | \( r = 0.709, \) \( P < 0.001 \) |               |               |               |
| BAP W2   |               |               |               |               | \( r = 0.777, \) \( P < 0.001 \) |               |               |
| BAP W3   |               |               |               |               |               | \( r = 0.791, \) \( P < 0.001 \) |               |
| BAP W4   |               |               |               |               |               |               | \( r = 0.696, \) \( P < 0.001 \) |

Post-PTX blood samples were collected at 24 and 72 h (D2 and D4, resp.) and at 1, 2, and 4 weeks (W1, W2 and W4, resp.) after the surgery. Spearman's correlation coefficients were calculated assuming a nonnormal distribution.

24 h following PTX. Serum NTX and TRAP values declined progressively over the 4-week period following the surgery. By contrast, BAP concentrations rose postoperatively within 24 h and peaked at 2 weeks post-PTX. These findings agree with those of previous studies [20] in which decreases in NTX and TRAP and increases in BAP were observed after PTX for SHPT. Significant correlations of NTX with iPTH, TRAP, BAP, TCa, and Pi were observed in the present study. However, NTX correlated significantly with iPTH and TRAP before (D0) but not at 4 weeks (W4) after surgery. Additionally, the mean percent decrease in serum NTX values was significantly smaller than that in serum TRAP values at all times following PTX. The finding that TRAP and NTX values, both of which reflect osteoclastic activity, did not correlate directly following PTX was unexpected.

NTX, which is formed during the process of bone resorption by osteoclasts, is proposed to serve as a valid marker of the process [21]. In patients without renal disease, NTX values fluctuate greatly in response to changes in bone resorption patterns and may vary as much as 50% on a daily
In conclusion, serum iPTH, TRAP, and NTX concentrations were observed before and 2 weeks after PTX. This observation is consistent with coupling of osteoblastic bone formation and osteoclastic bone resorption regardless of PTX. By contrast, TRAP and NTX concentrations did not correlate significantly at 4 weeks post-surgery, and the fractional changes in TRAP concentrations did not correlate with those for NTX at any time post-PTX. These findings favor the hypothesis that although osteoclast number is decreased after PTX, those osteoclasts that remain are still capable of degrading collagen. However, renal retention of NTX cannot be excluded. Other limitations of the current study include the small sample size, follow-up is limited to 4 weeks and also the lack of bone histomorphometric data.

In conclusion, serum iPTH, TRAP, and NTX concentrations decline rapidly following PTX for SHPT. The decline in these markers is attributable to suppression of bone resorption. Fractional decreases in serum TRAP are larger than those in serum NTX during the post-PTX period. Whether the latter observation indicates that bone collagen digestive ability declines more slowly than TRAP activity or reflects the renal retention of NTX warrants further study.

**Authors’ Contribution**

K. C. Hung and C. Y. Huang contributed equally to this work.

**Conflict of Interests**

The authors declare no conflict of interests.

**Acknowledgments**

This work was supported by Grant TSGH-C100-081 from the Tri-Service General Hospital (to P. Chu) and by Grant CTH-93-1-2A03 from the Cardinal-Tien Hospital (to K. C. Lu).
References

[1] J. Floege, J. Kim, E. Ireland et al., “Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population,” Nephrology Dialysis Transplantation, vol. 26, no. 6, pp. 1948–1955, 2011.

[2] M. L. Melamed, J. A. Eustace, L. C. Plantinga et al., “Third-generation parathyroid hormone assays and all-cause mortality in incident dialysis patients: the CHOICE study,” Nephrology Dialysis Transplantation, vol. 23, no. 5, pp. 1650–1658, 2008.

[3] F. Tentori, M. J. Blayney, J. M. Albert et al., “Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS),” American Journal of Kidney Diseases, vol. 52, no. 3, pp. 519–530, 2008.

[4] H. H. Malluche and M. C. Faugere, “Effects of 1,25(OH)2D3 administration on bone in patients with renal failure,” Kidney International, vol. 29, supplement 38, pp. S-48–S-53, 1990.

[5] D. J. Sherrard, H. Herz, Y. Pei et al., “The spectrum of bone disease in end-stage renal failure—an evolving disorder,” Kidney International, vol. 43, no. 2, pp. 436–442, 1993.

[6] L. S. Stiglen, L. M. Hegedüs, H. Beck-Nielsen, and B. Abrahamsson, “Osteoprotegerin levels in primary hyperparathyroidism: effect of parathyroidectomy and association with bone metabolism,” Calcified Tissue International, vol. 73, no. 3, pp. 210–216, 2003.

[7] A. Yajima, M. Inaba, Y. Tominaga, N. Nishizawa, K. Ikeda, and A. Ito, “Increased osteocyte death and mineralization inside bone after parathyroidectomy in patients with secondary hyperparathyroidism,” Journal of Bone and Mineral Research, vol. 25, no. 11, pp. 2374–2381, 2010.

[8] A. M. Parfitt, “A structural approach to renal bone disease,” Journal of Bone and Mineral Research, vol. 13, no. 8, pp. 1213–1220, 1998.

[9] S. C. Manolagas, “Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis,” Endocrine Reviews, vol. 21, no. 2, pp. 115–137, 2000.

[10] H. Tanaka, T. Mine, H. Ogasa, T. Taguchi, and C. T. Liang, “Expression of RANKL/OPG during bone remodeling in vivo,” Biochemical and Biophysical Research Communications, vol. 411, no. 4, pp. 690–694, 2011.

[11] H. Tanaka, A. Wakisaka, H. Ogasa, S. Kawai, and C. T. Liang, “Effect of IGF-I and PDGF administered in vivo on the expression of osteoblast-related genes in old rats,” The Journal of Endocrinology, vol. 174, no. 1, pp. 63–70, 2002.

[12] C. M. Zheng, P. Chu, C. C. Wu et al., “Association between increased serum osteoprotegerin levels and improvement in bone mineral density after parathyroidectomy in hemodialysis patients,” The Tohoku Journal of Experimental Medicine, vol. 226, no. 1, pp. 19–27, 2012.

[13] P. Chu, T. Y. Chao, Y. F. Lin, A. J. Jancikila, and L. T. Yam, “Correlation between histomorphometric parameters of bone resorption and serum type 5b tartrate-resistant acid phosphatase in uremic patients on maintenance hemodialysis,” American Journal of Kidney Diseases, vol. 41, no. 5, pp. 1052–1059, 2003.

[14] K. Iba, J. Takada, N. Hatakeyama, Y. Ozasa, T. Wada, and T. Yamashita, “Changes in urinary NTX levels in patients with primary osteoporosis undergoing long-term bisphosphonate treatment,” Journal of Orthopaedic Science, vol. 13, no. 5, pp. 438–441, 2008.

[15] Y. Maeno, M. Inaba, S. Okuno, T. Yamakawa, E. Ishimura, and Y. Nishizawa, “Serum concentrations of cross-linked N-telopeptides of type I collagen: new marker for bone resorption in hemodialysis patients,” Clinical Chemistry, vol. 51, no. 12, pp. 2312–2317, 2005.

[16] S. Epstein, I. R. Dissanyake, G. R. Goodman et al., “Effect of the interaction of parathyroid hormone and cyclosporine a on bone mineral metabolism in the rat,” Calcified Tissue International, vol. 68, no. 4, pp. 240–247, 2001.

[17] L. Caplan, A. H. Hines, E. Williams et al., “An observational study of glucocorticoid-induced osteoporosis prophylaxis in a national cohort of male veterans with rheumatoid arthritis,” Osteoporosis International, vol. 22, no. 1, pp. 305–315, 2011.

[18] A. Yajima, Y. Ogawa, A. Ikehara, T. Tominaga, T. Inou, and O. Otsubo, “Development of low-turnover bone diseases after parathyroidectomy and autotransplantation,” International Journal of Urology, vol. 8, no. 8, pp. S76–S79, 2001.

[19] A. Yajima, Y. Ogawa, H. E. Takahashi, Y. Tominaga, T. Inou, and O. Otsubo, “Changes of bone remodeling immediately after parathyroidectomy for secondary hyperparathyroidism,” American Journal of Kidney Diseases, vol. 42, no. 4, pp. 729–738, 2003.

[20] J. A. Balsa, J. I. Botella-Carretero, R. Peromino et al., “Chronic increase of bone turnover markers after biliopancreatic diversion is related to secondary hyperparathyroidism and weight loss. Relation with bone mineral density,” Obesity Surgery, vol. 20, no. 4, pp. 468–473, 2010.

[21] P. D. Delmas, R. Eastell, P. Garnero, M. J. Siebel, and J. Stepan, “The use of biochemical markers of bone turnover in osteoporosis. Committee of scientific advisors of the international osteoporosis foundation,” Osteoporosis International, vol. 11, supplement 6, pp. S2–S17, 2000.

[22] H. N. Rosen, A. C. Moses, J. Garber, D. S. Ross, S. L. Lee, and S. L. Greenspan, “Utility of biochemical markers of bone turnover in the follow-up of patients treated with bisphosphonates,” Calcified Tissue International, vol. 63, no. 5, pp. 363–368, 1998.

[23] P. Urena, A. Ferreira, V. T. Kung et al., “Serum pyridoline as a specific marker of collagen breakdown and bone metabolism in hemodialysis patients,” Journal of Bone and Mineral Research, vol. 10, no. 6, pp. 932–939, 1995.

[24] S. Mazzaferrro, M. Pasquali, P. Ballanti et al., “Diagnostic value of serum peptides of collagen synthesis and degradation in dialysis renal osteodystrophy,” Nephrology Dialysis Transplantation, vol. 10, no. 1, pp. 52–58, 1995.

[25] S. Palacios, J. L. Neyro, J. Ferrer et al., “Reduction of urinary levels of N-telopeptide correlates with treatment compliance in women with postmenopausal osteoporosis receiving alendronate,” Menopause, vol. 19, no. 1, pp. 67–74, 2012.

[26] M. McClung, R. Becker, P. Miller et al., “Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate,” Bone, vol. 41, no. 1, pp. 122–128, 2007.

[27] C. de la Piedra, N. A. Castro-Errecaborde, M. L. Traba et al., “Bone remodeling markers in the detection of bone metastases in prostate cancer,” Clinica Chimica Acta, vol. 331, no. 1-2, pp. 45–53, 2003.

[28] T. Tamada, T. Sone, T. Tomomitsu, Y. Jo, H. Tanaka, and M. Fukunaga, “Biochemical markers for the detection of bone metastasis in patients with prostate cancer: diagnostic efficacy and the effect of hormonal therapy,” Journal of Bone and Mineral Metabolism, vol. 19, no. 1, pp. 45–51, 2001.

[29] M. Katagiri, M. Fukunaga, T. Ohtawa, and T. Harada, “Prediction of bone mass in renal hyperparathyroidism by newly
developed bone metabolic markers: evaluation of serum levels of carboxy-terminal pyridinoline cross-linked telopeptide of type I collagen and carboxy-terminal propeptide of type I procollagen,” *World Journal of Surgery*, vol. 20, no. 7, pp. 753–757, 1996.

[30] P. Magnusson, C. A. Sharp, M. Magnusson, J. Risteli, M. W. J. Davie, and L. Larsson, “Effect of chronic renal failure on bone turnover and bone alkaline phosphatase isoforms,” *Kidney International*, vol. 60, no. 1, pp. 257–265, 2001.

[31] P. Ureña, O. Bernard-Poenaru, M. Cohen-Solal, and M. C. de Vernejoul, “Plasma bone-specific alkaline phosphatase changes in hemodialysis patients treated by alfalcacidol,” *Clinical Nephrology*, vol. 57, no. 4, pp. 261–273, 2002.

[32] L. T. Yam, “Clinical significance of the human acid phosphatases: a review,” *The American Journal of Medicine*, vol. 56, no. 5, pp. 604–616, 1974.

[33] J. J. Stepan, E. Silinkova Malkova, T. Havranek et al., “Relationship of plasma tartrate resistant acid phosphatase to the bone isoenzyme of serum alkaline phosphatase in hyperparathyroidism,” *Clinica Chimica Acta*, vol. 133, no. 2, pp. 189–200, 1983.

[34] S. Irie, N. Hayashida, T. Shinkawa et al., “Suitability of tartrate-resistant acid phosphatase type 5b as a screening marker for bone mineral density in community-dwelling elderly individuals,” *The Tohoku Journal of Experimental Medicine*, vol. 224, no. 2, pp. 105–110, 2011.

[35] K. C. Lu, W. Y. Ma, J. C. Yu, C. C. Wu, and P. Chu, “Bone turnover markers predict changes in bone mineral density after parathyroidectomy in patients with renal hyperparathyroidism,” *Clinical Endocrinology*, vol. 76, no. 5, pp. 634–642, 2012.

[36] M. Schoppet and C. M. Shanahan, “Role for alkaline phosphatase as an inducer of vascular calcification in renal failure?” *Kidney International*, vol. 73, no. 9, pp. 989–991, 2008.

[37] R. Shantouf, C. P. Kovesdy, Y. Kim et al., “Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients,” *Clinical Journal of the American Society of Nephrology*, vol. 4, no. 6, pp. 1106–1114, 2009.

[38] T. C. Franca, L. Griz, J. Pinho et al., “Bisphosphonates can reduce bone hunger after parathyroidectomy in patients with primary hyperparathyroidism and osteitis fibrosa cystica,” *Revista Brasileira de Reumatologia*, vol. 51, no. 2, pp. 131–137, 2011.

[39] D. Harmey, L. Hessle, S. Narisawa, K. A. Johnson, R. Terkeltaub, and J. L. Millán, “Concerted regulation of inorganic pyrophosphate and osteopontin by akp2, enpp1, and ank: an integrated model of the pathogenesis of mineralization disorders,” *The American Journal of Pathology*, vol. 164, no. 4, pp. 1199–1209, 2004.

[40] W. C. O’Neill, “Pyrophosphate, alkaline phosphatase, and vascular calcification,” *Circulation Research*, vol. 99, no. 2, p. e2, 2006.