Published in final edited form as:

J Clin Densitom. 2013 ; 16(1): 22–27. doi:10.1016/j.jocd.2012.11.004.

Bone Turnover Markers in Primary Hyperparathyroidism

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Keywords

primary hyperparathyroidism; bone turnover markers; PTH

Introduction

Primary hyperparathyroidism (PHPT) is a disorder characterized by hypercalcemia with an inappropriate normal or high PTH level. The clinical presentation of primary hyperparathyroidism has changed over the past several decades to a mild hypercalcemic state without obvious signs or symptoms [1]. Nevertheless, most patients with PHPT have reduced bone mineral density (BMD), particularly at the distal 1/3 radius (a site of cortical bone) and are in a high turnover state as determined by dynamic histomorphometry of bone biopsies and by circulating biochemical markers of bone turnover [2, 3]. In this article, we describe measurement and evaluation of bone turnover markers in PHPT.

Bone markers

Markers of bone resorption or bone formation generally reflect secretory or breakdown products of bone cells (osteoblasts, osteoclasts, or osteocytes) or bone collagen as it is being formed or resorbed. They are used as indirect tools to assess bone turnover and to provide information about the metabolic status of bone. In PHPT, a disorder of increased skeletal metabolism, these bone turnover markers can be helpful indices of the extent to which the hyperparathyroid process may be active in bone. While these markers reflect the remodeling activity in the skeleton, their measurement in the circulation or urine can be influenced by numerous factors such as day-to-day or diurnal variation, food intake, renal clearance, other hormonal disorders and other diseases. Moreover, methodological variability can complicate interpretation of the measurements [4]. Nevertheless, assessment of bone turnover markers in PHPT has been helpful in assessing the state of the skeleton in this disease.

Bone formation markers, products of osteoblast activity, can be assessed by the measurement of: total alkaline phosphatase (ALP), bone-specific alkaline phosphatase

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Disclosure summary: Work was supported by NIH grant DK32333.

(BALP), osteocalcin (OC), N-terminal cross-linking propeptides of type I procollagen (PINP) and C-terminal cross-linking propeptides of type I procollagen (P1CP).

Bone resorption markers are small fragments of collagen that result from its metabolic breakdown. These collagen degradation products are measured in the circulation or in the urine [5]. For a number of years, bone resorption markers were measured predominantly in the urine but now circulating resorption markers, as measured in serum, have tended to supersede urinary markers because of convenience and better assay precision [6]. Examples of bone resorption markers include: deoxypyridinoline (DPD), pyridinoline (PYD), hydroxyproline (OHP), C-terminal cross-linking peptide of type I collagen (ICTP), N-terminal cross-linking telopeptides of type I collagen (NTX), C-terminal cross-linking telopeptides of type I collagen (CTX), and hydroxylysine glycosides. The most frequently measured serum resorption marker is CTX while the most frequently measured urine resorption marker is the NTX [5]. Tartrate-resistant acid phosphatase (TRAP) and its isoform 5b (TRAP-5b) differs from all the others in being a secretory product of the osteoclast [7].

Increased bone turnover is characteristic of PHPT. Not surprisingly, bone turnover markers are elevated [8, 9]. In generally, subjects with more active disease, even if asymptomatic, will show levels of bone turnover markers that are higher than those with less active disease. Since asymptomatic PHPT presents most often in an indolent fashion, bone turnover markers are usually not frankly elevated but rather at the upper limits of normal [10, 11]. The work of Silverberg et al. [12] demonstrated this point in their cohort of 66 subjects whose baseline mean values of the bone formation marker ALP and resorption markers PYD, DPD and OHP were all at the upper limit of the normal range. Over a period of 6 years, there were no significant changes in any of these indices [12].

PHPT Treatment and Bone Markers

Primary hyperparathyroidism can be cured by surgical removal of the abnormal parathyroid gland(s) if they are symptomatic or if they are asymptomatic and meet surgical guidelines [13]. Surgical and non-surgical approaches to the management of PHPT are described in detail elsewhere in this issue of the Journal. The following sections focus on changes in the bone markers as a result of surgical or pharmacological intervention.

Surgery

With removal of the offending abnormal parathyroid gland(s) by parathyroidectomy (PTX), PTH levels fall immediately followed soon thereafter by normalization of the serum calcium concentration. Reductions in bone turnover markers as associated with BMD increments [10, 11, 14]. The post PTX period is associated first with rapid reductions in bone resorption markers followed by a more gradual reduction in bone formation markers. Thorsen et al. [15] followed the 2-year course of bone formation markers after PTX in 12 postmenopausal women. BALP and OC, which were elevated preoperatively, fell into the normal range while PICP and ICTP levels, which were within the normal range preoperatively, did not change during the 2-year postoperative period [15].

Christiansen et al. [11] reported in a shorter, 6-month study of 24 patients after PTX, marked reductions in both formation and resorption markers. Urinary NTX fell abruptly but ICTP first increased in the 1st postoperative month before also falling. The bone formation markers (OC, ALP, and BALP) declined much more slowly over the 6-month period. This study was extended for an additional 36 months [16]. All bone turnover markers were within the normal range by the end of the 36-month study period. Although previous studies had failed to show a correlation between bone turnover markers at baseline and BMD changes

after PTX [17], this study showed that the initial levels of bone markers were positively correlated with changes in lumbar spine BMD [11]. Another study reported similar positive associations between initial levels of P1NP and CTX and the change in BMD 1 year after surgery in 53 patients (FIGURE1) [18]. These results not only show that bone turnover markers normalize post-PTX but that patients with the highest turnover might be the ones destined to experience the greatest gains in BMD [11].

Tamura et al. [19] followed 11 older patients with PHPT (age 72.7 ± 8.5 yrs) who underwent PTX and found, 1 year after PTX, that bone turnover markers had substantially decreased from baseline values: OC -70%; BALP -58%, uNTx -51%, uDPD -45%. During the 5 subsequent years, the values remained lower than baseline values [19].

These studies, in the aggregate, show that bone turnover markers after PTX routinely fall into the normal range, with the most impressive reductions occurring within the first year. The reductions occur most rapidly in bone resorption markers followed thereafter by reductions in bone formation markers. The early reduction in bone resorption markers followed by a slower reduction in bone formation markers would provide a “window” when bone formation would be higher due to the initial and preferential reduction in bone resorption after PTX.

Other studies have attempted to identify a specific bone marker that can predict PTX outcomes and reflect beneficial effects on bone remodeling and microstructure. A perioperative study investigated the changes in CTX and P1NP 2 days after PTX in 41 postmenopausal women with PHPT [20]. As previously shown, bone turnover markers were elevated and higher than 2 post- and premenopausal control groups. Subjects were divided into 3 groups according to their initial bone marker levels compared to the postmenopausal controls: 1) high turnover-both bone markers (P1NP and CTX) are high; 2) high bone resorption - elevated CTX only; 3) normal turnover- P1NP and CTX levels normal. All 3 subgroups showed significant reductions in CTX 2 days after surgery. However, the high turnover group experienced a more marked decline [20]. In contrast, P1NP significantly increased in the high turnover and high resorption groups.

Guo et al. [8] tracked changes in the cytokine IL-6 after PTX in a 12-day study. Baseline levels of IL-6 were higher in PHPT patients compared to controls. They increased soon after PTX peaking by 1 day and declining thereafter. In a surgical control group, that did not undergo PTX, IL-6 also peaked postoperatively followed only then by a decline. Despite the high pre-operative levels of IL-6 in PHPT as reported by Guo et al. [21] and in previous studies [22], the peak was seen after surgery both in PHPT patients and in surgical controls indicating perhaps that such post-operative elevations in IL-6 represent a response to surgical trauma, per se, rather than reflecting a direct marker involved in the bone turnover process post-PTX [21]. On the other hand, the subsequent decline in IL-6 after PTX is in keeping with resolution of the mechanisms by which bone resorption is increased in PHPT.

Post-surgical changes in osteoprotegerin (OPG) in a group of 20 PHPT subjects approximately 1 year after PTX were studied by Stilgren et al. [23]. Baseline levels of OPG were within the normal range with a mean of 27.5 pg/mL (range: 13–73 pg/mL) and remained rather stable after PTX. All traditional bone turnover markers fell after PTX [23]. Correlations between bone markers and OPG levels were seen only after surgery. Interestingly, patients with the highest preoperative OPG concentration showed a trend towards smaller postoperative BMD changes in the lumbar spine and distal forearm.

Recently, sclerostin has been described as a marker that depicts bone formation. Sclerostin, a protein produced mainly by osteocytes, acts as a natural inhibitor of the Wnt anabolic signaling pathway. Recently, a new immunoassay has enabled measurement of circulating

sclerostin concentrations [24–27]. Different from other bone formation markers that are products of osteoblast activity, sclerostin influences differentiation and survival of these cells by inhibiting the Wnt pathway [27]. Sclerostin levels are thought to be correlated negatively with bone formation that is when sclerostin levels are high, bone formation is low. Patients with PHPT are shown to have lower sclerostin levels compared to euparathyroid and hypoparathyroid controls [28, 29]. In a small series of 27 patients followed for up to a year post-PTX, circulating sclerostin increases shortly after post-surgery but return to the age reference range within 10 days remaining stable throughout the other study visits [30].

Non-surgical pharmacological intervention in PHPT

Since many patients with asymptomatic PHPT do not meet criteria for surgery and, therefore, do not undergo PTX, non-surgical approaches have been utilized. Changes in bone turnover markers after pharmacological intervention have often been a component of the monitoring plan. The majority of these agents reduces calcium levels, at least transiently, and reduce bone turnover.

Estrogen—The effect of Hormone Replacement Therapy (HRT) on bone markers in women with PHPT has been reported in a few small trials, which date back to the 1970's [31]. Measurements of circulating bone markers of resorption or formation were not available during some of the earlier studies, but the historical urinary resorption marker, hydroxyproline (OHP) and traditional urinary calcium excretion measurement declined in PHPT postmenopausal women treated with estrogen for short or long term [32, 33]. A double blind, randomized, placebo-controlled trial enrolled 42 postmenopausal women with mild PHPT to receive HRT with conjugated estrogen (0.625mg) and medroxyprogesterone (5mg), or placebo for 2 years [34]. In the group taking HRT, ALP, urine OHP and uNTX decreased significantly from baseline and from placebo in the first 6 months of treatment. The markers remained suppressed for 2 years. Treatment did not affect levels of PTH or ionized calcium concentrations [34]. At the end of 4 years of HRT, in an extension of this trial, serum ALP and urine OHP excretion remained lower than baseline [35]. A previous study with a smaller number of participants noted a trend towards suppression of ALP and serum osteocalcin in patients taking estrogen therapy [36]. The changes in bone turnover markers were similar to changes seen in subjects who underwent PTX [8]. Reductions in bone turnover markers were associated with increments on BMD [37].

Selective Estrogen Modulator (SERM)—The SERM, raloxifene acts as a tissue-specific estrogen agonist in bone. While there are many trials reporting the effects of raloxifene in osteoporosis, there are very few studies in PHPT. In a small series of 3 patients, daily treatment with raloxifene for 12 months was associated with reductions in DPD by 61% and fasting calcium excretion by 56% along with increased BMD of the lumbar spine and femoral neck [38]. A short-term study conducted by Rubin et al. [39] enrolled 18 postmenopausal women with PHPT to test the hypothesis that raloxifene reduces calcium concentration and biochemical markers of bone turnover in PHPT. The study was placebo-controlled, double blinded, with a randomized 1:1 allocation to either placebo or raloxifene 60mg daily for 8 weeks. Markers of bone turnover and serum calcium declined significantly by 8 weeks in the group treated with raloxifene, while no changes were seen in the control group. By 8 weeks, OC fell from 11.4 ± 1.6 to 9.9 ± 1.6 nmol/L and serum NTX from 21.2 ± 3.4 to 17.3 ± 2.8 nmol BCE/L (for both, $p < 0.05$). PTH levels did not change in either group. After a 4-week washout, bone turnover markers returned to baseline levels [39]. Changes in bone turnover markers and calcium were similar to changes seen in PHPT patients treated with HRT or estrogen RT.

Calcimimetics—Several studies have demonstrated the efficacy of cinacalcet, a calcimimetic, in decreasing serum calcium and PTH levels in PHPT, and have reported its effect to reduced bone turnover markers [40–43]. Seventy-eight patients (aged 27–83) were enrolled in a multicenter, randomized, double-blind, placebo-controlled 1-year trial, randomized 1:1 (placebo:cinacalcet). Despite a decline in PTH levels by about 20%, measurements of bone turnover indices revealed that serum BALP and NTX and urine NTX increased in the cinacalcet group as compared to the placebo group [41]. In patients with persistent PHPT after PTX, the use of cinacalcet did not initially change the median serum concentrations of NTX or BALP after a titration phase [44]. An analysis of data from 3 multicenter clinical trials of cinacalcet in PHPT grouped patients according to disease severity: 1) history of failed parathyroidectomy, 2) no surgical intervention despite meeting surgical criteria, and 3) mild asymptomatic PHPT [45]. Serum BALP and NTx and urine NTx were not significantly different among the groups, but there was a trend for bone markers to increase according to the severity of the disease (group1 > group2 > group3). After 1 year of cinacalcet, no changes were seen in BALP, NTx or urine NTx in any of the three groups regardless of the decline of calcium levels [45]. Faggiano et al. [46] have investigated the effect of medical treatment with cinacalcet alone (n=10) or with alendronate (n=13). The combination group- cinacalcet and alendronate- showed a marked reduction of ALP compared to baseline and was significantly higher than the group receiving cinacalcet alone ($p<0.05$) [46].

Bisphosphonate—Early studies demonstrated an effect of older non-nitrogen-substituted bisphosphonates, namely disodium etidronate and dichloromethylene diphosphonate, in lowering urinary OHP in PHPT [47, 48]. Effects of treatment with alendronate on bone markers were evaluated in a cohort of patients with osteoporosis and mild PHPT [49]. Initial measurements revealed elevated levels of BALP, OC and urine PYD in all patients. Treatment with alendronate 10mg every other day for 2 years was successful in suppressing all 3 bone turnover markers. PYD fell by month 1 and OC and BALP by month 3, with all remaining suppressed throughout the treatment period. Bone turnover markers did not change in controls [49]. In a group of postmenopausal PHPT women receiving daily alendronate 10mg for 48 weeks, Chow et al. [50] showed significant reductions in BALP by 24 weeks, and in serum OC and uNTx by 48 weeks. Bone turnover markers rose 24 weeks after alendronate was discontinued. A randomized controlled trial of alendronate 10mg daily vs. placebo showed that bone turnover markers in those who received alendronate were reduced and maintained below baseline values for up to 2 years [51]. uNTx fell more promptly, reaching a nadir (–66%) within 3 months of treatment while BALP reached its nadir within 9 months (–54%). Bone turnover markers in the placebo group remained elevated and similar to baseline values until after 1 year when the placebo group crossed over to receive alendronate. At that point, bone turnover markers fell in a manner similar to the group that had initially received alendronate [51]. In a further analysis separating subjects by gender, Khan et al. [52] showed that alendronate therapy in men reduces BALP (–46.6%, $p=0.003$) and uNTx (–60.5%, $p=0.07$) similar to postmenopausal women after 1 year of treatment (BALP: –44.6%, $p<0.001$; uNTx –46.8%, $p=0.1$). Similarly, an open label trial with alendronate (10mg/day) showed that bone turnover markers were suppressed with treatment, but tended to return to baseline values after 18 months [53]. Reasner et al. [54] showed that a short course of risedronate acutely inhibits bone resorption and in a more delayed manner bone formation.

Conclusion

Bone turnover markers are a helpful indirect index of skeletal dynamics, and are elevated or in the high normal range in PHPT. Subjects with high bone turnover markers are likely to have more active skeletal disease. After PTX, bone resorption markers fall precipitously and

are followed gradually by a slower fall in bone formation markers. Non-surgical, pharmacological approaches to PHPT are also associated with reductions in bone turnover markers that persist for as long as the drug is used.

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Figure 1.

Relationship between percent changes in BMD 6 months/1year and pre-operative bone markers cross-linked C-terminal telopeptide of type I collagen (β CTX), and amino-terminal procollagen propetide of type I collagen (P1NP). (From J. Endocrinol. Invest. 35:640–644, 2012 with permission of Editrice Kurtis).