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Research Article

Bone Status and Circulating Sclerostin Levels Differ among Patients with Different Parathyroid Disorders

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Abstract

Parathyroid Hormone (PTH) shows both catabolic or anabolic actions on the skeleton and the anabolic actions of PTH are mainly mediated by inhibition of sclerostin expression in osteocytes. Different parathyroid disorders show different effects on bone status and circulating sclerostin levels. Studies regarding bone status including bone mass and bone turnover markers in pseudohypoparathyroidism are sparse and get inconsistent results. Previous studies suggested that pseudohypoparathyroidism may show partial resistance to PTH in skeleton. Therefore, we hypothesized that the bone status in pseudohypoparathyroidism may be between hyperparathyroidism and hypoparathyroidism. Therefore, this study was designed to compare the bone status including bone density and bone turnover markers, as well as circulating sclerostin levels, among patients with different parathyroid disorders. A total of 216 patients with hyperparathyroidism, pseudohypoparathyroidism and hypoparathyroidism were collected. Results showed that the Bone Mineral Density (BMD) of Lumbar Spine (LS), Femoral Neck (FN) and Total Hip (TH) were gradually decreased in hyperparathyroidism, pseudohypoparathyroidism and hypoparathyroidism. The levels of bone turnover markers were comparable between hyperparathyroidism and pseudohypoparathyroidism, and were significantly higher than those of hypoparathyroidism. Serum sclerostin levels were significantly lower in hyperparathyroidism. In hyperparathyroidism, sclerostin was positively correlated with BMD of LS and FN. In pseudohypoparathyroidism, sclerostin was positively associated with BMD of LS. Our study suggested that the bone status in pseudohypoparathyroidism is between hyperparathyroidism and hypoparathyroidism, and circulating sclerostin levels are different among patients with different parathyroid disorders and are correlated with BMD of LS and FN in hyperparathyroidism and pseudohypoparathyroidism.

Keywords: Bone status; Hyperparathyroidism; Hypoparathyroidism; Pseudohypoparathyroidism; Sclerostin

Introduction

Parathyroid Hormone (PTH) plays a key role in bone metabolism, primarily mediated by PTH-cAMP-PKA signal pathway. Depending on the ways in which PTH is administrated or elevated, PTH shows both catabolic or anabolic actions on the skeleton. Persistently high serum PTH concentrations, such as in hyperparathyroidism, have catabolic effects on bone (preferential involvement of cortical bone) [1], whereas intermittent mild increases have anabolic effects, primary involvement of cancellous bone [1]. Accordingly, different parathyroid disorders lead to different bone status. Primary hyperparathyroidism (PHPT) causes enhanced bone turnover and decreased bone mass, while hypoparathyroidism (HypoPT) leads to decreased bone turnover and increased bone mass. Pseudohypoparathyroidism (PHP) is caused by genetic mutations or epigenetic abnormity of GNAS, characterized by hypocalcemia and hyperphosphatemia in the presence of elevated PTH levels due to PTH resistance. Studies regarding the bone status including bone density and bone turnover markers in subjects with PHP are sparse and get inconsistent results.

Regarding bone mineral density (BMD), a study suggested that PHP1B patients showed significantly lower BMD Z-scores for the femoral neck (FN), lumbar spine (LS), and total hip (TH) compared with HypoPT subjects [2]. Another study also indicated that the Z scores of BMD of LS and radius were lower in patients with PHP1B than in those with idiopathic hypoparathyroidism (IHP) and postoperative hypoparathyroidism (OHP) [3]. However, when compared with normal controls, PHP1A patients showed higher total body BMD [4]. Furthermore, two brothers diagnosed as PHP1B, caused by a maternally inherited 3-kb deletion within STX16, have been found to have high bone mass [5]. Regarding bone turnover markers, a study showed that all bone metabolic markers in patients with PHP1B were significantly higher than those in patients with IHP and OHP [3]. Another study also revealed elevated bone turnover markers in PHP subjects compared with non-surgical hypoparathyroidism (Ns-HypoPT) [6]. These data may indicate that bones of most cases of PHP could respond to PTH, at least partly, and the skeletal response to PTH may be heterogeneous, which leads to the diverse skeletal phenotypes in PHP subjects. Therefore, we hypothesized that the bone status in PHP subjects may be between PHPT and HypoPT subjects. However, few studies have compared the bone status in subjects with PHPT, PHP and HypoPT simultaneously.

Previous studies suggested that different parathyroid disorders showed different effects on the circulating (sclerostin) SOST levels. PHPT subjects have decreased SOST levels, while HypoPT subjects have elevated SOST levels [7-9]. However, studies comparing the circulating SOST levels in PHPT, PHP and HypoPT subjects are unavailable. Therefore, this study was designed to compare the bone status including bone density and bone turnover markers, as well as circulating SOST levels, among patients with different parathyroid disorders.

Subjects and Methods

Subjects

This study was approved by the Institutional Review Boards of West China Hospital, Sichuan University (2018 NO.441). All subjects were given written, informed consent before participating in the study. A total of 216 patients with different parathyroid gland disorders were collected from 2007.1-2019.9 in the department of endocrinology of West China Hospital, Sichuan University. PHPT was defined by hypercalcemia associated with PTH levels in the upper range or above the PTH assay reference range (>6.9 pmol/L). PHP were defined as hypocalcaemia with elevated PTH levels not attributable to chronic renal insufficiency, vitamin D insufficiency, or other known causes of secondary hyperparathyroidism. HypoPT was defined as chronic hypocalcemia associated with PTH levels below the PTH assay reference range (<1.6 pmol/L). Exclusion criteria included: liver or kidney disease, Cushing's syndrome, diabetes mellitus, current treatment with glucocorticoids, calcitonin, raloxifene, or estrogens.

Laboratory and radiology studies

Fasted blood samples were collected from a vein in the forearm between 0800 and 0900 in the morning. After clot formation, serum was collected after centrifuging at 2,000 x g for 10 minutes and was stored at −80 °C until analysis. Circulating SOST levels were measured using an ELISA kit from abcam (ab221836, Cambridge, UK). The detection limit of the assay is 6 pg/mL with a range of 31.1 – 2000 pg/mL. The intra- and inter-assay precision is 4.8 and 8.6%, respectively. The levels of other biochemical indices, including serum calcium, phosphate, alkaline phosphatase (ALP), PTH, bone-specific alkaline phosphatase (B-ALP), N-MID osteocalcin (OCN), type 1 collagen cross-linked C-telopeptide (CTX), tartrate-resistant acid phosphatase 5b (TRAP5b), 25(OH)D3, thyroid stimulating hormone (TSH), free T4 (FT4) and urinary calcium and phosphate were measured in the department of laboratory medicine, West China Hospital, Sichuan University using standard protocols. BMD was measured at the lumbar spine (LS; L1–L4), TH, FN and distal one-third radius (1/3 radius) by dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, General Electric Company, U.S.). The results were expressed as BMD (g/cm^2) and/or Z-score. The Z score is the deviation (in standard deviations) from the normal age- and sex-matched mean.

Statistical Analyses

Data were analyzed using SPSS 16.0 software. Continuous data were checked for normal distribution by Shapiro–Wilk's test before each analysis. Continuous variables with normal distributions were expressed as mean±SD. Otherwise, data were presented as median with interquartile range (25-75) % and were log-transformed before analysis. Data in Table 1 were in

their original scale. The significance of group differences was evaluated using ANOVA for multiple comparisons. The Least-Square Deconvolution (LSD) was used to determine differences between two groups. Pearson's correlation was used to determine the correlation between two parameters. Partial correlation was used to eliminate the influence of potential confounding factors. Categorical variables were expressed as rate or percentage, and the Kruskal-Wallis H Test was used to compare the difference among three groups. The statistical significance was set at $p < 0.05$ (two-tailed).

Result

Clinical characteristics among HypoPT, PHP and PHPT patients

Due to the low prevalence of these diseases, especially HypoPT and PHP, in order to enlarge the sample size, patients who meet the diagnostic criteria and exclusion criteria were included in this study. Therefore, age, age of onset and disease duration were significantly different among the three groups, as shown in Table 1. The mean age was 45.4±18.8, 21.0±4.0 and 51.3±15.8 years in HypoPT, PHP and PHPT groups respectively. The mean age of onset was 39.3±19, 13.7±6.1 and 47.5±16.1 years in HypoPT, PHP and PHPT groups respectively. The mean disease duration was 6.4, 7.6 and 2.0 years in HypoPT, PHP and PHPT patients respectively. On average, PHP subjects were younger than patients with HypoPT and PHPT, mainly due to their younger age of onset, which is consistent with previous clinical observations [4,10]. Compared with patients with PHP and PHPT, HypoPT subjects showed higher mean height, body weight, body mass index (BMI) and lower ALP levels. TSH levels were higher in PHP patients than the other two groups, while FT4 levels were higher in HypoPT patients than the other two groups.

Comparison of BMD among HypoPT, PHP and PHPT patients

The BMD of L1-4, FN, TH and the Z-values of L1-4, TH were different among the three groups in the following order: PHPT<PHP<HypoPT (Figure 1). The Z-values of FN in HypoPT subjects were significantly higher than the other two groups. The BMD and Z-values of 1/3 radius in PHP and HypoPT patients were significantly higher than those of PHPT subjects. The BMD and Z-values of 1/3 radius were comparable between PHP and HypoPT patients. These data indicated that the bone mineral density of the PHP patients may be between the HypoPT and PHPT patients.

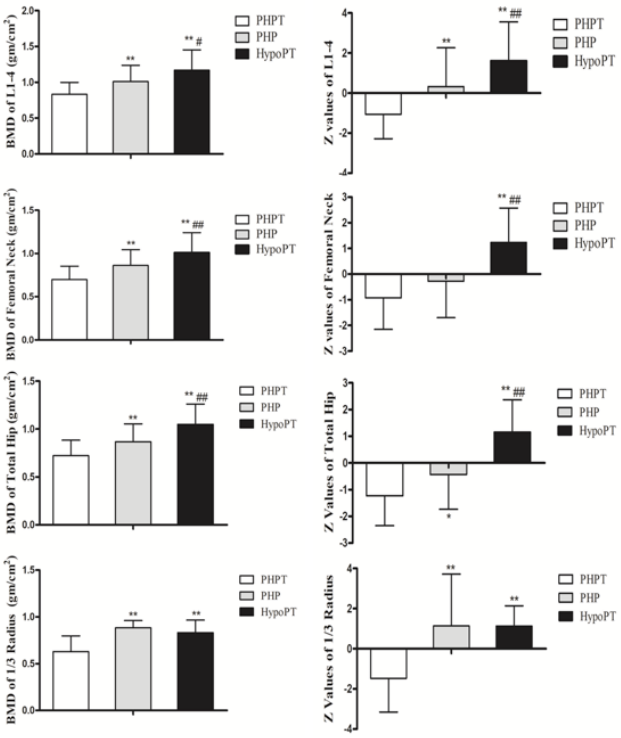

Figure 1: Comparison of BMD among HypoPT, PHP and PHPT patients. *p<0.05, vs PHPT; **p<0.01 vs PHPT; #p<0.05, vs PHP; ##p<0.01, vs PHP.

Comparison of bone indices among HypoPT, PHP and PHPT patients

As expected, PHPT subjects showed significant higher serum calcium, 24h urinary calcium levels and lower serum phosphate levels compared with HypoPT and PHP patients (Table 1). The serum calcium and phosphate levels, as well as urinary calcium levels were comparable between HypoPT and PHP patients. Also as expected, PTH levels were significantly higher in PHPT and PHP subjects than those of HypoPT subjects. The PTH levels were similar between PHPT and PHP subjects. There was no significant difference in 24h urinary phosphate levels among the three groups. The B-ALP, OCN, CTX levels were higher and 25(OH) D_3 levels were lower in subjects with PHPT and PHP than those of subjects with HypoPT. PHPT subjects had a higher TRAP5b levels compared with HypoPT subjects. The PTH, CTX, B-ALP, OCN and 25(OH)D_3 levels were comparable between PHPT and PHP patients, although PHPT subjects showed a tendency to have higher PTH, CTX and OCN levels compared with PHP subjects.

	HypoPT (n=49)	PHP (n=25)	PHPT (n=142)	P values from LSD		
				HypoPT vs PHP	HypoPT vs PHPT	PHP vs PHPT
Age (years)	45.4±18.8	21.0±4.0	51.3±15.8	0.000	0.023	0.000
Age of disease onset (years)	39.3±19	13.7±6.1	47.5±16.1	0.000	0.002	0.000
Disease duration (years)	3.5 (1.3, 10.5)	6.5 (3.5, 11.8)	2.0(0.5, 5.5)	0.000	0.002	0.000
Body weight (kg)	61.6±10.8	52.9±9.3	55.0±11.7	0.003	0.001	0.401
Height (cm)	162.0 (157.0, 167.0)	154.0 (151.0, 166.5)	157.0(150.5, 163.0)	0.303	0.045	0.995
BMI (kg/m^2)	23.8±3.5	21.2±2.7	22.0±4.4	0.021	0.022	0.401
ALP (μg/L) (50-135)	73.00(60.50, 89.00)	110.50(84.75, 142.75)	128.50(88.75, 234.50)	0.007	0.000	0.649
TSH (mU/L) (0.27-4.2)	2.21(1.50, 4.31)	5.79(3.89, 10.00)	2.42(1.63, 3.62)	0.001	0.997	0.000
FT4 (pmol/L) (12.0-22.0)	17.13±3.66	14.38±2.10	14.42±3.34	0.009	0.000	0.967
PTH (pmol/L) (1.6-6.9)	0.85 (0.52, 1.48)	23.70 (17.85, 39.44)	40.2(17.66, 105.7)	0.000	0.000	0.282
25(OH)D3 (ng/mL) (47.7-144)	54.18±20.76	39.18±11.21	34.35±16.14	0.004	0.000	0.281
Serum calcium (mmol/L) (adults:2.1-2.7; 2-12y: 2.2-2.7)	1.38 (1.19, 1.60)	1.44 (1.21, 1.63)	2.98(2.78, 3.26)	0.996	0.000	0.000
Serum phosphate (mmol/L) (adults:0.81-1.45; 0-12y:1.29-2.26)	1.72(1.46, 2.19)	1.88 (1.47, 2.66)	0.75(0.64, 0.89)	0.996	0.000	0.000
Urinary calcium (mmol /24 h) (2.5-7.5)	1.61(0.67, 3.02)	0.43(0.21, 0.87)	6.33(3.96, 9.71)	0.060	0.000	0.000
Urinary phosphate (mmol /24 h) (22-48)	12.65±6.98	12.32±6.44	15.02±7.70	0.867	0.070	0.118
B-ALP (μg/L) (11.4-24.6)	12.17(10.75, 15.85)	28.87 (22.59, 51.23)	33.07(19.56, 81.54)	0.001	0.000	0.994
OCN (μg/L) (24-70)	12.45(8.88, 19.53)	38.10(23.98, 73.78)	56.75(30.65, 103.60)	0.021	0.000	0.995
CTX (ng/mL) (0.30-0.584)	0.19 (0.12, 0.44)	0.86 (0.49, 1.10)	1.14(0.58, 2.02)	0.009	0.000	0.557
TRAP5b (U/L) (1.3–4.82)	2.59±1.64	4.58±2.23	5.22±2.90	0.161	0.011	0.590
BMD of LS	1.169±0.283	1.011±0.226	0.832±0.167	0.010	0.000	0.001

Abbreviations: B-ALP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; OCN, osteocalcin; CTX, type 1 collagen cross-linked C-telopeptide

Table 1: Baseline characteristics and biochemical indices.

Comparison of circulating SOST levels among HypoPT, PHP and PHPT patients

The mean SOST levels were 426.08±150.36, 162.84±89.01, 400.33±120.42 and 493.13±203.99 pg/mL in control, PHPT, PHP, and HypoPT subjects, respectively (Figure 2). Compared with control, PHPT subjects showed lower SOST levels. Compared with PHPT subjects, HypoPT and PHP subjects had significantly higher SOST levels. The SOST levels were comparable among control, PHP and HypoPT patients.

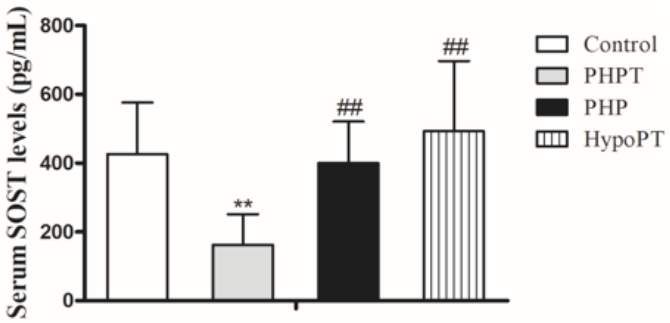

Figure 2: Comparison of circulating SOST levels among HypoPT, PHP and PHPT patients. **p<0.01 vs control; ##p<0.01, vs PHPT.

Correlation analysis of SOST

For the entire group, SOST showed a positive association with phosphate, OCN, BMD of L1-4 and FN, and a negative association with serum calcium and PTH levels (Table 2). After adjustment for age, the possible confounding factor, SOST was positively correlated with phosphate, BMD of L1-4 and FN, and was negatively correlated with calcium, B-ALP, and OCN levels. After adjustment for PTH levels, SOST was positively associated with BMD of L1-4 and FN, and was negatively associated with calcium. After adjustment for both the age and PTH, SOST was still positively associated with phosphate and BMD of L1-4 and FN, and was negatively associated with calcium. In PHPT subjects, SOST was positively associated with age. After adjustment for age, there was a positive correlation between SOST with BMD of L1-4 and FN. After adjustment for PTH, SOST was positively associated with age. After adjustment for age and PTH, SOST was still positively associated with BMD of L1-4 and FN. In PHP subjects, SOST was positively associated with age, and BMD of L1-4. After adjustment for age and PTH, SOST was still positively associated with BMD of L1-4. In HypoPT subjects, there was a positive association between SOST and age.

Parameters	Total Subjects		PHPT		PHP		HypoPT	
	r	p	r	p	r	p	r	p
Calcium	-0.696	0.000	-0.140	0.605	0.132	0.716	0.225	0.627
Phosphate	0.568	0.007	0.239	0.373	-0.462	0.179	-0.380	0.400
B-ALP	-0.403	0.070	-0.013	0.963	-0.120	0.777	-0.231	0.616
OCN	-0.278	0.222	0.083	0.761	0.540	0.637	-0.812	0.074
CTX	-0.132	0.569	0.014	0.959	0.329	0.387	-0.298	0.474
BMD of L1-4	0.700	0.000	0.575	0.020	0.969	0.001	0.270	0.557
BMD of FN	0.618	0.003	0.593	0.015	0.812	0.050	0.420	0.349

Abbreviations: B-ALP, bone-specific alkaline phosphatase; OCN, osteocalcin; CTX, type 1 collagen cross-linked C-telopeptide; BMD, bone mineral density; FN, femoral neck

Table 2: Correlation analysis of SOST after adjustment for age and PTH.

Discussion

The bone status including bone density and changes of bone turnover indices in patients with PHPT and HypoPT is clear. PHPT subjects show enhanced bone turnover and decreased bone mass, mainly at cortical bone. On the contrary, HypoPT subjects have inhibited bone turnover and increased bone mass, especially at trabecular bone. However, studies regarding the bone status in PHP subjects get discrepant results. Compared with background population, similar, lower or higher aBMD has been observed in patients with PHP [3,4,11]. For example, Long et al. reported that aBMD Z-score values in 22 patients with PHP1A were similar to the background population at the lumbar spine, total hip and femoral neck, while the total body BMD in PHP1A subjects was significantly greater than normal [4]. Compared with Ns-HypoPT, PHP patients had significantly lower total and trabecular volumetric BMD at the spine and hip, accompanied by significantly higher bone markers [6]. Xueying Chu et al. also reported that all BMD Z-scores in PHP1B patients were significantly lower than in IHP patients for the FN, LS, and TH [2]. Furthermore, high bone mass was found in two brothers diagnosed as PHP1B [5]. These data may indicate that PHP patients do not have a complete skeletal resistance to PTH, and the skeletal response to PTH in different sites or among different subgroups of PHP subjects is heterogenous, which leads to the diverse bone status in PHP subjects [12].

The effects of PTH on bone are mainly regulated by the stimulatory guanine nucleotide-binding protein (Gsα) mediated PTH/cAMP/PKA signal pathway. Gsα, coded by GNAS gene in human, is biallelically expressed in skeleton [13]. Theoretically, genetic abnormality caused by genetic mutations from either parent may impair the expression and function of Gsα, leading to partial bone resistance to PTH. Accordingly, we hypothesized that the bone status including bone density and bone turnover levels in PHP subjects may be between PHPT and HP subjects.

In this study, we compared the bone density at LS, FN, TH, and 1/3 radius as well as bone turnover markers among patients with different parathyroid gland functions. Our study revealed that bone density and Z-scores at L1-4 and TH were increased gradually, while bone turnover markers including B-ALP, N-MID and CTX levels were decreased gradually, among the three groups with PHPT, PHP and HypoPT, as expected. Our study may indicate PHP subjects show partial skeletal response to PTH. SOST, a glycoprotein secreted by osteocytes, acts as an inhibitor of bone formation mediated by Wnt pathway. Sclerostin expression is regulated by several factors including age, estrogen, and mechanical loading [14]. It has been proven that PTH is an inhibitor of SOST mediated by PTH1R expressed at osteocytes, and the down regulation of SOST in osteocytes is required for the anabolic effect of PTH on bone [15]. Decreased SOST levels were observed followed by continuous and intermittent PTH treatments in rodents [16,17]. Decreased SOST levels were also found after treatment with the PTH analogue teriparatide in elderly healthy men [18] and postmenopausal women [19]. Therefore, there is an inverse correlation between circulating sclerostin and PTH levels in human subjects. Several clinical studies have confirmed that PHPT subjects had significantly lower sclerostin levels, compared with euparathyroid controls [8, 20,21], and serum sclerostin was normalized following parathyroidectomy by the tenth day postoperatively [8]. On the other hand, hypoparathyroid subjects had significantly higher serum sclerostin levels compared with hyperparathyroid subjects and euparathyroid controls [9]. Currently, studies investigating the changes of circulating SOST levels in PHP patients were available.

Our study showed that PHPT subjects had significantly lower serum SOST levels compared with hypoPT and PHP subjects, as well as euparathyroid controls. Compared with controls, SOST levels in HypoPT subjects showed a tendency to increase, although the difference did not reach statistical significance, possibly due to the limited sample size. Our study suggests that different parathyroid functions influence the circulating levels of SOST, and the inhibitory effects of hyperparathyroidism on SOST levels are prominent. Previous studies indicated that SOST was positively correlated with age [22], and higher SOST levels were found in old compared with young [23]. In subgroup analysis, a significantly positive association was found between SOST and age in either parathyroid disorder. In our study, PHPT subjects were the oldest, while had the lowest SOST levels, which may indicate the inhibitory effects of PTH on SOST were beyond the influence of age.

It is intriguing that SOST is an inhibitor of bone formation, while most previous studies revealed a positive correlation between circulating SOST levels and BMD in human subjects. It was suggested that serum sclerostin acts as a partial reflection of osteocyte number. In a large cohort study, serum sclerostin levels are strongly positively associated with BMD in men, and this association is apparently related to higher Tb.vBMD, indicating sclerostin levels in men are strongly positively associated with better bone microarchitectural parameters, mainly trabecular architecture [24]. In postmenopausal women, serum sclerostin was also positively associated with spine ($r=0.35$, $p<0.0001$) and total hip ($r=0.25$, <0.0001) BMD [25]. Although no significant correlation was found between BMD and sclerostin in subjects with parathyroid disorder, a significantly positive relationship was found between sclerostin and bone mineral content in subjects with hypoparathyroidism [9]. In this study, after adjustment for confounding factors, SOST were positively correlated with spine and FN BMD in subjects with PHPT and PHP. Previous studies also revealed correlation between SOST and bone turnover markers. In postmenopausal women, serum sclerostin was weakly negatively associated with the bone markers procollagen type I N-terminal propeptide (PINP) and CTX and with intact PTH [25]. In primary hyperparathyroidism, SOST was negatively associated with PINP, while in hypoparathyroidism, SOST was positively associated with CTX [9]. Our study revealed no correlation between SOST with bone markers after adjustment for confounding factors in either parathyroid disorder. Therefore, our study indicates that different

parathyroid disorders influence the circulating SOST levels, with the most prominent inhibitory effects of PTH on SOST, which leads to significantly decreased SOST levels in PHPT subjects. Our study also suggests that SOST is closely associated with BMD in PHPT and PHP subjects.

The major limitation of this study includes the small sample size and unmatched age among groups, due to the rare nature of these diseases. These unmatched clinical features may have some effects on bone metabolism and circulating SOST levels. The estimated prevalence rates of PHP in Japan and Denmark are 0.34 in 100 000 and 1.1 in 100 000, respectively [26]. The prevalence of non-surgical hypoparathyroidism is also very low, with a prevalence in Denmark of 2/100,000 [6]. Previous studies also suggested that pseudohypoparathyroidism occurs at a younger age, while hyperparathyroidism usually occurs after middle age, consistent with our study. For example, in 18 Korean PHP patients, the mean age at diagnosis was 4.89 ± 3.54 years (range: 0.37-9.58) for PHP1A, and 9.95 ± 3.35 years (range: 4.83–14.33) for PHP1B [26]. For PHPT, although this condition can occur at any age, the average age at diagnosis is 55 years [27-29]. In addition, PHP subjects have not been divided into subgroups based on genotypes, and the different genotypes may lead to diverse phenotypes. In spite of these limitations, this study represents the first to compare the bone density, bone turnover markers and circulating SOST levels among patients with different parathyroid disorders including hyperparathyroidism, pseudohypoparathyroidism and hypoparathyroidism. Furthermore, real-world data is particularly important for the study of clinical phenotypes or molecular mechanisms of rare diseases.

Conclusion

The bone status including BMD and bone turnover markers in PHP subjects is between PHPT and HypoPT subjects, and different parathyroid disorders affect the circulating SOST levels. In PHPT and PHP patients, serum SOST levels are closely and positively correlated with BMD of L1-4 and FN.

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