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Original Research Article

The comparison of bone mineral density in primary hyperparathyroidim, vitamin D induced secondary hyperparathyroidism, and patients with both condition: a single center experience

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ABSTRACT

Background: To compare bone mineral densities via dual energy X-ray absorptiometry method (DXA) between various hyperparathyroidism (HPT) types such as primary, vitamin D induced secondary, and both conditions.

Methods: Participants who were aged between 18-45 years and had elevated parathyroid hormone levels were included. After initial evaluations, patients were divided into 3 groups according to diagnoses: primary HPT (pHPT), vitamin D induced secondary HPT (sHPT), and combined (primary+secondary) one. In addition to the bone mineral density (BMD), demographic and laboratory datas were recorded.

Results: Of 166 patients, 147 of the patients were female, 19 were male, and average age was 38.10±7.24 years. Significant difference was found in terms of age (p=0.03) between pHPT and sHPT. Blood calcium, PTH, 25-OH vitamin D, and daily urine calcium excretion levels were significantly higher and phosphorus levels were lower in the pHPT group compared to the sHPT and combined disease group. Both T and Z scores of the pHPT group were significantly lower than the sHPT group especially in the lumbar region. However, no significant difference was noted between pHPT and combined disease group with respect to T and Z scores in all regions.

Conclusions: The results of this study indicate that pHPT has a significantly worse impact on skeletal mineral density particularly in the lumbar region than sHPT. The addition of vitamin D deficiency to the clinical picture seems to have no significant influence on BMD in pHPT. To confirm and clarify these findings, prospective studies with larger number of participants are needed.

Keywords: Bone mineral density, Dual energy X-ray absorptiometry hyperparathyroidism, Vitamin D deficiency

INTRODUCTION

Hyperparathyroidism (HPT) is defined when a patient is found to have a significantly elevated parathyroid

hormone (PTH) level. This condition may be due to primary HPT (pHPT) which arises from various diseases of the parathyroid glands, such as adenoma or hyperplasia. pHPT is among the most common endocrine disorders

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following diabetes mellitus and thyroid disorders, and it is the most prevalent cause of hypercalcemia. Previously, clinicians had interpreted the clinical findings of pHPT with a simple, summarizing phrase: "bones, stones, groans, thrones, and psychiatric overtones". Therefore, many pHPT cases (with or without clinical hypercalcemia) were missed, causing a lower estimate of disease burden. Today, widespread use of autoanalyzers for PTH measurement has led to an increase in the incidence of the disease. Recent studies put the prevalence for pHPT in a narrow range that varies between 0.25-0.66% overall, with a female-to-male ratio of 3 to 1. Incidence increases with age and shows a significant peak after 50 years old.¹ Another reason for high PTH levels is secondary HPT (sHPT) which may stem from other conditions or diseases, such as vitamin D deficiency, chronic renal failure and celiac disease.² Additionally, a condition defined as tertiary hyperparathyroidism also exists; it is a form of HPT in which a long-standing, severe sHPT becomes chronic and does not regress even when the underlying cause for sHPT is corrected.3

In addition to the evident changes in blood biochemistry, the negative effects of HPT on the bone, including diminished bone mineral density (BMD) and bone structure deficits are well defined. In the literature, many studies have established these negative influences caused by HPT. 4,5 An abnormal vitamin D metabolism plays an important role in the pathogenesis of sHPT, especially in patients with vitamin D deficiency and chronic kidney disease which may contribute to the deleterious effects sustained by the bone. Vitamin D deficiency decreases the absorption of calcium from the intestine, leading to an increase in PTH level (thus, secondary), which in turn causes increased osteoclastic activity.6 It is well defined that both primary and secondary HPT can cause bone mineral problems, but according to this knowledge, there is currently no study comparing bone mineral densities of different HPT types like as primary, vitamin D-induced secondary, and their combination. Therefore, authors aim was to compare BMD via the scintigraphy method (DXA) and laboratory findings in patients under 45 years old who were grouped according to the following 3 diagnoses: primary HPT, vitamin D-induced secondary HPT, and combined HPT (primary HPT + vitamin D deficiency).

METHODS

Study group

This single-centre cross sectional study was conducted at the Internal Medicine and Endocrinology and Metabolism Diseases outpatient clinics of Uludag University Medical Faculty (Bursa, Turkey) between January 2011 and January 2012. The local ethics committee granted approval for the study and all participants signed the informed consent form for inclusion into the study (Reference number: 2012-10/12). The Helsinki Declaration and all relevant guidelines for appropriate patient care were followed during the study period and writing of the article.

We included a total of 166 participants who were between 18-45 years of age, and had elevated PTH levels. We excluded those who were over 45 years old, postmenopausal, pregnant, and had a history of malignancy, hysterectomy, and premature ovarian failure. Subjects using drugs or having diseases that interferes with bone metabolism such as steroids, chronic renal failure, inflammatory bowel disease, being treated for osteoporosis (OP), and lacking of information mentioned below in their medical records were also excluded. Three groups were formed according to patient diagnoses: the pHPT group, the vitamin D induced sHPT group, and the combined disease group (subjects with pHPT + vitamin D induced sHPT).

Definitions and measurements

Primary HPT was defined as: increased PTH levels accompanying normal/high Ca, normal/low P, >400 mg/day 24-hour urine calcium concentration, and >30 ng/mL concentration of 25-OH-D vitamin. Secondary HPT was defined as: increased PTH levels accompanying normal/low Ca, normal/high P, and <30 ng/mL concentration of 25-OH-D vitamin (in the absence of any other disease which can cause sHPT). Combined disease was defined as: increased PTH levels accompanying normal/high Ca, normal/low P, >400 mg/day 24-hour urine calcium concentration, <30 ng/mL concentrations of 25-OH-D vitamin (in the absence of any other disease which can cause sHPT).

Authors recorded all patients' age, gender, comorbid disorders, symptoms, and laboratory data. Patients PTH, vitamin D, urea, creatinine, serum electrolytes (sodium, potassium, chloride, calcium, phosphorus), serum albumin, and daily urinary calcium and phosphorus excretion were measured by chemiluminescence method (ARCHITECT, Abbott Diagnostics, IL, USA). Bone mineral density was measured via dual energy x-ray absorptiometry (DXA) (Hologic) by the Department of Nuclear Medicine. T and Z scores of the lumbar vertebrae (L1-2-3-4), overall lumbar, femur neck, trochanteric, intertrochanteric area, and total femur were recorded from DXA imaging reports.

Statistical analysis

Data were analyzed using the SPSS v22.0 software (SPSS Inc., Chicago IL). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Categorical data was presented as frequency and percent values, while continuous data was presented as mean \pm standard deviation (SD). The comparison of categorical variables were performed using the Pearson Chi-square and Fisher's exact tests.

One-way ANOVA and Kruskall Wallis tests were used to compare means and medians with regard to normality of distribution. The level of statistical significance was set at $p \le 0.05$.

RESULTS

One hundred and forty seven (88.6%) of the patients were female and 19 (11.4%) were male, average age of the participants was 38.10±7.24 years. Sociodemographic data of the study groups are shown in Table 1. Significant

difference was found in terms of age (p=0.03) between pHPT and sHPT, but no significant difference was noted between these three groups with respect to gender, comorbid disorders, and symptoms.

Table 1: Sociodemographic data of the study groups (HPT: hyperparathyroidism).

	Primary HPT	Secondary HPT	Primary HPT + Vitamin D deficiency
Diagnosis (%, n)	28.3/47	59.0/98	12.7/21
Gender (Female/male) (%)	83.0/17.0	90.8/9.2	90.5/9.5
Age (years)	40.55 ± 6.06	36.82±7.51	38.62±7.24
Comorbid disorders (%/n)			
Diabetes mellitus type 2	4.3/2	4.1/4	14.3/3
Hypertension	6.4/3	9.2/9	14.3/3
Coronary Artery Disease	2.1/1	3.1/3	4.8/1
Thyroid disorders	17.0/8	27.6/27	19.0/4
Urinary system disease	4.3/2	2.0/2	0.0/0
Symptoms (%/n)			
Weakness	25.5/12	18.4/18	38.1/8
Fatigue	14.9/7	10.2/10	23.8/5
Constipation	2.1/1	3.1/3	0.0/0
Abdominal pain	0.0/0	4.1/4	4.8/1
Depression	4.3/2	3.1/3	0.0/0
Polydipsia	0.0/0	1.0/1	0.0/0
Polyuria	0.0/0	1.0/1	0.0/0
Bone/joint pain	19.1/9	18.4/18	23.8/5
Renal stones	8.5/4	7.1/7	14.3/3

Table 2: Laboratory results of the groups (pHPT: primary hyperparathyroidism, sHPT: secondary hyperparathyroidism).

	рНРТ	sHPT	Primary HPT + Vitamin D deficiency	p
Urea (mg/dL) (10-50)	24 (11-47)	24 (11-135)	26 (12-127)	0.591
Creatinine (mg/dL) (0.6-1.3)	0.7 (0.5-1.2)	0.7 (0.5-15.1)	0.7 (0.4-9.8)	0.858
Sodium (mmol/L) (136-145)	139 (134-147)	139 (109-146)	138 (133-142)	0.359
Potassium (mmol/L) (3.5-5.1)	4.4 (3.1-5.4)	4.3 (3.5-5.2)	4.4 (3.7-5.0)	0.280
Chloride (mmol/L) (98-107)	105 (99-114)	105 (97-110)	104 (99-111)	0.492
Albumin (g/dL) (3.5-5.0)	4.1 (2.8-4.6)	4.1 (3.2-5.1)	4.15 (3.6-4.6)	0.566
Calcium (mg/dL) (8.4-10.2)	11.2 (9.7-18.9)	9.4 (7.6-11.6)	10.4 (8.0-11.6)	0.0001
Phosphorus (mg/dL) (2.3-4.7)	2.6 (1.1-4.00)	3.2 (2.0-5.5)	3.15 (1.8-6.1)	0.0001
Parathormone (pg /mL)(15-68.3)	234 (93.3-2600)	109 (54-1655)	131.5 (58.8-1495)	0.0001
25-OH vitamin D (μg/L) (>30)	13 (3.1-39.0)	9.6 (2-38)	9.02 (4-48.9)	0.005
Urinary calcium excretion (mg/ day) (80-320)	385 (14-1137)	155(21-515)	183.95 (85-577)	0.0001
Urinary phosphorus excretion (mg/day) (250-1000)	765(0-1842)	682.7(0-1930)	662 (0-1159.8)	0.541

The laboratory data of the study groups are presented in Table 2. There was significant difference between all three groups in terms of blood calcium, phosphorus, PTH, 25-OH vitamin D, and daily urinary calcium excretion levels. Blood calcium, PTH, and daily urine calcium excretion

levels were significantly higher and phosphorus levels were lower in the pHPT group compared to the sHPT and combined disease group (p=0.001, for all of four). Additionally, vitamin D levels were higher in the pHPT group than the other groups (p=0.005). There were no

significant differences between this groups in terms of other laboratory results.

The T and Z scores of the groups and their comparisons are shown in Table 3 and Table 4, respectively. T scores of the pHPT group were significantly lower than the sHPT group in the L1, L3, L4, overall lumbar, femur neck. Similarly, the Z scores of the same regions except L1 were also significantly worse in the pHPT group compared to the sHPT group. Likewise, authors found a significant difference between sHPT and combined group regarding T score (in L1, L2, L3, overall lumbar, femur neck) and Z score (in only the overall lumbar); results were better in

those with sHPT. However, no significant difference was noted between pHPT and combined disease group with respect to T and Z scores in all regions. Overall, 27.7% (n: 46) of the patients had undergone parathyroidectomy surgery; in regard to subgroups, 89.4% (n=42) of those in the pHPT group and 19.0% (n=4) in the combined disease group. Evaluation of the parathyroidectomy specimens showed that 76.1% of the samples were consistent with adenoma, 6.5% with hyperplasia, 2.2% with carcinoma, and 15.2% with normal parathyroid tissue. Four (9.5%) of the subjects who underwent parathyroidectomy experienced recurrence of HPT.

Table 3: T scores of the groups (pHPT: primary hyperparathyroidism, sHPT: secondary hyperparathyroidism).

	pHPT	sHPT	Primary HPT + Vitamin D deficiency	p
Lumbar 1	-1.25 (-6.30-2.90)	-0.50 (-2.90-6.50)	-1.05 (-3.90-0.70)	0.020
Lumbar 2	-0.20 (-6.90-17.00)	0.00 (-4.30-5.80)	-0.80 (-5.80-0.50)	0.033
Lumbar 3	-1.70(-7.40-4.10)	-0.50 (-4.10-5.00)	-1.15 (-4.80-0.20)	0.017
Lumbar 4	-1.70(-7.80-3.00)	-0.90 (-3.80-4.20)	-1.30 (-4.50-0.40)	0.029
Overall Lumbar	-1.60(-7.20-3.20)	-0.50 (-6.00-5.30)	-1.35 (-4.80-0.10)	0.012
Femur neck	-1.35 (-5.30-2.40)	-0.40 (-4.00-5.00)	-1.30 (-3.50-1.00)	0.007
Trochanter	-1.10 (-5.70-2.90)	-0.60 (-3.60-5.90)	-0.70 (-3.50-1.20)	0.245
Intertrochanteric	-0.40 (-3.90-2.40)	-0.10 (-3.00-4.00)	-0.10 (-2.70-3.10)	0.300
Total femur	-0.60 (-4.70-2.70)	0.10 (-3.10-5.30)	0.00 (-2.70-2.70)	0.361

Table 4: Z scores of the groups (pHPT: primary hyperparathyroidism, sHPT: secondary hyperparathyroidism).

	pHPT	sHPT	Primary HPT + Vitamin D deficiency	р
Lumbar 1	-1.05 (-6.00-3.30)	-0.30 (-2.60-6.50)	-0.75 (-3.90-1.10)	0.110
Lumbar 2	-1.05 (-6.50-3.40)	-0.20 (-4.10-5.80)	-0.75 (-5.80-0.90)	0.064
Lumbar 3	-1.30 (-7.00-4.50)	-0.30 (-3.80-5.00)	-0.80 (-4.80-0.40)	0.061
Lumbar 4	-1.55 (-7.50-3.50)	-0.70 (-3.40-4.30)	-0.85 (-4.50-0.60)	0.068
Overall lumbar	-1.40 (-6.80-3.70)	-0.30 (-3.30-5.30)	-0.75 (-4.80-0.50)	0.035
Femur neck	-1.00 (-5.00-2.80)	-0.10 (-3.50-5.10)	-0.60 (-2.50-1.30)	0.092
Trochanter	-0.80 (-5.50-3.30)	-0.40 (-3.30-5.90)	-0.50 (-2.50-2.00)	0.623
Intertrochanteric	-0.20 (-3.80-2.50)	0.00 (-2.80-4.10)	0.30 (-1.50-3.70)	0.300
Total femur	-0.25 (-4.50-3.00)	0.10 (-3.10-5.30)	0.40 (-1.40-3.40)	0.451

DISCUSSION

In this retrospective study comparing the DXA measurements of pHPT, vitamin D-induced sHPT, and combined disease patients, authors found that pHPT seems to affect BMD to a greater degree compared to sHPT. Even despite this anticipation, the pHPT and combined disease group were similar in terms of DXA imaging results. To authors knowledge, this is the first study in the literature comparing BMD results with regard to three different diagnoses causing HPT. From this point of view, authors believe that this study adds some important data about the characteristics of pHPT and sHPT to the literature. There are many studies which have shown the adverse effects of HPT, especially pHPT, on bone health. Jung et al, reported

that the cortical thickness of the femur neck was significantly decreased in patients with pHPT; whereas lumbar spine and femur mineral density remained unchanged, during 5 years of follow-up. However, the authors had included postmenopausal women in their patient group; as it is clearly known that menopause is a major risk factor for OP, we chose to exclude menopausal women from this study in order to avoid the effects of this confounding factor. In this group of patients, lumbar spine T scores were the worst. Silverberg et al, reported similar results with this study, they found that the regions most affected by HPT were the lumbar spine, femoral neck and radius. Additionally the study by Lumachi et al, supports authors argument, they reported that, in premenopausal women, BMD values of the lumbar spine significantly

improve after parathyroidectomy. There are also plenty of other studies showing there is significant improvement of bone dynamics after parathyroidectomy. In one of these studies, Rolighed et al, observed significant postoperative BMD improvement at the hip and spine, which is supported by other studies. Hill parathyroidectomy evidently improves BMD, observation leads to a small but statistically significant degradation in BMD after 5 years. However, in some studies, the mean T and Z scores of patients were worse in the distal radius compared to the femoral neck and lumber spine which is alike to this findings. Health Because the region of the distal one-third radius is not a routine measurement in this institution, authors are unable to make such comparison.

Chronic vitamin D inadequacy is another probable risk factor for HPT development. It has long been accepted that accompanying vitamin D inadequacy in pHPT is connected with higher PTH levels, greater adenoma size, lower BMD, especially at cortical sites. 15,16 However recent researches suggest that the impact of vitamin D inadequacy (when added on to pHPT) on BMD is controversial. While some studies are suggesting that coexisting vitamin D deficiency increases bone disease in pHPT, others are asserting it has no further effect on BMD.¹⁷⁻¹⁹ For instance, Walker et al, reported that, although 25-OH D deficiency increases PTH levels, vitamin D deficiency and insufficiency did not lead to degradation of lumbar spine bone health in patients with HPT.²⁰ In a recent study conducted in the United states, vitamin D deficiency was associated with more severe pHPT as reflected by PTH levels, but its impact on BMD were found to be very limited.

They interpreted this interesting deviation from prior studies' results with the possibility that earlier studies had been conducted in settings or regions where long-standing and/or severe vitamin D inadequacy/deficiency and low calcium consumption were widespread.²¹ In another study with results that were consistent with this paradigm shift, researchers found that, the actual increase of PTH itself rendered 25-OH D levels irrelevant in terms of effects on BMD.²² Authors detected a similar result with these studies, as the DXA results of the combined disease group were similar to that of those with pHPT. Also, there were no significant differences between these two groups in terms of laboratory results (blood PTH, calcium and phosphorus levels). When this results and above mentioned are taken into consideration, it can be speculated that vitamin D inadequacy has no additional negative effects on skeletal health in patients with pHPT.

This study has some limitations, firstly this research is a retrospective study and authors could not evaluate the follow-up results of patients. This study group was also limited in terms of patient numbers; however, in order to avoid negative effect of menopause on bone mineral density authors excluded menopausal patients and participants over 45 years old from this study, therefore this study subject number remained limited.

CONCLUSION

Primary hyperparathyroidism was found to affect BMD especially in the lumbar region more than sHPT. The addition of vitamin D deficiency seems to have no impact on BMD in pHPT, this laboratory data are also consistent with these findings.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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