Evaluation of Bone Mineral Density in Subjects with Primary Hyperparathyroidism by Dual Energy X-Ray Absorptiometry

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ABSTRACT

Objective: **Bone loss is a major complication of primary hyperparathyroidism (PHPT), and the extent of bone loss is an important factor for parathyroidectomy. Studies focused on this issue of bone loss in subjects with PHPT are quite rare in our country. This study will help the physicians to take proper action by giving an exact reflection of bone condition in subjects with PHPT. The purpose of this study was to evaluate the bone condition by measuring Bone Mineral Density (BMD), in subjects with PHPT using Dual Energy X-ray Absorptiometry (DEXA) and compare these findings with individuals without PHPT.**

Patients and Methods: **It was an analytical and cross sectional study (group comparison) carried out at National Institute of Nuclear Medicine and Allied Sciences (NINMAS) BSMMU campus, Dhaka from July 2015-December 2016. Subjects of PHPT diagnosed by biochemical evaluation (increased serum calcium and parathyroid hormone concentrations), between age ranges 15-45 years were selected as group-A. Individuals without biochemical evidence of PHPT or other major illness causing bone loss were selected as comparison group or as group-B. The subjects underwent BMD test by DEXA at lumbar spines from L1-L4 vertebra and the left femoral neck using Norland XR-46 densitometer. BMD was classified according to WHO criteria. Data presented on categorical form were analyzed using chi-squared test. While the data presented on continuous scale were analyzed using student's t-test. In each analysis, level of significance was 5% and P value <0.05 was considered significant. Data were processed and analyzed with the help of computer software SPSS, version 20.**

Results: **Total number of 90 subjects were selected for this study, 45 subjects with PHPT were in group-A and equal number of subjects without PHPT were in group-B. The findings derived from data analysis showed, a significantly more male participants in group-A. The mean age of group-A and group-B was 37.24 ± 8.03 years and 38.20 ± 5.74 years respectively. Mean BMI of group-A was 25.10 ± 4.35 kg/m2 in compare to 29.43 ± 5.17 kg/m2 in group-B. Higher BMI was noted in both groups. PHPT subjects with high BMI had low BMD. BMD expressed in absolute value (gm/cm2) and T score. BMD was significantly low in group-A (with PHPT) than in group-B (without PHPT), (p<0.0001). In group-A, prevalence of low BMD was 62.2% (osteopenia 37.8% and osteoporosis 24.4%) at lumbar spine and 84.5% (osteopenia 35.6% and osteoporosis 48.9%) at femoral neck. PHPT subjects had significant difference in both T score and BMD between lumbar spine and femoral neck.**

Conclusion: **Primary hyperparathyroidism (PHPT) is shown to be associated with significantly reduced BMD especially at femoral neck. Thus, an increased fracture risk should consider if it is left untreated.**

Key words: **Primary Hyperparathyroidism (PHPT), Parathyroid hormone (PTH), Bone Mineral Density (BMD), Dual Energy X-ray Absorptiometry (DEXA), Osteoporosis.**

INTRODUCTION

Hyperparathyroidism is an endocrine disorder characterized by increased synthesis and release of parathyroid hormone (PTH) from parathyroid gland (1). PHPT has prevalence in the general population of approximately 3 per 1000 with a female to male ratio of about 5:1 (2). Incidence of PHPT peaks in midlife and most commonly diagnosed in the fifth through seventh decades of life (3).

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in otherwise healthy outsubjects and therefore the clinical diagnosis of PHPT is largely based on serum laboratory test

results, as subjects often are asymptomatic (4). PHPT mainly diagnosed by its biochemical profile that includes Hypercalcaemia with elevated or inappropriately normal levels of intact PTH (the intact PTH is typically suppressed in PTH independent hypercalcaemia), normal to elevated urinary calcium and hypophosphataemia. Various modalities are available to localize abnormal parathyroid glands, such as- ultrasonography, parathyroid scintigraphy, combined ultrasonography and scintigraphy, CT (Computed Tomography), and MRI (Magnetic Resonance Imaging).

Parathyroid hormone (PTH) is a major regulator of bone remodeling, the process by which the skeleton is being renewed constantly throughout life. The primer of bone remodeling is bone resorption by osteoclasts and bone formation by osteoblasts. It is believed that, PTH mainly has an indirect stimulation on osteoclasts neighboring by osteoblasts. However, this increased resorption of bone is seen in both trabecular and cortical bone in PHPT and causes a temporary, but reversible, bone loss if the remodeling cavities are refilled with new bone. PTH normally secreted in response to low ionised calcium levels. It promotes increased osteoclast activity, causing the release of calcium and phosphate into the serum. It also acts on kidney to increase calcium and decrease phosphate reabsorption at the proximal tubule. The end result of producing too much PTH is therefore hypercalcaemia, hypophosphataemia and loss of bone density (5).

Bone mineral density (BMD) is a measure of mineral content of bone and is the most readily used method to determine bone health. BMD is used not only to measure the amount of bone mass but also to assess fracture risk and guide osteoporosis treatment initiation. Dual Energy X-ray Absorptiometry (DEXA) is currently the most widely available and standardized test, providing rapid, convenient and accurate (85-99%) assessment of BMD. It is an enhanced form of X-ray technology that is used to measure bone loss and can detect as little as 2% of bone loss per year. Measurements are usually taken at the lumbar vertebra L1-L4, and the femoral neck. WHO criteria of BMD is, Normal: T score $\geq$ -1.0, Osteopenia: T score between -1.0 and -2.5, Osteoporosis: T score $\leq$-2.5 (6).

Skeletal complications of advanced PHPT include clinically bone pains, muscle weakness, bone deformities and fracture. In recent onset of PHPT bone changes may be detected by DEXA. Thus the aim of this study was to evaluate BMD, according to WHO scoring with the use of DEXA at two sites – in lumbar vertebral bodies (L1–L4) and femoral neck. In PHPT bone loss is a major complication. Hence low bone mass ultimately results in fracture risk; it is necessary to identify these subjects and taking proper action accordingly.

PATIENTS AND METHODS

During the period of July 2015 to December 2016 this cross sectional Group comparison study was carried out in National Institute of Nuclear Medicine and Allied Sciences (NINMAS), BSMMU, Dhaka. Total 90 subjects of both sexes, age ranged from 15-45 yere ware included in the study. Of them in group-A, 45 subjects were patients of primary hyperparathyroidism, diagnosed biochemically by increased serum level of calcium and parathyroid hormone. 45 subjects were in group-B (without PHPT) who came to the institute for BMD examination for other reasons that does not affect bone metabolism. The subjects who had co-existing renal, hepatic, thyroid or celiac disease, tuberculosis, rheumatological, endocrine or metabolic bone disease and any malignancy were excluded from the study. The subjects who had been receiving or recently treated with calcium, vitamin D, biphosphonates, levo-thyroxine, lithium, heparin, phenothiazine, methotrexate or androgens were also excluded. Pregnant, lactating mother and post menopausal women were also excluded.

After taking informed written consent, subjects were interviewed and relevant information regarding their health status, previous disease, recent treatment, menstruation and lactating status were recorded on a formatted questionnaire form. BMI was calculated from the height and weight of the patients and were divided into five groups according to recent categorization of BMI. All the subjects underwent DEXA scan of spine and left femoral neck to measure bone mineral density by Norland XR-46 densitometer. The region of interest was L1-L2 vertebra in spine and left femoral neck. Analysis of data from DEXA was computerized and completely automated. Low bone mass was defined as osteopenia and osteoporosis according to WHO criteria. WHO study group recommended the definition of osteoporosis and osteopenia, based on BMD value of spine and femoral neck that expressed as T score. According to WHO criteria, Normal: T score ≥ -1.0, Osteopenia: T score between <-1.0 and >-2.5, Osteoporosis: T score ≤-2.5 (6).

Data were processed and analyzed with the help of computer software SPSS (Statistical Package for Social Sciences), version 20. Categorical data were expressed as frequencies and corresponding percentages and continuous data were presented as mean, standard deviation (SD). Data presented on categorical form were analyzed using chi-squared test. While the data presented on continuous scale were analyzed using student's t-test. In each analysis, level of significance was 5% and P value <0.05 was considered significant.

RESULTS

Characteristics of the subjects have shown in Table-1.

Table 1. Characteristics of the study subjects

Parameters	Group A n=45 No (%)	Group B n=45 No (%)	P value X^2 test
Male	28 (62.2)	9 (20)	0.0001
Female	17 (37.8)	36 (80)	
Mean Age	37.24±8.03	38.20±5.74	
Range	20-45	24-45	

Chi square test/Unpaired Student's 't' test

Mean BMI of group-A subjects was 25.10±4.35 kg/m2 ranging 1.43-34.83 in comparison to 29.43±5.17 kg/m2 ranging 21.09-46.31 in group-B subjects shown in Table 2.

Table 2. Body mass index of the study subjects

BMI (kg/m^2)	Group A N=45	Group B N=45	P value X^2 test
<18.49 (underweight)	2 (4.4)	0	0.015*
18.50-24.99 (healthy)	19 (42.2)	9 (20.0)	
25.00-29.99 (overweight)	17 (37.8)	18 (40.0)	
30.00-34.99 (obese)	7 (15.6)	13 (28.9)	
35.00 or more (severely obese)	00	05 (11.1)	
Mean±SD	25.10±4.35	29.43±5.17	(t test) 0.0001**
Range	15.43-34.63	21.09-46.31	

Chi square test/Unpaired Student's 't' test
* = Significant at P<0.05
*** = Significant at P<0.001

Prevalence of low BMD among study subjects has shown in Table-3 and Table-4.

Table 3. Distribution and comparison of BMD value and T- score in study subjects

Parameter	Group A N=45	Group B N=45	P value X^2 test
BMD (g/cm^2)			
Lumbar spine	0.89±0.20 (0.49-1.50)	1.01±0.09 (0.83-1.23)	0.001**
Femoral neck	0.65±0.23 (0.12-1.12)	0.98±0.08 (0.81-1.14)	0.0001***
Difference	0.24±0.25	0.03±0.12	
[b]P value (t test) (t test)	0.0001***	0.097ns	
T-Score			
Lumbar spine	-1.43±1.35 (-3.80-2.70)	-0.46±0.75 (-2.00-1.60)	0.0001***
Femoral neck	-2.38±1.52 (-7.38-0.50)	0.19±0.72 (-1.00-1.70)	0.0001***
Difference	0.95±1.40	-0.65±0.99	
[b]P value (t test) (t test)	0.0001***	0.0001***	

[a]Unpaired Student's 't' test ; [b]Paired Student's 't' test
** = Significant (P<0.01); *** = Significant (P<0.001)

Table 4. Status of BMD at lumbar spine and femoral neck of the study subjects

Status of BMD	Group A N=45	Group B N=45	P value X^2 test
At lumbar spine			
Normal	17(37.8)	37(82.2)	
Osteopenia	17(37.8)	8(17.8)	0.0001***
Osteoporosis	11(24.4)	0	
At femoral neck			
Normal	7(15.6)	45(100.0)	
Osteopenia	16(35.6)	0	0.0001***
Osteoporosis	22(48.9)	0	

Chi-square test
*** = Significant at P<0.001

Relationship between age, sex and BMI with BMD has shown in Table 5, Table 6 and Table 7. In both groups more number of subjects belonged to higher age group. A positive relationship of age and BMD at lumbar spine and negative relationship at femoral neck in group-A with an opposite phenomenon in group-B was noted. BMD was lower in female compare to male in both groups. PHPT subjects showed negative relationship in BMD vs. BMI.

Table 5. Relationship between Age and BMD of study subjects

Parameters	Group A N=45		Group B N=45	
	r	*P*	*r*	*P*
Age vs. BMD				
At lumbar spine	+0.122	0.425^{ns}	-0.094	0.539^{ns}
At femoral neck	-0.145	0.342^{ns}	+0.074	0.631^{ns}

Pearson's correlation coefficient (r) test
ns= not significant

Table 6. Relationship between Sex and BMD of study subjects

Parameters	Group A N=45		Group B N=45	
	r	*P*	*r*	*P*
Sex vs. BMD				
At lumbar spine	-0.058	0.704^{ns}	-0.203	0.180^{ns}
At femoral neck	-0.002	0.991^{ns}	+0.024	0.878^{ns}

Spearman's rho (ρ) correlation coefficient (r) test
ns= not significant

Table 7. Relationship between BMI and BMD of study subjects

Parameters	Group A N=45		Group B N=45	
	r	*P*	*r*	*P*
BMI vs. BMD				
At lumbar spine	-0.090	0.555^{ns}	-0.013	0.931^{ns}
At femoral neck	-0.043	0.777^{ns}	+0.289	0.054^{ns}

Pearson's correlation coefficient (r) test
ns= not significant

DISCUSSION

Most of the studies focused that, incidence of PHPT increased with age of the patient and peak incidence reported between 40 to 70 years. Current epidemiological study of PHPT done in North America with the findings of midlife peak incidence of PHPT in both gender (2). In the present study, mean age of group-A (with PHPT) was 37.24± 8.03 years and 38.20±5.74 years in group-B (without PHPT). Majority of subjects belongs to age group 36-45 years, with (60%) of the participants in group-A and (71.1%) in group-B was observed in this age group.

Aging influences BMD and with older age, reduction of mineralization of the skeleton is expected. Several studies have shown an age related reduction of BMD. However, in this study at lumbar spine positive relationship of BMD with aging in group-A and negative relationship in group-B was observed. In the statement of Vignali, et al. (7) the finding that age is not a risk factor for vertebral fractures in PHPT. Subjects could be due to the relative protective effect of the disease on cancellous bone. Indeed, in PHPT person's cancellous bone is maintained over time more effectively than in normal aging individuals. A negative relationship of BMD with advancing age in group-A and a positive relationship of BMD in group-B at femoral neck also noticed in this study.

Primary hyperparathyroidism naturally occurs in both gender but women are more prone to develop the

disease than men. In spite of this, in this study a male predominance (62.2% male) of participants in group-A and (20% male) in group-B was observed. This male predominance do not correlate with previous findings of female predominance of PHPT, may be due to social factors. In developed countries, women are routinely screened for osteoporosis as well as calcium measurement, which often results in asymptomatic and frequent diagnosis of hypercalcaemia that is not practice in this sub continent (8). This type of gender discrimination was not reflected in the relationship of sex with BMD, where in female low BMD was more compare to male both at lumbar spine and femoral neck in two groups.

Significantly, higher BMI in PHPT group compare to the healthy group pronounced in most of the previous studies. Sillin, H. (9) in her study found, 26.27±4.6 BMI in cases and 24.16±3.5 BMI in controls. In the present study, in group-A only 2(4.4%) subjects were in <18.50 BMI group and 19(42.2%) in 18.5-24.99 (healthy) BMI group, rest of the 41(91.2%) subjects were in ≥25 BMI group with a Mean±SD of 25.10±4.35. Similarly in group-B, out of 45 subjects only 9 were in 18.50-24.99(healthy) BMI group and rest of the 49 were in ≥24.99 BMI group with a Mean±SD of 29.43±5.17. In group-B BMI was significantly higher than group-A. Explanation behind this is unclear, small sample size may be a reason.

In spite of these high BMI, subjects with PHPT shows negative relationship with BMD at both lumbar spine and femoral neck. Mechanism behind this finding is unclear, though a nested case-control study in a cohort of subjects on the effect of hyperparathyroidism on BMI and BMD was carried out at United Kingdom and found, association of both high BMI and an increased osteoporotic risk, with significantly reduced BMD and concluded saying that, reduced BMD in the presence of an increased BMI may be due to certain unique circumstances found in hyperparathyroidism, such as presence of extra PTH-secreting cells in adipose tissue, or the sequestration of vitamin D in adipose tissue, which may lead to further PTH secretion and BMD loss (10).

In the present study, BMD was expressed in absolute value and T score. BMD was classified according to WHO criteria. Prevalence of low BMD was more in subjects with PHPT in compare to subjects without PHPT. At lumbar spines in group-A, equal number of subjects (37.8%) were normal and osteopenic 17 and rest 11(24.4%) were osteoporotic, where as in group-B, 37(82.2%) were normal, 8(17.8%) were osteopenic, none had osteoporosis. This pattern correlates with other studies (9, 11). Although lumbar spine is relatively spared in milder forms in some studies, Feder et al. (12) have shown vertebral osteopenia in 15% of patients at diagnosis. Similarly at femoral neck in group-A, 7(15.6%) were normal; 16(35.6%) were osteopenic and 22(48.9%) were osteoporotic, where in group-B all of the subjects were normal. These findings correlated with other studies (9, 13).

In this study, T score at lumbar spine were, -1.43±1.35 (mean ± SD) in group-A and -0.46±0.75 (mean ± SD) in group-B. On the other side, at femoral neck T score were -2.38±1.52 (mean ± SD) in group-A and 0.19±0.72 (mean ± SD) in group-B respectively. In the mean time, at lumbar spine BMD were 0.89±0.20 (mean ± SD) in group-A and 1.01±0.09 (mean ± SD) in group-B. Similarly in the present study at femoral neck BMD were 0.65±0.23 (mean ± SD) in group-A and 0.98±0.08 (mean ± SD) in group-B. There were statistical significant differences between two groups in all of these findings. In their study to see the morphometric vertebral fractures in postmenopausal women, Vignali, et al. (7) have found, lumbar spine BMD of 0.818±0.142 with -2.06±1.27 T score in cases and 0.797±0.105 BMD with -2.25±0.94 T score in controls. In addition BMD of 0.647±0.108 with -1.78±0.94 T score at femoral neck in cases and 0.664±0.105 BMD with -1.63±0.92 T score in controls.

Several studies have shown decreased bone mineral content or density in subjects with PHPT. Researches (7, 9, 10, 11, 12) showed that, the reduction of BMD varied between skeletal regions, generally tending towards a higher degree of cortical than trabecular bone loss more on cancellous bone. In contrast, a large cohort study by Larsson, et al. (14) found no increased risk of hip fractures in PHPT.

Based upon the densitometric and histomorphometric findings, it may be expected that cortical skeleton would be at greater risk fracture compared to cancellous bone. This pattern of bone involvement is typically reflected in reduced DEXA values at the femoral neck (a site enriched in cortical bone) and relative preservation of lumbar spine (sites primarily consisting of cancellous bone). In their study on skeletal diseases in PHPT of 52 subjects by Silverberg, et al. (15) found , greatest reduction in bone mineral density at the site of predominantly cortical bone, the radius (0.54 ± 0.1 g/cm; 79 ± 2% of expected), whereas the site of predominantly cancellous bone, the lumbar spine (1.07 ± 0.03 g/cm2), was normal (95 ± 3% of expected). The site of mixed composition, the femoral neck (0.78 ± 0.14 g/cm2), gave an intermediate value (89 ± 2% of expected). Preferential involvement of cortical bone with apparent preservation of cancellous bone in PHPT was confirmed by percutaneous bone biopsy.

In this study, presented data were in agreement with those of previous shorter-term studies. Here in group-A, BMD at lumbar spine was 0.89±0.20 with a significant difference (p=0.0001) at femoral neck of 0.65±0.23. Correspondingly, T score at lumbar spine (-1.43±1.35) also shows significant difference with that of femoral neck (-2.38±1.52). In addition, at lumbar spine among 45 PHPT subjects, according to T score 17 were normal, 17 osteopenic and only 11 appeared osteoporotic. Dissimilarly, at femoral neck, 22 were osteoporotic, 16 were osteopenic and only 7 subjects were normal.

In a study (11) bone loss in patient with PHPT evaluated by quantitative bone SPECT. Another study (16) measured bone loss by radiogrammetry of metacarpals, Norland-Cameron photon absorptiometry of the radius, quantitative computed tomography (QCT) of the spine, industrial radiography of the hands, and conventional radiography of thoracolumbar spine. In this study BMD was measured at lumbar spines from L1-L4 vertebra and left femoral neck using DEXA by Norland XR-46 densitometer, which is considered as gold standard in osteoporosis diagnosis.

CONCLUSION

In conclusion, PHPT appears to be associated with reduced BMD, documented especially at femoral neck (site enriched in cortical bone). Measurement of BMD by DEXA in subjects with PHPT can assess bone turnover, and it can predict early rapid cortical bone loss. Low BMD values may indicate the need for parathyroidectomy to prevent irreversible bone loss.

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