Status of Bone Mineral Density in Patients with Hyperthyroidism

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Abstract

Vitamin D deficiency is widely prevalent in patients with hyperthyroidism along with lower bone mineral density. Against this background, the present study aims to analyze the status of bone mineral density in patients with hyperthyroidism along with age and sex matched controls. 70 consecutive patients and controls were analyzed for thyroid function test, BMD parameters and DEXA scan. The values of BMD parameters were analyzed at the baseline in both patients & control group. The baseline values of vitamin D and PTH of both the groups were 19.24±10.15 Vs 28.38±14.56 and 69.81±57.41Vs 58.53±46.49 respectively. BMD at spine and Hip were -1.38±1.31 Vs -0.26±0.80 and -1.02±1.11 Vs -0.22±0.93 respectively. The BMD of total body was 1.044±0.10 Vs 1.160±0.08. Vitamin D deficiency was found to be prevalent in patients with hyperthyroidism along with significantly reduced BMD compared to controls. The occurrence of osteopenia was higher than osteoporosis in the patient group at both lumbar spine and hip region.

Keywords: **Hyperthyroidism, thyrotoxicosis, vitamin D, India, bone mineral density, BMD**

Background & Introduction

Graves' disease is a common endocrine disorder. Patients with active Graves' disease have widespread systemic manifestations involving all organ systems such as CNS, respiratory, cardiovascular, reproductive, gastrointestinal and skeletal system. The effects are due to the metabolic actions of excess thyroid hormones. Patients with Graves' disease in India present late in the course of the disease and therefore have severe thyrotoxicosis. Several novel clinical features of thyrotoxicosis have been reported from India [1-4].

Thyroid hormones have direct catabolic effect on bone mineral homeostasis leading to increased bone mineral resorption and calcium loss through kidneys [5]. Osteomalacia which presents as severe vitamin D deficiency has been reported such as hyperpigmentation of skin, steatorrhea, reduced lung function and vitamin D deficiency [6-7].

Vitamin D deficiency and low BMD have also been reported from New Delhi- India; however, there is a paucity of data and still a lot of scope for further research in Indian population. The present study was planned keeping this in view [8].

Aim of the Study

The study was aimed to assess the parameters related to bone mineral homeostasis such as calcium, phosphorous, alkaline phosphatase, 25-hydroxy vitamin D [25 (OH) D], parathyroid hormone (PTH) and bone mineral density in patients with thyrotoxicosis and varying degrees of vitamin D deficiency. An attempt was also made to compare the BMD parameters with age and sex matched controls to analyze the difference.

Recruitment of Study Subjects

The present study was conducted after obtaining the approval from Institutional Ethics Committee (IEC). All patients and controls were given written informed consent prior to their recruitment in the study. Newly diagnosed 70 consecutive patients (43 females and 23 males) with hyperthyroidism aged > 16 years attending endocrine clinic of Maulna Azad Medical College and Lok Nayak Hospital, New Delhi during the year 2007-2010, were recruited. Exclusion criteria included postmenopausal, pregnant and lactating women, presence of chronic liver disease and renal failure, history of ingestion of steroids, antitubercular drugs, ketoconazole, diuretics or calcium and vitamin D supplements. The cases can have hyperthyroidism due to Graves' disease, toxic multinodular goiter (MNG) and solitary toxic nodule (STN). Graves' disease was diagnosed based upon the criteria suggested by Wayne's clinical score for thyrotoxicosis [9].

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Diagnosis of hyperthyroidism included serum T_3, free T_4 and TSH levels were in hyperthyroid range, high 2-h and 24-h radioactive iodine uptake (RAIU) and diffuse thyromegaly demonstrated clinically, thyroid scan or on ultrasound and diagnosis of toxic MNG and STN essentially involved thyroid scan. Average duration of sun exposure and the surface area of the body-exposed daily to direct sunlight were also assessed. Nutritional status was assessed by estimating the average composition of the daily diet in terms of energy, carbohydrate, protein, fat and calcium by use of a semi quantitative food frequency questionnaire and published data on the nutrient composition of Indian food [10]. It is known that dairy products and food fat are not fortified in with vitamin D in India.

Sample Collection

Fasting venous samples of all the study subjects were drawn at 0800-0900 hrs without venostasis in calcium free test tubes. Serum was separated in a refrigerated centrifuge at 800 x g for 15 minutes at 4°C, and stored in multiple aliquots at –20°C for serum FT_4, TSH, 25 (OH) D and PTH assays. All hormone assays was batched together. Serum calcium, phosphorous and alkaline phosphatase were estimated on the day of collection.

Serum free T4, TSH was done using commercial available kits (Vishat Diagnostics, Mumbai). Serum 25(OH) D and parathyroid hormone (PTH) estimation were measured by Radioimmunoassay (RIA) and radioimmunometric (IRMA) assay respectively using commercial available kits (DiaSorin Inc Stillwater,USA). Intra-assay coefficient of variation ranged from 4.0% to 7.2% for FT4 and TSH. The normal range in our lab is 52-167nmol/L for serum T4, 0.3-0.4mU/l for THS. Normal kit range for PTH is 13-54ng/l. Normal level of serum calcium, phosphorous, serum alkaline phosphatase are 2.25-2.7mmol/l, 0.8-1.5mmol/l and 3-13KA units respectively.

DEXA Scan

Bone mineral density (BMD) was measured using Lunar Prodigy (GE, USA) densitometer. BMD was measured at both hips and lumbar spine (L_1-L_4) at anteroposterior regions. BMD was expressed as bone mineral content/cm^2 area examined. The bone mineral density values were obtained and were compared with the normal values of the young adult reference population with age and sex matched Caucasians population as provided by WHO classification. After DEXA findings the patients were classified into normal, osteopenic and osteoporotic range.

Results

Table.1 Biochemical indices of different parameters of patients with hyperthyroidism with age and sex matched controls

Variables	Patients (N=70)	Controls (N=70)	P Value
Age(Yr)	39±10.01	38.8±10.01	0.9061
BMI (Kg/m^2)	20.58±3.46	24.51±2.03	**0.0001**
Sun Exposure (min/day)	62.17±48.13	81.23±64.47	0.0506
Creatinine (mg/dl)	0.95±0.73	0.88±0.25	0.449

Calcium (mg/dl)	9.46±0.53	9.48±0.74	0.854
Phosphate (mg/dl)	3.46±0.5	3.7±1.0	0.0747
24hrs Dietary Calcium	416.41±269.5	558.47±259.16	**0.0005**
Alkaline Phosphates (IU)	234±134.7	130.92±75.82	**0.0001**
PTH (pg/ml)	69.81±57.41	58.53±46.49	0.2033
25 (OH) D (ng/ml)	19.24±10.15	28.38±14.56	**0.0001**
T. Billurubin	35.04±32.93	27.34±12.08	0.069
ALT	27.14±18.53	35.12± 21.24	0.019
AST	053±0.14	0.57±0.20	0.431
BMD at Spine (T score)	-1.38±1.31	-0.26±0.80	**0.0001**
BMD at Hip (T score)	-1.02±1.11	-0.22±0.93	**0.0001**
BMD Total body (m^2)	1.044±0.10	1.160±0.08	**0.0001**
Values are mean ± SD			

The average duration of illness was 3 years with respective treatment. The mean age of the patients was 39±10.01 years. The baseline lab investigations i.e. billurubin, AST, ALT, ALT, creatinine and urea were 0.53±0.14, 35.04±32.93, 27.14±18.53, 23.55±8.74, 0.95±0.73 and 12.59±56.7 respectively. The mean TSH and Free T4 of patients were 0.54±1.79 µIU/ml and 9.90±21.58 µg/dl respectively.

There were 28 women (40%) and majority of the patients were thyrotoxic state. The average sun exposure was 9% of the total body in 53 patients (75%) and 17 patients (25%) had 18% of the total body exposure. The bone mineral parameters such as parathyroid hormone (PTH), 25(OH) D, alkaline phosphatase, calcium and phosphorous were 69.81±57.41pg/ml, 19.24±10.15 ng/ml (p>0.0001), 234±134.7 IU/ml, 9.46±0.53 mg/dl (p>0.0001) and 3.46±0.5 mg/dl respectively.

BMD at lumbar spine (L1-L4) and femur region were -1.38±1.31 and -1.02±1.11 respectively which was highly significant (p>0.0001). The values of Z

score of AP spine and femur were also recorded and the values were -0.82±1.14 and -0.56±1.21 respectively which was not statistically significant may be because of age matched control population. The total body BMD and 24hrs dietary calcium were also found significant higher in patient group as compared to controls.

Discussion

It is not uncommon to find vitamin D deficiency in Indian population including hyperthyroidism. Several studies have demonstrated low serum vitamin 25(OH) D levels in different populations across India [11-14]. Patients with active thyrotoxicosis in India are at an increased risk of osteomalacia or osteoporosis due to associated vitamin D deficiency [15]. However, some studies have documented normal serum levels of 25(OH) vitamin D in thyrotoxicosis patients whereas others showed subnormal vitamin D levels [16-17].

Earlier, few reports showed subnormal 25 (OH) D levels in patients with hyperthyroidism. Besides, there is scarcity of data from Indian subcontinent regarding the effect of thyrotoxicosis on bone [18-21].

Udayakumar and colleagues recently reported significantly low BMD in patient with thyrotoxicosis [22]. Goswami et al. reported widespread vitamin D deficiency in healthy individuals residing in Delhi due to skin pigmentation and poor sunlight exposure [8].

Dhanwal et al. reported high vitamin D deficiency in Northern India. It is relevant to see its impact on bone loss in patients with hyperthyroidism. 26% of thyrotoxic patients had concomitant vitamin D deficiency with pronounced bone loss [23]. In a study done by Jyotsna et al. too, insufficient vitamin D levels were found along with reduced BMD in hyperthyroidism patients [24].

However, the current study found 60% of vitamin D deficiency in hyperthyroidism patients. Furthermore, in entire group of patient's population vitamin D insufficiency was found in 11 patients (15.71%), deficiency in 36 patients (51.42%). Only 23 (32.85%) of the patients had optimal vitamin D levels.

In a study done by Velentzas et al., significantly lower plasma 25 (OH) D levels were reported in thyrotoxic patients compared to value observed in controls [19], which is in accordance with the current study (Refer Table 1).

Another study done by Yamashita et al. has also reported subnormal levels of 25 (OH) D levels in 40% in females and 18% in males in a series of 208 patients with Graves' disease [17]. Similarly, we have also found hypovitaminosis D in 30.57% in female and 21.42% in male group respectively.

It is well known that hyperthyroidism is an important cause of secondary osteoporosis [20]. Results of BMD show that 50% of the patients had osteopenia and 15% osteoporosis at AP spine region. At hip region, the percentages of osteopenia and osteoporosis were and 48.5% and 10% respectively. The occurrence of osteopenia was higher at both hip and spine region than osteoporosis.

However, milder form of vitamin deficiency with subnormal levels of serum 25(OH) D can cause chemical osteomalacia characterized by low to normal serum calcium, phosphorous, increased serum alkaline phosphates and PTH levels without symptoms and signs.

Patients with hypovitaminosis D and secondary hyperthyroidism represent increased bone loss at lumbar spine and hip region [24].

Serum alkaline phosphatase in majority of the patients was significantly higher (98%) as compared to controls. Secondary hyperparthyroidism (SHTP) was also observed in 35 patients (50%).

The levels of Vitamin D were negatively correlated with age (-.153), PTH (-.214), ALP (-.225), and BMD at hip region (-.018). However, it was not significantly associated with BMD at spine region (Refer Table 2).

There were certain limitations of the study. Few of the patients were at postmenopausal stage which might affect the vitamin D status along with secondary hyperparathyroidism. It was also affected by the dietary calcium intakes of the subjects and their socio-economic status as majority of the patients belonged to low socioeconomic group. The majority of the female patients belonged to Islamic/Muslim religion and wore veil routinely which may influence vitamin D levels in these groups of patients.

Table 2: Correlation of Different variables

Correlation Variables	Age	PTH	Vitamin D
Age	1	.043	-.153
ALP	-.118	.271*	-.225
Calcium	-.085	-.187	.249*
P04	-.076	-.006	.005
PTH	.043	1	-.214
Vit D	-.153	-.214	1
BMD at Spine	-.315**	-.036	.101
BMD at Femur	-.113	-.143	-.018
BMD total body	-.126	-.050	-.008
24 dietary Cal	-.086	-.081	.099

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Conclusion

Patients with hyperthyroidism have significantly reduced bone mineral density with concomitant vitamin D deficiency as compared to controls. The occurrence of osteopenia is almost similar both at spine and hip region as compared to osteoporosis.

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