Vitamin D Supplementation improves Bone Mineral Density in Patients with Hyperthyroidism

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Abstract

Background: **Diseases of the thyroid gland are a common occurrence in India. Thyrotoxicosis causes acceleration of bone remodeling and even though it is one of the known risk factors for osteoporosis, the metabolic effects of thyroxine on bone is a little- discussed subject.**

Materials & Methods: **70 consecutive patients with hyperthyroidism attending endocrine clinic of Maulana Azad Medical College. Serum total calcium, phosphorous, urinary creatinine and alkaline phosphatase were measured by standard methods. Serum T4, serum 25(OH)D estimations were done by radioimmunoassay assay. Serum intact PTH and TSH concentration was measured by immune-radiometric assay using commercial kits. Bone mineral density was measured using Hologic DR 4500A densitometer. Bone mineral density was measured at both hips, and lumbar spine (L_2-L_4) using anteroposterior view. 50% of the patients were randomized for vitamin D supplementation.**

Results: **The mean age of the patients was 39±10.01 years. The baseline vitamin D of the patients was 19.24±10.15 ng/ml. The values of vitamin D in randomized and non-randomized patients were 27.82±16.43 vs 11.82±6.58 ng/ml (p>0.0001) respectively. Patients who received vitamin D had acquired optimum level of vitamin significantly, whereas, BMD at lumbar spine was also found increased after post treatment of vitamin D. However, it was not significantly raised when compared with the pre treatment. BMD at hip region was found elevated after post-treatment. There was an improvement noticed in total body BMD as well.**

Conclusion: **Patients with active thyrotoxicosis, acquired optimum vitamin D levels, elevated lumbar spine and hip BMD after one year of vitamin D supplementation. Vitamin D supplementation is necessary to be advocated in patients with hyperthyroidism.**

Keywords: **Parathyroid hormone (PTH), Vitamin D deficiency (VDD), Radio-immuno-assay (RIA), Bone mineral density (BMD).**

Background

Little is known about the impact of concomitant vitamin D deficiency on bone mineral density in hyperthyroidism with common occurrence in India. Thyrotoxicosis, a clinical syndrome characterized by manifestations of excess thyroid hormone, is one of the commonly recognized conditions of the thyroid gland. Thyrotoxicosis causes acceleration of bone remodeling[1-11] and even though it is one of the known risk factors for osteoporosis, the metabolic effects of thyroxine on bone is a little-discussed subject. There are largely limited studies in India as to whether these changes are reversible. In this study, we note the incidence and profile of bone involvement in

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thyrotoxicosis patients by dual energy x-ray absorptiometry (DEXA) scan and the effect of treatment on the bone mineral density (BMD) after control of thyrotoxicosis.[12]

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 with severe thyrotoxicosis, late in their clinical course. Several novel clinical features of thyrotoxicosis have been reported from All India Institute of Medical Sciences (AIIMS), New Delhi, representing clinical abnormalities as occur in the late stages of natural history of Graves' disease.[13-16]

Studies reported widespread vitamin D deficiency in healthy individuals residing in Delhi due to skin pigmentation and poor sunlight exposure.[17] Patients with Graves' disease in India have marked proximal muscle weakness due to skeletal muscle myopathy. Majority of patients have increased skin pigmentation during thyrotoxic state.[18] Thyroid hormones have direct catabolic effect on bone mineral homeostasis leading to increased bone mineral resorption and calcium loss through kidneys.[19]

Increased skin pigmentation and related vitamin D deficiency coupled with excessive urinary calcium loss, caused by thyrotoxicosis, may well be responsible for causing significant abnormalities in bone mineral homeostasis in thyrotoxic patients in India. There have been reports of osteomalacia in patients with thyrotoxicosis from India[20-21] and elsewhere[22-25] yet there is no scientific systematic study till date to examine the effect of thyrotoxicosis on bone mineral homeostasis in people with vitamin D deficiency.

We therefore, conducted this study to assess 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.

Aim of the Study

Our aim was to assess the effect of vitamin D supplementation in vitamin D deficient and sufficient patients with hyperthyroidism and response by studying the BMD along with parameters related to bone mineral density after one year of vitamin D supplementation.

Materials & Methods

70 consecutive patients with hyperthyroidism attending endocrine clinic of Maulana Azad Medical College, New Delhi in the past three years (2008-2011) were included. 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 will be diagnosed based upon criteria suggested by Volpe Wayne's clinical score for thyrotoxicosis, serum T_3, T_4 and TSH levels in hyperthyroid range, high 2-h and 24-h radioactive iodine uptake (RAIU) and diffuse thyromegaly demonstrated clinically, thyroid scan or on ultrasound. Diagnosis of toxic MNG and STN essentially involved thyroid scan.

All patients were subjected to detailed history and clinical examination using a pre-designed pro forma. History included assessment of severity of hyperthyroidism using Wayne's score, osteomalacia/ osteoporosis discriminatory score described by McKenna et al.,[26] documenting average duration of sun exposure and surface area of the body- exposed daily assessed direct sunlight exposure. Fasting venous samples of all study subjects was 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 T_4, TSH, 24(OH)D and PTH assays. All hormone assays were batched together. Serum calcium, phosphorous and alkaline phosphatase were estimated on the day of collection. Serum total calcium, phosphorous, urinary creatinine and alkaline phosphatase were measured by standard methods. Documenting average duration of sun exposure and surface area of the body-exposed daily assessed direct sunlight exposure. 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. Dairy products and food fat are not fortified in with vitamin D in India. Serum T4, serum 25(OH)D estimation was done by radioimmunoassay assay. Serum intact PTH and TSH concentration was measured by immune-radiometric assay using

commercial kits. Intra-assay coefficient of variation ranged from 4.0% to 7.2% for T4 and TSH. The normal range in our lab is 52-167nmol/L for serum T4, and 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.

Bone mineral density was measured using Hologic DR 4500A densitometer. It was measured at both hips, and lumbar spine (L_2-L_4) using anteroposterior view. The bone mineral density was expressed as bone mineral content/cm^2 area examined. The bone mineral density value obtained was compared with the normal values of the young adult reference population and age and sex matched Caucasians as provided by WHO (Appendix 6). T and Z scores represent the number of standard deviation from the estimated mean peak bone mineral density of adult young reference and age, sex matched population respectively.

Hyperthyroid subjects were stratified into vitamin D sufficient and deficient group. A cut off level of 10ng/ml was used to designate vitamin D deficient group based on the mean-2SD value of the patients who had 370 minutes of sun exposure and 10% body surface area exposed during winter. Data was expressed as mean ± SD. Student "t" test was used to establish whether differences existed within study groups. Chi-square test was used to assess differences in the frequency of different indices between vitamin D deficient and sufficient group. Pearson correlation test was used to assess relationship among study variables.

Out of 70 patients, 35 patients (50%) were randomized to receive vitamin D (Cholecalciferol sachet once a month with milk (60,000 IU)) along with Calcium tablets (Calcium 500 mg BD). BMD measurement (DEXA) was done after one year of treatment effect along with BMD laboratory parameters and results were compared at the baseline and post treatment.

Results

Baseline characteristics of the parameters are given in table 1. The average duration of illness was 3 years with respective treatment. The mean age of the patients was 39±10.01 years. The mean TSH and free T4 of patients were 0.54±1.79 μIU/ml and 9.90±21.58 μg/dl respectively. The baseline lab investigations such as bilirubin, SGOT, SGPT, and creatinine were 0.53±0.14, 27.14±18.53, 35.04±32.93 and 0.95±0.73 respectively. The bone mineral parameters such as parathyroid hormone (PTH), 25(OH)D, alkaline phosphatase, calcium and phosphorous were 69.81±57.41, 19.24±10.15, 234±134.7, 9.46±0.53 and 3.46±0.5 respectively. The 24hrs dietary calcium intake was 416.41±269.5. The bone mineral density at lumbar spine, hip and total body were-1.38±1.31,-1.02±1.11 and 1.044±0.10 respectively.

There were 28 women patients (40%) and majority of the patients were at thyrotoxic state. The average sun exposure was 9% (whole body) in 53 patients and rest of 17 patients had 18% of the total body exposure.

S. No	Parameters	Values
1.	Age (Years)	39±10.01
2.	BMI (Kg/m^2)	20.58±3.46
3.	Sun Exposure (min/day)	62.17±48.13
4.	Creatinine (mg/dl)	0.95±0.73
5.	Calcium (mg/dl)	9.46±0.53
6.	Phosphate (mg/dl)	3.46±0.5
7.	24hrs Dietary Calcium (mg/24hrs)	416.41±269.5
8.	Alkaline Phosphates (IU)	234±134.7
9.	Parathyroid hormone (pg/ml)	69.81±57.41
10.	25(OH)D (ng/ml)	19.24±10.15
11.	T. Billurubin (mg/dl)	0.53±0.14
12.	SGOT (U/L)	27.14±18.53
13.	SGPT (U/L)	35.04±32.93
14.	BMD at Spine (T score) (g/cm^2)	-1.38±1.31
15.	BMD at Hip (T score) (g/cm^2)	-1.02±1.11
16.	BMD Total body (m^2)	1.044±0.10

*values are given in Mean ± SD

Table 1.Baseline characteristics of different parameters in whole group (N=70)

Parameters such as T. Bilirubin, AST, ALT, Urea and Creatinine in both randomized and non randomized patients were 0.525±0.15 vs 0.52±0.21, 27.71±16.38 vs 27.14±32.93, 23.42±6.66 vs 25.79±14.38, 24±7.37 vs 24.14±11.11, and 0.82±0.22 vs 1.39±3.47 respectively. The BMD parameters such as PTH, 25(OH)D, Alkaline phosphatase, calcium and phosphorous were 71.43±70.36 vs 80.63±64.13, 27.82±16.43 vs 11.82±6.58 (p>0.0001), 193.38±167.38 vs 175±179.64, 9.42±0.52 vs 9.57±0.52 and 3.5±0.91 vs 4.0±1.38 respectively. The DEXA findings were analyzed in both the groups at different regions such as AP spine (L1-L4), Femur (hip), and total body BMD were-1.102±1.39 vs-1.40±1.44,-0.72±1.22 vs-1.02±1.11 (p>0.0001) and 1.036±0.116 vs 0.983±0.08 (p>0.0001) respectively (table 2).

S. No.	Parameters	Randomized group	Non- randomized group	p Value
1	Age (years)	39±10.01	39±10.01	0.906
2	Calcium (mg/dl)	9.42±0.52	9.57±0.52	0.238
3	Phosphorus (mg/dl)	3.5±0.91	4.0±1.38	0.078
4	Alkaline Phosphatase (Ka/U)	193.38±167.38	175±179. 64	0.659
5	SGOT (U/L)	27.71±16.38	27.14±32.93	0.865
6	SGPT (U/L)	23.42±6.66	25.79±14.38	0.375
7	T. Bilirubin (mg/dl)	0.525±0.15	0.52±0.21	0.912
8	Urea (mg/dl)	24±7.37	24.14±11.11	0.968
9	Creatinine (mg/dl)	0.82±0.22	1.39±3.47	0.335
10	PTH (pg/ml)	71.43±70.36	80.63±64.13	0.569
11	25(OH)D (ng/ml)	27.82±16.43	11.82±6.58	**0.0001**
12	T Score (AP Spine)	-1.102±1.39	-1.40±1.44	0.3815
13	T Score (Femur/hip)	-0.72±1.22	-1.02±1.11	**0.0001**
14	BMD (Total Body)	1.036±0.116	0.983±0.08	0.0296

*P value of all parameters was < 0.01. P values are calculated by one sample t-test and were considered significant (< 0.05).

Table 2.Characteristics of different parameters in groups

Our next effort was to see the BMD related parameters within randomized and nonrandomized groups for comparison. The patients who received vitamin D had acquired optimum level of vitamin significantly, whereas, BMD at lumbar spine was also found increased after post treatment of vitamin D. However, it was not significantly raised when compared with the pre treatment. BMD at hip region was found elevated after post treatment. There was an improvement noticed in total body BMD as well (table 3).

S. No.	Parameter	Pre treatment	Post treatment	P Value
1	Calcium (mg/dl)	9.394±0.56	9.422±1.22	0.9022
2	Phosphorous (mg/dl)	3.47±0.69	3.59±0.91	0.5363
3	Alkaline phosphatase (Ka/U)	233.57±130.27	193.38±167.38	0.2662
4	PTH (pg/ml)	63.70±58.19	71.43±70.36	0.6181
5	25(OH)D (ng/ml)	18.18±11.01	27.82±16.43	**0.0053***
6	BMD Lumbar Spine	-1.44±1.31	-1.102±1.39	0.2988
7	BMD Hip/ femur	-0.968±1.23	-0.723±1.22	0.4057
8	Total body BMD	1.0336±0.12	1.0362±0.116	0.9268

*P value of all parameters was < 0.01. P values are calculated by one sample t-test and were considered significant (< 0.05).

Table 3.BMD parameters in Randomized patients

Other bone mineral parameters were also noticed such as calcium, phosphorous and alkaline phosphatase. There was an improvement in calcium levels, and significant decline was observed in alkaline phosphatase. Only phosphorous levels were found a bit elevated after the vitamin D treatment. In a similar fashion, same parameters were looked upon in the non randomized group. There was a significant jump found in PTH levels and their vitamin D levels were also lower than the baseline levels. However, BMD at lumbar spine was found slightly elevated. BMD at hip was found lower along with total body BMD (table 4).

S. No.	Parameter	Pre treatment	Post treatment	Value
1	Calcium (mg/dl)	9.528±0.52	9.522±0.52	0.9616
2	Phosphorous (mg/dl)	3.454±0.43	4.00±1.38	0.0287
3	Alkaline phosphatase (Ka/U)	234.42±142.9	175.05±179.64	0.0212
4	PTH (pg/ml)	75.93±57.65	80.63±64.13	0.7481
5	25(OH)D (ng/ml)	20.29±9.4	11.82±6.58	0.0001
6	BMD Lumbar Spine	-1.322±1.35	-1.48±1.44	0.6373
7	BMD Hip/ femur	-1.088±1.03	-.085±1.14	0.9908
8	Total body BMD	1.054±0.086	0.983±0.23	0.0917

* P value of all parameters was < 0.01. P values are calculated by one sample t-test and were considered significant (< 0.05)

Table 4.BMD parameters in Non- Randomized patients

No change was recorded in calcium levels but phosphorous levels were found elevated. Surprisingly, alkaline phosphatase levels came down lower. This might also have been because of the ongoing anti-thyroid treatment.

Discussion

There is a high vitamin D deficiency in Northern India. Tt is relevant to see its impact on bone loss in patients with hyperthyroidism. In a study by Jyotsna et al. on hyperthyroid Graves patients, BMD was found to be significantly lower at hip, spine and forearm. Serum 25(OH)D levels < 20 ng/ml was found in 70 (87.5%) patients.[27]

Dhanwal et al., showed that 26% of thyrotoxic patients in India have concomitant vitamin D deficiency and they have more pronounced bone loss. With this study as background, it is important to study the bone mineral homeostasis in more thyrotoxic patients and impact of vitamin D supplementation in the group with vitamin D deficiency.[28]

Our observation showed vitamin D insufficiency in 11 patients (15.71%), deficiency in 36 patients (51.42%) and only 23 patients (32.85%) had optimal vitamin D levels.

Serum levels of 25(OH)D, $1,25(OH)_2D$ and other metabolites of vitamin D have been studied by various investigators. Most of the studies have documented lower serum levels of 25(OH)D in hyperthyroidism.[17-18] Velentzas et al. and Mosekilde et al. reported significantly lower plasma 25(OH)D levels in thyrotoxic patients when compared to the value observed in controls.[29] Yamashita et al. have reported subnormal levels of 25(OH)D in 40% of females and 18% of males in a series of 208 patients with Graves' disease. The subnormal levels of mean plasma 25(OH)D in the above studies was postulated to be due to reduced intestinal absorption of vitamin D due to steatorrhea or hepatic enzyme induction, reduced sun exposure or deficient vitamin D intake in diet.[30]

Subjects with hyperthyroidism high serum calcium, low PTH and high phosphorous levels suppress renal 25(OH)D 1 hydroxylase activity leading to decrease in $1,25(OH)_2D$ levels (47). Serum 24, $25(OH)_2D$ levels are increased in patients with hypothyroidism and correlates with serum thyroid hormone levels.

Hyperthyroidism is an important cause of secondary osteoporosis. Our study shows that patients with active thyrotoxicosis have reduced lumbar spine BMD. However, BMD measurements were found to have increased after therapy within randomized group of patients. Early studies have used conventional radiography to assess bone mineral content.[24] During 1970-80s, single photon absorptiometry and dual photon absorptiometry were used to quantify bone mineral density at various sites. Tsai K S et al. studied bone mineral density in 24 untreated patients with hyperthyroidism using dual photon absorptiometry and showed significant increase after one year of treatment with anti- thyroid drugs and propranolol.[31] From 1991 onwards, dual energy absorptiometry (DEXA) is available for bone mineral density measurements. DEXA allows rapid, accurate and highly reproducible assessment of mineral content with a minimal exposure to radiation. Bayley et al., studied bone mineral and muscle mass using in vivo neutron activation analysis in patients with hyperthyroidism before and after treatment. In this method, stable ^{48}Ca is converted to radioactive ^{49}Ca and radioactivity recorded corresponds to mineral content. The latter is normalized to body size and expressed as calcium bone index (Ca BI). Muscle mass was also measured by counting the radioactive ^{40}K in a whole body counter and then normalized with body size.[32] Reversibility of both bone mineral mass and body muscle mass was recorded after one year of treatment with radioiodine therapy. In this study, BMD indicates

50% osteopenia and 15% osteoporosis at lumbar spine region and 48.5% and 10% at hip region respectively.

Krolner et al. investigated 25 patients with hyperthyroidism and demonstrated 12.5% lower bone mineral content at lumbar spine when compared to healthy controls and lumbar bone mineral content increased by 3.7% after 1 year of antithyroid therapy.[6] Additionally, most of the subsequent studies have shown significant increase in bone mineral density following treatment.[27] In a study we have shown that patients with hyperthyroidism have significant bone loss[33] as compared to Caucasians[28], concomitant vitamin D deficiency exacerbates bone loss in these patient with hyperthyroidism. Sworczak et al. showed that vitamin D supplementation can help to improve bone mineral density in patients with hyperthyroidism.[34] Further studies are required to assess reversibility of bone loss after treatment with anti- thyroid drugs and effects of calcium and vitamin D supplementation on recovery of bone loss in patients with hyperthyroidism from vitamin D deficient population.

Conclusion

Metabolic bone disease should be looked for in all thyrotoxic patients, especially patients complaining of bone pain and those with elevated bone enzymes. Our study shows that patients with active thyrotoxicosis have optimum vitamin D levels, raised lumbar spine BMD and significantly elevated hip BMD after one year of vitamin D supplementation. Therefore, vitamin D supplementation is necessary to be advocated in patients with hyperthyroidism keeping in mind its rising prevalence worldwide.

Conflict of Interest: None

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