Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/463

Original Article

Multiple Effects of Hypothyroidism on Bone Mineral Density and Its Association with Vitamin D, Serum Calcium: A Cross-sectional Study

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Abstract

Introduction: Hypothyroidism is one of the most common endocrine disorders worldwide. Thyroid stimulating hormones (TSH) directly affects the remodeling of bone through TSH receptor found on osteoblast and osteoclast precursor cells. The physiological variation of thyroid hormones is associated with changes in bone mineral density (BMD) and nonvertebral fracture risk in healthy postmenopausal women.

Material and Methods: The study population included 94 females suffering from hypothyroidism and 75 healthy female subjects of 20-60 years age group. Thyroid function test including serum total triiodothyronine, free thyroxine, and TSH was measured by enzyme-linked immunosorbent assay (ELISA) method. Serum calcium level was measured by Arsenazo III Method. Whereas, Vitamin D was estimated by ELISA method. BMD was measured by dual electron X-ray absorptiometry at the femoral neck.

Results: Results of the present study revealed that serum calcium level of Group I hypothyroid female patients was significantly low in comparison to Group II control female subjects ($P < 0.0001$). Vitamin D was significantly low in hypothyroid female patients in comparison of euthyroid female subjects (24.31 ± 13.41 ng/dl vs. 42.79 ± 9.67 ng/dl, $P < 0.0001$). Further, BMD in hypothyroid female patients was significantly high in comparison of euthyroid female subjects (−0.97 ± 0.22 g/cm^2 vs. -1.06 ± 0.34 g/cm^2, $P < 0.04$). X-ray of both group participants showed an insignificant difference in a long bone (femur).

Conclusion: Findings of the present study suggest thyroid hormones play an important role in strengthening and remodeling of bones as decreased thyroid hormones are associated with a decrease in serum calcium and Vitamin D. Further, increased BMD in hypothyroid patients induces stiffness of bones which further increases the risk of fracture. Moreover, present research suggests that serum calcium, Vitamin D and BMD should be investigated to prevent the risk of fracture in hypothyroid patients.

Key words: Bone mineral density, Hypothyroid, Serum calcium, Vitamin D

INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders worldwide.[1] The prevalence of hypothyroid is 10-11% in India.[2] Insufficient production of thyroid hormones is considered as hypothyroidism.[3] Hypothyroid is related to the weight changes of the body, heart thyroid gland and bones.[4] Any changes of normal thyroid function in euthyroid individuals are related with body weight variations.[5] Thyroid stimulating hormones (TSH) directly affects the remodeling of bone through TSH receptor found on osteoblast and osteoclast precursor cells.[6] TSH has a positive correlation with body mass index (BMI) in women; though, this correlation is insignificant in male.[5] Women having subclinical hypothyroidism have reduced femoral neck bone mineral density (BMD).[6] The variations in thyroid function are primary, while changes in body weight and bones are secondary.[5] The physiological variation of thyroid hormones is associated with changes in BMD and nonvertebral fracture risk in healthy postmenopausal women.[7] Serum calcium levels are decreased in subclinical hypothyroid and overt hypothyroidism compared to euthyroid while a negative

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www.ijss-sn.com

Month of Submission : 07-2017
Month of Peer Review : 08-2017
Month of Acceptance : 09-2017
Month of Publishing : 09-2017

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correlation between serum TSH levels and serum calcium.[8] Osteoporosis is one of the widespread metabolic diseases of bone in which the bone becomes thin and fragile, creating an increased risk of fracture.[9] According to the World Health Organization (WHO) BMD 2.5 or more standard deviations (SD) below that of a young adult (T score) at any site is osteoporosis.[10] The defective thyroid function may be one of the important causes of osteoporosis.[11] Nonetheless, hyperthyroidism poses a negative effect on bone metabolism while hypothyroidism in does not affect bone density in premenopausal females.[10,11] Bone strength is predicted by both BMD and bone architecture.[12] In general, thinned cortices reduce the number of trabeculae, and endosteal reabsorption is hallmark features of osteoporosis in radiography.[13] The WHO classified BMD into categories of normal (T-score <−1), Osteopenia (−1< T-score<−2.5), Osteoporosis (T-score <−2.5), and severe osteoporosis (T-score <−2.5 with a fragility fracture).[14]

There is still controversy about the relation between thyroid hormones, osteoporosis and BMD in female hypothyroid patients. Therefore, the present study was designed to fulfill in these lacunae in our understanding of impact of hypothyroid disorder on long bones, serum calcium, and Vitamin D in female patients.

MATERIALS AND METHODS

This was a cross-sectional study which was conducted in the Department of Anatomy, Rama Medical College, Kanpur, Uttar Pradesh. The study population was consisting of females both suffering from hypothyroid and healthy, between 18 and 60 years of age. The study population was divided into two groups, Group I (hypothyroid group) included 59 females suffering from hypothyroid, whereas, Group II (control group) consisted 52 healthy female subjects. All the participants of the present study both hypothyroid patients and controls were recruited from Rama medical college and Hospital, Kanpur. Female hypothyroid patients with BMI 20-40 kg/m^2 were included while hypothyroid patients are suffering from any type of chronic disease, e.g., diabetes mellitus, tuberculosis, renal failure, and hypertension were excluded from the study. Patients on hormone replacement therapy, antihypertensive medicines or on any other medication were not included in this study. This research was approved by the Ethical Committee of Rama Medical College and Hospital, Kanpur. All the participants gave their informed written consent before participating in the study.

Methodology

Anthropometric parameters

The height of the participants was measured using standard height scale.[15] Weight was measured by the standard portable weighing machine.[15] BMI was calculated using the formula - BMI = weight (kg)/height (m^2).

Biochemical parameters

Thyroid functions were assessed by measuring serum total triiodothyronine (T3), free thyroxine (FT4), and TSH by enzyme-linked immunosorbent assay (ELISA) method (kits manufactured by Avantor Performance Materials, India).[16] Serum concentration of total cholesterol, serum concentration of triglycerides, and serum concentration of high-density lipoprotein were estimated by the enzymatic cholesterol oxidase - peroxidase (CHOD-POD) method, glycerol phosphate oxidase - Papanicolaou test (GPO-PAP) method and CHOD-POD/phosphotungstate method, respectively, (kit manufactured by Erba Mannheim, India).[16] Serum concentration of low-density lipoprotein was measured using Friedewald's formula.[16] Serum calcium level was measured using Arsenazo III Method while kit manufactured by Diagnostics Pvt., Ltd. India was used. Whereas, Vitamin D was estimated by ELISA method (kit manufactured by Cayman chemical company, Ann Arbor, USA).[16] ELISA reader and biochemistry analyzer E-C5VZ (10 k), respectively, manufactured by Robonik (India) Pvt., Ltd. and Transasia (India) were used for biochemistry analysis. X-ray of long bone was done by MDX - 100 (100 mA, 100 KVP fixed X-ray machine) manufactured by recorders and Medicare Systems Pvt., Ltd, Panchkula (HR). BMD was measured dual electron X-ray absorptiometry using the Hologic machine (QDR 4500; Discovery a Hologic, Waltham, Massachusetts) at the femoral neck.[17]

$$\text{T}-\text{score} = \frac{\text{Subject's BMD value} - \text{Mean yong normal BMD value}^{6}}{\text{ISD young normal BMD}}$$

Statistical Analysis

Baseline characteristics of the study participants were expressed in mean ± SD. Unpaired student *t*-test was used to analyze if there were any difference in different parameters of both groups. A $P < 0.05$ was considered statistically significant. IBM Statistical Package for the Social Sciences Statistics 21 manufactured by IBM USA will be used for entire calculations.

RESULTS

All the results of the present study were expressed as mean ± SD. Table 1 summarizes that there was an insignificant change in age ($P > 0.05$) of both groups participants. Further, it is evident from Table 1, that there was a significant difference between weight ($P < 0.001$) and BMI ($P < 0.0012$) of Group I hypothyroid female patients and Group II control female subjects.

Table 2 summarizes that T3 ($P < 0.0001$) and FT4 ($P < 0.0001$) were significantly low in Group I hypothyroid female patients in comparison to Group II normal female subjects. Further, TSH was significantly high in Group I patients in comparison of Group II subjects ($P < 0.0001$). Results of the present study revealed that serum calcium level of Group I hypothyroid female patients was significantly low in comparison to Group II control female subjects ($P < 0.0001$). Furthermore, there was a significant difference in total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein of Group I and Group II (Table 2).

Figure 1 shows that Vitamin D was significantly low in hypothyroid female patients (24.31 ± 13.41 ng/dl) in comparison of euthyroid female subjects (42.79 ± 9.67 ng/dl). The $P < 0.00001$. Further, it is evident from Figure 2 that BMD in hypothyroid female patients was significantly high in comparison of euthyroid female subjects (−0.97 ± 0.22 g/cm^2 vs. −1.06 ± 0.34 g/cm^2, $P < 0.04$).

It is evident from Figure 3 that X-ray of both group participants showed an insignificant difference in a long bone (femur).

DISCUSSION

Thyroid disorder has been found associated with alteration of bone growth.[18] Moreover, hypothyroid causes increase risk of fracture of bones[19] finding of this study showed that serum calcium level of hypothyroid female patients was significantly low in comparison of euthyroid females. Our findings are consistent with the previous studies of Shivaleela *et al.*[20] and Kavitha *et al.*[8] as they observed the similar low concentration serum calcium in hypothyroid patients in comparison to control subjects. Calcium is one of the most important nutrients of the body which is reserved in the bones.[21] This low serum calcium level in hypothyroid female as observed in the present study seems to be due to a decrease of hypothyroid hormones cause reduced basal metabolic rate which in turn leads to decreasing turnover of calcium.[8,20] Decrease of calcium for

Table 1: Baseline characteristics of the participants

Parameters	Group I	Group II	*P*
Age (years)	33.29±11.26	33.85±11.55	<0.7486^{NS}
Height (m)	154.18±6.71	155.19±6.55	<0.3251^{NS}
Weight (kg)	55.73±5.46	53.44±5.86	<0.001**
BMI (kg/m^2)	23.19±2.71	22.22±1.81	<0.0012**

Values expressed as mean±SD, NS: Nonsignificant, **(*P*<0.05) significant.
BMI: Body mass index, SD: Standard deviation

Table 2: Comparison of thyroid hormones in both groups

Parameters	Group I	Group II	*P*
T3	0.33±0.16	1.07±0.2	<0.0001**
FT4	0.9±0.46	1.24±0.4	<0.0001**
TSH	30.73±15.42	2.35±1.41	<0.0001**
Serum calcium	7.66±1.21	9.09±0.62	<0.0001**
TC	213.2±29.16	195.16±24.26	<0.0001**
TG	125.99±27.74	109.84±21.57	<0.0001**
HDL	41.39±5.59	42.86±7.42	<0.147^{NS}
LDL	146.39±27.3	130±23.79	<0.0001**

Values expressed as mean±SD, NS: Nonsignificant, **(*P*<0.05) significant.
T_3: Triiodothyronine, FT_4: Free thyroxine, TSH: Thyroid stimulating hormones, SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TC: Total cholesterol, TG: Triglyceride

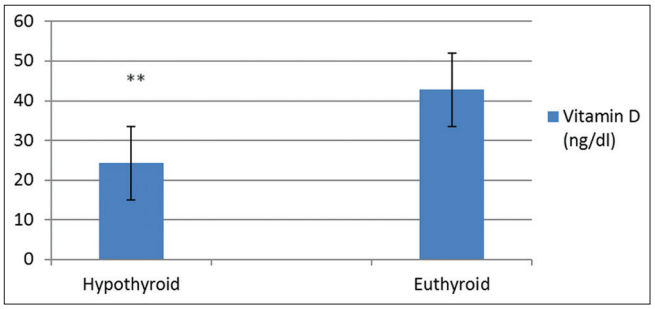

Figure 1: Comparison of Vitamin D in both groups, **P<0.05 significant

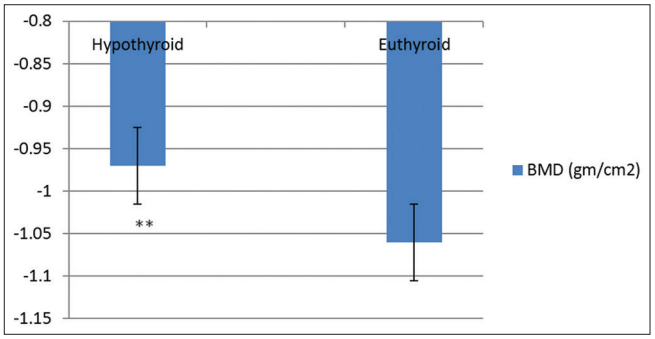

Figure 2: Comparison of bone mineral density in both groups, **P<0.05 significant

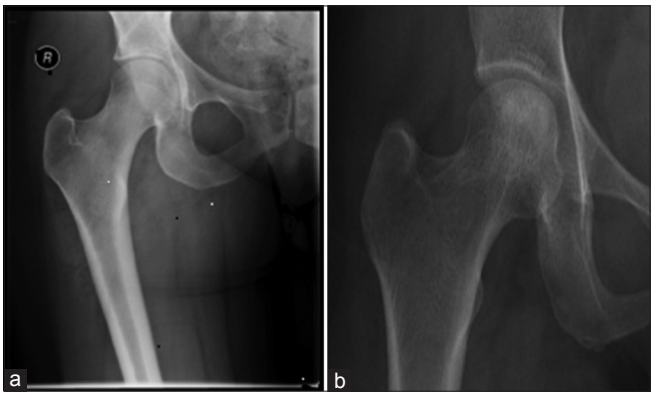

Figure 3: Comparison of femur X-ray of both groups, (a) hypothyroid patients, (b) euthyroid subjects

a long time can significantly depilate the calcium storage of body and leads weakness of bones.[21] In addition, decrease calcium level has been found associated with osteoporosis in females.[22]

Further, the present study recorded a significant low level of Vitamin D in hypothyroid patients in comparison of euthyroid females. The results of the present study are very similar to the previous studies Mackawy *et al.*[23] and Kivity *et al.*[24] as they observed low level of Vitamin D in hypothyroid disorder. Moreover, result of our study is consistent with the result of Chio *et al.*[25] in which they observed similar decrease level of Vitamin D in hypothyroid patients. Vitamin D is essential for absorption of calcium from stomach; requirement of Vitamin D is fulfilled by exposure to sun light, diet, and supplementation.[26] This decrease of Vitamin D in hypothyroid female patients primarily may be due to defective absorption from the intestine, second due to improper activation of Vitamin D.[27] Decrease of Vitamin D induces hypocalcaemia.[28] Vitamin D plays a permissive role in formation and remodeling of bones.[18]

Finding of the present study showed that BMD level of hypothyroid female patients was significantly high in comparison of euthyroid females. Our findings are in harmony with the previous study of Grimnes *et al.*[29] as they recorded a significant increase of BMD in hypothyroid female patients in comparison of euthyroid subjects. Further, increased BMD level as recorded in the present study is consistent with the previous studies of Marwaha *et al.*,[30] Kavitha *et al.*,[8] and Morris.[31] Thyroid hormones are indispensable for the growth and remodeling of the bone.[32] This increase of BMD in hypothyroid female patients in comparison to euthyroid female subjects may be due to a decreased rate of metabolism during hypothyroidism which leads to reducing rate of bone resorption process results in a higher net gain of bone.[33] There is a decrease of osteocalcin, and alkaline phosphate during hypothyroidism leads to osteosclerosis and increase of BMD.[34] Further, decrease serum calcium level and reduce Vitamin D level induces the poor bone quality as serum calcium and Vitamin D are essential for remodeling of bone as well as maintenance normal BMD level of bones.[7] TSH has direct effects on bone remodeling, which is mediated through the TSH receptor found on osteoblast and osteoclast precursor cells.[11] Therefore, an increase of thyroid hormones causes increased cortical thickness and decreased osteoblast activity which results in prolonged and slow maturation of bones.[32] Furthermore, reduced and decelerated bone remodeling due to hypothyroid disorder induces decreased bone matrix protein like osteocalcin while increased mineralization causes sclerosis of bones which further, increased the risk of bone fracture in hypothyroid patients.[20,32] Nonetheless, decrease of serum calcium as well as reduce the level of Vitamin D leads to deprived quality of bone; moreover, increased BMD with osteosclerosis leads to increased stiffness of bones increased the susceptibility for fracture in hypothyroid patients.[18]

CONCLUSION

Findings of the present study suggest thyroid hormones play an important role in strengthening and remodeling of bones as decreased thyroid hormones are associated with a decrease of serum calcium and Vitamin D. Further, increased BMD in hypothyroid patients induces stiffness of bones which further increases the risk of fracture. Moreover, present research suggests that serum calcium, Vitamin D and BMD should be investigated to prevent the risk of fracture in hypothyroid patients. Moreover, our study encourages the screening of serum calcium and Vitamin D in hypothyroid patients as well suggests supplementation of calcium and Vitamin D to hypothyroid patients. However, more studies on larger populations are warranted to establish a clear relation between hypothyroid and bone health.

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How to cite this article: Bhatnagar S, Srivastva RK, Jahan S, Ranjan R. Multiple Effects of Hypothyroidism on Bone Mineral Density and Its Association with Vitamin D, Serum Calcium: A Cross-sectional Study. Int J Sci Stud 2017;5(6):120-124.

Source of Support: Nil, **Conflict of Interest:** None declared.