

Effect of Suppressive Dose of Thyroxine and High Dose of Calcium-D3 on Bone Mineral Density in Post-thyroidectomy DTC with Incidental Parathyroidectomy Patients

¹Tania Sultana, ¹Pupree Mutsuddy, ¹Sadia Sultana, ^{1,2}Debabrata Aich Majumder, ^{1,2}Mashrufa Sultana

¹National Institute of Nuclear Medicine & Allied Sciences (NINMAS)

²Directorate General of Health Services (DGHS)

Correspondence Address : Dr. Tania Sultana, MD Resident (Nuclear Medicine), NINMAS, Block-D, BSMMU Campus.
E-mail: t.sultana.kmc20@gmail.com

ABSTRACT

Background: Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy, which is successfully treated with total thyroidectomy or near-total thyroidectomy followed by radioactive iodine ablation/radioactive iodine therapy of remnant tissue. Incidental parathyroidectomy is a common complication during total thyroidectomy or near-total thyroidectomy, leading to hypoparathyroidism, requiring calcium and vitamin D supplementation to maintain calcium homeostasis. These patients are also treated with levothyroxine (LT4) to suppress thyroid-stimulating hormone (TSH) and prevent recurrence or metastasis, which is known to impact bone mineral density (BMD) due to increased bone turnover. As osteoporosis is a significant public health concern, this study evaluates the effects of long-term TSH suppression and calcium-D3 therapy on BMD in post-thyroidectomy DTC patients.

Objective: The primary aim of this study was to assess the impact of prolonged TSH suppressive therapy and high-dose calcium-D3 supplementation on BMD in DTC patients with incidental parathyroidectomy during thyroidectomy followed by radioactive iodine ablation.

Patients and Methods: This observational cross-sectional study was conducted at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), BSMMU campus, Dhaka, over a period of 18 months from February 2023 to July 2024. A total of 103 post-thyroidectomy DTC patients aged between 20 and 45 years, all of whom had incidental parathyroidectomy, were included. BMD was measured using dual-energy X-ray absorptiometry (DEXA) at the lumbar spine (LS) (L1-L4 vertebrae) and both femoral necks (FN). Independent variables, including the duration of therapy, daily doses of LT4, and calcium-D3, were analyzed in relation to BMD Z-scores and T-scores.

Result: Study included 103 participants (M= 12, F= 91) with a mean age of 34.5 ± 6.3 years. The average duration of LT4 and calcium-D3 therapy was 7.23 ± 2.99 years. According to BMD Z-scores, four patients had low bone mass at the lumbar spine and one at the left

femoral neck. Osteoporosis, as defined by T-scores, was found in one patient at the lumbar spine, while osteopenia was observed in 22 patients at the lumbar spine and five at the femoral neck. No significant association was found between LT4/calcium-D3 therapy duration and BMD scores at the lumbar spine or femoral neck. Similarly, no significant correlation was observed between therapeutic doses, age, body mass index and BMD Z-scores or T-scores ($p > 0.05$).

Conclusion: Long-term TSH suppression combined with calcium-D3 supplementation in premenopausal females and young male DTC patients does not significantly affect bone mineral density.

Keywords: Differentiated Thyroid Carcinoma (DTC), Levothyroxine (LT4), Calcitriol (D3), Hypoparathyroidism, Bone Mineral Density (BMD).

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INTRODUCTION

Thyroid cancer, the most prevalent endocrine malignancy, accounts for about 2.2% of all cancer cases (1). The global incidence of thyroid cancer has significantly increased, ranking as the thirteenth most common cancer diagnosis globally, and it affects women six times more than men. Differentiated thyroid carcinoma (DTC) comprises papillary and follicular subtypes. Among the two types (papillary and follicular carcinoma) of DTC, about 90% are papillary thyroid carcinomas (PTC) and 4% are follicular thyroid carcinomas (FTC) (2). DTC originates from thyroid follicular cells, and its prognosis is good. The 5-year relative survival rate of DTC is 98.4% (1). On the other hand, incidental parathyroidectomy during thyroidectomy accounts for 7.9% of cases, even among skilled surgeons (3). The treatment modalities of DTC include total

thyroidectomy (TT) or near-total thyroidectomy (NTT) followed by radioactive iodine ablation (RAIA) of remnant tissue. These patients are followed up with a high dose of levothyroxine (LT4) to suppress TSH to prevent recurrence or metastasis. TSH suppression by LT4 is used to maintain TSH levels below the normal range (≤ 0.1 mIU/L) for high- and intermediate-risk DTC patients (4). TSH suppression lowers the incidence of recurrence and reduces morbidity and mortality in DTC patients. Long-term TSH suppression may cause subclinical hyperthyroidism, which is associated with some adverse effects like osteoporosis, atrial fibrillation, and major cardiovascular events (5). So, TT or NTT, all DTC patients are vulnerable to bone mass loss and decreased bone mineral density (BMD), which finally results in low BMD. The most common complication of TT/NTT is the unintentional removal of the parathyroid gland. There are two main causes of hypoparathyroidism: one is autoimmune destruction of the parathyroid glands, and another is incidental parathyroidectomy during thyroidectomy (6). So, after TT/NTT, these patients are suffering from hypoparathyroidism, which is evidenced by postoperative biochemical hypocalcemia with low PTH level, and this occurs due to incidental parathyroidectomy, parathyroid gland injury, or devascularization (7). Bone disease develops in hypoparathyroidism due to significantly impaired bone remodeling caused by the absence or low amounts of parathyroid hormone or parathormone (PTH) (8). Parathyroid glands release PTH, which plays an important role in calcium homeostasis by stimulating calcium release from bone into the bloodstream, increasing reabsorption of calcium from the kidney, and also altering inactive vitamin D to active vitamin D3 (calcitriol), which improves calcium absorption in the intestine (9).

The BMD test determines how much calcium and other minerals are present in a specific area of bone. This test detects osteoporosis and predicts the likelihood of fractures. BMD depends on various factors like heredity, sex, age, dietary factors, physical exercise, endocrine factors, and exposure to risk factors like certain drugs. Bone loss begins at the age of 40, grows significantly in the 60s, and reaches a peak in the 80s (10). Primary osteoporosis is due to bone loss that occurs during the aging process in men and hormonal changes in males and females. Secondary osteoporosis is due to certain diseases like chronic

obstructive pulmonary disease, chronic kidney disease, hyperthyroidism, hyperparathyroidism, malignancy, diabetes, and also exposure to some drugs like prolonged use of corticosteroids, thyroid hormone, proton pump-inhibiting drugs, anxiolytics, sedatives, neuroleptics, and antidepressants (11). Several techniques have been proposed for measuring BMD, but dual X-ray absorptiometry (DXA) is used worldwide and is considered the 'Gold Standard' for the diagnosis of osteoporosis. Bone densitometry is the single best approach for measuring bone health. According to WHO recommendations, BMD values were expressed in g/cm² and determined by T- and Z-scores. A T-score ≤ -2.5 SD was defined as osteoporosis, between -2.5 and -1.0 SD as osteopenia, and ≥ -1.0 as normal, and a Z-score above -2 defines normal bone mass, and -2 and less defines low bone mass (12, 13). Osteoporosis is a condition that does not show visible signs until a fragility fracture occurs. It is essential to diagnose osteoporosis or low bone mass as soon as possible and start fracture prevention therapy. LT4 is a TSH suppressant, and calcium D3 is used to maintain calcium homeostasis in post-surgical hypoparathyroidism patients with DTC. This study aimed to discover whether prolonged use of this medicine affects bone mass in persons with DTC aged 20 to 45 years. As a result, extra relevant measures may be implemented following the BMD to lower the chance of a subsequent disease and its consequences.

PATIENTS AND METHOD

This descriptive observational study was conducted at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Bangladesh, for eighteen months (from February 2023 to July 2024), and the study population included both males & females (aged 20 to 45 years) DTC patients having the criteria of high and intermediate risk and who enrolled for follow-up with the clinical diagnosis of total thyroidectomy with incidental parathyroidectomy followed by RAIA with a long-term TSH suppressive dose of levothyroxine and a high dose of calcium-D3 supplementation. Duration of levothyroxine supplement ≥ 5 years, patients having serum TSH level < 0.1 mIU/day with serum PTH < 13 pg/ml. Patients with any form of drugs affecting bone metabolism, such as glucocorticoids, heparin, lithium, warfarin, antiepileptics, aromatase inhibitors, methotrexate, proton pump inhibitors, etc., with a history of vertebral or femoral fracture, were treated with

any agents that could interfere with bone metabolism. Those with a history of alcohol intake, rheumatoid arthritis, chronic amenorrhea of more than 3 months, late menarche, early menopause, oophorectomy, or any serious medical disorder were excluded. Independent variables were age (< 45 years), weight, height, BMI (Kg/m²), duration of calcium-D3 and TSH suppressive therapy, dose of calcium-D3 and levothyroxine, and serum TSH and serum calcium, and dependent variables were BMD contents (gm/cm²) and BMD T-score and Z score. The study subjects were divided according to the duration of levothyroxine, calcium-D3 supplementation, BMI, etc. The study subjects were divided according to the duration of levothyroxine and calcium-D3 supplementation into three groups of five-year segments: Group 1: 5–9 years, Group 2: 10–15 years, and Group 3: > 15 years. BMD was measured at the lumbar spine (levels L1-4), right femoral neck, and left femoral neck by the MEDIX DR Bone Densitometer Dual Emission. X-ray Absorptiometry is based on T-score, according to the WHO criteria, and based on Z-score according to ISCD recommendations for 20-45 years of age (12, 13). The diagnosis of osteoporosis was made based on a T-score of -2.5 standard deviations or below at the lumbar spine and the femur neck. A T-score that fell between the range of -2.5 to -1.0 standard deviations was considered to be osteopenia, whereas a T-score of -1.0 SD or above was considered to be normal (12). On the other hand, the diagnosis of low bone mass was made based on a Z-score. According to ISCD recommendations, a Z-score of -2.0 or lower was defined as “below the expected range for age,” and a Z-score above -2.0 was defined as “within the expected range for age” (13). Serum TSH, serum calcium, and PTH were measured. Study subjects were further divided into normal BMD, osteopenia, and osteoporosis according to T score and Z score. The effects of the duration of levothyroxine and calcium-D3 supplementation on BMD were measured.

Data processing and statistical analysis: Statistical analysis was carried out by using the Statistical Package for the Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel to analyze frequency and percentage. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. The chi-square test was used to analyze the categorical variables, shown with cross-tabulation. P values <0.05 were considered statistically significant.

RESULTS

Most patients were in the age group of 30-39 years (49.5%), with a mean age of 34.5±6.30 years, ranging from 20 to 45 years. The sample had a female predominance, with 88.3% female and only 11.7% male. Clinically 86.4% of the patients were diagnosed with papillary thyroid carcinoma (PTC), and 13.6% were diagnosed with follicular variant papillary thyroid carcinoma (FV PTC). Most patients (93.2%) had lymph node metastasis in post-surgical histopathology reports. The mean duration of supplementation was 7.23±2.99 years, with a range of 5 to 20 years. The study examined the bone mineral density (BMD) status in the lumbar spine and both femoral necks of the participants, as determined by the T-score and Z-score. Z-score revealed that for the Rt. FN, all patients (100%) had normal bone mass, and for the Lt. FN, 99.0% had normal bone mass with just 1.0% having low bone mass. About 96.1% of patients had normal bone mass, with only 3.9% having low bone mass at the LS. According to the T-score, the study found that most patients had normal BMD while 4.9%, 5.8%, and 22.4% had low BMD (osteoporosis and osteopenia) at Rt. FN, Lt. FN, and LS, respectively. All the 103 patients observed in this study, based on both T and Z-score, the data shows no significant association between the duration of levothyroxine therapy and BMD score at either the lumbar spine or right and left femonecks. cks. The p-value suggests a lack of statistical significance (p > 0.05).

Table 1. Demographic characteristics of the study population

Variables	n (%) or value (N=103)
Age (in years)	
20-29	27 (26.2)
30-39	51 (49.5)
40-45	25 (24.3)
Mean ($\pm$ SD)	34.5 (6.30)
Min	20
Max	45
Sex	
Male	12 (11.7)
Female	91 (88.3)
Clinical diagnosis	
PTC	89 (86.4)
FV PTC	14 (13.6)
Lymph node metastasis	
With LN metastasis	96 (93.2)
Without LN metastasis	7 (6.8)

Table 2. Distribution of the study population by duration of levothyroxine, calcium-D3 supplementation

Duration of supplementation (years)	n (%) or value N=103
5-9	86 (83.5)
10-15	12 (11.7)
>15	5 (4.9)
Mean $\pm$ SD	7.23 $\pm$ 2.99
Minimum	5
Maximum	20

Table 3. Distribution of the study subjects by BMD

BMD	n (%) N=103
Right femoral neck (Rt. FN) Z- score	
Normal bone mass	103 (100)
Low bone mass	0 (0)
Left femoral neck (Lt. FN) Z- score	
Normal bone mass	102 (99)
Low bone mass	1 (1)
Lumbar spine (LS) Z- score	
Normal bone mass	99 (96.1)
Low bone mass	4 (3.90)
Rt. FN T-score	
Normal	98 (95.1)
Osteopenia	5 (4.9)
Lt. FN T- score	
Normal	97 (94.2)
Osteopenia	6 (5.8)
LS T- score	
Normal	80 (77.7)
Osteopenia	22 (21.4)
Osteoporosis	1 (1)

Table 4. Relationship between BMD T-score and Z-score among different Body Mass Index (BMI) groups of the study population (n=103)

Variables	n (%)					p-value
BMI (kg/m ²)	Underweight (<18.5) (n=3)	Normal (18.5-22.9) (n=24)	Overweight (23-24.9) (n=18)	Pre-obese (25-29.9) (n=39)	Obese (≥30) (n=19)	
Rt. FN Z-score						
Normal bone mass	3 (100)	24 (100)	18 (100)	39 (100)	19 (100)	-
Low bone mass	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Lt. FN Z-score						
Normal bone mass	3 (100)	23 (95.8)	18 (100)	39 (100)	19 (100)	0.505
Low bone mass	0 (0)	1 (4.2)	0 (0)	0 (0)	0 (0)	
LS Z-score						
Normal bone mass	3 (100)	22 (91.7)	17 (94.4)	38 (97.4)	19 (100)	0.064
Low bone mass	0 (0)	2 (8.3)	1 (5.6)	1 (2.6)	0 (0)	
Rt. FN T-score						
Normal	3 (100)	21 (87.5)	17 (94.4)	38 (97.4)	19 (100)	0.328
Osteopenia	0 (0)	3 (12.5)	1 (5.6)	1 (2.6)	0 (0)	
Lt. FN T-score						
Normal	3 (100)	22 (91.7)	16 (88.9)	37 (94.9)	19 (100)	0.629
Osteopenia	0 (0)	2 (8.3)	2 (11.1)	2 (5.1)	0 (0)	
LS T-score						
Normal	2 (66.7)	16 (66.7)	13 (72.2)	31 (79.5)	18 (94.7)	0.480
Osteopenia	1 (33.3)	8 (33.3)	5 (27.8)	7 (17.9)	1 (5.3)	
Osteoporosis	0 (0)	0 (0)	0 (0)	1 (2.6)	0 (0)	

*A Chi-square test was done to measure the level of significance
p-value <0.05 was considered as significant.

Table 5. Relationship between Association of BMD T-score and Z-score among three duration groups of calcium-D3 and levothyroxine suppressive therapy of the study population

Variables	n (%)			p-value
Duration of Calcium-D3 and LT4 suppressive therapy	5-9 years (n=86)	10-15 years (n=12)	>15 years (n=5)	
Rt. FN Z-score				
Normal bone mass	86 (100)	12 (100)	0 (100)	-
Low bone mass	0 (0)	0 (0)	0 (0)	
Lt. FN Z-score				
Normal bone mass	85 (98.8)	12 (100)	0 (100)	0.905
Low bone mass	1 (1.2)	0 (0)	0 (0)	
LS Z-score				
Normal bone mass	82 (95.3)	12 (100)	5 (100)	0.663
Low bone mass	4 (4.7)	0 (0)	0 (0)	
Rt. FN T-score				
Normal	82 (95.3)	11 (91.7)	5 (100)	0.749
Osteopenia	4 (4.7)	1 (8.3)	0 (0)	
Lt. FN T-score				
Normal	80 (93)	12 (100)	0 (100)	0.533
Osteopenia	6 (7)	0 (0)	0 (0)	
LS T-score				
Normal	64 (74.4)	11 (91.7)	5 (100)	0.503
Osteopenia	21 (24.4)	1 (8.3)	0 (0)	
Osteoporosis	1 (1.2)	0 (0)	0 (0)	

*A Chi-square test was done to measure the level of significance
p-value <0.05 was considered as significant.

DISCUSSION

The study included 103 patients, with the majority being female (88.3%) and it specifically focused on patients who had been on TSH-suppressive therapy and calcium-D3 supplementation for at least five years. The findings provide insights into the relationship between long-term thyroid hormone suppression, calcium-D3 supplementation, and BMD. The relationship between TSH suppressive therapy and BMD has been a subject of concern due to the known effects of thyroid hormones on bone metabolism. Suppressive doses of LT4 are used to prevent recurrence or metastasis in patients with DTC by maintaining TSH levels below normal.

The results of the study provide insights into the clinical attributes of the participants, their BMD status, and the correlations with the duration of long-term LT4, calcium-D3 treatment, and BMD. However, no statistically significant relationships were observed. The results provide insights into the BMD outcomes in patients undergoing long-term calcium-D3 and TSH suppressive therapy and are categorized by duration of therapy. The average duration of levothyroxine (LT4) and calcium-D3 medication was 7.23 ± 2.99 years, ranging from 5 to 20 years (Table 2). The study population was divided into groups based on the duration of therapy (5-9 years, 10-15 years, and >15 years), but no significant differences in BMD were observed between these groups (Table 5). According to the Z-score, no significant association was found between LT4 therapy duration and BMD Z-scores at the LS, Rt. FN, or Lt. FN. The majority of participants, regardless of bone mass, had taken levothyroxine therapy for up to 20 years. No participants with low bone mass had been on LT4 therapy for >9 years. The majority of participants across all duration groups had taken LT4 therapy for up to 20 years. The p-value suggests a lack of statistical significance ($p > 0.05$). Results also showed that most patients maintained normal bone density throughout therapy durations according to the T-score. In Rt. and Lt. FN T-scores, osteopenia was more common in the 5-9-year group and 10-15-year group but not in the >15-year group. In the LS, a larger proportion of patients showed osteopenia (24.4%), suggesting a decrease with longer therapy durations. Only one patient had osteoporosis in the 5-9-year group. One of the findings of this study was the lack of a significant association between the duration of TSH

suppressive therapy and calcium-D3 supplementation and BMD. This suggests that within the time frame studied, the duration of therapy did not have a cumulative negative effect on BMD. Leonova et al. reported a similar finding after a 10-year follow-up period (14). Similarly, a comparable finding was reported by Ku et al. that there was no significant relationship between the duration of LT4 therapy and BMD Z-scores at the LS and FN in premenopausal women as well as in men of the same age group (15). Some researchers also discovered that TSH suppression had no significant effect on BMD after a median duration of suppression (9, 16, 17). It is important that the patients in this study were younger, premenopausal individuals, who may have a lower risk of developing osteoporosis compared to older or postmenopausal women. Additionally, the concurrent calcium-D3 supplementation may have played a protective role, preventing the gradual bone loss that might otherwise occur with long-term TSH suppression.

This study found no significant association between the duration of TSH suppressive therapy and decreased BMD in the LS or FN regions. This finding contrasts with the hypothesis that prolonged TSH suppression increases bone turnover and decreases BMD, particularly in patients at risk of osteoporosis. Previous studies have demonstrated that long-term TSH suppression may induce subclinical hyperthyroidism, which can accelerate bone resorption, leading to decreased bone density in both premenopausal (18) and postmenopausal women (19). However, in the current study, which focused on younger men and premenopausal women, the findings suggest that TSH suppression did not have a significant detrimental effect on BMD. This discrepancy could be attributed to the age of the study population, as younger individuals may have higher baseline bone density, which could offer some protection against bone loss induced by thyroid hormone suppression. The findings of this study have several important clinical implications. This study suggests that long-term TSH suppression combined with high-dose calcium-D3 supplementation does not significantly impair bone health in young, premenopausal DTC patients with incidental parathyroidectomy. This provides reassurance to clinicians and patients that TSH suppression, which is essential for preventing thyroid cancer recurrence, can be safely administered without increasing the risk of osteoporosis in this patient population.

CONCLUSION

The study shows that long-term TSH suppression medication and calcium-D3 supplementation have no significant effect on bone metabolism, despite low bone mass in some patients, and no significant relationship between therapy duration and BMD.

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