# Effects of Long Term TSH Suppressive Dose of Levothyroxine on Bone Mineral Density in Differentiated Thyroid Carcinoma Patients after Radioactive Iodine Ablation

[1,2] Mashrufa Sultana, [1]Pupree Mutsuddy, [2]Amanat Hasan, [1,2]Debobrata Aich Majumder, [1]Tania Sultana

[1]National Institute of Nuclear Medicine & Allied Sciences (NINMAS)
[2]Directorate General of Health Services (DGHS)

**Correspondence Address :** Dr. Mashrufa Sultana, MD (Nuclear Medicine), NINMAS, Block-D, BSMMU Campus. e-mail: mashrufa.sultana@gmail.com

## ABSTRACT

***Background:*** Differentiated thyroid carcinoma (DTC) which includes both papillary and follicular subtypes, is a type of thyroid cancer that has a high probability of being differentiated thyroid carcinoma entails a total thyroidectomy, followed by radioactive iodine ablation (RAIA), and then the administration of suppressive dose levothyroxine. Patients with long term TSH suppression might be at risk for developing osteoporosis, experiencing a loss of bone mass, and eventually experiencing a decrease in bone mineral density.

***Objective:*** To determine the effects of long term TSH suppressive dose of levothyroxine on bone mineral density in patients with differentiated thyroid carcinoma after radioactive iodine ablation.

Patients and Methods: This descriptive observational study was conducted in National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Bangladesh for eighteen months and the study population was the differentiated thyroid carcinoma patients with history of total thyroidectomy followed by radioactive iodine ablation. The age ranged from 20 to 45 years who has history of long term TSH suppressive doses of levothyroxine for more than five years. Bone mineral density was measured at the lumbar spine (L1-L4 vertebrae), right (Rt.) femoral neck, and left (Lt.) femoral neck. The study's results provide insights into the clinical attributes of the participants, their bone mineral density status, and the correlations of duration of levothyroxine's treatment with bone mineral density.

***Result:*** Most patients were premenopausal (35-39- and 40-45-years age groups), female (84%), and overweight and obese. In this study, the total number of differentiated thyroid carcinoma patients was 118, with a mean age of 37.08 ± 5.48 years for levothyroxine suppression therapy. The majority of individuals, namely 108 out of 118, adhere to a levothyroxine medication regimen for 15 years. The study examined the bone mineral density status in the participants' lumbar spine, as determined by the T-score and Z-score. Out of the total 108 subjects, 62% had normal bone mineral density, 24% had osteopenia, and 4% had osteoporosis. Based on the T-score, the results indicated that a majority of people (67%) exhibited normal bone mineral density, while the other participants had low bone mineral density. Within the low bone mineral density group, 29% of people had osteopenia, whereas 4% developed osteoporosis. Regarding the femoral neck (Rt.) and femoral neck (Lt.), the majority of subjects, 97% and 94%, respectively, had normal bone mineral density, whereas the remaining participants had low bone mineral density (both osteopenia and osteoporosis). The study found that 6.7% of patients had low bone mass in their lumbar spine, while the rest had normal bone mass. There was no significant association between levothyroxine therapy duration and bone mineral density scores in either lumbar spine or femoral necks.

***Conclusion:*** Despite concerns regarding TSH suppression and its potential impact on bone metabolism, our study suggests that prolonged levothyroxine therapy does not adversely affect bone mineral density.

***Keywords:*** Differentiated Thyroid Carcinoma, Radioactive Iodine Ablation, Bone mineral density, Thyroid stimulating hormone , Levothyroxine

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## INTRODUCTION

Thyroid cancer accounts for around 2.2% of all cancer cases, making it the most common endocrine malignancy. The incidence rate of this particular disease was ranked 10th among all malignancies (1, 2). Differentiated thyroid carcinoma (DTC) is responsible for about 90% of all thyroid cancer (3). DTC includes both papillary and follicular subtypes that have a high probability of being successfully cured with good treatment outcomes. Currently, the method that is utilized for the management of persons who have DTC entails the usage of total thyroidectomy, followed by radioactive iodine ablation, and then the administration of suppressive amounts of levothyroxine. An increase in the rate of cell proliferation is induced as a result of the existence of a thyroid-stimulating hormone (TSH) receptor on the cellular membrane. Consequently, levothyroxine is administered to patients in suppressive dosages for

treatment. The goal of suppressive therapy is to prevent recurrence or metastasis. Levothyroxine is used for the goal of suppressing TSH, which means that it efficiently regulates TSH levels so that they should remain below the usual range of 0.1 mIU/L (4). Even though DTC affects people of both sexes, it is more widespread among young women than it is among young men. The overall prognosis for DTC is positive, with a 10-year survival rate of 98% of patients (5). However, there have been reports that imply that the extended suppression of thyroid-stimulating hormone (TSH) might potentially lead to negative side effects of levothyroxine on bone metabolism, as well as major cardiovascular events and atrial fibrillation. This might be as a result of persistent subclinical hyperthyroidism. Consequently, those who have undergone treatment for TSH suppression after undergoing a total thyroidectomy may be at risk for developing osteoporosis, experiencing a loss of bone mass, and eventually experiencing a decrease in bone mineral density (6).

Bone mineral density (BMD) is the ratio of the total area of bone to the mineral content of the bone, which is mostly composed of calcium and phosphorus and usually expressed as gm/cm$^2$. BMD is affected by a wide range of factors, some of which include but are not limited to age, gender, genetic predisposition, dietary habits, endocrine factors (such as estrogen and parathyroid hormone), physical activity, and possible exposure to risk factors. The prevalence of osteoporosis is significant across a wide variety of people, regardless of their gender or ethnic origin, and it is anticipated that the frequency of this condition would grow with increasing age. This condition does not manifest any symptoms until fractures become obvious. This can lead to significant secondary health problems and can be fatal in certain cases. The loss of bone can be attributed to either main or secondary causes, depending on the circumstances. It is believed that important contributing variables include the natural process of aging in males as well as hormonal shifts that occur in both males and females (7). Several disorders can be linked to secondary osteoporosis, which include chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), hyperthyroidism, hyperparathyroidism, metabolic syndrome, cancer, and depression. Secondary osteoporosis can be brought on by extended exposure to medications. These medications include corticosteroids, thyroid hormones, proton pump inhibitors, anxiolytics, sedatives, neuroleptics, and antidepressants (8).

Subclinical hyperthyroidism, which can be caused by a wide variety of factors, has been shown to result in a 2% yearly bone loss rate, according to some studies. In contrast, several studies have discovered that these individuals do not exhibit any statistically significant changes in bone metabolism measurements when compared to healthy controls. Many studies have shown that the majority of people who have subclinical hyperthyroidism and differentiated thyroid carcinoma are women who have gone through menopause. On the other hand, there is no evidence of a substantial increase in risk among males or women who have not yet reached menopause. An excessive quantity of thyroid hormone has been connected to a decrease in the volume of trabecular bone, as well as an increase in porosity and a reduction in the thickness of the cortical bone, according to the findings of a research effort. Osteoporosis does not manifest any visible signs until a fragility fracture occurs. Early recognition and timely intervention of osteoporosis or low bone mass therapy are crucial for preventing fractures.

## PATIENTS AND METHODS

This descriptive observational study was conducted at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), BSMMU during September 2022 to February 2024. The study population included both male and female (aged 20 to 45 years) registered differentiated thyroid carcinoma (DTC) patients who enrolled for lifelong follow-up after total thyroidectomy followed by RAIA to maintain long-term TSH suppression with suitable dose of levothyroxine. Duration of levothyroxine supplement $\geq$ 5 years, patients having serum TSH level <0.1 mIU/L with normal levels of FT3, serum PTH, and calcium were included in the study. Patients consuming high calcium supplements, patients with vertebral or femoral fracture history with drugs that interfere with bone metabolism, history of alcohol intake, rheumatoid arthritis, or other major medical illness were excluded.

Independent variables were age, sex, body mass index (kg/m2), duration of therapy, thyroid-stimulating hormone (TSH), and dose of levothyroxine, and dependent variables were bone mineral density contents

(gm/cm2) and bone mineral density T-score and Z-score. The study subjects were divided according to duration of levothyroxine, BMI, etc.

The study subjects were divided according to the duration of levothyroxine supplementation into four groups of five-year segments: **Group 1: 6–10 years, Group 2: 11–15 years, Group 3: 16–20 years, and Group 4: 21–26 years**. Bone mineral density 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. Based on T-score, according to the WHO criteria, and based on Z-score according to ISCD recommendations, for 20-45 years of age (9, 10). The diagnosis of osteoporosis was made based on a T-score of -2.5 standard deviations or below at the lumbar spine and both femoral necks. 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 (9). 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" (10). Serum TSH, serum calcium, and PTH were measured. Study subjects were further divided into normal bone mineral density, osteopenia, and osteoporosis according to T score and Z score. The effects of the duration of levothyroxine on bone mineral density were measured.

Data Processing and 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 premenopausal (35-39- and 40-45-year age groups), female (84%), and overweight and obese. Only 16% of patients were male. Most of the subjects were above 35 years. In this study, the total number of differentiated thyroid carcinoma patients was 118, with a mean age of 37.08 ± 5.48 years for levothyroxine suppression therapy. The majority of individuals, namely 108 out of 118, adhere to a levothyroxine medication regimen for 15 years. The study examined the bone mineral density status in the lumbar spine of the participants, as determined by the T-score and Z-score. Out of the total 108 subjects, 62% had normal bone mineral density, 24% had osteopenia, and 4% had osteoporosis. Based on the T-score, the results indicated that a majority of people (67%) exhibited normal bone mineral density, while the other participants had low bone mineral density. Within the low bone mineral density group, 29% of people had osteopenia, whereas 4% developed osteoporosis. Regarding the femoral neck (Rt.) and femoral neck (Lt.), the majority of subjects, 97% and 94%, respectively, had normal bone mineral density, whereas the remaining participants had inadequate bone mineral density. Based on Z score, eight patients (6.7%) were found with low bone mass in the lumbar spine, whereas the rest of the patients had normal bone mass in the lumbar spine. All the 118 patients observed had normal bone mass in both femoral necks. In this study, based on both T and Z scores, the data show no significant association between the duration of levothyroxine therapy and bone mineral density scores at either the lumbar spine or the right and left femoral necks. The p-value suggests a lack of statistical significance ($p > 0.05$).

**Table 1. Demographic characteristics of study population (n = 118)**

| Characteristics | Mean ± SD | Range |
|---|---|---|
| Age (years) | 37.08 ± 5.48 | 20 to 45 |
| BMI (kg/m$^2$) | 25.99 ± 4.30 | 15.82 to 42.19 |
| TSH level (mlU/L) | 0.03 ± 0.02 | 0.09 to 0.01 |
| PTH level (pg/ml) | 44.88 ± 32.43 | 17.8 to 249 |
| FT3 level (mlU/L) | 5.57 ± 1.41 | 2.76 to 9.53 |
| Calcium level(mg/dl) | 9.14 ± 0.63 | 8.06 to 10.95 |
| Duration of Levothyroxine Therapy (years) | 10.11 ± 4.07 | 6 to 26 |
| Levothyroxine dose (mcg) | 144.49 ± 33.67 | 75 to 225 |

| Age Category (in year) | Number of Female (%) | Number of Male (%) | Total (%) |
|---|---|---|---|
| 20-24 | 4 (3%) | - | 4(3%) |
| 25-29 | 8 (7%) | 1(1%) | 9 (8%) |
| 30-34 | 17(14%) | 3 (3%) | 20 (17%) |
| 35-39 | 29(25%) | 6 (5%) | 35 (30%) |
| 40-45 | 41 (35%) | 9 (8%) | 50 (42%) |
| Total | 99 (84%) | 19 (16%) | 118 (100%) |

Mean ± SD (Range) = 37.08 ± 5.48 years (20-45 years)

**Table 2. Distribution of BMI among study subjects (n=118) :**

| BMI | Frequency | Percentage |
|---|---|---|
| Underweight (<18.5) | 5 | 4% |
| Healthy Weight (18.5-22.9) | 21 | 18% |
| Overweight (23-24.9) | 25 | 21% |
| Obesity (≥25) | 67 | 57% |
| Total | 118 | 100% |

Mean ± SD (Range) = 25.99 ± 4.30 kg/m$^2$ (15.82-42.19 kg/m$^2$)

**Table 3. Relationship between bone mineral density at Lumbar spine and duration of levothyroxine therapy based on T-score:**

| BMD at Lumbar Spine | Duration of levothyroxine therapy (in years) | | | | p-value* |
|---|---|---|---|---|---|
| | 6-10 | 11-15 | 16-20 | 21-26 | |
| Normal | 47 (64%) | 27 (77%) | 3 (50%) | 2 (50%) | 0.67 |
| Osteopenia | 22 (30%) | 7 (20%) | 3 (50%) | 2 (50%) | |
| Osteoporosis | 4 (6%) | 1 (3%) | - | - | |
| Total | 73 (100%) | 35 (100%) | 6 (100%) | 4 (100%) | |

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

**Table 4. Relationship between bone mineral density at Femoral Neck based on T-score and duration of levothyroxine therapy**

| BMD at Femoral Neck | Duration of levothyroxine therapy (in years) | | | | | | | | p-value* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 6-10 | | 11-15 | | 16-20 | | 21-26 | | Rt. | Lt. |
| | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | .06 | .32 |
| Normal | 72 (99%) | 70 (96%) | 33 (94%) | 32 (91%) | 6 (100%) | 6 (100%) | 3 (75%) | 3 (75%) | | |
| Osteopenia | 1 (1%) | 3 (4%) | 2 (6%) | 3 (9%) | - | - | 1 (25%) | 1 (25%) | | |
| Osteoporosis | - | - | - | - | - | - | - | - | | |
| Total | 73 (100%) | 73 (100%) | 35 (100%) | 35 (100%) | 6 (100%) | 6 (100%) | 4 (100%) | 4 (100%) | | |

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

**Table 5. Relationship between bone mineral density at Lumbar spine and duration of levothyroxine therapy based on Z-score:**

| BMD at Lumbar Spine | Duration of levothyroxine therapy (in years) | | | | p-value* |
|---|---|---|---|---|---|
| | 6-10 | 11-15 | 16-20 | 21-26 | |
| Normal bone mass | 67 (92%) | 33 (94%) | 6 (100%) | 4 (100%) | **0.95** |
| Low bone mass | 6 (8%) | 2 (6%) | - | - | |
| **Total** | **73 (100%)** | **35 (100%)** | **6 (100%)** | **4 (100%)** | |

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

**Table 6. Relationship between bone mineral density at Femoral Neck and duration of levothyroxine therapy based on Z-score:**

| BMD at Femoral Neck | Duration of levothyroxine therapy (in years) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 6-10 | | 11-15 | | 16-20 | | 21-26 | | p-value* | |
| | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. | Rt. | Lt. |
| Normal | 73 (100%) | 73 (100%) | 35 (100%) | 35 (100%) | 6 (100%) | 6 (100%) | 4 (100%) | 4 (100%) | 1 | 1 |
| **Total** | **73 (100%)** | **73 (100%)** | **35 (100%)** | **35 (100%)** | **6 (100%)** | **6 (100%)** | **4 (100%)** | **1** | | |

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

## DISCUSSION

Tumor recurrence and metastasis are frequently prevented in patients diagnosed with differentiated thyroid carcinoma with the administration of a suppressive amount of levothyroxine after thyroidectomy. Long-term care remains a concern about the possible impact of hyperthyroidism on the bone health of individuals who undergo total thyroidectomy for thyroid cancer. In order to tailor TSH suppression and guide therapeutic measures in a targeted and individualized way, it is imperative to identify high-risk populations that are susceptible to deteriorating bone health following thyroidectomy. The objective of this study was to examine the impact of the administration of levothyroxine at a long-term TSH-suppressive dosage on bone mineral density in individuals diagnosed with differentiated thyroid cancer. The results of the study provide insights into the clinical attributes of the participants, their bone mineral density status, and the correlations with the length of long-term levothyroxine treatment and bone mineral density. However, no statistically significant relationships were observed. This phenomenon was also documented in previous research conducted on individuals with differentiated thyroid carcinoma, including children, adolescents, and young adults (11).

The findings of our study suggest that the mean ± standard deviation (SD) for levothyroxine suppression therapy in the age group was 37.08 ± 5.48 years, with a range of 20-45 years. Most of the participants were premenopausal women, overweight and obese. Among them, 25% were overweight and 67% were obese. Only 16% of patients were male. Most of the subjects were above 35 years. Our study found that the average duration of levothyroxine medication was 10.11 ± 4.07 years (Table 1). Here, we observed a correlation (Table 3) between bone mineral density in the lumbar spine and the duration of levothyroxine therapy. Notably, none of the patients who had levothyroxine therapy for more than 15 years had osteoporosis. The majority of individuals, namely 108 out of 118, adhered to a levothyroxine medication regimen for 15 years. Out of the total subjects, 62% had normal bone mineral density, 24% had osteopenia, and 4% had osteoporosis. Conversely, there were 10 patients (4%) who were above 15 years, and among them, 4% had normal bone mineral density, whereas 4% had osteopenia. A previous research study showed that bone loss is evident in

all patients with differentiated thyroid carcinoma during 24 months of levothyroxine-suppressive medication (12).

A study was carried out between the bone mineral density in the right and left femoral necks and the duration of levothyroxine medication. About 97% of patients who underwent levothyroxine treatment for up to 15 years had the right femoral neck exhibit normal bone mineral density, and in 94% of subjects, the left femoral neck had normal bone mineral density. There was no osteoporosis in both cases, and the majority of subjects had levothyroxine medication for 15 years (Table 4). There was a study that involved a systematic review and meta-analysis, which revealed that the bone mineral density of premenopausal women was considerably greater in the group receiving TSH suppression medication compared to the control group (13). There was no notable disparity observed across the group in males. Research revealed no disparities in bone mass and T-score among the lumbar spine, neck, and entire femur (10).

In this study, based on Z-score, among 100 out of 118 subjects, the data shows no significant association between the duration of levothyroxine therapy and bone mineral density Z-scores at the lumbar spine. Among eight participants with low bone mass, none had been on levothyroxine therapy for more than 15 years. The p-value obtained from the Chi-square test suggests that the relationship observed is not statistically significant ($p > 0.05$). Similar to the lumbar spine, no significant relationship was observed between the duration of levothyroxine therapy and bone mineral density Z-scores at the femoral neck (Rt.) and femoral neck (Lt.). Notably, no participants in the low bone mass group were observed in this analysis. Again, the majority of participants across all duration groups had taken levothyroxine therapy for up to 15 years. By analyzing all the data, it is assumed that some factors, like premenopausal women, suppressive doses according to weight, and high BMI, might have contributed to the non-significant association.

## CONCLUSION

Despite concerns regarding TSH suppression and its potential impact on bone metabolism, our study suggests that prolonged levothyroxine therapy does not adversely affect bone mineral density. These findings underscore the safety and efficacy of levothyroxine treatment in maintaining bone health in patients with differentiated thyroid carcinoma, providing reassurance to clinicians and patients. Nevertheless, continued monitoring and further research are necessary to fully understand the complex interactions between levothyroxine therapy, TSH suppression, and bone health.

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