Original Article

Factors related to bone mineral density in female patients receiving TSH-suppressive doses of levothyroxine for thyroid cancer

Araya Boonyaleepan M.D.
Tarit Taerakul M.D.
From Department of Radiology, Rajavithi Hospital, Bangkok, Thailand.
Address correspondence to A.B.(arayaboonyaleepan@yahoo.com)

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Abstract

Background: Patients with thyroid cancer receive a high-dose thyroid hormone therapy after total thyroidectomy for suppression of thyroid stimulating hormone (TSH); this may affect bone mineral density (BMD). Identifying the common factors that affect BMD (including the duration of a high dose of thyroid hormone treatment) may, therefore, aid the delivery of appropriate and comprehensive care in such cases.

Objective: To identify the factors related to BMD in female patients with thyroid cancer.

Materials and Methods: This cross-sectional study evaluated data pertaining to the BMD and demographic characteristics of female patients with thyroid cancer. The patients were aged at least 40 years and received a high-dose thyroid hormone replacement therapy after total thyroidectomy at the Rajavithi Hospital between January 2004 and December 2019. The relationships between BMD and associated factors were analyzed using Pearson's correlation and multiple linear regression. A p-value of less than 0.05 was considered statistically significant.

THE ASEAN JOURNAL OF RADIOLOGY
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Results: A total of 100 female patients with a mean age of 55.37 ± 11.36 (40-82) years and mean body mass index (BMI) of 24.8 ± 4.96 (15-40) were included; 60 and 56 of them were postmenopausal and coffee drinkers, respectively. High-dose thyroid hormone replacement therapy was received for a mean duration of 94.59±50.36 (3-210) months and 13 patients had a history of fractures; 60%, 30%, and 10% had normal BMD, osteopenia, and osteoporosis, respectively. The factors affecting BMD included the BMI (p-value <0.001) and postmenopausal status (p-value <0.001). Subgroup analyses showed the BMI to be the factor affecting BMD in the premenopausal group (p-value <0.001). Age, BMI, and calcium supplement intake were found to have an effect on the BMD in the postmenopausal group (p-value= 0.003, 0.002, and 0.020, respectively). The duration of high-dose thyroid hormone intake had no effect on the BMD in both the overall population (p-value= 0.558) and the subgroups based on the menopausal status (p-value = 0.437 and 0.380 in premenopausal and postmenopausal groups, respectively).

Conclusion: In female patients who were treated for thyroid cancer, the factors affecting the BMD included the BMI in the premenopausal group and the age, BMI, and calcium supplementation in the postmenopausal group.

Keywords: Bone mineral density, BMD, High-dose thyroid hormone, Thyroid cancer, TSH-suppressive dose of thyroxine.

Introduction

Osteoporosis is a disease characterized by a reduction in bone mineral density (BMD) [1]. It is more common in postmenopausal women, and its incidence and severity increase with age. In Thailand, more than 50% of women aged over 70 years are affected by this disease [2]; it increases the likelihood of fractures, which are a major source of medical expenses in the elderly, and result in both increased morbidity and mortality [3-10]. Notably, the hospital mortality rate in Thailand is 2.1% [11], and the average cost of treatment for osteoporotic hip fractures was 116,458.60 Baht in 2004 [12].

Thyroid hormones affect bone resorption rather than formation, leading to a decrease in BMD and potentially leading to osteoporosis [13]. Patients with thyroid cancer are treated by surgical removal of the entire thyroid gland, after which they receive a radioactive iodine therapy to destroy the residual thyroid gland and remaining cancer. This is typically followed by high doses (thyroid stimulating hormone [TSH]-suppressive dose) of thyroid hormone therapy for more than 1 year. Investigating the impact of the duration of the high-dose thyroid hormone therapy on the BMD, and identifying the common factors affecting BMD in these patients, may, therefore, be useful in delivering appropriate and comprehensive care in such cases. The factors considered in this study included basic demographic characteristics, details pertaining to thyroid hormone treatment, and data collected for calculation of the FRAX score [14,15]; these included the age, BMI, income, the educational level, the menopausal status, coffee consumption, alcohol consumption, smoking habits, exercise habits, calcium intake, vitamin D intake, the duration of a high-dose thyroid hormone therapy, the duration of normal-dose thyroid hormone replacement before BMD measurement, the history of fractures in adulthood, the history of hip fractures in parents, the receipt of steroid medication, the history of rheumatoid arthritis, and the presence of secondary osteoporosis.

The objective of this study was to determine factors related to the BMD in patients with thyroid cancer who were receiving a high-dose thyroid hormone therapy after total thyroidectomy.

Operational definitions

The BMD is the quantity of mineral in the bone; it affects the bone strength, and is expressed in terms of the mineral mass per square centimeter of bone (gm/cm^2). The T-score is a numerical value obtained by comparing the patient's BMD (BMD_p) with that of a healthy young adult having a peak bone mass (BMD_y), and is calculated as follows: T-score = $(BMD_p - BMD_y)/SD_y$, with SD_y denoting the standard deviation in BMD of a healthy young adult. The Z-score is a numerical value obtained by comparing the patient's BMD (BMD_p) with that of age-matched

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

individuals (BMD_{am}), and is calculated based on the following formula: Z-score = (BMD_p – BMD_{am})/SD_{am}, with SDam indicating the standard deviation of BMD in age-matched individuals.

A normal BMD is diagnosed when the T-score is ≤ -1. An abnormal BMD encompasses 2 entities, namely, osteopenia and osteoporosis. Osteopenia is diagnosed when the T-score is between -1 and -2.5 and osteoporosis is diagnosed when the T-score is ≥ -2.5. For the spine, the L1–L4 region is used unless focal artifacts (such as spurs) require exclusion of individual vertebra to avoid falsely high BMD.

The BMI is a measure of obesity in adults aged 20 years and over and is calculated using the following formula: BMI = body weight (kg) / (height [m])^2. The premenopausal group included all women who menstruated until menopause. The postmenopausal group included all women who had been menopausal for more than a year.

Coffee consumption, alcohol consumption, smoking habits, exercise habits, calcium intake, vitamin D intake, and the receipt of steroid medication were evaluated based on the current status. In cases where any factor was present, further details were obtained regarding the amount or frequency. In this context, a unit of alcohol varies slightly between different countries, and contains 8-10 g of alcohol. This is equivalent to a standard glass of beer (285 ml), a single measure of spirits (30 ml), a medium-sized glass of wine (120 ml), or a single measure of an aperitif (60 ml).

High-dose thyroid hormone (TSH-suppressive dose of levothyroxine) therapy is administered to patients at higher than normal levels to suppress TSH levels to below0.3 μIU/ml [1].

Patients were considered to have a history of previous fractures in adulthood if they had a history of fracture from any cause. A history of hip fractures in the parents was considered to be positive in cases where the patient's mother or father had a history of hip fracture. Rheumatoid arthritis was considered to be present in

cases with a confirmed diagnosis of rheumatoid arthritis. Secondary osteoporosis was considered to be present in cases where the patient had a disorder strongly associated with osteoporosis. These included: type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, malabsorption, and chronic liver disease.

Materials and methods

This was a cross-sectional study. Bone density measurements and other data were obtained from female patients who were aged at least 40 years and were receiving a high-dose thyroid hormone therapy after total thyroidectomy for thyroid cancer at the Rajavithi Hospital between January 2004 and December 2019.

The data collected included independent variables, namely, age, BMI, income, the educational level, the menopausal status, coffee consumption, alcohol consumption, smoking habits, exercise habits, calcium intake, vitamin D intake, the duration of high-dose thyroid hormone treatment (to maintain TSH < 0.3 μIU/mL), the duration of normal-dose thyroid hormone replacement before BMD measurement, the history of fractures in adulthood, the history of hip fractures in parents, the receipt of steroid medication, the history of rheumatoid arthritis, and the presence of secondary osteoporosis. The dependent variables comprised of the BMD; T-score; and Z-scores of the lumbar spine (L1-L4 vertebrae), total hip, and femoral neck. The BMD was measured by dual-energy X-ray absorptiometry (DXA) using the Prodigy system, GE Healthcare, USA.

Statistical analysis

The sample size for this study was calculated using the mean difference (mean change) from high-dose thyroid hormone treatment estimation formula (Wayne WD, 1995) [16]:

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

$$n = \frac{(Z_{\alpha/2})^2 x (SD)^2}{d^2}$$

n = sample size
$z_{\alpha/2}$ *= statistical value under the standard curve when the level of statistical significance (α = 0.05) is 1.96*
SD = standard deviation
d = precision estimate from 20% change in mean BMD from high-dose thyroid hormone treatment.

In the study by Kim et al. [17], the post-treatment BMD of the lumbar spine had a mean (±standard deviation) value of 1.161±1.278; where *d* = 20% of mean (d =1.161x0.20=0.232)

$$n = \frac{(1.96)^2 x (1.278)^2}{(0.232)^2}$$

$$n = 97$$

The sample group (*n*=100) was selected by systematic sampling based on the hospital number.

Descriptive statistics

Categorical data have been reported as numbers and percentages. Normally distributed continuous data have been reported as the mean with standard deviation, while non-normally distributed continuous data have been presented as the median (with minimum and maximum).

Inferential statistics

Kolomogorov- Smirnov test was used for testing the normality of the data distribution. It was found that p-value = 0.200, interpreted that the data were normal distribution. The lowest T-score was used to represent the individual BMD value for analysis. The relationships between the BMD and associated factors were analyzed using Pearson's correlation and multiple linear regression. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Human Research Ethics Committee, Rajavithi Hospital.

The certificate of approval number was 64115.

Results

A total of 100 female patients who had undergone total thyroidectomy for thyroid cancer and subsequently received a high-dose thyroid hormone therapy were included. The mean age was 55.37 ± 11.36 (40-82) years, mean BMI was 24.8 ± 4.96 (15-40), and median income was 10,000 (600 - 300,000) Baht per month; 70, 27, and 3 participants received education up to the undergraduate level, the bachelor's degree, and the postgraduate level, respectively. A total of 40 and 60 participants were premenopausal and postmenopausal, respectively, and 56 were coffee drinkers who had an average intake of 5.2±2.87 (0.5-14) cups per week. Ten of the subjects consumed alcohol, but none consumed more than 3 units per day. None of the patients smoked, and 63 were physically active; 20 exercised more than 3 days a week. Among the 56 patients taking calcium supplements, the average intake was 2,389±1,978 (250 to 9,000) mg/day. A total of 30, 17 and 13 patients received vitamin D, D2, and D3 supplementation, respectively. The mean duration

THE ASEAN JOURNAL OF RADIOLOGY
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of the high-dose thyroid hormone treatment was 94.59±50.36 (3 - 210) months and the average period of normal-dose thyroid hormone replacement before BMD measurement was 29.74 ± 39.97 (0 – 216) months. Thirteen patients had a history of fractures and 4 reported a history of fractures in their parents; 1 patient each had rheumatoid arthritis and secondary osteoporosis, and none received steroids (Table 1).

Table 1. *Demographic data and clinical characteristics of the study population.*

Characteristics	Patients (n = 100)
Age (years), mean ±SD	55.37±11.36
BMI (kg/m²) mean ±SD	24.81±4.96
<18.0, n (%)	3 (3.0)
18.0-23.0, n (%)	43 (43.0)
>23.0, n (%)	54 (54.0)
Monthly income median (min-max)	10,000.0 (600-300,000.0)
Less than 10,000 Baht, n (%)	53 (53.0)
10,001 to 15,000 Baht, n (%)	18 (18.0)
15,001 to 20,000 Baht, n (%)	10 (10.0)
Over 20,001 Baht, n (%)	19 (19.0)
Education	
Lower than bachelor degree, n (%)	70 (70.0)
Bachelor degree, n (%)	27 (27.0)
Higher than bachelor degree, n (%)	3 (3.0)
Postmenopausal	
No, n (%)	40 (40.0)
Yes, n (%)	60 (60.0)

Characteristics	Patients (n = 100)
Coffee drinkers	
No, n (%)	44 (44.0)
Yes, n (%)	56 (56.0)
Amount (cups/week), mean ±SD	5.21±2.87
(min-max)	(0.5-14.0)
Alcohol drinkers	
No, n (%)	90 (90.0)
Yes, n (%)	10 (10.0)
Smokers	
No, n (%)	100 (100.0)
Yes, n (%)	0 (0.0)
Exercise	
No, n (%)	37 (37.0)
Yes, n (%)	63 (63.0)
Exercise more than 3 days (n=63)	
No, n (%)	43 (68.3)
Yes, n (%)	20 (31.7)
Calcium supplements	
No, n (%)	44 (44.0)
Yes, n (%)	56 (56.0)
Amount of intake (mg/day) mean ±SD. (min-max)	2,389.8±1978.1 (250-9,000)
Vitamin D supplements	
No, n (%)	70 (70.0)
Yes, n (%)	30 (30.0)
- Vitamin D2, n (%)	17 (56.7)
- Vitamin D3, n (%)	13 (43.3)

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

Characteristics	Patients (n = 100)
Duration of high-dose thyroxine (months) mean ±SD (min-max)	94.59±50.36 (3-210)
Duration of normal-dose thyroxine (months) mean ±SD (min-max)	29.74±39.97 (0-216)
History of fracture	
No, n (%)	87 (87.0)
Yes, n (%)	13 (13.0)
History of fracture in parents	
No, n (%)	96 (96.0)
Yes, n (%)	4 (4.0)
Receipt of steroids	
No, n (%)	100 (100.0)
Yes, n (%)	0 (0.0)
Rheumatoid arthritis	
No, n (%)	99 (99.0)
Yes, n (%)	1 (1.0)
Secondary osteoporosis	
No, n (%)	99 (99.0)
Yes, n (%)	1 (1.0)

Data are presented as the number (%) or mean ±SD. or median (min-max)
BMI = body mass index, SD = standard deviation

The results of analysis of the BMD, T-scores, and Z-scores at the lumbar spine, total hip, and femoral neck are shown in Table 2. A total of 60 patients were diagnosed with normal BMD. The remaining 40 patients had abnormal BMD, with 30 and 10 demonstrating the presence of osteopenia and osteoporosis, respectively (Figure 1).

Table 2. *Bone mineral density of female patients with thyroid cancer after administration of TSH-suppressive doses of levothyroxine (n = 100).*

Bone mineral density	Mean	Standard Deviation	Minimum	Maximum
Lumbar BMD(gm/cm^2)	1.073	0.19	0.657	1.514
Lumbar T-score	-0.3	1.57	-3.8	3.4
Lumbar Z-score	0.8	1.34	-2.1	4.1
Total hip BMD(gm/cm^2)	0.935	0.16	0.479	1.298
Total hip T-score	-0.2	1.24	-3.8	2.7
Total hip Z-score	0.7	1.10	-2.1	3.0
Femoral neck BMD (gm/cm^2)	0.864	0.15	0.444	1.157
Femoral T-score	-0.4	1.20	-3.9	2.0
Femoral Z-score	0.7	1.01	-1.9	2.8

BMD = Bone mineral density

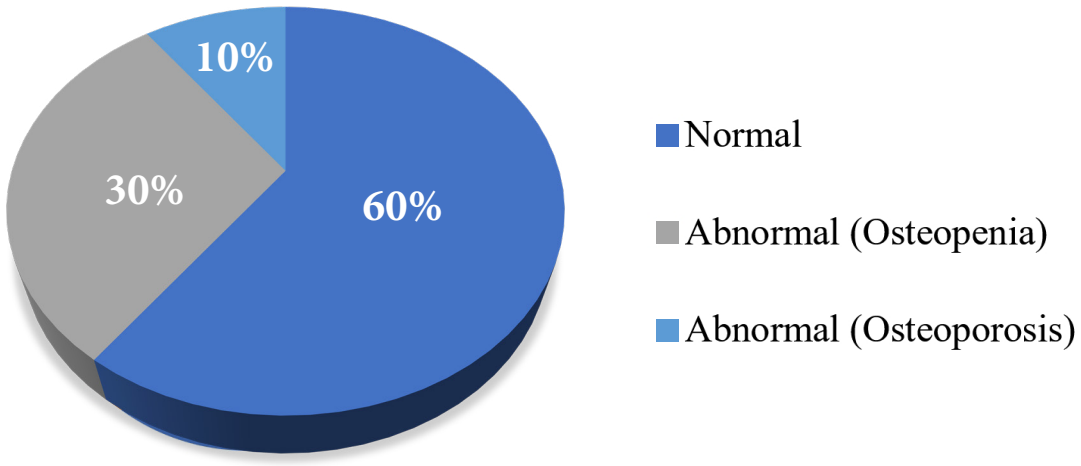

Figure 1. *Diagnosis on BMD measurement.*

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

Table 3 shows the results of Pearson's correlation analysis between the BMD and various factors. The BMI (r=0.571, p-value <0.001) and coffee consumption (r=0.210, p-value =0.036) were found to be the factors with statistically significant positive correlation with the BMD. The factors showing statistically significant negative correlation with the BMD included age (r=-0.535, p-value <0.001), the duration of a high-dose hormone therapy (months) (r=-0.510, p-value <0.001) and the postmenopausal status (r=-0.510, p-value <0.001).

Table 3. *Correlation between BMD and various factors.*

Factors	Bone mineral density	
	Correlation (r)	p-value
Duration of high-dose thyroid hormone therapy (months)	-0.510	<0.001*
Age (years)	-0.535	<0.001*
BMI (kg/m^2)	0.571	<0.001*
Monthly income (Baht)	0.031	0.764
Education	0.010	0.919
Coffee consumption	0.210	0.036*
Vitamin D supplementation	0.094	0.352
Alcohol consumption	0.080	0.430
Calcium supplementation	0.083	0.412
Exercise	0.024	0.809
Postmenopausal status	-0.510	<0.001*
Fracture history	-0.141	0.163

**Significant at p<0.05*

As shown in Table 4, multiple linear regression of the various factors that correlated with the BMD showed the BMI to have a statistically significant positive correlation (p-value <0.001); conversely, postmenopausal status demonstrated a statistically significant negative correlation with the BMD (p-value <0.001). The duration of high-dose hormone therapy and coffee consumption showed no correlation with the BMD (p>0.05).

Table 4. *Factors associated with BMD on multiple linear regression.*

Factors	B	Standard error	Standard beta	p-value
BMI	0.107	0.021	0.422	<0.001*
Duration high-dose thyroid hormone therapy	-0.001	0.002	-0.046	0.558
Coffee consumption	0.321	0.193	0.127	0.100
Postmenopausal status	-0.917	0.207	-0.359	<0.001*
(Constant)	-2.943	0.609		

R= 0.678, R^2 = 0.460, p-value < 0.001, B= regression coefficient

Table 5 shows the results of Pearson's correlation analysis between the pre-menopausal and postmenopausal subgroups. In the premenopausal group, the BMI was found to be the factor demonstrating a statistically significant positive correlation with the BMD (r=0.651, p-value <0.001). In the post-menopausal group, age demonstrated a statistically significant negative correlation with the BMD (r=-0.426, p-value <0.001); however, the BMI (r=0.411, p-value <0.001), coffee consumption (r=0.315, p-value <0.014), and calcium supplementation (r=0.289, p-value <0.025) showed a statistically significant positive correlation with the BMD.

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

Table 5. *Correlation between the BMD and various factors in the premenopausal and postmenopausal subgroups.*

Factors	Bone mineral density			
	Premenopausal subgroup		Premenopausal subgroup	
	Correlation (r)	p-value	Correlation (r)	p-value
Duration of high-dose thyroid hormone therapy (months)	-0.126	0.437	-0.115	0.380
Age (years)	0.202	0.211	-0.426	0.001*
BMI (kg/m^2)	0.651	<0.001*	0.411	0.001*
Monthly income (Baht)	-0.138	0.397	0.008	0.955
Education	-0.215	0.183	0.003	0.982
Coffee consumption	0.074	0.648	0.315	0.014*
Vitamin D supplementation	0.116	0.474	0.147	0.263
Alcohol consumption	-0.130	0.423	0.062	0.636
Calcium supplementation	0.064	0.695	0.289	0.025*
Exercise	-0.294	0.066	0.001	0.999
Fracture history	0.152	0.350	-0.244	0.060

**Significant at p<0.05*

Table 6 shows the results of multiple linear regression analysis in the postmenopausal subgroup. Age, BMI, and calcium supplementation demonstrated a statistically significant correlation with the BMD (p-value <0.001).

Table 6. *Factors associated with BMD in the postmenopausal group (on multiple linear regression).*

Factors	B	Standard error	Standard beta	p-value
Age	-0.040	0.013	-0.327	0.003*
BMI	0.097	0.030	0.336	0.002*
Coffee consumption	0.485	0.248	0.208	0.055
Calcium supplementation	0.599	0.249	0.249	0.020*
(Constant)	-1.753	1.157		

R= 0.644, R^2 = 0.415, p-value <0.001, B= regression coefficient

Discussion

In the present study, the 100 female patients with thyroid cancer had a mean age of 55.37 ± 11.36 (40–82) years and a mean BMI of 24.81 ± 4.96. The mean duration of the high-dose thyroid hormone treatment extended for 94.59±50.36 (3-210) months, and 60% of the patients were postmenopausal. The mean values of the measured lumbar spine, total hip, and femoral neck BMD were 1.073, 0.935 and 0.864 g/cm^2, respectively; the respective mean T-scores were -0.3, -0.2 and -0.4, respectively, and the corresponding mean Z-scores were 0.8, 0.7 and 0.7, respectively. The majority (60%) of patients were found to have a normal BMD; 30% and 10% had osteopenia and osteoporosis, respectively.

In their study, Limpaphayom et al. [18] evaluated the BMD in 1773 Thai women aged 11 to 80 years and found the highest BMD in the age range of 30-34 years. The mean BMD of the spine and femoral neck were found to be 0.957 and 0.814 g/cm^2, respectively. The BMD declined significantly after the age of 35 years, and there was rapid deterioration by the age of 50 years. In their study, Gomes et al. [19] compared 109 postmenopausal women who received high-dose thyroid hormone therapy for thyroid cancer with women of the same age who had a

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

normal thyroid status. The mean age of the patients was 58.4 ± 8.3 years; the mean TSH level was 0.21± 0.28 μIU/ml and the lumbar spine and total femur T-scores were -1.09±1.43 and -0.12±1.18, respectively. No differences were found between the lumbar spine and total femur T-scores of the subjects and controls.

This study found that the BMI had a direct effect on the BMD; this is in agreement with the findings reported by Fawzy et al. [20]. They evaluated the relationship between the BMI and BMD in a sample of 101 individuals, 39 and 62 of whom had normal and low BMD, respectively. A low BMD was observed in 82.4% of the normal BMI group; in the overweight and obese groups, the corresponding proportions were 78.1% and 44.2%, respectively. Notably, the latter figure was statistically significant ($p<0.001$). Hariri et al. [21] studied 198 patients with type 2 diabetes mellitus who were aged 50 to 90 years and found a positive relationship between the BMI and BMD T-scores in the hip and spine regions. They concluded that a low BMI (<18.5 kg/m^2(may be a risk factor for osteoporosis in adults with diabetes, whereas a normal/high BMI could protect them against this disease. In their cross-sectional study, Ma et al. [22] analyzed data from the datasets of the National Health and Nutrition Examination Survey 2005–2006, 2007–2008, 2009–2010, 2013–2014, and 2017–2018. A total of 10,910 participants (5,654 males and 5,256 females) aged over 50 years were enrolled. In addition to finding a simple linear positive association between the BMI and BMD, they observed the existence of a saturation value, which persisted during site-, sex, age-, and race-specific subgroup analyses. They, therefore, concluded that maintaining the BMI at a reasonable value (approximately 26 kg/m^2) may provide the most significant benefit in older adults in terms of maintenance of an optimal BMD and reduction of other obesity-related diseases.

In postmenopausal women, estrogen deficiency increases the rate of both bone resorption and formation; the rate of resorption is much higher, resulting in a rapid decline in the BMD. The present study confirmed that a postmenopausal status correlates with a decrease in the BMD. In this context, Finkelstein et al. [23] conducted a longitudinal cohort study in 1902 African-American, Caucasian, Chinese, and Japanese women who were premenopausal or early perimenopausal

at baseline. The BMD of the lumbar spine and total hip was evaluated across a maximum of six annual visits. Changes in the BMD during the premenopausal or early perimenopausal period were minimal. However, the values declined substantially in the late perimenopausal period, with an average loss of 0.018 and 0.010 g/cm^2·yr from the spine and hip, respectively ($P < 0.001$ for both). In the postmenopausal subgroup, the rates of loss from the spine and hip were 0.022 and 0.013 g/cm^2·yr, respectively ($P < 0.001$ for both).

On subgroup analysis in our study, the factors associated with BMD in the postmenopausal group were the BMI, age, and calcium supplementation. Our results were consistent with those reported by Chen et al. [24]. Their retrospective study included 69 Taiwanese women (44 premenopausal and 25 postmenopausal) with differentiated thyroid cancer who had undergone a regular thyroid hormone suppressive therapy for more than 3 years (mean: 7.3 +/- 3.0 years; range: 3 to 15 years). They found a strong correlation between the BMD and age, BMI, and serum calcium levels. However, no correlation was found with the degree of TSH suppression or the duration of TSH suppression therapy. In their prospective study, Kung et al. [25] evaluated 46 postmenopausal women with thyroid carcinoma for 2 years; they evaluated the rate of bone loss and assessed whether calcium supplementation with or without intranasal calcitonin could decrease the rate of bone loss. All patients were receiving a stable dose of thyroxine (170 +/- 60 micrograms/day or 3.0 +/- 1.4 micrograms/kg/day) for more than one year and all had TSH levels of 0.03 μIU/L or less; the BMD was measured at 6-month intervals. The subjects were randomized into three groups: 1) intranasal calcitonin (200 IU daily) for 5 days/week with 1000 mg calcium daily, 2) calcium alone, or 3) placebo. The results showed that at the end of the second year, both groups 1 and 2 had stable bone mass; however, group 3 showed a significant loss in bone mass (lumbar spine: 5.0%, hip: 6.7%, trochanter: 4.7%, and Ward's triangle: 8.8%; $P < 0.05$).

The negative impact of TSH-suppressive doses of thyroxine on BMD has been debated. In 2017, Chang et al. [26] performed a retrospective study using data from the Korea National Health and Nutrition Examination Survey between 2008 and 2011. Among the 18618 patients included, 80 (11 male and 69 female) had

THE ASEAN JOURNAL OF RADIOLOGY
ISSN 2672-9393

thyroid cancer; no significant difference was found between the groups with and without thyroid cancer in terms of the incidence of osteopenia and osteoporosis (p = 0.783). Subgroup analyses of women and postmenopausal women also showed similar results (p = 0.685 and p =0.095, respectively).

In their study, Zhang et al. [1] investigated the effects of thyrotropin suppression on lumbar spine density in 225 postmenopausal women with differentiated thyroid carcinoma.The patients were divided into 2 groups; 154 received TSH-suppressive doses of thyroxine (median TSH <0.3 μIU/ml) and 71 (control group) did not receive TSH-suppressive doses (median TSH >0.3 μIU/ml). There was no significant difference between either group in terms of the lumbar spine BMD at baseline and at 6, 12, and 24 months before and after treatment (t=1.37, p=0.17; t=-0.128, p=0.89; and t=-0.547, p=0.89 at 6, 12, and 24 months, respectively). Comparison of the BMD before and 2 years after TSH-suppressive therapy demonstrated a 1.9% reduction; at 24 months, a significant difference was found between the TSH-suppressed and control groups in terms of the number of patients with osteopenia and osteoporosis (103/152 vs. 32/68, χ^2=2.88, p=0.004). However, no significant difference was found at either 6 months (72/154 vs. 35/70, χ^2=0.45, p=0.65) or 12 months (71/154 vs. 30/69, χ^2=0.36, p=0.72).

In 1996, Ongphiphadhanakul et al. [27] studied the effect of TSH-suppressive doses of levothyroxine on BMD in Thai women.The study included 27 (18 premenopausal and 9 postmenopausal) women, who received at least 150 micrograms of thyroxine per day for over two years for the treatment of nodular thyroid disease. Comparison of their Z-scores with those of 54 age-matched healthy controls showed that postmenopausal women who received thyroxine for a prolonged period demonstrated a statistically significant reduction in anteroposterior spinal (-0.69 ± 0.20 vs 0.05 ± 0.17, $p < 0.01$), femoral neck (-0.61 ± 0.35 vs 0.18 ± 0.24, $p < 0.05$), and femoral trochanter (-0.64 ± 0.37 vs 0.13 ± 0.22, $p < 0.05$) BMD; no significant difference was found in premenopausal women. In 2006, Mazokopakis et al. [28] performed a comparative study on the femoral BMD in premenopausal women with thyroid cancer who received TSH-suppressive doses of thyroxine. On measuring the BMD before and at 12 and

48 months after receiving thyroxine, they concluded that administration of the TSH-suppressive therapy for at least one year may lower the BMD in the femoral neck, femoral trochanter, and Ward's triangle in premenopausal women.

In their systemic review, Yoon et al. [29] identified and analyzed data from 11 published controlled cross-sectional studies (including approximately 571 patients with well differentiated thyroid cancer and 836 controls). TSH suppression was associated with a lower total hip (weighted mean difference: -0.023; 95% confidence interval: -0.047 to 0.000; p=0.050) and spine (weighted mean difference: -0.041; 95% confidence interval: -0.057 to -0.026; p<0.001) BMD in postmenopausal women with differentiated thyroid cancer; however, no such association was found in male and premenopausal female patients. In our study, no correlation was observed between the duration of TSH-suppressive doses of thyroxine and BMD. Subgroup analyses in the premenopausal and postmenopausal groups showed the same results. Other factors that did not have any effect on the BMD included income, the educational level, coffee consumption, alcohol consumption, smoking habits, exercise habits, vitamin D intake, the duration of normal-dose thyroid hormone replacement before BMD measurement, the history of fractures in adulthood, the history of hip fractures in parents, the receipt of steroid medication, history of rheumatoid arthritis, and presence of secondary osteoporosis.

This study has certain limitations, which may partly be attributed to the retrospective design. First, patients who had osteoporosis before treatment for thyroid cancer could not be excluded, as almost all patients had never undergone testing for BMD. A proportion of the patients consumed calcium and vitamin D owing to postoperative hypoparathyroidism. Second, TSH testing was performed every 3-6 months during the follow-up visits; there may have, therefore, been some discrepancy in the recorded duration of TSH-suppressive therapy. Third, although we had initially planned to only include insufficiency fractures in adulthood, difficulties in identification of such cases prompted the inclusion of all fractures irrespective of the cause.

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Although this study had only 100 samples, the analysis results from the G*Power software showed that there was a high level of power (0.996).

The findings from this study showed that the duration of TSH-suppressive levothyroxine administration had no effect on the BMD. This provides a valuable reference for decision-making during the treatment. The BMI demonstrated a positive correlation with the BMD; patients should, therefore, be advised not to maintain a BMI that is considerably low. As calcium supplementation had a positive effect on the BMD in postmenopausal patients, calcium supplementation may be useful for preventing osteoporosis in postmenopausal patients with low BMI.

Conclusion

In female patients with thyroid cancer, the BMI and postmenopausal status were found to be related to the BMD. In the premenopausal group, the BMD was affected by the BMI. However, the age, BMI, and calcium supplementation were found to affect the BMD in the postmenopausal group. The majority of the subjects had normal BMD.

The period of receiving high doses of levothyroxine had no effect on BMD, so in the cases of patients with high thyroglobulin (Tg) who require high doses of levothyroxine over a long period of time, patients and their physicians may not have to worry as much about the negative effects on BMD. In postmenopausal patients with low BMI, calcium supplementation should be considered to prevent osteoporosis.

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