# The Comparative Study of Bone Mineral Density between Premenopausal Women Receiving Long Term Suppressive Doses of Levothyroxine for Well-differentiated Thyroid Cancer with Healthy Premenopausal Women

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***Objective:*** *To compare bone mineral density (BMD) of lumbar spines (LS) and femoral neck (FN) by Dual energy X-ray absorptiometry (DEXA) in premenopausal well-differentiated thyroid carcinoma women S/P total or near total thyroidectomy with a control group and the effect of Levothyroxine ($LT_4$) to BMD between short term and long term treatment.*

***Material and Method:*** *DEXA were performed at LS (L1-L4) and FN in 22 premenopausal thyroid carcinoma women S/P total or near total thyroidectomy followed by I-131 ablation and long term suppressive dose $LT_4$ and 22 healthy premenopausal women.*

***Results:*** *Mean BMD of LS and FN were not significantly different between thyroid cancer group and control (LS 1.023 +/- 0.088 VS 0.980 +/- 0.075 g/cm$^2$,p > 0.05, FN 0.800 +/- 0.068 VS 0.770 +/- 0.061 g/cm$^2$, p > 0.05). Period of time taking suppressive doses $LT_4$ was divided into 3 groups (2-5 yrs, 6-10 yrs and 11-14 yrs). Mean LS BMD +/- S.D of 2-5 yrs, 6-10 yrs and 11-14 yrs therapy are 1.042 +/- 0.135, 1.004 +/- 0.044 and 1.042 +/- 0.055 respectively (p > 0.05). Mean FN BMD +/- S.D of 2-5 yrs, 6-10 yrs and 11-14 yrs therapy are 0.808 +/- 0.084, 0.781 +/- 0.067 and 0.816 +/- 0.013 respectively (p > 0.05).*

***Conclusion:*** *The suppressive doses $LT_4$ was not the risk factor of osteoporosis. Although, there was no statistically significant difference of BMD between short and long-term suppressive doses $LT_4$ groups, the present sample size was not enough to conclude that long-term suppressive doses $LT_4$ did not decrease BMD.*

***Keywords:*** *Bone mineral density, Levothyroxine suppressive doses, Thyroid cancer.*

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Thyroid cancer is the most common endocrine malignancy. The incidence was 40 in 1,000,000 of population or 1% of all cancers[1]. Well-differentiated thyroid carcinoma composed of papillary carcinoma (80-90%) and follicular carcinoma (10-20%)[2]. Well-differentiated thyroid carcinoma was a very good prognosis malignancy and low mortality rate provided a long life expectancy[3]. The recommendation of treatment was total or near total thyroidectomy followed by I-131 ablation and Levothyroxine ($LT_4$ or Eltroxin®) suppressive doses therapy[4]. The usefulness of $LT_4$ were both substitutive and suppressive therapy. The aim of substitutive therapy was to relieve hypothyroid symptoms so that serum Thyroid stimulating hormone (TSH) should be kept about 1 mU/L. Suppressive therapy aimed to completely inhibit TSH secretion by pituitary gland. This prevented recurrent tumor and inhibits carcinoma progression[3]. Thus, $LT_4$ should be given at a dose sufficient to suppress TSH to a low level ($\leq$ 0.1 mU/L)[3,5]. These patients were categorized as subclinical hyperthyroidism subjects.

Hyperthyroidism is known as a risk factor for osteoporosis and increases the risk of fracture[6]. There was increased bone resorption in overt hyperthyroidism. The rate of bone resorption was increased as the higher level of thyroid hormone[7,8]. The risk factors were menopausal status, a family history of osteoporosis, aging, sedentary lifestyle, low calcium intake, hypogonadism, vitamin D deficiency, smoking, excessive alcohol consumption and some medication (such as glucocorticoids, excessive thyroid hormone, medroxyprogesterone acetate, luteinizing hormone-releasing hormone agonists, anti-seizure medications, cyclosporine A, aluminium, lithium)[6,9].

The effect of suppressive doses of $LT_4$ on bone mass were controversial.

Because there was an estrogen effect to accelerate in reduction of bone mineral density (BMD) in postmenopausal women, so the authors included only premenopausal group in the present study.

The aim of the present study was to compare BMD between the well-differentiated thyroid carcinoma premenopausal women S/P total or near total thyroidectomy with I-131 ablation who were receiving long term suppressive doses $LT_4$ with the control group and the effect on BMD between short term and long term treatment.

**Material and Method**

The present study was an analytic, crossectional study. The authors included 22 well-differentiated thyroid carcinoma premenopausal women S/P total or near total thyroidectomy followed by I-131 ablation and long-term follow up (at least 2 years) in our clinic with a suppressive dose $LT_4$. All of them were free disease. They gave informed consent. Review all of the patient's history, the serum Thyroglobulin, free $T_4$ and TSH level was checked every 6 months and $LT_4$ dose was adjusted to keep the TSH level under or equal to 0.1 mU/L. The exclusion criteria were pregnancy, hyper or hypoparathyroidism, receiving hormonal replacement therapy, bisphosphonate, calcitonin, calcium, vitamin D, steroid, cyclosporin A, lithium, anti-seizure drug, post bilateral salphingo-oophorectomy, hypogonadism, bony metastasis and underlying any other thyroid disease. The presented data collections were the patient's age, body weight, height, BMI and period of time taking $LT_4$. Then, the BMD of LS (L1-L4) and FN were performed in the 22 thyroid cancer patients and 22 premenopausal healthy women by Dual energy X-ray absorptiometry (DEXA), Hologic QDR4500. Results were analyzed by Mann Withney U-test, using SPSS software.

## Results

The findings are summarized in Table 1. The present study demonstrated the factors, which may effect BMD such as age, weight, height and BMI, were not significantly different between the 2 groups. The period of time that patients had taken $LT_4$ suppressive dose was between 2-14 years (mean 7 years). None of the subjects were smokers, drinkers or had a previous history of pathological fracture. Only 3 of the controls had a family history of the osteoporosis, but none of thyroid cancer patients had.

BMD of LS in thyroid cancer patients was between 0.849-1.217 (T-score - 1.8 to +1.54) and controls was between 0.859-1.122 (T-score - 1.71 to +0.68).

BMD of FN in thyroid cancer patients was between 0.696-0.953 (T-score - 1.99 to +0.58) and controls was 0.651-0.912 (T-score - 2.43 to +0.17).

Mean BMD of LS and FN were also not significantly different between the thyroid cancer group and controls (LS 1.023 +/- 0.088 VS 0.980 +/- 0.075 $g/cm^2$, $p > 0.05$, FN 0.800 +/- 0.068 VS 0.770 +/- 0.061 $g/cm^2$, $p > 0.05$).

The authors divided the thyroid cancer patients into 3 groups by the period of time using $LT_4$ suppressive doses therapy (Table 2). In LS BMD, mean +/- S.D of 2-5 yrs, 6-10 yrs and 11-14 yrs therapy were 1.042 +/- 0.135, 1.004 +/- 0.044 and 1.042 +/- 0.055 respectively ($p > 0.05$). In FN BMD, mean +/- S.D of 2-5 yrs, 6-10 yrs and 11-14 yrs therapy were 0.808 +/- 0.084, 0.781 +/- 0.067 and 0.816 +/- 0.013 respectively ($p > 0.05$). Thus, the period of time using suppressive dose $LT_4$ therapy had no effect on BMD.

## Discussion

The standard treatment of well-differentiated thyroid cancer was total or near thyroidectomy followed by I-131 ablation, thus all the patients had almost always permanent hypothyroidism. As above-mentioned, they needed long term $LT_4$ therapy for substitute hypothyroid symptoms and suppressive therapy to prevent recurrent tumor and inhibit tumoral progression. In this case, the authors had to keep TSH level less or equal 0.1 mU/L, which was lower than the normal population and categorized as subclinical hyperthyroidism. Because thyroid cancer patients

**Table 1.** The comparison of data collection in thyroid cancer during long term LT4 suppressive dose therapy and controls

| | Thyroid cancer (N = 22) | | Control (N = 22) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Age** (year) | 38.00 (26-50) | 7.264 | 39.77 (27-49) | 6.039 | 0.38 |
| **BW** (kg) | 56.60 (44-88) | 10.560 | 55.64 (40-67.5) | 6.710 | 0.72 |
| **Height** (cm) | 156.27 (150-170) | 5.230 | 155.82 (150-164) | 3.800 | 0.74 |
| **BMI** | 23.157 (17.46-30.44) | 3.862 (17.09-27.68) | 22.917 | 2.694 | 0.81 |
| **BMD** Lumbar ($g/cm^2$) | 1.023 (0.849-1.217) | 0.088 | 0.980 (0.859-1.122) | 0.075 | 0.081 |
| **BMD Femoral Neck** ($g/cm^2$) | 0.800 (0.696-0.953) | 0.068 | 0.770 (0.651-0.912) | 0.061 | 0.184 |
| **Period of time taking** $LT_4$ (year) | 7.00 (2-14) | 3.423 | - | - | - |

( ) = range

**Table 2.** Mean and standard deviation classified by the range of time receiving $LT_4$

| | The range of time receiving $LT_4$ (year) | N | BMD LUMBAR | | BMD FEMORAL NECK | |
|---|---|---|---|---|---|---|
| | | | Mean | SD | Mean | SD |
| 1. | 2-5 years | 8 | 1.042 | 0.135 | 0.808 | 0.084 |
| 2. | 6-10 years | 11 | 1.004 | 0.044 | 0.781 | 0.067 |
| 3. | 11-14 years | 3 | 1.042 | 0.055 | 0.816 | 0.013 |

needed long-term suppressive doses $LT_4$ treatment, the present study aimed to confirm the side effects of $LT_4$ in osteoporosis.

The authors found no significant difference of BMD at LS and FN regions between thyroid cancer patients and controls. This meant suppressive doses $LT_4$ did not decrease BMD. In the present study, there was no significant difference in BMD between short-term and long-term treatment. However, because of the small sample size (8, 11 and 3 patients in short, middle and long-term $LT_4$ therapy, respectively), thus the period of time taking suppressive doses $LT_4$ may not represent the effect on BMD in the large population.

Many previous studies had different ideas about bone loss and bone mineral density in thyroid disease. Kisakol G et al[8] studied 13 patients with subclinical hyperthyroid secondary to untreated Graves' disease, 20 patients with subclinical hypothyroidism and 10 healthy subjects. They concluded that the bone turnover and urine calcium excretion were increased in the subclinical hyperthyroid group.

Limonova Z et al[10] measured lumbar BMD in thyroid cancer patients (13 men, 20 premenopausal and 25 postmenopausal women) who had undergone thyroidectomy and were treated by suppressive doses $LT_4$ for 1-21 years. They found that the lumbar BMD reduced in only the postmenopausal group compared to controls and concluded that it was unsafe for postmenopausal women using suppressive dose $LT_4$ therapy. Corresponding with the prior study, Kung AW et al[11] also measured BMD using DEXA in 34 postmenopausal thyroid cancer women S/P total thyroidectomy with I-131 ablation followed by suppressive doses $LT_4$. They found lower BMD in total body, lumbar spines, femoral neck, trochanter and ward's triangle regions in thyroid cancer patients compared to controls.

However, a different conclusion was discussed by Florkowski CM et al[12] and Gorres G et al[13]. These researches included thyroid cancer men and women with suppressive doses $LT_4$. They concluded that $LT_4$ suppressive doses therapy was not a risk factor for osteoporosis.

The discrepancies of those researches were probably due to the difference of clinical, design study and BMD measurement techniques. Nowadays, DEXA is the gold standard in bone mass measurement. In the present study, the authors excluded postmenopausal women, because the low estrogen level may effect bone loss. Thus, the authors included only premenopausal group. The authors tried to get rid of the other risk factors of osteoporosis, which included hyper or hypoparathyroidism, some medication effecting bone mass (such as hormonal replacement therapy, bisphosphonate, calcitonin, calcium, vitamin D, steroid, cyclosporin A, lithium, anti-seizure drug), post bilateral salphingo-oophorectomy, hypogonadism, bony metastasis and any underlying thyroid disease. The body weight also effected BMD[15]. The present study demonstrated no significant difference in mean body stature (body weight, height and BMI) between the thyroid cancer group and controls.

In the present study, the authors found that there was no significant difference of BMD at the lumbar spines and femoral neck regions between treated thyroid cancer patients who received LT4 suppressive dose treatment and the controls. This meant suppressive doses of $LT_4$ was not a risk factor of osteoporosis. Although, there was no statistically significant difference of BMD between short and long-term suppressive doses $LT_4$ groups, the presented sample size was not enough to conclude that long-term suppressive doses $LT_4$ did not decrease BMD.

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## การศึกษาเปรียบเทียบความหนาแน่นของกระดูก ในผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่เป็นมะเร็งต่อมไทรอยด์ชนิด well-differentiated และได้รับยาฮอร์โมนไทรอยด์ขนาด suppressive doses เป็นเวลานานกับกลุ่มเปรียบเทียบ

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***วัตถุประสงค์:*** *เพื่อศึกษาความหนาแน่นของกระดูกที่บริเวณกระดูกสันหลังส่วนเอว (Lumbar spines) และสะโพก (Femoral neck) ด้วยเครื่องตรวจความหนาแน่นของกระดูกแบบ Dual energy X-ray absorptiometry (DEXA) ในผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่เป็นมะเร็งต่อมไทรอยด์ชนิด well-differentiated และได้รับยาฮอร์โมนไทรอยด์ขนาด suppressive doses เป็นเวลานาน เทียบกับหญิงวัยก่อนหมดประจำเดือนปกติ และเปรียบเทียบความหนาแน่นของกระดูกระหว่างกลุ่มผู้ป่วยที่ได้ฮอร์โมนไทรอยด์ในระยะสั้นกับระยะยาว*

***วัสดุและวิธีการ:*** *เป็นงานวิจัยแบบ Analytic, crossectional study โดยตรวจความหนาแน่นกระดูกบริเวณกระดูกสันหลังส่วนเอวและสะโพก ด้วยเครื่อง DEXA ในผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่เป็นมะเร็งไทรอยด์ชนิด Well-differentiated และเคยได้รับการผ่าตัดต่อมไทรอยด์ออกทั้งหมดหรือเกือบทั้งหมด ตามด้วยการให้ไอโอดีนรังสี (I-131) และได้ฮอร์โมนไทรอยด์เสริมขนาด Suppressive doses นานอย่างน้อย 2 ปี จำนวน 22 คน เทียบกับหญิงวัยก่อนหมดประจำเดือนปกติ 22 คน*

***ผลการศึกษา:*** *ค่าเฉลี่ยของความหนาแน่นของกระดูกบริเวณกระดูกสันหลังส่วนเอว และสะโพก ไม่มีความแตกต่างกันอย่างมีนัยสำคัญระหว่าง 2 กลุ่ม โดยค่าเฉลี่ยความหนาแน่นของกระดูกสันหลังส่วนเอวระหว่างผู้ป่วยและกลุ่มเปรียบเทียบคือ 1.023 +/- 0.088 VS 0.980 +/- 0.075 g/cm$^2$, p > 0.05, ส่วนสะโพก 0.800 +/- 0.068 VS 0.770 +/- 0.061 g/cm$^2$, p > 0.05. ระยะเวลาที่กินยา Suppressive doses $LT_4$ แบ่งเป็น 2-5, 6-10 and 11-14 ปี พบว่า ไม่มีความแตกต่างของความหนาแน่นของกระดูกอย่างมีนัยสำคัญ*

***สรุป:*** *ไม่มีความแตกต่างอย่างมีนัยสำคัญของความหนาแน่นของกระดูกที่กระดูกสันหลังส่วนเอว และสะโพกในผู้ป่วยมะเร็งไทรอยด์ชนิด Well-differentiated ที่ได้รับฮอร์โมนไทรอยด์ขนาด Suppressive doses เป็นเวลานาน สรุปได้ว่า Suppressive doses $LT_4$ ไม่เพิ่มความเสี่ยงต่อโรคกระดูกพรุน สำหรับการกินยาฮอร์โมนไทรอยด์ในระยะสั้นและยาวต่าง ๆ กัน แม้ว่าจะไม่มีความแตกต่างทางสถิติอย่างมีนัยสำคัญ แต่จำนวนประชากรน้อยเกินไปที่จะสรุปได้ว่า การกินยาฮอร์โมนไทรอยด์ในระยะยาวไม่ทำให้ความหนาแน่นของกระดูกลดลง*