A Comparative Study of Bone Mineral Density between Premenopausal Women with Hyperthyroidism and Healthy Premenopausal Women

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Objective: *To compare bone mineral density (BMD) of the lumbar spine (L1-L4), total hip (TH), and femoral neck (FN) analyzed by Dual Energy X-ray Absorptiometry (DXA) in premenopausal women with hyperthyroidism and in healthy premenopausal women.*

Material and Method: *Cross-sectional study included 49 premenopausal women with hyperthyroidism and 49 healthy premenopausal women. Age, weight and body mass index (BMI) were comparable in both groups. All subjects had a BMD measurement by DXA in the region of L1-L4, TH and FN and the unpaired t-test was used to analyze.*

Results: *The mean BMD of premenopausal women with hyperthyroidism at L1-L4, TH and FN was 0.928, 0.838 and 0.774 g/cm^2, which were lower than those of healthy premenopausal women; 0.991, 0.917 and 0.832 g/cm^2, respectively (p-value is less than 0.05). Time interval that had elapsed for active hyperthyroidism was not associated with the decrease of BMD at L1-L4, TH and FN in hyperthyroid women.*

Conclusion: *The BMD of L1-L4, TH and FN in premenopausal women with hyperthyroidism were significantly lower than those of healthy premenopausal women. Therefore, overt hyperthyroidism could be associated with bone loss and may be a risk factor for the development of osteoporosis. However, time interval of active hyperthyroidism was not related to the decrease of BMD in hyperthyroid women.*

Keywords: *Bone mineral density, Premenopausal women, Hyperthyroidism, Dual energy X-ray absorptiometry (DXA)*

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Over the past decade, osteoporotic fractures have been recognized as one of the most serious problems in public health. For a 50-year-old white woman, the lifetime risk of suffering a fragile fracture of the spine, hip or forearm is estimated to be 30-40%. For men, the risk of an osteoporotic fracture is about one third of that in women. These fractures cause pain, disability and incur health care costs[1].

On the other hand, thyrotoxicosis which is a common and important thyroid disorder, can affect many systems of the body including the skeletal system. The authors use the term thyrotoxicosis as a clinical syndrome of hypermetabolism from increased the serum concentration of free thyroxine (FT_4) or free triiodothyronine (FT_3), or both. The term hyperthyroidism is used to mean sustained increases in thyroid hormone biosynthesis and secretion by the thyroid gland. Although many patients with thyrotoxicosis have hyperthyroidism, others, for example, those, for whom thyrotoxicosis is caused by thyroiditis or exogenous thyroid hormone administration, do not[2]. This disorder occurs in almost one percent of all Americans and affects women five to ten times more often than men.

Graves Disease is the most common cause of hyperthyroidism and is attributable to immunoglobulins that activate the TSH receptor of follicular cells. A simple way of classifying the various causal disorders is to measure FT_3, FT_4, thyroid-stimulating hormone (TSH), and 24-hr uptake with I-131[3]. The other causes of hyperthyroidism are toxic multinodular goiter and toxic adenoma.

Thyroid hormone can act directly on bone to increase resorption and alter normal metabolism. In theory, thyrotoxicosis accelerates the rate of bone

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remodeling. The increased turnover of bone that develops in thyrotoxicosis is characterized by an increase in the number of osteoclasts, the number of resorption sites and ratio of resorptive to formative bone surfaces, with the net result of bone loss[4,5].

Nevertheless, the effect of hyperthyroidism on osteoporosis risk remains controversial. Besides, it is known that low estrogen levels in postmenopausal women also cause bone loss. Therefore, the authors excluded postmenopausal women in the presented study.

The aim of this research was to compare BMD between premenopausal women with hyperthyroidism and healthy premenopausal women, and to study the change of BMD on the time interval that elapsed for hyperthyroidism.

Material and Method

The present study was an analytic, cross-sectional study. The authors included 49 premenopausal women with hyperthyroidism and 49 healthy premenopausal women who underwent BMD measurement in Phramongkutklao hospital between December 2007 and June 2008. For the hyperthyroid subjects, the diagnosis of hyperthyroidism was proven by increased 24-hr thyroid uptake or increased FT_3, FT_4 with decreased TSH. All subjects gave informed consent. The presented data collection included age, body weight, height, history of menstruation, and other underlying diseases and treatments. For the hyperthyroid women, the authors recorded the interval of time that elapsed between the initial diagnosis of hyperthyroidism and the BMD measurement, previous medication or surgery, thyroid function test (FT_3, FT_4, TSH) and measured thyroid uptake. The exclusion criteria comprised metabolic disease (such as hyper or hypoparathyroidism), other thyroid diseases (such as thyroid cancer), osteoporosis receiving antiresorptive drugs, patients receiving hormonal replacement therapy, steroids, cyclosporin A, lithium, anti-seizure drugs, females whose BMI were more than 25 or less than 19, pregnancy, post bilateral salphingo-oophorectomy, hypogonadism, and bony metastasis. Patients taking only calcium and/or vitamin D supplements were not excluded.

All subjects had a BMD measurement by Dual Energy X-ray Absorptiometry (DXA), Hologic Discovery, at the lumbar spine and hips.

Statistical analysis

The data were analyzed by using SPSS for Microsoft Windows version 15.0 (Chicago, IL). Baseline characteristic was presented using descriptive statistics. Comparison of quantitative variables such as mean BMD and standard deviation (SD) between two groups was done by unpaired t-test. A p-value of less than 0.05 was considered as statistical significance different.

Results

The data in Table 1 demonstrates the factors, affecting BMD such as age, weight, and BMI. It suggests that these factors were not significantly different between premenopausal women with hyperthyroidism and controls. The authors divided the subjects into four groups by age at the time of BMD measurement (Table 2): (1) less than 20 years, (2) 21-30 years, (3) 31-40 years and (4) more than 40 years. Most of the hyperthyroid patients and controls were between 21-30 years old, n = 19 (38.78%) and n = 20 (40.82%), respectively. Hence, it seems that the BMD change due to aging did not affect both groups.

Clearly, all hyperthyroid subjects had active hyperthyroidism. In the hyperthyroid group, the lowest 24hr-thyroid uptake was 41.59%, while the highest was 99.27%. Most of the hyperthyroid patients' 24hr-thyroid uptakes were between 81 to 90% (Table 3).

The mean BMD of premenopausal women with hyperthyroidism at the lumbar spine, total hip and femoral neck were 0.928, 0.838 and 0.774 g/cm^2, while

Table 1. The comparison of data collection between premenopausal women with hyperthyroidism and controls.

	group	n	mean	SD	p
Age (year)	Hyperthyroid	49	33.45	7.71	0.462
	Control	49	34.59	7.61	
Weight (kg)	Hyperthyroid	49	53.98	6.22	0.959
	Control	49	53.92	5.35	
BMI (kg/m^2)	Hyperthyroid	49	22.36	2.56	0.139
	Control	49	21.68	1.91	

those of controls were 0.991, 0.917 and 0.832 g/cm^2, respectively (Table 4). The summarized finding shows that the BMD of hyperthyroid women in these regions was significantly lower than those of the controls (p-value was less than 0.05).

The time interval that had elapsed between the initial diagnosis of hyperthyroidism and BMD measurement was also divided into four groups: (l) less than four years (n = 18), (2) four to six years (n = 16), (3) seven to nine years (n = 7) and (4) more than nine years (n = 8), as shown in Table 5. The presented data indicated that time interval of active hyperthyroidism was not associated with the decrease of BMD at L1-L4, TH and FN.

Table 2. All subjects in each group classified by the range of age

Range of age (year)	Hyperthyroid n (%)	Control n (%)
≤ 20	1 (2.04%)	0 (0%)
21-30	19 (38.78%)	20 (40.82%)
31-40	16 (32.65%)	13 (26.53%)
> 40	13 (26.53%)	16 (32.65%)
Total	49 (100%)	49 (100%)

Discussion

In the normal population, BMD increases in childhood and adolescence and stabilizes between 20

Table 3. The number and percentage of the hyperthyroid patients classified by thyroid uptake

Percent of 24hr. -thyroid uptake	Number of patient	Percent of patient
41-50%	4	8.16%
51-60%	3	6.12%
61-70%	9	18.37%
71-80%	10	20.41%
81-90%	15	30.61%
> 90%	8	16.33%
Total	49	100%

Table 4. The comparison of BMD measurement at lumbar spine, total hip and femoral neck between premenopausal hyperthyroid women and controls.

Region of BMD measurement	Group	n	mean	SD	p-value
L1-L4	Hyperthyroid	49	0.928	0.11	0.002*
	Control	49	0.991	0.09	
Total Hip	Hyperthyroid	49	0.838	0.11	<0.001*
	Control	49	0.917	0.09	
Femoral neck	Hyperthyroid	49	0.774	0.11	0.006*
	Control	49	0.832	0.08	

*Significant p-value less than 0.05

Table 5. The mean and standard deviation of BMD at the lumbar spine, total hip and femoral neck classified by the range of time taking in hyperthyroid premenopausal women

Time interval (year)	Number of patient (percent)	Lumbar spine		Total Hip		Femoral Neck	
		mean	SD	mean	SD	Mean	SD
<4	18 (36.73)	0.904	0.021	0.796	0.024	0.763	0.028
4-6	16 (32.65)	0.979	0.032	0.889	0.021	0.808	0.029
7-9	7 (14.29)	0.868	0.042	0.814	0.048	0.745	0.037
> 9	8 (16.33)	0.932	0.012	0.849	0.040	0.780	0.031
*p-value		0.066		0.079		0.558	

*By using ANOVA

to 29 years old. After this interval, it gradually decreases. It may rapidly decline in post menopausal women or in patients with risk factors such as receiving steroids, or hyperparathyroidism. In the Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Position Development Conference, a recommendation was made that osteoporosis cannot be diagnosed in females prior to menopause and in males younger than age 50. The Z-score, not the T-score, is preferred for diagnosis. A Z-score of -2.0 or lower is defined as "below the expected range for age," and a Z-score above -2.0 is "within the expected range for age". In the present study, the authors included premenopausal women with hyperthyroidism and healthy premenopausal women. Accordingly, osteoporosis cannot be diagnosed in these subjects. However, it is possible patients defined as "below the expected range for age" when they are post menopausal or older than age 50, may be at risk for the development of osteoporosis.

Many previous studies had different ideas about bone loss and BMD in hyperthyroidism. Kisakol G et al[6] 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 increased in the subclinical hyperthyroid group.

Helen Karga et al[7] reported that overt symptomatic hyperthyroidism is associated with decreased BMD during the first three years after diagnosis and treatment of the disease. After this interval, women with hyperthyroid do not have different BMD from controls, apparently because of the recovery of the bone density lost early during the course of the disease. Similarly, Udayakumar N et al[8] measured BMD by DXA at the lumbar spine in young men and women with thyrotoxicosis. They concluded that after control of thyrotoxicosis by anti-thyroid drugs and surgery, the mean BMD of the subjects significantly increased after one year. Another correspondent research by Rosen CJ and Adler RA[9] studied lumbar BMD in 11 hyperthyroid patients and 10 controls in 1986 measured by DPA and in 1991 by DXA. All of the hyperthyroid patients were successfully treated and remained euthyroid for more than three years. They found that decreased bone density associated with thyrotoxicosis is reversible after effective treatment.

The discrepancies of those research studies were probably due to the difference of clinical design study and BMD measurement technique. The present study was analytic, cross-sectional study. It showed an advantage over the other studies due to additional comparison of age, weight and BMI. The authors excluded postmenopausal women because low estrogen levels may cause bone loss. Moreover, all hyperthyroid patients exhibited proven active hyperthyroidism. Some of them had newly diagnosed symptomatic hyperthyroidism; the others were previously treated with active hyperthyroidism. The results of the present study were related to the many previous studies suggesting that hyperthyroidism was associated with bone loss in premenopausal women. Nevertheless, the authors also found that the time interval that had elapsed for active hyperthyroidism was not associated with the decrease of BMD in hyperthyroid women.

Conclusion

In conclusion, the BMD of L1-L4, TH and FN in premenopausal women with hyperthyroidism were significantly lower than those of the controls. Hence, active hyperthyroidism could be associated with bone loss and may be a risk factor for the development of osteoporosis. However, time interval of active hyperthyroidism was not related to the decrease of BMD in hyperthyroid women.

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การศึกษาเปรียบเทียบความหนาแน่นของกระดูก ในผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่เป็นโรคต่อมไทรอยด์เป็นพิษ กับหญิงวัยก่อนหมดประจำเดือนที่ไม่เป็นโรคต่อมไทรอยด์เป็นพิษ

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วัตถุประสงค์*: เพื่อเปรียบเทียบความหนาแน่นของกระดูกในผู้ป่วยหญิงวัยก่อนหมดประจำเดือน ที่เป็นโรคต่อมไทรอยด์เป็นพิษ กับหญิงวัยก่อนหมดประจำเดือนที่ไม่เป็นโรคต่อมไทรอยด์เป็นพิษ*

วัสดุและวิธีการ*: การวิจัยภาคตัดขวางครั้งนี้เป็นการเปรียบเทียบผลการตรวจความหนาแน่นกระดูก (BMD) โดยใช้วิธี Dual energy X-ray absorptiometry (DXA) ที่บริเวณกระดูกสันหลัง (L1-L4), กระดูกสะโพกโดยรวม (total hip, TH) และคอของกระดูกสะโพก (femoral neck, FN) ของผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่ได้รับการวินิจฉัยว่าเป็นโรคต่อมไทรอยด์เป็นพิษ จำนวน 49 คน กับกลุ่มเปรียบเทียบ จำนวน 49 คน โดยอายุเฉลี่ย น้ำหนัก และดัชนีมวลกายทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*

ผลการศึกษา *: ผู้ป่วยหญิงวัยก่อนหมดประจำเดือน ที่ได้รับการวินิจฉัยว่าเป็นโรคต่อมไทรอยด์เป็นพิษมีค่าเฉลี่ยความหนาแน่นกระดูกที่บริเวณ L1-L4, TH และ FN เท่ากับ 0.928, 0.838 และ 0.774 g/cm^2 โดยทั้ง 3 ค่าต่ำกว่ากลุ่มเปรียบเทียบอย่างมีนัยสำคัญทางสถิติ ซึ่งวัดค่าเฉลี่ยความหนาแน่นกระดูกได้เท่ากับ 0.991, 0.917 และ 0.832 g/cm^2 ตามลำดับนอกจากนี้ยังพบว่าการลดลงของความหนาแน่นกระดูกทั้ง 3 ส่วน ไม่ขึ้นกับระยะเวลาการป่วยของโรคต่อมไทรอยด์เป็นพิษ*

สรุป*: ค่าความหนาแน่นของกระดูกที่บริเวณ L1-L4, TH และ FN ของผู้ป่วยหญิงวัยก่อนหมดประจำเดือนที่เป็นโรคต่อมไทรอยด์เป็นพิษต่ำกว่ากลุ่มเปรียบเทียบอย่างมีนัยสำคัญทางสถิติที่ระดับ 0.05 ดังนั้นสรุปได้ว่าโรคต่อมไทรอยด์เป็นพิษทำให้มวลกระดูกลดลง ซึ่งอาจก่อให้เกิดความเสี่ยงของโรคกระดูกพรุนได้ในอนาคต อย่างไรก็ตามระยะเวลาการป่วยของโรคต่อมไทรอยด์เป็นพิษไม่สัมพันธ์กับการลดลงของความหนาแน่นกระดูก*