ORIGINAL ARTICLE

Endogenous subclinical hyperthyroidism may not lead to bone loss in premenopausal women

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Abstract

Background: Osteoporosis is defined as the decrease in bone mineral density. It is a serious health problem showing the predisposed person with increased bone fracture risk. Hyperthyroidism is one of the major causes of secondary osteoporosis. The aim of this study was to assess bone mineral density in premenopausal women with endogenous subclinical hyperthyroidism.

Methods: A total of 168 subjects were included in this case-control study, of whom 86 and 82 participants were premenopausal women with subclinical hyperthyroidism and healthy premenopausal subjects, respectively. The patients with subclinical hyperthyroidism who were not receiving L-thyroxine treatment were included. The women in postmenopausal state or having chronic disease were excluded. The bone mineral densities of all subjects with dual energy X-ray absorptiometry were examined.

Results: The Z scores (femur and L1-4) of the study group were -0.15 ± 1.15 and -0.23 ± 1.03, respectively. The Z scores of the control group were -0.39 ± 1.08 and -0.55 ± 0.98, respectively. The differences between the groups were not statistically significant (p=0.14, 0.34, respectively).

Conclusion: Our data suggest that contrary to exogenous subclinical hyperthyroidism, endogenous subclinical hyperthyroidism may not decrease bone mineral density in premenopausal women and it may not a risk factor for osteopenia or osteoporosis. Hippokratia 2014; 18 (3): 240-244.

Keywords: Subclinical hyperthyroidism, bone mineral density, premenopausal women

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Introduction

Osteoporosis is a skeletal disorder characterized by a loss of bone osteoid that reduces bone integrity and resulting in an increased risk of fractures[1]. The treatment of bone fracture and management of complications is rather expensive. Since bone is a dynamic system with ongoing formation and resorption which are in equilibrium under normal circumstances, a variety of conditions may shift the balance towards resorption with consequent osteoporosis. Hyperthyroidism is one of the major causes of secondary osteoporosis[2-4]. However the effect of subclinical hyperthyroidism (SH), which is defined as reduced serum thyroid stimulating hormone (TSH) concentrations but normal free T4 (fT4) and free T3 (fT3) values, on bone mineral density (BMD) remains controversial[4,5]. Studies reporting the effect of SH on bone mineral density are either in postmenopausal women or in patients with exogenous SH under L-thyroxine (L-T4) treatment[6,7] whereas menopause itself is an important risk factor for osteoporosis. Likewise the contribution of L-T4 treatment on osteoporosis is well known[4-6,8-10]. Reserved estrogen production which is not present in postmenopausal women plays a protective role against irreversible bone loss in premenopausal women[11]. However the number of studies conducted on premenopausal women with SH regarding reduction in BMD is unsatisfactory and conflicting[4,5]. Therefore the aim of the present study was to investigate the bone mineral density in premenopausal women with endogenous subclinical hyperthyroidism in which secondary osteoporosis was excluded.

Materials and Methods

This case-control study was carried out in the internal medicine outpatient clinics of Haseki Training and Research Hospital from January 1st 2008 to June 1st 2009. The institutional review board of the hospital approved this experiment, and informed consent was obtained from all subjects. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

A total of 168 subjects were included in this study. The study group consisted of 86 premenopausal women with subclinical hyperthyroidism and the control group consisted of 82 healthy premenopausal subjects. Patients with a low TSH level with normal fT4 and fT3 concentra-

tions were considered as subclinical hyperthyroidism. The thyroid function tests (TFT) of the patients with SH were assessed retrospectively. Among them, treatment naive patients with persistent SH for at least 3 months were invited and included. Furthermore, newly diagnosed SH patients were followed up for 3 months without any treatment and patients with persistent TFT values were also included.

The exclusion criteria included postmenopausal state, chronic illness (malignancy, renal or hepatic insufficiency, diabetes or other endocrinopathies like primary hyperparathyroidism, hyperprolactinemia, hypogonadism, endogenous or exogenous Cushing syndrome), steroid treatment (systemic, inhaled or topical), significant immobility, chronic alcohol and tobacco consumption or unwillingness to participate in the study. Subjects over 50 years of age were also excluded. All patients matching inclusion and exclusion criteria were selected for the study.

In the study group, 44 of the patients had Graves disease, 18 had solitary thyroid nodule. Twenty-four patients had multinodular goiter. Thyroid ultrasonography, antibody levels and scintigraphic evaluations helped the determination of these disorders. Thyroid ultrasonographies were performed by a radiologist with Xario SSA-790 model ultrasound (Toshiba, 2006, Japan).

All participants underwent bone densitometry investigation. Total body and regional bone mineral density levels were measured by a dual energy X-ray absorptiometry (DEXA) (Norland XR-46 X-ray, Fort Atkinson, Wis) was used to measure BMD in the lumbar vertebrae (L1-L4) and in the classical locations of the proximal femur such as the femoral neck with precision error is defined as ± 2%[10,11]. Z scores "-2.0 or lower" below expected range for age while >-2.0 "within expected range for age" were considered as osteoporosis compared to the age matched cohort according to World Health Organisation[12].

A venous blood sample for biochemical tests was collected in the morning after an overnight fasting. Serum glucose, creatinine, calcium, phosphorus levels were analysed on the Beckman Coulter Synchron LX 20 (Massachusetts, USA) using commercially available kits. Prolactin, TSH and fT4, fT3 concentrations were examined by chemiluminescent enzyme immunoassay (Abbott C 16000, Longford, Ireland). Intact parathyroid hormone (iPTH) levels, serum anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibody were examined by chemiluminescent enzyme immunoassay (Immulite 2500, Los Angeles, USA). Radio-immunoassay method was used when measuring vitamin D (25OHD) levels in Cobas e411 analyser (Mannheim, USA; reference value: 10-68 ng/ml).

The MedCalc 12.7 software (MedCalc, Belgium) program was used for all statistical analyses, and the data were reported as the mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to show the normal distribution of quantitative measurements; the Chi-square or Fischer's exact test were used to test the statistical significance of the differences in frequencies (the rate of osteopenia and osteoporosis); and the t-test or Mann Whitney U test was used for the comparison of the quantitative measurements (biochemical measurements and Z scores) between the two groups. An odds ratio was used to analyse the degree of association between the TSH and Z scores, and BMD values. Multiple linear regression test (enter method) was used to analyse the relationship between a dependent variable (BMD femur and L1-L4) and one or more independent variables (predictor variables or explanatory variables). The probability of making a Type I error (alpha, significance) is 0.05 in all tests.

Results

The average age of the study group (33.28 ± 9.54 years) and control (34.12 ± 7.91) were matched (p=0.66). There was no difference between control and SH group with regard to body mass index (BMI) either (25.78 ± 5.59 vs 24.68 ± 3.73; p=0.29). The groups were successfully matched for all biochemical parameters (FT4, FT3, iPTH, Ca, 25OHD, P, glucose, creatinine and prolactin) except TSH (Table 1). The BMD values of groups were summarized in Table 2. Z score of lumbar 1-4 regions of

Table 1: Biochemical measurements and clinical characteristics of the study (86 premenopausal women with subclinical hyperthyroidism) and control (82 healthy premenopausal subjects) groups.

	Study group (n=86)	Control group (n=82)	p
Age	33.2 ± 9.5	34.1 ± 7.9	0.66
BMI (kg/m²)	25.7 ± 5.5	24.6 ± 3.7	0.29
TSH (uIU/mL)	0.17 ± 0.10	1.99 ± 0.93	<0.001
fT4 (ng/dL)	1.11 ± 0.15	1.03 ± 0.22	0.07
fT3(ng/dl)	2.88 ± 0.46	2.83 ± 0.44	0.58
iPTH (pg/mL)	67.1 ± 19.3	59.0 ± 23.6	0.08
Ca (mg/dl)	9.2 ± 0.3	9.2 ± 0.4	0.64
25OHD (ng/mL)	18.1 ± 10.7	22.5 ± 10.7	0.06
P (mg/dl)	3.63 ± 0.63	3.43 ± 0.82	0.22
Glucose (mg/dL)	91.6 ± 7.2	89.6 ± 8.0	0.23
Prolactin (ng/mL)	13.63 ± 6.02	13.43 ± 6.11	0.74
Creatinine (mg/dL)	0.75 ± 0.12	0.74 ± 0.16	0.76

BMI: body mass index, n: number of subjects, TSH: thyroid stimulating hormone, TFT: thyroid function test, fT4: free T4, fT3: free T3, iPTH: Intact parathyroid hormone, Ca: calcium, 25OHD: vitamin D, P: phosphorus.

Table 2: Bone mineral density values of the spine and the femoral neck of the study (86 premenopausal women with subclinical hyperthyroidism) and control (82 healthy premenopausal subjects) groups.

	Study group (n=86)	Control group (n=82)	p
Lumbar 1-4 Z score	-0.23 ± 1.03	-0.55 ± 0.98	0.14
Femur neck Z score	-0.15 ± 1.15	-0.39 ± 1.08	0.34
Lumbar 1-4 T score	-0.63 ± 1.01	-0.33 ± 1.03	0.18
Femur neck T score	-0.76 ± 1.11	-0.63 ± 0.98	0.57
BMD femur g/cm2	0.83 ± 0.14	0.84 ± 0.12	0.82
BMD L1-4 g/cm2	0.92 ± 0.16	0.91 ± 0.15	0.91

BMD: bone mineral density, n: number of subjects, L1-4: Lumbar 1-4.

groups were comparable (-0.23 ± 1.03 vs. -0.55 ± 0.98; p=0.14). Similarly, Z score of femur necks were also comparable (-0.15 ± 1.15 vs. -0.39 ± 1.08; p=0.34). T score of lumbar 1-4 regions of groups were comparable (-0.63 ± 1.01 vs. -0.33 ± 1.03; p=0.18). Similarly, T score of femur necks were also comparable (-0.76±1.11 vs. -0.63 ± 0.98; p=0.57).

Twenty women (46.5%) in the study group had osteopenia whereas they were 17 (41.4%) in the control group. This result was not statistically significant (p=0.80). Three patients (6.9%) in the study group had osteoporosis. In control group the number of women with osteoporosis was two (4.8%) (p=0.95; Table 3).

In correlation analyses; serum TSH levels were not significantly correlated with Z scores and BMD values of femur neck and lumbar 1-4 levels (p>0.05, respectively; Table 4).

Multiple regression analyses (enter method) was performed with BMD femur and L1-L4 as dependent variables and with duration of disease, etiology of SH as independent variables. A significant correlation was not found between BMD femur and duration of disease (p = 0.814), and etiology of SH (p=0.998) (Table 5). Similarly, a significant correlation was not found between BMD L1-L4 and duration of disease (p=0.656), and etiology of SH (p=0.674) (Table 6).

Discussion

Although the effect of subclinical hyperthyroidism on bone tissue is somewhat controversial, our study clearly demonstrated that BMD of premenopausal women with endogenous SH was not lower than normal population. Some of previous studies demonstrated that low TSH levels cause a decrease in bone mineral density[4,13,14]. On the other hand some of them claimed that it does not have an effect[11,15]. However, most of the studies suggesting a decrease in bone mineral density in women with SH showed the data of either postmenopausal women or women with suppressed TSH values under L-T4 treatment[16]. The study of Tauchmanova et al[7], revealed that endogenous SH results with a significant increase in bone turnover markers and a decrease in bone mass in postmenopausal women. Consistently, one meta-analysis demonstrated significantly lower BMD in postmenopausal women receiving L-T4 in suppressive doses[11]. Greenspan et al[17], concluded that postmenopausal women

Table 3: The frequency of osteopenia and osteoporosis of the study (86 premenopausal women with subclinical hyperthyroidism) and control (82 healthy premenopausal subjects) groups.

	Study group (n=86)	Control group (n=82)	p
Osteopenia N (%)	20 (46.5%)	17 (41.4%)	0.80
Osteoporosis N (%)	3 (6.9%9	2 (4.8%)	0.95

n: number of subjects.

Table 4: Correlation of thyroid stimulating hormone (TSH) with lumbar 1-4 Z score, femur neck Z score, bone mineral density (BMD) femur and BMD lumbar 1-4.

L1-4 in the study group

	TSH
Lumbar 1-4 Z score	r=0.09
	p=0.56
Femur neck Z score	r=0.02
	p=0.86
BMD femur g/cm^2	r=-0.09
	p=0.54
BMD L1-4 g/cm^2	r=-0.10
	p=0.51

BMD: bone mineral density, TSH: thyroid stimulating hormone.

Table 5: Multiple regression analyses (enter method) performed with bone mineral density (BMD) femur as dependent variable and with duration of disease, and etiology of subclinical hyperthyroidism (SH) as independent variables.

Independent variables	Coefficient	SE	$r_{partial}$	p
(Constant)	0.8271			
Etiology of SH	0.00007042	0.03467	0.0003211	0.9984
Duration of disease	0.004794	0.02024	0.03742	0.8140

BMD: bone mineral density, SE: Standard Error, SH: subclinical hyperthyroidism, $r_{partial:}$ partial correlation coefficient.

Table 6: Multiple regression analyses (enter method) performed with bone mineral density (BMD) L1-4 as dependent variable and with duration of disease, and etiology of subclinical hyperthyroidism (SH) as independent variables.

Independent variables	Coefficient	SE	$r_{partial}$	p
(Constant)	0.8699			
Etiology of SH	0.01626	0.03847	0.06668	0.6748
Duration of disease	0.01008	0.02246	0.07077	0.6561

BMD: bone mineral density, L1-4: lumbar 1-4, SE: Standard Error, SH: subclinical hyperthyroidism, $r_{partial:}$ partial correlation coefficient.

with a history of SH should have skeletal status assessed according to the results indicating the adverse effect of LT4 on bone. Although thyroxin is considered as the most suitable hormone therapy without any serious effects, the balance between sufficient thyroxine hormone and iatrogenic subclinical hyperthyroidism may easily be deteriorated[18]. Accordingly, De Rosa et al[19], also showed that L-T4 treatment significantly increased the bone mineral turnover and might contribute to a BMD reduction in both pre- and post-menopausal women. It is generally accepted that no or only a very small loss of bone mineral density is present in premenopausal women[20]. Sufficient estrogen production is accepted as the main reason for the lack or only minimal loss of bone mass in premenopausal women[21]. Additionally, Uzzan et al[22], found that thyroxine hormone therapy was associated with significant bone loss in postmenopausal women (but not in premenopausal women), whereas, thyroxine hormone therapy was associated with bone loss in premenopausal women (spine and hip), but not in postmenopausal women.

The present study is reinforced with the study of Gürlek et al[23]. They suggested that endogenous subclinical hyperthyroidism is not associated with increased bone turnover, and BMD is not reduced in premenopausal women, at least in the short term. However, the sample size of their study was low.

Based on the consideration that L-T4 treatment may be causing a decrease in BMD, we pooled the study group among premenopausal women who were not receiving LT4 treatment. Földes at al[24], indicated that BMD was not decreased in premenopausal patients with endogenous subclinical hyperthyroidism resulting from a solitary autonomously functioning thyroid nodule. According to Rosario[25], BMD was not low in the lumbar spine in patients before menopause, whereas a lower BMD was observed in postmenopausal patients.

Our findings suggest that, in accordance with the literature[23-25], endogenous subclinical hyperthyroidism does not have a negative effect on bone mineral density in premenopausal women. Reduced BMD can occur in postmenopausal individuals who were administered thyroxine hormone therapies and who developed exogenous hyperthyroidism.

In conclusion, contrary to exogenous subclinical hyperthyroidism, endogenous subclinical hyperthyroidism has no significant effect on bone mineral density of premenopausal women.

Conflict of interest

The authors declare no conflict of interest.

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