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The Effect of Hyperthyroidism on Bone Mineral Density in Premenopausal Women

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Abstract

Background: The effects of subclinical hyperthyroidism and clinical hyperthyroidism on bone metabolism in premenopausal women are contradictory.

Methods: Sixteen hyperthyroid (31.3±9.5 yrs), 23 subclinical hyperthyroid (33.7±7.3 yrs) and 20 healthy (31.7±8.1 yrs) premenopausal women were evaluated. Bone mineral density (BMD) was assessed by dual energy X-ray absorptiometry (DXA). Osteocalcin, total alkaline phosphatase (tALP), homocysteine, β-2 microglobulin, hsCRP and deoxypyridinoline (DPD) concentrations were assessed. Demographic and anthropometrical parameters; and osteoporotic risk factors were evaluated.

Results: Serum calcium, tALP, osteocalcin, β-2 microglobulin and DPD were significantly different in hyperthyroid group. However there was no difference for any of the study parameters between control and subclinical hyperthyroid group. BMD was similar for all the three groups. Thyroid hormones were correlated with osteocalcin, β-2 microglobulin, tALP, lumbar vertebrae and femur BMD. Osteocalcine and tALP were significantly and negatively correlated with vertebral and femoral total BMD. Homocysteine was not different within groups but significantly correlated with tALP.

Conclusions: There is limited and conflicting data about the effects of subclinical hyperthyroidism on bone turnover in premenopausal period. Despite we could not establish any difference for bone turnover markers between control group and subclinical hyperthyroid patients; with tight correlations between thyroid hormones; we can conclude that subclinical hyperthyroid patients are prone to osteoporosis even in premenopausal period.

Keywords: Premenopausal women; Subclinical hyperthyroidism; Hyperthyroidism; Bone mineral density; Osteoporosis

Introduction

Adequate concentrations of thyroid hormones are necessary for bone development and maturation whereas excess concentrations enhance bone turnover and cause osteoporosis [1]. Although this phenomenon is most obvious in patients with overt hyperthyroidism (H) some studies suggest that even mild subclinical hyperthyroidism (SH) is associated with increased bone resorption [2] and accelerated bone loss [3,4]. Although the loss of bone mineral density in postmenopausal women with hyperthyroidism is well defined [5], the reports on the results of SH in premenopausal women are contradictory. In suggestion to the actions of thyroid hormones, subclinical hyperthyroidism has to have similar osteoporotic effects in premenopausal period.

Materials and Methods

The study was approved by the Ethics Committee of Inonu University Faculty of Medicine and all of the participants gave written informed consent. Twenty three subclinical hyperthyroid, 16 hyperthyroid and 22 euthyroid (as the control group) premenopausal women who attended the Endocrinology Outpatient Clinic of Inonu University Faculty of Medicine were recruited. The patients with a history of chronic cardiac, renal, pulmonary or hepatic parenchymal diseases, patients with a history of diabetes, Cushing's disease, parathyroid problems and anemia, and patients using any drugs that can influence calcium and bone metabolism were excluded. Regards of known influencing effects on osteoporosis, smoking status, caffeine intake, the number of parities, the duration of lactation for each newborn and the presence of veiling was also noted.

Each patient underwent a general physical examination, including the measurement of height (in nearest cm. without shoes), body weight (in nearest kg. without coats), waist circumference (WC; minimum circumference measured between iliac crest and lateral costal margin, in cm) and hip circumference (HC; maximum circumference over hips, in cm). Body mass index (BMI; kg/m^2) was calculated as body weight divided by height squared meter. Waist-to-hip ratio (WHR) was defined as waist circumference divided by hip circumference.

The serum samples were drawn between 8 and 9 am, after an overnight fast of 12 to 14 hours. Serum glucose, creatinine, calcium, phosphor, magnesium, ALP, total protein and albumin concentrations were analyzed using a spektrophotometric auto-analyzer (Olympus AU 600; Olympus Diagnostica GmbH, Hamburg, Germany). Serum thyroid stimulating hormone (TSH), total T3 (TT3), total T4 (TT4), free T3 (FT3), free T4 (FT4), thyroid antibodies, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and intact parathyroid hormone (PTH) and urinary deoxypyridinoline (DPD)

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were analyzed by using chemiluminescent enzyme immunoassay technique (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). Deoxypyridinoline (DPD) values were assessed related to urinary creatinine secretion with a normal range 3.0–7.4 nM DPD/ mM creatinine for women.

Osteocalcin and thyroid receptor antibody (TRAC) were assessed by microELISA technique (Brio SEAC and Biotek ELX 800; BioSource Europe S. A, Nivelles, Belgium). 25(OH) vitamin D3 and homocysteine were assessed by high performance liquid chromatography method (Shimadzu; Chromsystems Instruments Chemicals GmbH, Munich, Germany). Serum high sensitive C reactive protein (hsCRP) and beta–2 microglobulin levels were analyzed by nephelometric method (Dade Behring BN II; Dade Behring Marburg GmbH, USA).

Bone mineral density was analyzed by using dual-energy x-ray absorptiometry (DEXA) [Hologic QDR 4500 W (SIN 49584), Waltham, MA, USA], through lumbar vertebrae (L1-L4) and left femur (neck, trochanteric region, intertrochanteric region and Wards triangle).

Statistical Analysis

Statistical analyses were carried out by employing the Statistical Package for Social Sciences software 13.0 for Windows package software (SPSS, Inc., Chicago, IL, USA). Data was expressed as means ± standard deviation (SD). Normality of distribution for continued variables in groups was determined by the Shapiro Wilk test. The ANOVA was used to compare parametric data and least significant difference (LSD) test was used for comparison of variables. The correlations between the study parameters were assessed by using Pearson's correlation. The groups were compared using the chi-square test for smoking status, caffeine intake, veiling, parity and lactation. A p value ≤ 0.05 was considered to be statistically significant. The data was presented as mean ± standard derivation.

Results

The study group was consisted of 23 subclinical hyperthyroid and 16 hyperthyroid premenopausal women while 20 healthy euthyroid premenopausal women served as the control group. The thyroid hormone and thyroid antibody values of the groups are documented in table 1. The subjects were comparable for age and anthropometrical parameters. The data was shown in table 2. The women were comparable for smoking status, caffeine intake, veiling, parity and duration of lactation ($p>0.05$ with chi squared test for each). Serum calcium, ALP, osteocalcine, β-2 microglobulin and urinary DPD were significantly different in hyperthyroid group compared to both SH and control groups. There was not any significant difference for any of the study parameters between SH and control subjects. The parameters showing bone turnover and their statistical meanings between groups are documented in tables 3 and 4. There was no difference for bone mineral density and T scores of either femur or lumbar vertebrae with dual-energy x-ray absorptiometry (DXA) between any of the groups (Table 5). Thyroid hormones (FT3 and FT4) were positively and significantly correlated with ALP, serum Ca, osteocalcine and beta-2 microglobulin, whereas negatively and significantly correlated with both femur and lumbar vertebrae total BMD. The correlation coefficients are documented in table 6. Serum tALP was significantly and positively correlated with DPD (r=0.453, p=0.0001), beta-2 microglobulin (r=0.305, p=0.019), homocysteine (r=0.533, p=0.0001) and negatively with lumbar vertebrae total BMD (r=-0.468, p=0.0001), and femur total BMD (r=-0.371, p=0.004). As supporting the increment of bone formation in hyperthyroidism, osteocalcine was significantly and positively correlated with thyroid hormones (r=0.574 for TT3,

	Control	Subclinical hyperthyroid	Hyperthyroid	p
TSH (mIU/mL)	1.14±0.97	0.20±0.10	0.03±0.04	0.0001
TT3 (ng/dL)	135.89±33.46	146.05±34.43	326.06±138.54	0.0001
TT4 (ug/dL)	8.72±1.54	8.72±2.39	15.77±4.02	0.0001
FT3 (pg/mL)	3.27±0.43	3.02±0.53	8.28±4.15	0.0001
FT4 (ng/dL)	1.33±0.18	1.36±0.21	2.98±1.24	0.0001
Anti-TPO (IU/mL)	68.49±220.69	112.59±288.68	255.29±333.69	NS
Anti-Tg (IU/mL)	135.97±360.54	297.31±815.69	140.22±234.40	NS
TRAC (U/L)	2.82±1.29	2.63±1.49	10.92±13.31	0.001

Table 1: Thyroid hormones and thyroid antibodies.

	Control	Subclinical hyperthyroid	Hyperthyroid
Age (years)	31.70±8.08	33.70±7.30	31.38±9.45
Height (cm)	159.60±5.39	160.69±5.20	162.31±6.03
Weight (kg)	59.43±9.98	66.71±13.36	63.85±14.49
BMI (kg/m^2)	23.39±4.13	25.80±4.65	24.15±4.48
Waist (cm)	78.75±11.30	83.95±11.19	82.50±11.91
Hip (cm)	97.25±7.87	102.91±9.39	100.93±9.86
WHR	0.80±0.08	0.81±0.05	0.81±0.54

p is non-significant for all the parameters
BMI: Body mass index
WHR: Waist to-hip-ratio

Table 2: The demographic and anthropometrical features of the groups.

0.521 for TT4, 0.578 for FT3, 0.653 for FT4 and p= 0.0001 for all); and negatively correlated with lumbar vertebrae total BMD (r=-0.370, p=0.004), and femur total BMD (r=-0.366, p=0.004).

Discussion

The aim of this study was to define the status of bone mineral density and bone turnover in premenopausal women with different degrees of hyperthyroidism either clinical or subclinical. Hyperthyroidism is already known to have worsening effects on bone mineral density especially in postmenopausal period [5]; however the data about the premenopausal period is under debate. In current study thyroid hormones were significantly correlated with tALP, serum calcium and osteocalcine as supporting their function in increased bone turnover; and negatively correlated with both femur and vertebrae BMDs as reflecting the bone mineral content decrement in their excess secretion. Although there was no difference in bone mineral density between any of the hyperthyroid groups than controls, biochemical markers were noticing out the early changes in bone turnover in either states in premenopausal period.

Either serum Ca concentration or urinary Ca excretion supposed to increase in hyperthyroidism and commonly do not differ from euthyroids in subclinical form of the disease, data is controversial [6-8]. In current study serum Ca concentrations were significantly higher in hyperthyroid patients while urinary Ca excretion was comparable with other groups. Although we were not able to analyze bone ALP, concordant to previous data as showing increased bone formation, the subjects with hyperthyroidism were found to have increased tALP [9-11].

	Control	Subclinical hyperthyroid	Hyperthyroid
*Calcium (mg/dL)	9.35±0.47	9.33±0.39	9.88±0.69
Phosphor (mg/dL)	3.42±0.51	3.69±0.44	3.67±0.72
Magnesium (mg/dL)	1.95±0.19	1.98±0.22	1.92±0.28
*ALP IU/L	175.75±75.30	181.43±34.10	356.06±210.86
iPTH (pg/mL)	67.46±25.43	70.36±58.92	80.38±55.68
Urinary Ca (mg/dL)	10.49±5.28	11.31±5.88	11.44±6.86
Homocysteine (umol/L)	10.15±3.17	10.66±3.77	14.59±11.58
25 (OH)2 vitamin D_3 (ng/mL)	16.83±11.44	18.17±11.94	13.76±11.69
hsCRP (mg/L)	3.31±2.56	3.60±4.13	3.58±2.96
*Beta-2 microglobulin (mg/L)	1.44±0.36	1.42±0.51	1.79±0.60
*DPD (nMol/mMol cr)	8.23±13.28	8.72±13.63	17.97±15.30

* significantly different parameters between groups whereas *p* values are documented in Table 4. iPTH: intact parathormon, hsCRP: high sensitive C-reactive protein

Table 3: Bone turnover parameters of the groups.

	Control *vs.* SH.	Control *vs.* H.	SH. *vs.* H.
Serum Ca	NS	0.003	0.002
ALP	NS	0.0001	0.0001
Osteocalcin	NS	0.0001	0.0001
β-2 microglobulin	NS	0.03	0.02
Deoxypyridinoline	NS	0.04	0.04

SH: subclinical hyperthyroid, H: hyperthyroid, ALP: Alkaline phosphatase

Table 4: Differences between the three groups for bone turnover markers.

	Control	Subclinical Hyperthyroid	Hyperthyroid
Femur neck BMD	0.78±0.09	0.82±0.12	0.76±0.12
Femur neck T Score	-0.61±0.85	-0.24±1.11	-0.80±1.09
Femur total BMD	0.90±0.12	0.94±0.16	0.84±0.14
Femur Total T Score	-0.28±1.03	0.07±1.23	-0.76±1.21
L total BMD	0.99±0.14	0.99±0.10	0.91±0.11
L Total T Score	-0.49±1.34	-0.45±0.95	-1.18±1.06

Table 5: DXA parameters for femur and lumbar vertebrae (BMD is g/cm^2).

	FT3		*FT4*	
	p	*r*	*p*	*r*
ALP	0.0001	0.674	0.0001	0.664
Serum Ca	0.001	0.427	0.0001	0.503
Osteocalcine	0.0001	0.578	0.0001	0.653
Beta-2 microglobulin	0.0001	0.485	0.006	0.351
Lumbar total BMD	0.026	-0.289	0.027	-0.287
Femur total BMD	0.033	-0.278	0.019	-0.305

Table 6: The correlating parameters with thyroid hormones.

Serum osteocalcine levels are the other contradictory subject in various reports which both reported to be elevated [7] or unchanged [12,13] in subclinical subjects, whereas the data is inadequate in premenopausal period [14]. In current study osteocalcine was found to be correlated with the markers of osteoblastic process i.e. ALP, Ca as a marker reflecting the increased bone formation in both stages of the diseases. Its negative correlation with BMD values lead us to conclude osteocalcine as a strong and early marker of osteoporotic process before the changes defined through DXA in premenopausal period.

DPD is the other marker reported to be increased in postmenopausal SH women compared to controls whereas reported to be unchanged in premenopausal women [14]. On the other hand the results are incomparable [7,13]. In current study hyperthyroid women were found to have significantly increased urinary DPD values compared to controls whereas there were not any significance in SH women compared to controls. But its correlations with ALP and homocysteine inspire a weak or at least not an early existing parameter in premenopausal period which has to be confirmed in further studies.

There is limited data about the association of beta-2 microglobulin and osteoporosis [15-17]. In a study conducted through postmenopausal women, salmon calcitonin treatment was found to have lowering effects on beta-2 microglobulin concentrations [18]. To our knowledge this molecule has not been considered in thyroid abnormalities accompanied with bone turnover. In current study, beta-2 microglobulin concentration was significantly higher in hyperthyroid women with positive correlations to ALP. The increment of the molecule might indicate the increment of bone turnover, as a marker prior to DXA alterations.

Although showing no statistical significance serum homocysteine concentration was higher in hyperthyroid group whereas comparable within control and subclinical subjects. Although higher homocysteine concentrations were reported to increase osteoclastic activity [19] with a correlation of decreased BMD [20], the data is contradictory [21]. However serum calcium and urinary DPD excretion was reported to be correlated with homocysteine [21]. Supporting the latter data despite showing no relation to BMD, serum homocysteine concentration

was correlated with tALP and urinary DPD excretion as reflecting the accelerated bone turnover and osteoclastic bone resorption.

hsCRP is a valuable parameter reflecting inflammatory processes i.e. atherosclerosis. In a study conducted through postmenopausal osteoporotic women by Ferrari et al. [22] a negative but significant correlation between hsCRP and BMD was revealed. On the other hand Lee et al. [23] could not define any difference for the molecule between SH and hyperthyroid patients. In current study we could neither define any difference in hsCRP concentrations between the groups, nor any correlation to any of the study parameters. Younger age of our subjects may cause the contradiction to the correlations which were revealed by Ferrari et al. [22] as inflammations could show a parallelism to advanced age.

Although long term TSH suppressive treatment was revealed to decrease BMD in both premenopausal and postmenopausal periods [6,24-26], the accurate effects of endogenous subclinical hyperthyroidism on bone metabolism is under debate. In the studies reported by Foldes et al. [27], Lee et al. [8] and Gurlek A and Gedik O [13] femur and lumbar vertebrae BMD values of premenopausal subclinical hyperthyroid women were not different compared to control subjects. The results for BMD were similar in the study reported by Faber et al. [12] whereas the increment of bone turnover was defined via biochemical markers. Except for significant correlations with biochemical markers mentioned above, we could not define any difference for both BMD and T-scores of femur and lumbar vertebrae between the three groups. Young age or short duration of hyperthyroidism may prevent the subjects from obvious bone loss.

The lack of long term follow up of bone mineral density in subclinical hyperthyroid patients and awareness of hyperthyroid/subclinical hyperthyroid state durations are the limitations of this study.

As reflecting early markers of osteoporosis, tALP, serum calcium concentration, beta-2 microglobulin and urinary DPD concentrations were significantly different in hyperthyroid group compared to subclinical hyperthyroid and euthyroid groups, while none of the study parameters showed significant difference in subclinical hyperthyroid women compared to control subjects. However the significant correlations inspire a possible bone loss as long as subclinical hyperthyroid process lasts, which has to be confirmed with more extensive trials.

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