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Early postmenopausal bone loss in hyperthyroidism

Anat Ben-Shlomo [a], Philippe Hagag [a,b], Sandra Evans [c], Mordechai Weiss [a,b,*]

[a] *Endocrine Institute, 'Assaf Harofeh' Medical Center, Zerifin 70300, Israel*
[b] *Sakler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[c] *Department of Biochemistry, 'Assaf Harofeh' Medical Center, Zerifin 70300, Israel*

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Abstract

Objectives: To evaluate the effect of hyperthyroidism on bone in relation to the menopausal state. *Methods:* Fifty-nine hyperthyroid (HYPER), 40 hypothyroid (HYPO), and 51 control euthyroid (EUTH) women were studied. Bone mineral density (BMD) was assessed by dual X-rays absorptiometry (DXA) at the lumbar spine, and at the femoral neck. A multi-site QUS device evaluated speed of sound (SOS) at the radius (RAD), tibia (TIB), metatarsus (MTR), and phalanx (PLX). Bone markers used were serum bone specific alkaline phosphatase (BSAP) and urinary deoxypyridinoline (DPD). *Results:* At all sites, SOS was lower in HYPER than in EUTH (RAD $P < 0.05$, TIB $P < 0.01$, MTR $P < 0.05$, PLX $P = 0.01$). The low SOS was only noted at the early postmenopausal period. BMD at the femoral neck but not at the lumbar spine was lower in HYPER as compared to EUTH ($P < 0.05$). Both femoral neck and tibia were the sites with the highest odds ratio for being hyperthyroid (2.3 and 2.04, respectively). There was no correlation between BMD or SOS and FT_4, TT_3 or duration of hyperthyroidism. BSAP and DPD positively correlated with FT_4 and TT_3 ($P < 0.05$). *Conclusions:* This study suggests that hyperthyroidism affects bone mineralization especially during the early postmenopausal period, and the effect is mainly at the cortical bone. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

1. Introduction

Thyroid hormones are essential for bone development in fetal life, modeling in childhood and remodeling cycles in adult life [1–3]. The bone-formation phase of the remodeling cycle in hyperthyroid patients (HYPER) is shortened and results in thinning of the mineralized osteoid. Opposite changes are observed in hypothyroid subjects (HYPO). The thyroid hormone effect on bone remodeling is evident in both trabecular and cortical bone although it is more pronounced in compact bone [4–6]. The postmenopausal period is characterized by two distinct phases. The first 5–10 years are associated with high bone turnover that is followed by a slow bone-loss period that lasts for decades.

Therefore, it is possible that the increased bone turnover of hyperthyroidism may differently affect bone mineralization in these two postmenopausal stages. However, even the recent meta-analyses [7,8] suggesting lower BMD in hy-

* Corresponding author. Tel.: +972-8-9779270; fax: +972-8-9779642.
E-mail address: mweis@asaf.health.gov.il (M. Weiss).

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perthyroid postmenopausal women did not separate early- from late-postmenopausal subjects.

While determining bone mineral density (BMD), most commonly by dual X-rays absorptiometry (DXA) and quantitative ultrasound (QUS), bone turnover is evaluated by measuring bone marker levels. Out of the several QUS parameters, speed of sound (SOS) is the most widely used. QUS provides information on bone properties additional to BMD [9,10] that accounts for 30% variance in bone strength not explained by DXA-determined BMD.

Even though plenty of information on QUS role in osteoporosis is available, little is known regarding its role in other metabolic bone diseases [9]. A recent report [11] suggested lower QUS parameters at the heel of HYPER women as compared to normative database, but not to euthyroid (EUTH) controls of the same population. Moreover, the hyperthyroidism effect on bone was not related to the menopausal state of the women evaluated. Considering the discordance in BMD among various measurement-sites [12], this single-site QUS report [11] may not properly estimate the hyperthyroidism effect on the entire skeleton.

We, therefore, evaluated the effect of hyperthyroidism on bone by DXA, multi-site peripheral QUS and bone-marker levels in hyperthyroid, hypothyroid and euthyroid control females. Bone effect of hyperthyroidism was related to the menopausal state of the participants.

2. Subjects and methods

2.1. Subjects

One hundred and fifty consecutive female patients (median age 57.5 years, range 36–79) presenting to the Endocrine Institute of the 'Assaf Harofeh' Medical Center were included in this study. Women were categorized into three groups: HYPER-59, HYPO-40 and EUTH goitrous controls-51. Both HYPER and HYPO groups comprised of women with overt and subclinical disease according to TSH and serum thyroid hormone levels. Neither HYPO nor EUTH patients were previously hyperthyroid. It was verified that all thyroid-related treatment was administered at our tertiary center.

Candidates were excluded from the study when they had a metabolic bone disease such as hyper- or hypoparathyroidism, premature menopause (before the age of 40), Paget's disease, osteomalacia, osteogenesis imperfecta or renal osteodystrophy. Women with debilitating disease such as severe cardio-pulmonary, chronic liver, collagen vascular or malignant disease (other than differentiated thyroid cancer) were also excluded from the study. Previous treatment with bone-affecting medications such as bisphosphonate, calcitonin, fluoride, anabolic steroid, glucocorticoid, anticonvulsant, thiazide, or higher than recommended doses of vitamin A and D precluded enrolling in the study. Subjects using estrogen for any period of time, but discontinued it more than a year before presenting, were allowed to participate in the study. The time lag from discontinuation of estrogen use was based on patients' memory. Not all patients were evaluated by either every diagnostic modalities or had SOS measurements at all sites.

2.2. Laboratory tests

The reference normal values for TSH, total triiodothyronine (TT_3) and free thyroxine (FT_4) are 0.4–4 mU/l, 1.1–2.8 nmol/l, and 9–26 pmol/l, respectively. A commercial kit (Pyrilinks–D, Meta-Biosystems Inc, Mountain View, CA) was used to determine morning spot urinary deoxypyridinoline (DPD) level. Normal DPD reference values are: 3–7.4 nM/mM of creatinine. The sensitivity of the assay is 1.1 nM, intra- and inter-assay CV, not including that of creatinine, are 8.4 and 4.8%, respectively. Serum bone-specific alkaline phosphatase (BSA) activity was measured (ALKPHASE-B, Meta-Biosystems Inc) with sensitivity of 0.7 U/l, intra- and inter-assay CV of 5.8 and 5.2%, respectively. Normal reference values for females aged 25–44 are 11.6–29.6 and 14.2–42.7 U/l for women older than 45 years of age.

2.3. Bone mass measurements

SOS was determined as previously reported [13]. Briefly, SOS was measured using the Sunlight Omnisense™ (Sunlight Technologies Ltd., Rehovot, Israel (Omnisense)). Three cycles of SOS measurements along the distal third of the radius of the non-dominant limb (RAD), mid-shaft tibia (TIB) fifth metatarsus (MTR) and the proximal phalanx of the index finger (PLX) using an acoustic gel were performed. While scanning the limb, the SOS was determined about every 0.1 s to yield SOS profile at the RAD. The data thus obtained were checked for consistency and if that was not the case a fourth cycle was performed. The system computes the average of the 95 percentile of the 3 or 4 cycles performed and reports the SOS. Finally, the *T*- and *Z*-scores are provided following comparison to the female Caucasian Reference Database.

BMD of the lumbar spine (L_2–L_4) and femoral neck was obtained by DXA (Hologic QDR 1000®) and presented as the age-adjusted *Z*-score. The reference database was that supplied by the manufacturer.

Table 1
Patient characteristics (median (range))

	Euthyroids ($N=51$)	Hyperthyroids ($N=59$)	Hypothyroids ($N=40$)
Age (years)	57 (36–78)	59 (36–79)	59 (36–79)
Postmenopausal (%)	74.5	76.3	67.5
BMI (kg/m^2)	28 (19–41)	27 (21–37)	28 (19–39)
TSH (IU/l)	1.5 (0.4–4.6)[a]	0.1 (0.0–0.4)[a]	8.1 (5.1–99.9)
FT_4 (pmol/l)	16.1 (13.3–24.8)[b]	20.7 (8.5–56.3)	12.4 (5.0–18.0)[c]
TT_3 (nmol/l)	2.0 (1.2–2.7)[b]	2.9 (2.7–10.0)[d]	1.8 (0.6–2.3)
Duration[e] (years)	3.0 (0.2–17)[f]	2.0 (0.2–30)[f]	2.0 (0.2–7.0)

[a] $P<0.0001$, as compared to the other two groups.
[b] $P<0.05$, as compared to hyperthyroids.
[c] $P<0.0001$, as compared to euthyroids.
[d] $P<0.005$, as compared to euthyroids.
[e] Duration = recall diagnosis of euthyroid goiter or disease or follow-up period.
[f] $P=0.001$, as compared to hypothyroids.

2.4. Ethical consideration

Every participant signed an informed consent. The institutional and governmental ethical committees approved this study.

2.5. Statistical analysis

T- or Chi-square tests were used to compare means, S.D. and S.E. of the three study groups. Pearson product–moment correlation was used to explore association between variables. Following scattering of data, transformation was not selected, nor were outliners excluded. Correlation of less than ten pairs are not reported. The area under the curves was determined as described by Hanley and McNeil [14]. The proportion of pre- to postmenopausal women was similar in the three study groups. Therefore, this variable was not included in the various statistical analyses. *P* values lower than 0.05 were considered significant throughout the study.

3. Results

Patient characteristics are shown in Table 1. The subjects' age and the proportion of pre- to postmenopausals were similar in all three groups. Thyroid function tests varied according to disease classification. Although not significantly, BMI was highest in the HYPO, intermediate in the EUTH, and lowest in HYPER. TSH serum level was lowest in HYPER, intermediate in EUTH and highest in HYPO. Even though the range of TSH of the HYPO was wide (5.1–99.9 IU/l), all HYPO women had higher than normal serum TSH levels. As expected, serum levels of FT_4 and TT_3 were inversely related to those of TSH in the three disease groups. The median recall disease duration was higher in EUTH when their goiter was diagnosed as compared to HYPO and HYPER groups (3, 2, and 2 years, respectively).

BMD, SOS and bone-marker levels are shown in Table 2. Bone marker levels were similar in all study groups. SOS at all measurement sites was the highest in EUTH, intermediate in HYPO and lowest in HYPER group (except for SOS at the

Table 2
BMD, SOS and bone marker levels in the three study groups

		Euthyroids		Hyperthyroids		Hypothyroids	
		N	Median (range)	*N*	Median (range)	*N*	Median (range)
BMD (*Z*-score)	L_2–L_4	27	0.36 (−2.57–3.14)	42	−0.24 (−2.87–3.67)	20	−0.01 (−1.78–2.09)
	Femoral neck	27	0.28 (−1.25–1.94)	42	−0.16 (−2.16–2.62)[a]	19	0.04 (−2.41–2.55)
SOS (*Z*-score)	Radius	42	−0.22 (−4.79–4.65)	42	−0.55 (−2.73–4.19)[a]	29	−0.11 (−2.09–6.19)
	Tibia	42	0.61 (−3.69–2.61)	44	0.22 (−3.91–3.42)[b]	29	0.37 (−5.35–3.71)
	Metatarsus	31	0.61 (−1.50–2.76)	26	0.21 (−1.35–2.90)[a]	17	0.489 (−2.43–2.364)[a]
	Phalanx	40	0.43 (−2.43–3.43)	40	−0.29 (−2.17–2.12)[c]	25	−0.03 (−2.13–2.66)
Bone markers	BSA[d] (U/l)	24	23.0 (8.5–50.0)	35	19.5 (9.0–31.0)	16	17.0 (12.0–40.0)
	DPD[e] (nM/mM)	26	8.5 (1.2–15.1)	38	9.3 (5.1–29.7)	16	8.1 (2.6–25.9)

[a] $P<0.05$, as compared to euthyroids.
[b] $P<0.01$, as compared to euthyroids.
[c] $P=0.01$, as compared to euthyroids.
[d] BSA = bone-specific alkaline phosphatase.
[e] DPD = deoxypyridinoline.

MTR of the HYPO group). At all four-measurement sites SOS of the HYPER was significantly lower as compared with the EUTH group. Only at the MTR SOS of the HYPO was also lower than in the EUTH group.

In the HYPER, at all four-measurement sites, SOS *Z*-score was lower than in the EUTH only at the early postmenopausal period (Fig. 1). While the nadir of SOS was at the age quintile of 50–59 years, before the menopause and following the age of 70 no change in age-adjusted SOS was evident.

DXA-determined BMD at the femoral neck was lower in HYPER as compared to the EUTH group. Similar to QUS, the age-adjusted BMD was lower in the HYPER only at the age group of 50–59 years (data not shown). However, BMD at the lumbar spine was independent of the thyroid state. Comparable results were obtained when data were analyzed in logistic regression in a model that adjusts for age and BMD (Table 3). The femoral neck and the TIB were the sites with the highest odds ratios for HYPER, as compared to EUTH (2.3 and 2.04, respectively). The area under the curve of the ROC (Fig. 2) was significantly greater than 0.5 for both the femoral neck and the TIB. As the diagnosis of hyperthyroidism was based on the gold-standard thyroid function tests, the bone measurement data discriminates HYPER from EUTH women. Certainly, this method is not to be used as a diagnostic mean for hyperthyroidism.

In the HYPER group there was a significant correlation within diagnostic modality and no similar inter modality correlation was noted. The two DXA measurement sites were correlated ($r=0.64$, $P=0.0001$). However, SOS *Z*-score at the TIB correlated with those of the RAD and MTR ($r=0.33$, $P=0.039$ and $r=0.65$, $P=0.0003$, respectively) but not with that of the PLX. No correlation was observed between the two bone marker levels.

There was no correlation between duration of hyperthyroidism or thyroid hormone levels and BMD or SOS. On the contrary, BSAP positively correlated with FT_4 and with TT_3 ($r=0.60$, $r=0.37$, $P<0.05$, respectively) and so did DPD ($r=0.70$, $r=0.73$, $P<0.05$, respectively).

WHO classification of osteoporosis, based on BMD [15], applied to our cohort of patients

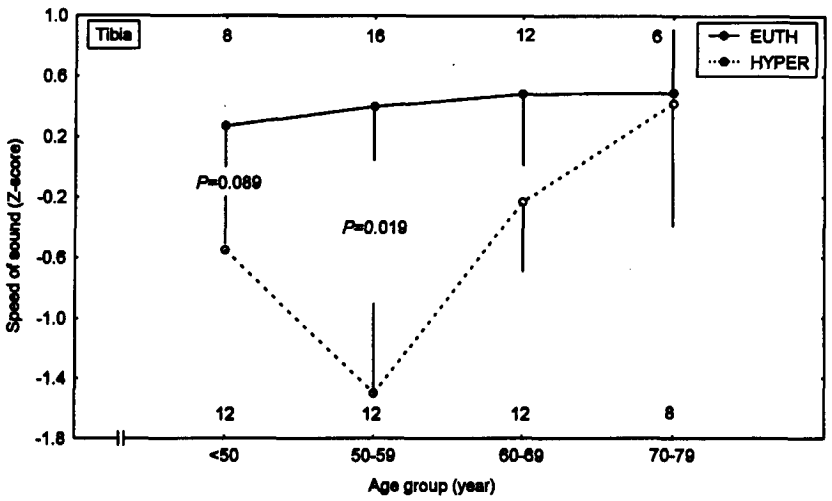

Fig. 1. Age-adjusted SOS at the TIB stratified into various age groups. The horizontal values imply the number of women in every age strata of the two groups of patients. The vertical bars indicate S.E.M.

(Table 4) reveals a higher proportion of 'osteoporotic' women in the HYPER as compared to EUTH when SOS was determined at the RAD ($P = 0.036$). Similarly, SOS measurements at the TIB identified more women with T-score < -2.5 in the HYPER as compared to the EUTH ($P = 0.015$). Using DXA, this rate was similar in HYPER and EUTH groups. However, at the femoral neck more women of the HYPER as compared to the EUTH group were with T-score < -2.5 ($P = 0.086$).

4. Discussion

This study provides in vivo evidence that unlike osteoporosis, hyperthyroidism affects compact more than cancellous bone. Moreover, this detrimental effect is mainly evident at the high bone turnover state of the early postmenopausal period.

Thyroid hormones exert profound effects on bone turnover [1–6,11,26]. In hyperthyroidism, both resorption and formation phases are increased. However, as bone formation does not match bone resorption, in trabecular thickness decreases leading to trabecular perforation, and higher cortical porosity. Opposite changes are noted in hypothyroidism. In both diseases osteoid seam thickness diminishes due to prolonged mineralization lag time [1].

Hyperthyroidism-related bone disease is clinically relevant in thyroid suppressive therapy, and in spontaneous hyperthyroidism. Most of the earlier studies suggested low BMD in overt hyperthyroidism [16–21]. Whereas some reported detrimental effect of subclinical hyperthyroidism of either etiology on BMD [22–24], others provided cross-sectional and prospective data for normal BMD [25,26]. The recent meta-analysis [7,8] suggests that suppressive doses of thyroxin

Table 3
Logistic regression for age and BMI adjusted SOS and hyperthyroidism and expressed in a receiver-operator curve

	AUC (95% C.I.)	Odds ratio (95% C.I.)
BMD		
L_2–L_4	0.57 (0.43–0.71)	1.36 (0.80–2.29)
Femoral neck	0.73 (0.60–0.86)	2.23 (1.18–4.23)
SOS		
Radius	0.66 (0.54–0.77)	1.89 (1.12–3.19)
Tibia	0.66 (0.55–0.78)	2.04 (1.21–3.44)
Metatarsus	0.65 (0.50–0.79)	1.88 (1.03–3.44)
Phalanx	0.67 (0.55–0.78)	1.87 (1.13–3.07)

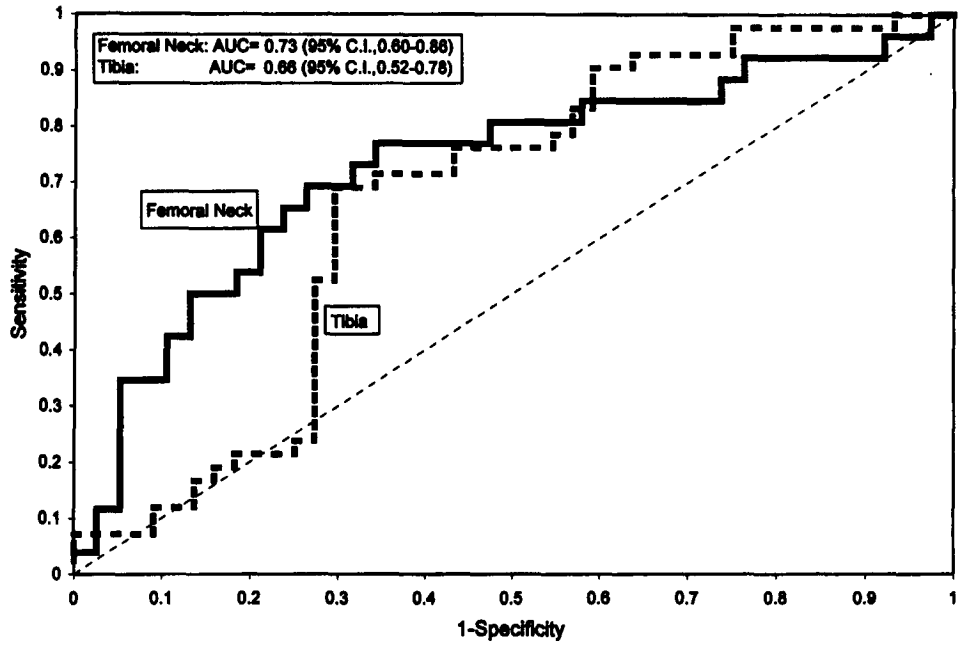

Fig. 2. Discrimination of HYPER women by BMD at femoral neck and SOS at the TIB. Data are expressed in receiver operator characteristic curves.

Table 4
Women with T-score < -2.5 in relation to number of women tested.

	Euthyroids		Hyperthyroids		Hypothyroids	
	N^a	%[b]	N^a	%[b]	N^a	%[b]
BMD						
L_2–L_4	27	22.2	42	23.8	20	25
Femoral neck	27	11.1	42	28.6	19	10.5
SOS						
Radius	42	21.4	42	42.9[c]	29	20.7
Tibia	42	11.9	44	34.1[c]	29	13.8
Metatarsus	31	3.2	26	3.8	17	5.9
Phalanx	40	10	40	25	25	28

[a] N = number of women tested.
[b] % = percentage of women with T-score < -2.5.
[c] $P < 0.05$ as compared to the euthyroids.

are detrimental to BMD only in postmenopausal women. Greenspan et al. [27] recently reviewed the published data, and concluded that both overt- and subclinical hyperthyroidism decreases BMD. This effect is evident at both axial and appendicular skeleton, and mainly at cortical bone. Although the effect is more evident in postmenopausal women, it is also present in premenopausal subjects [4,7,8,27].

Previous studies did not relate BMD to early or late postmenopausal state of women evaluated. Our data suggest that the BMD-detrimental effect of hyperthyroidism is mainly at the high bone turnover state of early postmenopausal phase.

Therefore, it is possible that women at different stages of the postmenopausal period were mixed and leading to conflicting conclusions.

Our data of lower BMD at the femoral neck, but not at the lumbar spine, correlate with many [1,4,22,23,27–29] but not all [11,30] previous studies claiming greater detrimental effect of hyperthyroidism on cortical as compared with trabecular bone. This site-specific effect of thyroid hormone is supported by ample evidence in rats [31,32].

In contrast to DXA that measured lower BMD only at the hip, SOS measured by Omnisense was affected by hyperthyroidism at all measurement sites. Most previous studies evaluating thyrotoxic bone disease used BMD determined by photon absorptiometry [4,27] as an end point. Only recently QUS and DXA compared bone involvement women [11]. However, the authors did not separate between pre- and postmenopausal women. Moreover, they did not include euthyroid control subjects, and the data were only compared to the normative database. Considering these drawbacks, our data correlate these previous QUS conclusions [11].

The age-adjusted low SOS values noted in the HYPER group is more pronounced during the first 10 years following menopause. In this stage previous studies reported a rapid decline in SOS [33], along with higher serum and urinary levels of bone markers [34,35]. This suggests that the high turnover state of early postmenopausal stage predisposes bone to the detrimental effect of hyperthyroidism.

The Omnisense is unique in its ability to determine SOS at multiple skeletal sites. Therefore, it is interesting to note that skeletal involvement in hyperthyroidism is not homogeneous. SOS at various measurement sites was 0.7–1.0 S.D. lower in HYPER as compared to the EUTH group. Further observations are needed to appreciate the unexplained lower SOS observed only at the MTR of the HYPO patients. More thyrotoxic as compared with euthyroid women met the WHO criterion for osteoporosis when SOS was determined at the RAD and TIB. This rate was similar in both groups when the SOS was measured at the other two sites. Analysis of DXA data suggested a comparable trend only at the hip, but not reaching statistical significance probably due to small measurements performed.

In this study SOS, BMD, and bone marker did not correlate with either duration of hyperthyroidism or thyroid hormone levels. Our BMD data correlate previous studies [21,24,36], but contrast others [11] that suggested a correlation between QUS parameter, BMD and duration of hyperthyroidism. The lack of correlation with disease duration and thyroid hormone levels of our data may result from inaccurate recall data by the patient. We used peak thyroid hormone levels throughout the follow-up period as a determinant of the intensity of hyperthyroidism. It is possible that the thyrotoxic bone disease may rather be related to mean thyroid hormone levels in relation to the duration of hyperthyroidism. It is still possible that there is indeed no correlation between bone parameters and indicators of hyperthyroidism. The fact that neither bone marker was elevated even though SOS, and femoral neck BMD were lower in the HYPER is unclear. The similar mean BMI values in all study groups argue against the possibility that depressed muscle mass in hyperthyroid patients interfere with the determination of DPD through the correction by creatinine. It contrasts a previous cross sectional study of hyperthyroid patients in whom higher bone marker levels were noted in patients with high bone turn-over [37]. However, our data correlate the previous prospective study reporting no change in the levels of biochemical markers in postmenopausal women treated with T_3 for 7 days [38].

The lack of hyperthyroidism-mediated bone loss in late postmenopausal women reported here correlate previous reports of women older than 65 years of age [39], and of women who were menopausal for 15 years [40]. MEDLINE search did not disclose any paper reporting of bone status limited to early postmenopausal women.

This study has several significant limitations, the most important is the cross sectional design. The recall of the duration of hyperthyroidism may misindicate the real length of the disease. As this study was carried out at a tertiary care center this may suggest that women with more severe forms

of hyperthyroidism were included. However, the fact that patients with subclinical and overt hyperthyroidism were enrolled makes this possibility less likely. As was not the case in this study, it is desired that all participants should be evaluated by all diagnostic modalities. We cannot rule out that EUTH women were previously subclinically hyperthyroid, thus affecting their bone mineralization.

In conclusion, this study suggests that hyperthyroidism affects bone mineralization especially during the early postmenopausal period. This effect is mainly at the cortical bone. This argues for early institution of hormonal replacement therapy in early menopausal thyrotoxic women. Additional prospective studies enrolling more women are needed to evaluate the findings.

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