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Original article

Changes in bone mineral density and trabecular bone score in Graves' disease patients after anti-thyroid therapy

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Abstract

Objective: The purpose of this study was to evaluate changes in bone quantity based on bone mineral density (BMD) and bone quality based on trabecular bone score (TBS) in Graves' disease patients after anti-thyroid therapy.
Research design and method: This retrospective study included premenopausal female and male patients with Graves' disease who received BMD measurement more than two times during treatment. BMD and thyroid function tests with free thyroxine (FT4), total triiodothyronine (T3), thyroid stimulating hormone (TSH), and TSH receptor antibody (TRAb) levels were collected two times during follow-up. TBS was calculated using TBS insight® software (version 2.1) from dual-energy X-ray absorptiometry images.
Results: Thirty Graves' disease patients (17 males, 56%; 13 premenopausal females, 44%) with a mean age of 35.3 ± 9.9 years were included. The mean follow-up period was 20.7 ± 8.5 months. The median levels of FT4, TSH and TRAb improved at follow-up [2.55 ng/dL (Interquartile range (IQR) 2.07−3.78) to 1.28 ng/dL (IQR 1.23−1.39), 0.015 mIU/L (IQR 0.01−0.04) to 0.89 mIU/L (IQR 0.35−1.55), 17.0 IU/L (IQR 5.0−40.3) to 5.0 IU/L (5.0−6.0), respectively; $p < 0.001$]. Median BMD (lumbar spine) values also improved from 1.118 g/cm^2 (IQR 1.000−1.119) to 1.167 g/cm^2 (IQR 1.050−1.219) ($p = 0.001$) at follow-up. TBS increased from 1.377 (IQR 1.299−1.422) to 1.390 (IQR 1.327−1.430) after treatment ($p = 0.038$).
Conclusion: Both bone quality and density improved after anti-thyroid treatment in premenopausal female and male Graves' disease patients.

Keywords: Graves' disease; Bone mineral density; Trabecular bone score

1. Introduction

Hyperthyroidism is a risk factor for osteoporosis due to increased bone turnover rate stimulated by thyroid hormone [1−3]. A meta-analysis found that BMD score decreases and fracture risk increases in hyperthyroid patients [3]. Several studies have shown that the increased fracture risk returns almost to normal after treatment with anti-thyroid therapy even without specific osteoporosis treatment, but not all studies agree [3−5]. Most studies have focused on data from bone densitometry (BMD) [1−3,5].

Bone strength associated with osteoporotic fracture is determined by material formation and structural considerations [6]. Although BMD measurement by dual-energy X-ray absorptiometry (DXA) is an effective, non-invasive, and quantitative method to assess fracture risk, it has a limited ability to reflect bone structure. Trabecular bone score (TBS) is a new texture parameter in DXA image analysis [7−10], and so does not require any additional radiation exposure or time by the patient. TBS measures gray level variations in DXA images of the lumbar spine and incorporates them into a score [8,10], allowing a reflection of bone quality by estimating

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bone microarchitecture status [7,8,10]. Several recent studies of secondary osteoporosis associated with conditions like diabetes and hyperparathyroidism have used TBS [11,12]. But, to the best of our knowledge, no study has addressed bone quality changes using TBS, and only a few studies using BMD, in Graves' disease.

Therefore, we evaluated changes in BMD and TBS in Graves' disease patients treated with anti-thyroid therapy.

2. Materials and methods

2.1. Study design and participants

We retrospectively reviewed the medical records of premenopausal female and male patients with Graves' disease between March 2005 and May 2014 at Ajou University Hospital. Diagnosis of Graves' disease was based on patient history, physical examination, ^{99m}Tc thyroid scan and serum free thyroxine (FT4), total triiodothyronine (T3), thyroid stimulating hormone (TSH), and TSH receptor antibody (TRAb) levels. We defined Graves' disease patients who has hyperthyroidism, increased levels of serum FT4, T3 and decreased levels of TSH, with elevated diffuse radioiodine uptake in thyroid scan or elevated TSH receptor antibody [13]. Patients who received more than two BMD measurements during the treatment period were selected. Patients with a history of spine fracture, severe hepatic and/or renal disease, alcoholism, hyperparathyroidism or other major medical conditions were excluded. No patients had taken calcium, vitamin D supplements or other drugs that can affect bone metabolism.

2.2. Measurement

Subject height and weight were measured at each BMD examination. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters. Basal serum FT4, T3 and TSH levels were assessed with an Advia Centaur Immunodiagnostic system (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The reference ranges were 0.89−1.76 ng/dL for fT4, 76−190 ng/dL for T3 and 0.55−4.78 mIU/L for TSH. TRAb levels were measured by radio-receptor assay (TSH Rezak; Medipan Diagnostica, Germany; normal values <15%). BMD was measured with dual X-ray absorptiometry (GE Lunar®) in the lumbar spine (LS) and femur. For lumbar spine BMD, when the specific vertebrae were not suitable for analysis due to degenerative changes or any other reasons, BMD was calculated excluding the affected vertebrae. Our center's coefficient of variation for BMD is 0.937% in the LS. All DXA scans were analyzed, and TBS was calculated using TBS insight® software (version 2.1) with DXA images on the same vertebrae as in the BMD measurements. The coefficient of variation for TBS measurement is 1.408% in the LS at our center. This study was approved by Institutional Review Board of Ajou University Hospital (IRB No. AJIRB-MED-MDB-14-247). And we retrospectively reviewed patient medical records, thus Institutional Review Board agreed waiver of requirement of informed consent for this study.

2.3. Statistical analysis

Wilcoxon signed rank test was used to compare changing patterns of parameters with treatment, and a subgroup analysis was done with newly diagnosed patients. All results are expressed as medians and interquartile ranges (IQR). A p-value <0.05 was considered statistically significant. All calculations were performed using SPSS 18.0 software (SPSS, Inc. Chicago, IL, USA).

3. Results

A total of 17 (56.6%) males and 13 (43.3%) premenopausal females with Graves' disease with a mean age 35.3 ± 9.9 years were included. The mean follow-up period was 20.7 ± 8.5 months. In terms of thyroid function tests, free T4 and TRAb levels decreased at follow-up [2.55 ng/dL (IQR 2.07−3.78) to 1.28 ng/dL (IQR 1.23−1.39), 17.0 IU/L (IQR 5.0−40.3) to 5.0 (5.0−6.0) IU/L, respectively; $p < 0.001$], while TSH level increased at follow-up [0.015 mIU/L (IQR 0.01−0.04) to 0.89 mIU/L (IQR 0.35−1.55), $p < 0.001$; Table 1]. Median BMD (LS) values were 1.118 g/cm^2 (IQR 1.000−1.119) at baseline and significantly increased at follow-up without any specific osteoporosis treatment as thyroid function tests improved [1.118 g/cm^2 (IQR 1.000−1.119) to 1.167 g/cm^2 (IQR 1.050−1.219), $p = 0.001$; Fig. 1]. Z-score increased along with BMD [−0.7 (IQR −1.25−0.2) to −0.3 (IQR −0.95−0.05)]. TBS also increased at follow-up [1.377 (IQR 1.299−1.422) to 1.390 (IQR 1.327−1.430), $p = 0.038$; Fig. 1]. These findings indicate that median bone density improved after anti-thyroid treatment in Graves' disease patient, as seen in previous studies.

Among the 30 patients, 19 were newly diagnosed with Graves' disease. The median follow-up period for BMD was 16 months (IQR 12-29) in newly diagnosed patients. Changes in FT4, TSH and TRAb level at follow-up in newly diagnosed patients were similar to those observed in all 30 patients. BMD improved from 1.11 g/cm^2 (IQR 0.97−1.19) to 1.15 g/cm^2 (IQR 1.06−1.23) after anti-thyroid therapy in the newly diagnosed group ($p = 0.001$). TBS also improved after

Table 1
Characteristics of 30 Graves' disease patients (20.7 ± 8.5-month follow-up).

	Initial	Follow up	p
Age, years	36.0 (29.5−44)	37.5 (30.8−46.0)	<0.001
Height, cm	165.35 (159.95−171.98)	165.60 (160.65−171.63)	0.390
Weight, kg	59.5 (52.7−68.0)	62.3 (56.18−69.8)	<0.001
BMI, kg/m^2	21.4 (19.9−24.1)	22.2 (20.8−25.6)	<0.001
T3, ng/dL	220 (139−381)	102 (89−111)	<0.001
Free T4, ng/dL	2.55 (2.07−3.78)	1.28 (1.23−1.39)	<0.001
TSH, mIU/L	0.015 (0.01−0.04)	0.89 (0.35−1.55)	<0.001
TRAb, IU/L	17.0 (5.0−40.3)	5.0 (5.0−6.0)	0.001
Z-score	−0.7 (−1.25−0.20)	−0.3 (−0.95−0.05)	0.042

Data are expressed as median (Interquartile ranges; 25 percentile-75 percentile).
Reference values: T3: 65−150 ng/dL; Free T4: 0.89−1.76 ng/dL; TSH: 0.55−4.78 mIU/L; TRAb: <15% (gray zone 9−14%).
BMI, body mass index; TSH, Thyroid-stimulating hormone; TRAb, Thyroid-stimulating hormone receptor antibody.

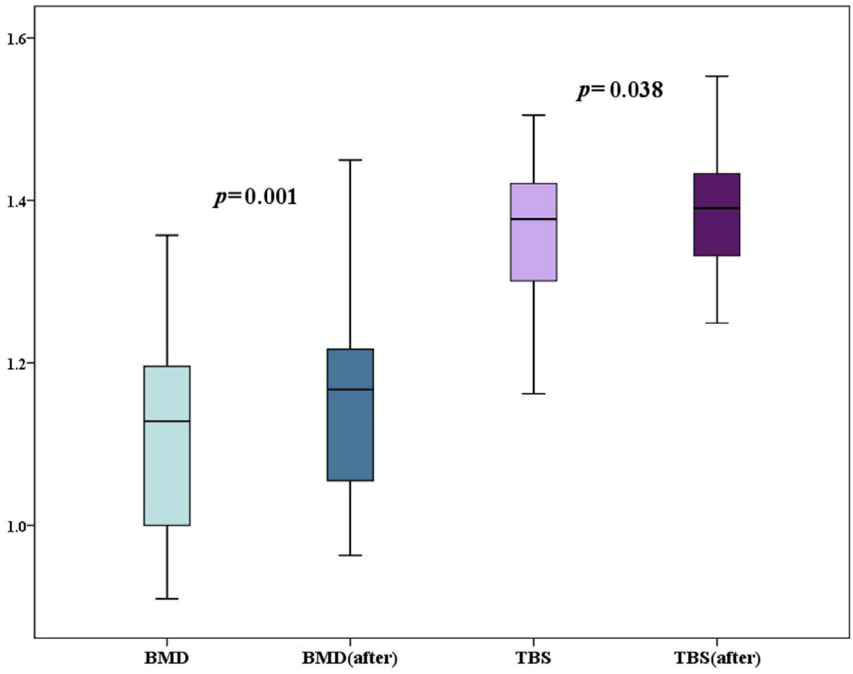

Fig. 1. Changes in bone mineral density (BMD) and trabecular bone score (TBS) in lumbar spine in premenopausal and male Graves' disease patients after anti-thyroid treatment (n = 30).

treatment [1.41 (IQR 1.38−1.46) to 1.43 (IQR 1.37−1.49), respectively, p = 0.038; Table 2]. For the 11 patients who were on anti-thyroid treatment when they took the first BMD measurements, there were no significant differences between initial and follow-up BMD and TBS (p = 0.182 and p = 0.347, respectively).

4. Discussion

The aim of this study was to evaluate changes in bone density represented by BMD and bone quality using TBS in Graves' disease patients after anti-thyroid therapy.

Hyperthyroidism is a hypermetabolic state with elevated levels of thyroid hormone. Graves' disease is one usual cause of hyperthyroidism and a known risk factor of osteoporosis. The mechanism of osteoporosis in Graves' disease is mainly acceleration of bone turnover rate. Osteoclastic bone resorption rate is faster than osteoblastic remineralization, reducing bone mass. The bone remodeling cycle is shortened by almost half, and about 10% of mineralized bone mass is reduced in every cycle in severe Graves' disease [14].

Several studies have also demonstrated other associated mechanisms. Thyroid hormone plays important roles in skeletal growth and bone mass maintenance. T3in particular is associated with bone development and growth [15]. The thyroid gland mainly secretes pro-hormone T4 in response to TSH stimulation [16]. Most circulating T3 is converted from T4 by type 2 iodothyronine deiodinase enzymes (D2) [17].

Table 2
Characteristics of newly diagnosed 19 and already diagnosed 11 Graves' disease patients.

	Newly diagnosed patients (n = 19)			Previously diagnosed patients (n = 11)		
	Initial	Follow up	p	Initial	Follow up	p
Age, years	35 (30−43)	36 (31−45)	<0.001	39 (28−45)	41 (30−50)	0.003
Height, cm	163.0 (159.0−141.6)	163.0 (158.8−171.3)	0.39	167.1 (163.2−173.5)	167.5 (163.3−173.8)	0.622
Weight, kg	55.2 (52.2−62.4)	60.5 (52.7−66.4)	<0.001	67.0 (60.9−72.9)	68.4 (60.4−73.0)	0.247
BMI, kg/m^2	20.8 (19.4−23.4)	21.9 (20.4−25.4)	<0.001	23.6 (21.3−25.8)	23.8 (21.9−26.4)	0.248
T3, ng/dl	239 (208−407)	103 (91−110)	<0.001	132 (124−161)	99 (81−127)	0.012
Free T4, ng/dL	3.44 (2.52−4.10)	1.28 (1.23−1.37)	<0.001	2.10 (1.67−2.29)	1.28 (1.21−1.43)	0.003
TSH, mIU/L	0.01 (0.01−0.04)	0.63 (0.14−1.40)	<0.001	0.02 (0.01−0.04)	1.08 (0.38−2.17)	0.003
TRAb, IU/L	27 (11−57)	5 (5−5)	<0.001	10 (5−20)	5 (5−16)	0.263
BMD (LS), g/cm^2	1.11 (0.97−1.19)	1.15 (1.06−1.23)	0.001	1.19 (1.01−1.21)	1.18 (1.04−1.22)	0.182
TBS (LS)	1.41 (1.38−1.46)	1.43 (1.37−1.49)	0.038	1.31 (1.28−1.39)	1.35 (1.28−1.37)	0.347
Z-score (LS)	−0.8 (−1.20−0.30)	−0.2 (−0.90−0.40)	0.010	−0.5 (−1.38−−0.08)	−0.55 (−1.59−−0.10)	0.929
Treatment period, month	16 (12−29)			36 (20−40)	52 (47−73)	

Data are expressed as median (Interquartile ranges; 25 percentile-75 percentile).
Reference values: T3: 65−150 ng/dL; Free T4: 0.89−1.76 ng/dL; TSH: 0.55−4.78 mIU/L; TRAb: <15%(gray zone 9−14%).
BMI, body mass index; TSH, Thyroid-stimulating hormone; TRAb, Thyroid-stimulating hormone receptor antibody; LS, Lumbar spine.

The action of T3 happens through binding to thyroid hormone receptors (TRs), a nuclear receptor superfamily [15,16]. Because T3 binds to TRs with a 100-fold higher affinity than T4, T3 enters the cell nucleus to take the TR ligand binding site [18]. T3 receptors (TRs) α and β, encoded by the genes THRA and THRB, respectively, are expressed in chondrocytes, osteoblasts and osteoclasts [16,17,19]. TRα is more dominant than TRβ, with almost 10-fold higher ranges in bone [20]. T3 is also associated with skeletal growth control by indian hedgehog (Ihh) and local feedback mechanism of PTHrP, which inhibits differentiation and growth of proliferating chondrocytes [21−23]. TSH is a known independent factor associated with bone resorption that, when bound to the TSH receptor in osteoblast and osteoclast precursors, inhibits bone turnover rate [24]. Other skeletal responses to thyroid hormones are less well understood, including growth hormone, insulin-like growth factor1 and Wnt-β catenin pathways [19,20,25−27].

Studies about the reversibility of bone loss after thyroid function normalization with treatment have yielded variable results in hyperthyroid patients. Krolner et al. found a 5% increase in bone mineral contents after a two-year treatment period in thyrotoxicosis patients [28]. Rosen et al. also reported an 11% lumbar bone density increase after thyroid function normalization [29]. In contrast, Toh et al. reported insignificant recovery of bone mineral contents (BMC) after euthyroid status in hyperthyroid patients in a longitudinal prospective study [30]. Overall, our observations are consistent with the majority of previous studies, which found that bone mineral density recovered some, but not completely, after hyperthyroid treatment [1,2,28,29,31].

Bone strength, which is closely related to bone fragility, depends not only on bone quantity, as represented by BMD, but also bone quality. Few studies have been done to measure bone quality, which is assessed by many factors including bone turnover rate, bone microarchitecture and microdamage accumulation. Acotto et al. reported poor bone architecture and decreased elasticity as measured by quantitative ultrasound in hyperthyroidism patients [32], but did not describe changes in these parameters after anti-thyroid treatment.

To our knowledge, this is the first report about changes in bone quality as represented by TBS in Graves' disease patients after anti-thyroid treatment.

Our study has some limitations. We did not include bone turnover markers, such as serum alkaline phosphatase, serum osteocalcin, urine N-telopeptide and urine C-telopeptide. Because of the retrospective design, these data could not be fully collected.

In conclusion, both bone density and quality improved after anti-thyroid treatment in premenopausal female and male patients with Graves' disease.

Conflicts of interest

Authors report no conflicts of interest.

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