Osteoporosis and Sarcopenia 3 (2017) 149–154

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: http://www.elsevier.com/locate/afos

Original article

The main autoimmune and nonautoimmune etiologies of endogenous hyperthyroidism do not seem to influence the increased prevalence of morphometric vertebral fractures and osteoporosis in Portuguese men

Ana Paula Barbosa [a, b, *], Mário Rui Mascarenhas [a, b], Manuel Bicho [c], João Janeiro [d], António Gouveia Oliveira [e]

[a] University Clinic of Endocrinology, Lisbon University Medical School, Lisbon, Portugal
[b] Endocrinology, Diabetes and Metabolism Department, Santa Maria University Hospital, Lisbon, Portugal
[c] Genetics Laboratory, Environmental Health Institute, Lisbon University Medical School, Lisbon, Portugal
[d] Imagiology Department, Santa Maria University Hospital, Lisbon, Portugal
[e] Pharmacy Department, Health Sciences Center, Federal University Rio Grande do Norte, Natal, Brazil

ARTICLE INFO

Article history:
Received 17 May 2017
Received in revised form
17 July 2017
Accepted 17 August 2017

Keywords:
Hyperthyroidism
Men
Fractures
Bone mineral density
Vertebral fracture assessment

ABSTRACT

Objectives: The purpose of this study was to evaluate the effects of hyperthyroidism and their etiology on bone mineral density (BMD), on body soft tissue composition, on the prevalence of vertebral fractures detected by vertebral fracture assessment (VFA) and on the trabecular bone score (TBS).
Methods: From an initial population of 119 Portuguese men (78 with hyperthyroidism [HT]+ 41 controls [CTs]) admitted to the Endocrinology Department we selected 41 men aged over 50 with clinical hyperthyroidism to participate; each one was matched by age and height with a control person. BMD (g/cm^2) at the lumbar spine, hip, radius 33% and whole body and the total body masses (kg) were studied by dual-energy X-ray absorptiometry (DXA). VFA with Genant semiquantitative method was used to detect fractures. The TBS was obtained from lumbar spine DXA images. No patient had been treated previously for hyperthyroidism or osteoporosis. Adequate statistical tests were used.
Results: In the hyperthyroidism group, total lean mass (CT 58.16 ± 7.7 vs. HT 52.3 ± 5.7, P = 0.03) and distal radius BMD (CT 0.769 ± 0.05 vs. HT 0.722 ± 0.08, P = 0.005) were lower; there was a significantly higher prevalence of osteoporosis (CT 9.7% vs. HT 29.3%, P = 0.015) and vertebral fractures (CT 2.4% vs. HT 24.4%, P = 0.007). TBS was similar in both groups (CT 1.328 ± 0.11 vs. HT 1.356 ± 0.11, P = not significant). Comparing patients with Graves' disease with patients with toxic goiter, there were no differences regarding BMD, BMD qualification, prevalence of fractures and TBS and just total lean mass was significantly lower in patients with Graves' disease.
Conclusions: These results suggest that in a group of hyperthyroid men aged over 50 there are significant decreases in cortical bone BMD and lean mass and a higher prevalence of osteoporosis and silent vertebral fractures, but the etiology of the hyperthyroidism does not seem to influence it. Besides the antithyroid drugs, some patients may benefit from bone-directed treatments.

1. Introduction

Thyroid dysfunction is one of the most common causes for consultation in Endocrinology Departments. A meta-analysis to evaluate its incidence and prevalence in Europe found 6.7% of undiagnosed thyroid dysfunction, being 1.72% for undiagnosed hyperthyroidism and 0.75% for previously diagnosed hyperthyroidism [1]. The prevalence of hyperthyroidism is about 10 times more common in women than in men in nondeficient iodine populations and is about 0.5%–2%. The more important etiologies are Graves' disease and toxic multinodular goiter, while autonomously functioning adenoma and thyroiditis are not so common [2].

In animal models, namely in thyroid receptor (TR)β mutant mice, the studies show an accelerated skeletal development and

* Corresponding author. University Clinic of Endocrinology, Lisbon University Medical School, Lisbon, Portugal.
E-mail address: ana_pbarbosa@hotmail.com (A.P. Barbosa).
Peer review under responsibility of The Korean Society of Osteoporosis.

http://dx.doi.org/10.1016/j.afos.2017.08.099

adult osteoporosis due to supraphysiological stimulation of skeletal TRα due to disruption of the hypothalamus-pituitary-thyroid axis. The studies also show that T3 exerts catabolic actions in adult bone and that those effects of disrupted or increased T_3 action seem to predominate over the skeletal responses to thyroid-stimulating hormone (TSH) [3].

In hyperthyroidism, the excess of circulating thyroid hormones can lead to an increase of bone resorption, either by acting directly on osteoclasts or indirectly on osteoblasts [4]. Also TSH seems to be a negative regulator of bone remodeling, inhibiting the formation, the survival of osteoclasts and the differentiation of osteoblasts [5,6]; however, this effect has not been totally clarified because experiments in mice with a loss-of-function TSH receptor, the bone loss seems to be independent of TSH levels [7].

The hyperthyroidism is a known important cause of secondary osteoporosis and of increase in fracture risk. One study in a male population investigated for the etiology of osteoporosis, found that a previous history of hyperthyroidism was present in about 5% [8].

However, most studies are done in postmenopausal women and in patients with exogenous hyperthyroidism due to thyroxine use after thyroidectomy for thyroid carcinoma.

The clinical studies in men with endogenous hyperthyroidism are very scarce, namely those addressing the osteoporotic fractures risk and the possible impact of the several etiologies of endogenous hyperthyroidism (autoimmune, toxic goiter) on that risk. This subject is important especially for the older populations because they are already prone to osteoporosis and to fragility fractures, which can be associated with precocious mortality [9]. Recent studies in male populations, show that accelerated loss of bone mineral density (BMD) at the hip is a risk factor for mortality that is not explained by comorbidity burden, change in weight or physical activity [10].

Vertebral fractures are among the most common fractures in osteoporosis. About 69% of patients with vertebral fractures are unaware of them, not only because they are very frequently asymptomatic, but also because patients are not routinely or accurately imaged. It is important to diagnose it, because their presence predicts the occurrence of future osteoporotic fractures all over the skeleton [11,12]. They occur more frequently in patients with a dual-energy X-ray absorptiometry (DXA) diagnosis of low bone mass rather than osteoporosis, showing that besides BMD, other factors contribute to the risk of osteoporotic fractures [12].

Vertebral fracture assessment (VFA) by DXA is a spine imaging with DXA scanners which may represent a better alternative to conventional radiography in the diagnosis of vertebral fractures, due to lower radiation dose and also to greater convenience for the patient as it can be done at the same time of DXA [13]. Despite not being used routinely in our country and in other bone metabolic units around the world, we find it very useful in clinical practice to detect prevalent fractures [14–16]. A previous study by our group in young hyperthyroid men, showed an increased prevalence of vertebral fractures detected by VFA [17].

In the last years, trabecular bone score (TBS) was defined as an indirect index of bone microarchitecture and of bone quality. It is determined from the grey-level texture metric variation analysis of the 2-dimensional lumbar spine DXA images, quantifying local variations in pixels intensities. The experimental variogram method is used to estimate the bone microarchitecture. An increased TBS assessment associates with better bone microarchitecture, while a reduced TBS estimation correlates with fragile skeletal microarchitecture. It was shown that TBS is associated with the structure of the bone tissue and it may detect differences between DXA scans that show identical BMD amounts. It is an easy tool and clinical studies suggest that it improves (in addition to clinical risk factors and BMD) the prediction of fracture risk not only in osteoporosis but also in some metabolic bone diseases. TBS seems also to be more sensitive than BMD in identifying secondary osteoporosis, namely hyperparathyroidism, adrenal adenomas and iatrogenic Cushing [18–20]. As far as we know, there are no TBS data in men with endogenous hyperthyroidism.

So, the aims of this cross-sectional case-control study were to evaluate the effects of endogenous clinical hyperthyroidism and their main etiologies in the body composition (BMD and total body fat and lean masses), in the TBS and in the prevalence of silent vertebral fractures using VFA technology (confirmed by X-ray) of a population of Portuguese men aged more than 50 years.

2. Methods

From an initial population of 119 men (78 with hyperthyroidism + 41 controls) which were admitted to the Endocrinology Department for diagnosis and treatment, we selected 41 men aged over 50 years with clinical hyperthyroidism to participate in this study. For each patient, an age (limits 6–11 months) and stature (limits 1–3 cm) matched control person without diseases or medications affecting bone metabolism, was drawn from a random sample of patients of the Endocrinology Department. Exclusion criteria for both patients and controls were: subclinical hyperthyroidism, hypo/hyperparathyroidism, hypogonadisms, diabetes mellitus, hypo/hypercortisolism, vitamin D deficiency, inflammatory bowel disease, malabsorption diseases, liver/renal diseases, medications affecting the skeleton, and alcohol habits.

Regarding the etiology of the patients with hyperthyroidism, 20 cases were Graves' disease, 14 cases were toxic multinodular goiter and 7 cases were toxic nodule.

No patient had previously been treated empirically for osteoporosis or reduced bone mass or hyperthyroidism. We cannot be sure of the duration of the hyperthyroidism before the beginning of antithyroid medication but possibly it ranged at least from 3 to 12 months.

Also, past history of fragility fractures and symptoms of vertebral fracture were excluded in both patients and controls. All patients and controls had a full clinical examination and body mass index (BMI) (kg/m^2) was calculated.

In both groups, BMD (g/cm^2) at the lumbar spine (L_1–L_4), at the hip (femoral neck and total), at the distal radius (1/3 or 33%) and at the whole body and total body tissue composition including soft body lean and fat masses (kg) were studied by DXA using the QDR Discovery W radiological densitometer (Hologic Inc., Marlborough, MA, USA) of the Lisbon Clinic of Endocrinology Diabetes and Metabolism, Lda. The fractured vertebrae were excluded from de analysis.

According to the International Society of Clinical Densitometry official positions, in both groups the BMD was qualified by the lowest T-score obtained at the lumbar spine, at the hip and at the distal radius (33%) in osteoporosis, low BMD and normal BMD [21].

TBS was obtained from the pixel grey-level texture metric variation analysis of the 2-dimensional lumbar spine DXA images (iNsight software, Medimaps, Mérignac, France) [21]. The normal range for TBS in European men is considered: higher or equal to 1.310 - high TBS, low fracture risk; between 1.230 and 1.310 - medium TBS, medium fracture risk; less or equal to 1.230 - low TBS, high fracture risk [22,23].

The lateral images of thoracolumbar spine in DXA scan (VFA) were used to detect fractures and those were classified according to type (wedge, biconcave, crush) and severity (% of deformity) by Genant semiquantitative method, by one qualified endocrinologist. This method combines the qualitative visualization of the spine with the morphometric measurements of the vertebral body height in 6 points [14].

Table 1
The anthropometric data and of total body masses in the hyperthyroidism and in the control groups.

Variable	Control (n = 41)	Hyperthyroidism (n = 41)	P-value
Age, yr	62.8 ± 7.8	62.9 ± 8.0	NS
Weight, kg	82.6 ± 13.1	76.3 ± 12.8	0.029
Height, m	1.69 ± 0.05	1.69 ± 0.06	NS
Body mass index, kg/m^2	28.8 ± 4.1	26.6 ± 3.7	0.012
Lean mass, kg	58.16 ± 7.7	52.3 ± 5.7	0.039
Fat mass, kg	23.16 ± 6.7	19.6 ± 5.8	NS

Values are presented as mean ± standard deviation.
NS, not significant.

Table 2
The BMD at several skeletal sites and TBS in the hyperthyroidism and control groups.

Variable	Control (n = 41)	Hyperthyroidism (n = 41)	P-value
BMD, g/cm^2			
L_1–L_4	1.035 ± 0.12	1.038 ± 0.22	NS
Femoral neck	0.854 ± 0.15	0.800 ± 0.13	NS
Total hip	1.024 ± 0.13	0.967 ± 0.13	NS
Distal radius (33%)	0.769 ± 0.05	0.722 ± 0.08	0.005
Whole body	1.184 ± 0.08	1.143 ± 0.12	NS
TBS L_1–L_4	1.328 ± 0.11	1.356 ± 0.10	NS

Values are presented as mean ± standard deviation.
BMD, bone mineral density; TBS, trabecular bone score; NS, not significant.

All patients had thoracolumbar spine X-ray (on frontal and lateral projections) on the same day or within a few days which was reviewed by one qualified radiologist. In a few instances where there was disagreement, a second radiologist was consulted. Conventional radiographs were electronic images produced by digital X-ray equipment and were viewed using a high-resolution viewing workstation designed for medical image reading. Their final reports were established as the gold standard for proven vertebral fractures, and only the positive cases in both VFA and X-ray were considered and included in the results.

Fasting blood samples were collected for measurement of serum chemistries, blood counts and hormones. Serum free T3, free T4, and thyroid-stimulating hormone (TSH) were assayed by an electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland) and total calcium and phosphorus were assayed by enzymatic colorimetry (Roche Diagnostics).

All patients and controls gave their informed consent, according to the approved protocol by the ethic committee of the institution and based on Helsinki declaration.

The data were statistically analyzed using the Statgraphics Centurion XVI version 16.1.07.01 (Statpoint Technologies, Inc., The Plains, VA, USA). All the results are expressed as mean ± standard deviation. After testing for normal distribution, the Student t-test was used to compare the differences in parametric data between the groups. The Fisher exact test was used to compare the number of fractures in both groups. P-value of <0.05 was considered statistically significant.

3. Results

The mean age, height, weight, BMI, and total body lean and fat masses of the groups are shown in Table 1. In the hyperthyroidism group, there was a significant decrease in the mean total lean body mass (Table 1). Regarding BMD at the several skeletal sites, we found significant decreases in the mean BMD at the distal radius (Table 2 and Fig. 1).

The means of TBS in both groups were in the considered normal range and there were no significant differences between the groups (hyperthyroidism [range, 1.063–1.515; mean, 1.356 ± 0.10] vs. control [range, 1.079–1.493; mean, 1.328 ± 0.11]), as shown in Table 2. Moreover, in the hyperthyroidism group, TBS values were similar between the 10 men with fractures and those without it (1.354 ± 0.05 vs. 1.359 ± 0.05 respectively, P = 0.9). In the control group, TBS correlated with weight, total femur BMD and total fat and lean masses, while in the hyperthyroidism group this tool correlated just with whole body BMD and T-score.

The prevalence of decreased BMD and osteoporosis, as well as, the prevalence of vertebral fractures (detected by both VFA and X-ray) were significantly increased in the hyperthyroidism group (Table 3). Also in this group, fractures were detected in 10 cases by both VFA and X-ray.

In the control group, the only fracture detected was in T11 mild wedge, while in the hyperthyroidism group 7 fractures were

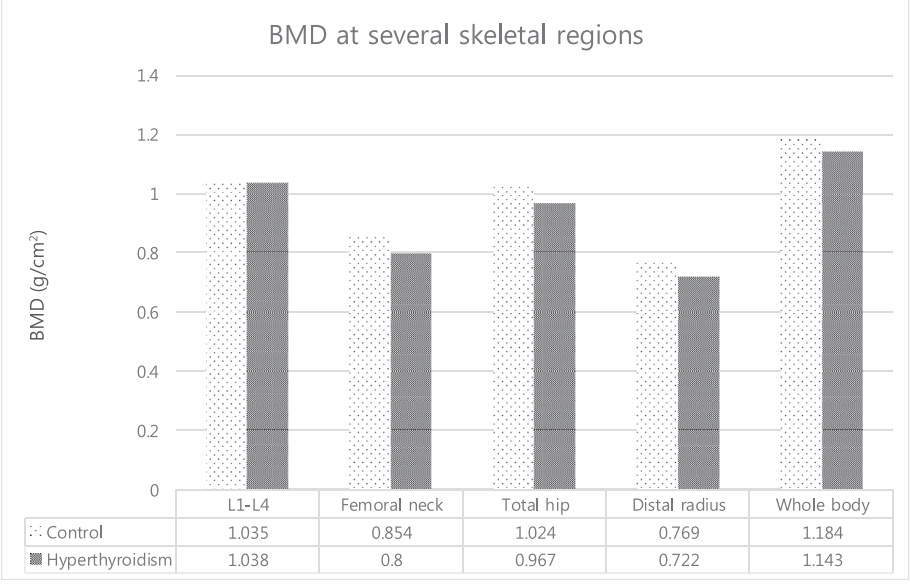

Fig. 1. Bone mineral density (BMD) at several skeletal sites in control and in hyperthyroidism groups.

Table 3
The BMD qualification and the number of vertebral fractures in the hyperthyroidism and control groups.

	Control (n = 41)	Hyperthyroidism (n = 41)	P-value
BMD qualification			
Normal	20 (48.8)	9 (21.9)	
Reduced	17 (41.5)	20 (48.8)	0.015
Osteoporosis	4 (9.7)	12 (29.3)	
Vertebral fractures	1 (2.4)	10 (24.4)	0.007

Values are presented as number (%).
BMD, bone mineral density.

localized in the thoracic spine and 3 at the lumbar spine, 2 biconcave moderate degree and 8 wedge mild degree. BMD qualification of the 11 men with fractures was: control group - reduced BMD; hyperthyroidism group - reduced BMD in 3, osteoporosis in 1, and normal in 6.

In the hyperthyroidism group, there were significant increases in bone formation markers (osteocalcin and total alkaline phosphatase) and in β-crosslaps (CTX) after age-adjustment (Table 4).

When we compared patients with Graves' disease with patients with toxic goiter, BMD at all skeletal sites, BMD qualification, prevalence of fractures and TBS were similar in both groups, but the total lean mass was significantly lower in patients with Graves' disease (Table 5A). Also, there were significant increases regarding free T4 and total alkaline phosphatase in the Graves' disease group (Table 5B).

4. Discussion

In hyperthyroidism, the duration of the bone remodeling cycle, which usually lasts about 7 months, can occur almost half that time (3–4 months) because the rate of bone turnover is accelerated, both bone resorption and formation are increased, so, the natural existing balance disappears leading to a bone resorption phase exceeding the bone formation phase; consequently there is an incomplete substitution with new bone cells and loss of mineralized bone. This progressively leads to a reduced BMD and osteoporosis development, reduced bone strength and consequently to a higher osteoporotic fracture risk. It usually affects both axial and appendicular skeleton, however it is usually more pronounced in areas with predominant cortical bone like the femoral neck and the distal radius [24,25].

This study was done in a population of men aged over 50, with non-iatrogenic clinical hyperthyroidism naïve of treatment, and we found that there was a slight tendency for a lower mean BMD in all skeletal regions except the lumbar spine, and a significant decrease of mean BMD at the distal radius. These results could be explained by the small number of patients, but we can also speculate that some small vertebrae deformities (but not fractures, which were excluded), could contribute to small increases in areal BMD at the lumbar spine.

El Hadidy et al. [26] studied a hyperthyroid male population aged 23–65 years and found a significant decrease in the "lower half radius" BMD by DXA, which was related to both severity and duration of the hyperthyroidism; however, no other skeletal regions were studied and fractures prevalence was not assessed. In our present study men were aged more than 50 years and the scans were performed at the radius 1/3 or 33%. A previous study by our group in younger hyperthyroid men, showed significant BMD decreases in all skeletal regions and an increase in the prevalence of vertebral fractures detected by VFA [17].

Another study evaluating BMD at both lumbar spine and femoral neck, but in normal euthyroid men around 50 years-old, suggested that serum TSH concentration at the lower end of the reference range may be associated with a lower BMD [27].

The studies in men about the impact of the several etiologies of endogenous clinical hyperthyroidism on BMD and vertebral fractures prevalence are very scarce; the same study by El Hadidy et al. [26] found that z-scores of BMD at the lower half of the left radius in patients with Graves' disease was not significantly different from those with toxic multinodular goiter. In females, all these etiologies of hyperthyroidism cause an increase in the prevalence of osteoporosis, but they do not seem to influence the impact on BMD [28]. Also in our study, there were no differences in the BMD between patients with Graves' disease and patients with toxic goiter, but there was a significant reduction in the total lean mass in patients with Graves' disease, probably because of

Table 4
The biochemical, hormonal and bone markers data in the hyperthyroidism and in the control groups.

Variable	Control (n = 41)	Hyperthyroidism (n = 41)	P-value
TSH, μU/mL	1.63 ± 0.7	0.12 ± 0.1	0.000
Free T4, ng/dL	1.16 ± 0.1	2.2 ± 1.6	0.000
Free T3, pg/mL	3.43 ± 0.5	6.8 ± 5.7	0.029
Calcium, mg/dL	9.37 ± 0.2	9.59 ± 0.4	NS
Phosphorus, mg/dL	3.12 ± 0.4	3.05 ± 0.4	NS
iPTH, pg/mL	52.26 ± 18.7	51.08 ± 32.4	NS
Total alkaline phosphatase, UI/L	62.87 ± 12.7	106.06 ± 48.5	0.000
Bone alkaline phosphatase, μg/L	15.8 ± 4.2	22.3 ± 13.5	NS
Osteocalcin, ng/mL	9.48 ± 5.8	15.71 ± 12.8	0.045
CTX, ng/mL	0.2 ± 0.1	0.7 ± 0.3	0.045[a]

Values are presented as mean ± standard deviation.
TSH, thyroid-stimulating hormone; iPTH, intact parathyroid hormone; CTX, β-slaps; NS, not significant.
[a] After age-adjusted; but the difference between the means is nonsignificant without correction.

Table 5A
The BMD qualification, the number of vertebral fractures and the lean mass in patients with Graves' disease and toxic goiter.

	Graves (n = 20)	Toxic goiter (n = 21)	P-value
BMD qualification			
Normal	5 (25.0)	4 (19.1)	
Reduced	9 (45.0)	11 (52.4)	NS
Osteoporosis	6 (30.0)	6 (28.6)	
Vertebral fractures	3 (15.0)	7 (33.3)	NS
Lean mass, kg	52.16 ± 5.4	56,92 ± 9,1	0.000
Trabecular bone score	1.353 ± 0.11	1.360 ± 0.09	NS

Values are presented as number (%) or mean ± standard deviation.
BMD, bone mineral density.

Table 5B
The biochemical, hormonal and bone markers data in the Graves' disease and in the toxic goiter groups.

Variable	Graves (n = 20)	Toxic goiter (n = 21)	P-value
TSH, μU/mL	0.05 ± 0.1	0.2 ± 0.1	NS
Free T4, ng/dL	2.8 ± 1.9	1.6 ± 1.0	0.019
Free T3, pg/mL	8.2 ± 6.9	5.4 ± 4.0	NS
Calcium, mg/dL	9.5 ± 0.4	9.7 ± 0.4	NS
Phosphorus, mg/dL	3.1 ± 0.5	3.0 ± 0.4	NS
iPTH, pg/mL	46.5 ± 30.2	55.4 ± 26.3	NS
Total alkaline phosphatase, UI/L	128.7 ± 54.8	84.8 ± 29.8	0.007
Osteocalcin, ng/mL	18.6 ± 14.7	13.1 ± 10.6	NS
CTX, ng/mL	0.90 ± 0.4	0.51 ± 0.2	NS

Values are presented as mean ± standard deviation.
TSH, thyroid-stimulating hormone; iPTH, intact parathyroid hormone; CTX, β-crosslaps; NS, not significant.

the more severe and/or longer duration of the hyperthyroidism which is very hard to define.

Weight loss and gastrointestinal changes like increased gut motility and consequent malabsorption of proteins, minerals and vitamins, are frequently seen in hyperthyroidism; this explains the significant decreases observed in total body lean mass and BMI in the hyperthyroidism group. Moreover, the weight reduction trend which is associated with a low bone mass, could also contribute to the BMD decrease in the hyperthyroidism group, because we found significant differences in both weight and total body fat mass between groups.

The Rotterdam study, done in a large sample of elderly Caucasian men and women, suggested that besides the effect of weight on bone density, there is also a direct effect of thyroid function on bone tissue [29].

In the hyperthyroidism group, we found 10 vertebral fractures confirmed by both VFA and X-ray, from mild to moderate degrees, and with a BMD qualification from normal to osteoporosis. So, the decreases in BMD may contribute, but cannot totally explain the increase in fracture risk observed in this population. Total lean mass could be another important factor, as well as parameters related to bone quality.

A population-based study of around 11,000 patients with diffuse and nodular toxic goiter with a mean age of 60 years old of both sexes, showed that fracture risk was only significantly increased at the time of diagnosis decreasing to normal after it [30].

Several studies done in patients with thyroxine-induced hyperthyroidism showed that fracture risk was higher in older men and, mainly, in women with a very suppressed TSH [31,32]. However, until now, it has not been clarified that iatrogenic hyperthyroidism does affect bone in a totally similar way as hyperthyroidism due to toxic goiter or autoimmune diseases.

Regarding TBS, the clinical studies in men are scarce and in men with hyperthyroidism are just a few. In our study, the means of TBS in both hyperthyroidism and control groups were in the considered normal range and there were no significant differences between the groups. A possible explanation is that in this endocrine disease the cortical bone is usually more affected than the trabecular one, which is the bone evaluated in TBS. By the other hand, small vertebral deformations (another complication of osteoporosis but not as severe as fragility bone fractures) may lead to artifacts in the analysis of the 2-dimensional lumbar spine DXA images, and/or TBS values obtained from those images. Another explanation could be that the time with nontreated hyperthyroidism was not long enough to develop bone microarchitecture changes measured by TBS.

In a retrospective case-control study, Leib et al. [20] showed that men with fragility fractures had lower TBS values than men without it, but it was not clear a causative direct association between the decrease in TBS and fracture risk.

Ock et al. found in Graves' disease male and female patients a significant increase of TBS values from 1.377 to 1.390 after antithyroid therapy, however it was a noncontrolled study and those scores are considered within normal range [22,23,33].

In our study, we found significant increases in bone formation markers (osteocalcin and total alkaline phosphatase) and in CTX only after age-adjustment. Moreover, the patients with Graves' disease had significantly higher levels of total alkaline phosphatase than patients with toxic goiter. Studies in both men and women with hyperthyroidism, show that bone formation and bone resorption markers are increased and correlate with the disease severity [26,34,35].

The strength of this study resides in the fact of being done in a male population, not previously treated for hyperthyroidism, osteoporosis or low bone mass and showing that they already had some bone and lean masses decreases as well as vertebral fractures and increase in bone turnover markers.

A limitation for this study could be the relatively low number of patients.

Future studies with bigger male populations and evaluating the effects of antithyroid treatment will be important to better understand the bone disease of endogenous hyperthyroidism.

5. Conclusions

In this controlled study of men aged over 50, with endogenous hyperthyroidism, we found a significant decrease in cortical BMD, namely at distal radius as well as a significantly increased prevalence of reduced BMD and osteoporosis and of asymptomatic vertebral fractures. The results of this study using VFA technology (confirmed by X-ray), suggest that BMD and lean mass changes in men aged over 50 with nontreated endogenous hyperthyroidism may contribute to the development of osteoporosis and fragility vertebral fractures, but there are very probably other implicated factors related to bone quality. The lean mass and the total alkaline phosphatase are more affected in Graves' disease than in toxic goiter.

These data support the urgency of detecting silent fractures in this endocrine disease especially in elderly people, in order to start a treatment for both thyroid and bone. Moreover, we suggest that hyperthyroid men should perform DXA, routinely, not only at lumbar spine and femur, but also at the distal radius.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

References

[1] Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014;99:923–31.
[2] Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99:39–51.
[3] Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev 2010;31:139–70.
[4] Britto JM, Fenton AJ, Holloway WR, Nicholson GC. Osteoblasts mediate thyroid hormone stimulation of osteoclastic bone resorption. Endocrinology 1994;134:169–76.
[5] Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y, et al. TSH is a negative regulator of skeletal remodeling. Cell 2003;115:151–62.
[6] Sun L, Zhu LL, Lu P, Yuen T, Li J, Ma R, et al. Genetic confirmation for a central role for TNFα in the direct action of thyroid stimulating hormone on the skeleton. Proc Natl Acad Sci U. S. A 2013;110:9891–6.
[7] Bassett JH, O'Shea PJ, Sriskantharajah S, Rabier B, Boyde A, Howell PG, et al. Thyroid hormone excess rather than thyrotropin deficiency induces osteoporosis in hyperthyroidism. Mol Endocrinol 2007;21:1095–107.
[8] Ryan CS, Petkov VI, Adler RA. Osteoporosis in men: the value of laboratory testing. Osteoporos Int 2011;22:1845–53.
[9] Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995;332:767–73.
[10] Cawthon PM, Patel S, Ewing SK, Lui LY, Cauley JA, Lyons JG, et al. Bone loss at the hip and subsequent mortality in older men: the osteoporotic fractures in men (MrOS) study. JBMR Plus 2017;1:31–5.
[11] Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999;14:821–8.
[12] Jager PL, Jonkman S, Koolhaas W, Stiekema A, Wolffenbuttel BH, Slart RH. Combined vertebral fracture assessment and bone mineral density measurement: a new standard in the diagnosis of osteoporosis in academic populations. Osteoporos Int 2011;22:1059–68.
[13] Rea JA, Chen MB, Li J, Blake GM, Steiger P, Genant HK, et al. Morphometric X-ray absorptiometry and morphometric radiography of the spine: a comparison of prevalent vertebral deformity identification. J Bone Miner Res 2000;15:564–74.
[14] Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment

using a semiquantitative technique. J Bone Miner Res 1993;8:1137–48.
[15] Steiger P, Cummings SR, Genant HK, Weiss H. Morphometric X-ray absorptiometry of the spine: correlation in vivo with morphometric radiography. Study of Osteoporotic Fractures Research Group Osteoporos Int 1994;4:238–44.
[16] Chappard C, Kolta S, Fechtenbaum J, Dougados M, Roux C. Clinical evaluation of spine morphometric X-ray absorptiometry. Br J Rheumatol 1998;37:496–501.
[17] Barbosa AP, Mascarenhas M Rui, Silva CF, Távora I, Bicho M, do Carmo I, et al. Prevalence of silent vertebral fractures detected by vertebral fracture assessment in young Portuguese men with hyperthyroidism. Eur J Endocrinol 2015;172:189–94.
[18] Bousson V, Bergot C, Sutter B, Levitz P, Cortet B. Scientific Committee of the Groupe de Recherche et d'Information sur les Ostéoporoses. Trabecular bone score (TBS): available knowledge, clinical relevance, and future prospects. Osteoporos Int 2012;23:1489–501.
[19] Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res 2014;29:518–30.
[20] Leib E, Winzenrieth R, Aubry-Rozier B, Hans D. Vertebral microarchitecture and fragility fracture in men: a TBS study. Bone 2014;62:51–5.
[21] Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 international society for clinical Densitometry position development conference on bone densitometry. J Clin Densitom 2013;16:455–66.
[22] McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res 2016;31:940–8.
[23] Harvey NC, Gluer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice: a consensus report of a European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Working Group. Bone 2015;78:216–24.
[24] van de Ven AC, Erdtsieck RJ. Changes of bone mineral density, quantitative ultrasound parameters and markers of bone turnover during treatment of hyperthyroidism. Neth J Med 2008;66:428–32.
[25] Greenspan SL, Greenspan FS. The effect of thyroid hormone on skeletal integrity. Ann Intern Med 1999;130:750–8.
[26] El Hadidy el HM, Ghonaim M, El Gawad SSh, El Atta MA. Impact of severity, duration, and etiology of hyperthyroidism on bone turnover markers and bone mineral density in men. BMC Endocr Disord 2011;11:15.
[27] Kim BJ, Lee SH, Bae SJ, Kim HK, Choe JW, Kim HY, et al. The association between serum thyrotropin (TSH) levels and bone mineral density in healthy euthyroid men. Clin Endocrinol (Oxf) 2010;73:396–403.
[28] Svare A, Nilsen TI, Bjøro T, Forsmo S, Schei B, Langhammer A. Hyperthyroid levels of TSH correlate with low bone mineral density: the HUNT 2 study. Eur J Endocrinol 2009;161:779–86.
[29] van der Deure WM, Uitterlinden AG, Hofman A, Rivadeneira F, Pols HA, Peeters RP, et al. Effects of serum TSH and FT4 levels and the TSHR-Asp727Glu polymorphism on bone: the Rotterdam Study. Clin Endocrinol (Oxf) 2008;68:175–81.
[30] Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. Thyroid 2002;12:411–9.
[31] Lee JS, Buzková P, Fink HA, Vu J, Carbone L, Chen Z, et al. Subclinical thyroid dysfunction and incident hip fracture in older adults. Arch Intern Med 2010;170:1876–83.
[32] Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. BMJ 2011;342:d2238.
[33] Ock SY, Chung YS, Choi YJ. Changes in bone mineral density and trabecular bone score in Graves' disease patients after anti-thyroid therapy. Osteoporos Sarcopenia 2016;2:175–9.
[34] Garnero P, Vassy V, Bertholin A, Riou JP, Delmas PD. Markers of bone turnover in hyperthyroidism and the effects of treatment. J Clin Endocrinol Metab 1994;78:955–9.
[35] Harvey RD, McHardy KC, Reid IW, Paterson F, Bewsher PD, Duncan A, et al. Measurement of bone collagen degradation in hyperthyroidism and during thyroxine replacement therapy using pyridinium cross-links as specific urinary markers. J Clin Endocrinol Metab 1991;72:1189–94.