Prevalence of silent vertebral fractures detected by vertebral fracture assessment in young Portuguese men with hyperthyroidism

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Abstract

Background: Hyperthyroidism is a risk factor for reduced bone mineral density (BMD) and osteoporotic fractures. Vertebral fracture assessment (VFA) by dual-energy X-ray absorptiometry (DXA) is a radiological method of visualization of the spine, which enables patient comfort and reduced radiation exposure.

Objectives: This study was carried out to evaluate BMD and the prevalence of silent vertebral fractures in young men with hyperthyroidism.

Design: We conducted a cross-sectional study in a group of Portuguese men aged up to 50 years and matched in hyperthyroidism (n = 24) and control (n = 24) groups.

Materials and methods: A group of 48 Portuguese men aged up to 50 years was divided and matched in hyperthyroidism (n = 24) and control (n = 24) groups. BMD (g/cm²) at L₁–L₄, hip, radius 33%, and whole body as well as the total body masses (kg) were studied by DXA. VFA was used to detect fractures and those were classified by Genant’s semiquantitative method. No patient had previously been treated for hyperthyroidism, osteoporosis, or low bone mass. Adequate statistical tests were used.

Results: The mean age, height, and total fat mass were similar in both groups (P ≥ 0.05). The total lean body mass and the mean BMD at lumbar spine, hip, and whole body were significantly decreased in the hyperthyroidism group. In this group, there was also a trend for an increased prevalence of reduced BMD/osteoporosis and osteoporotic vertebral fractures.

Conclusions: The results obtained using VFA technology (confirmed by X-ray) suggest that the BMD changes in young men with nontreated hyperthyroidism may lead to the development of osteoporosis and vertebral fractures. This supports the pertinence of using VFA in the routine of osteoporosis assessment to detect silent fractures precociously and consider early treatment.
Introduction

Overt hyperthyroidism is a clinical condition caused by exaggerated levels of circulating thyroid hormones which causes relatively common complications to heart and bone especially in the elderly. Indeed, hyperthyroidism has been recognized as an important cause of secondary osteoporosis and a risk factor for hip fracture in women. Moreover, osteoporotic fractures are associated with a risk of precocious mortality, especially in the elderly (1).

In adult life, after acquiring peak bone mass, the excess of circulating thyroid hormones leads to an increase in bone resorption, by acting either directly on osteoclasts or indirectly on osteoblasts (2). Furthermore, thyrotropin (TSH) is a negative regulator of bone remodeling, inhibiting the formation and survival of osteoclasts and the differentiation of osteoblasts (3). Also, it has been proposed that low TSH levels, per se, can predispose to osteoporosis and fragility fractures (4, 5, 6). However, the studies investigating the effects of endogenous subclinical hyperthyroidism on the skeleton are scarce, with most of them reflecting the effect of supraphysiologic doses of thyroid hormone to suppress TSH secretion in the treatment of differentiated thyroid carcinoma or nontoxic goiter and providing conflicting results (7).

Vertebral fractures are among the most common in osteoporosis and are very frequently asymptomatic fractures. About 69% of patients with vertebral fractures are unaware of them, not only due to the absence of symptoms but also because of not being routinely or accurately imaged. Vertebral fractures occur more frequently in patients known to have low bone mass more than osteoporosis diagnosis by dual X-ray absorptiometry (DXA) (8). Their presence is important because of predicting the occurrence of future fragility fractures all over the skeleton (9).

Vertebral fracture assessment (VFA) by DXA is spine imaging with DXA scanners and 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 as DXA (10).

VFA presents some drawbacks such as the fact that it requires special training and is time consuming. Moreover, the visualization of levels higher than D7 may not be accurately visualized. However, globally, it is very useful in clinical practice and research for detection of prevalent fractures (11, 12, 13).

The aims of our study were to evaluate the effects of hyperthyroidism in bone mineral density (BMD) and in total body fat and lean masses and also the prevalence of silent vertebral fractures in a population of Portuguese men aged up to 50 years, using the VFA technology. This is a very important scientific issue because the clinical studies investigating these effects are relatively scarce, especially in men and in younger populations.

Subjects and methods

Forty-eight men aged up to 50 were divided and matched in the hyperthyroidism group (n = 24) and in the control group (n = 24). From 30 initial patients with hyperthyroidism, who were referred to the Endocrinology Department for diagnosis and treatment, only 24 were included in the study. Exclusion criteria for both patients and controls included hypo/hyperparathyroidism, hypogonadisms, diabetes mellitus, hypo/hypercortisolism, vitamin D deficiency, inflammatory bowel disease, malabsorption diseases, liver/renal diseases, and medications affecting the skeleton including l-thyroxin (T₄). For each patient, an age- (limits 6–11 months) and stature- (limits 1–3 cm) matched control person was drawn from a random sample of the general population.

Regarding the etiology of hyperthyroidism, 21 cases were due to Graves’ disease and in three cases due to toxic multinodular goiter.

No patient had previously been treated empirically for osteoporosis or reduced bone mass or hyperthyroidism. We cannot be sure of the duration of hyperthyroidism before the beginning of anti-thyroid 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 their BMI (kg/m²) was calculated.

In both groups, BMD (g/cm²) at the lumbar spine (L₁–L₄), at the hip (femoral neck and total), at the distal radius (1/3 or 33%) is a skeletal region at which cortical bone predominates, 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., Bedford, MA, USA) of the Lisbon Clinic of Endocrinology Diabetes and Metabolism, Lda.

According to International Society for Clinical Densitometry (ISCD) recommendations, in both groups BMD was qualified by the lowest Z-score obtained at the lumbar spine, at the hip, and at the distal radius (33%) in osteoporosis and in low and normal BMD (14).
The lateral images of thoracolumbar spine in DXA scan (VFA) were used to detect fractures and were classified according to the type (wedge, biconcave, and crush) and severity (% of deformity) by Genant’s semiquantitative method, by one endocrinologist. This method combines the qualitative visualization of the spine with the morphometric measurements of the vertebral body height in six points (11).

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 two radiologists. In a few instances where there was disagreement, a third radiologist was consulted. Conventional radiographs were electronic images produced by digital X-ray equipment, which 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 these positive cases were included.

Fasting blood samples and 24-h urine were collected for measurement of serum chemistries, blood counts, and thyroid hormones. The levels of serum free tri-iodothyronine (T3), free T4, and TSH were assayed by an electrochemiluminescence immunoassay (Roche) and total calcium and phosphorus were assayed by enzymatic colorimetry (Roche).

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

**Statistical analyses**

The data were statistically analyzed using the Statgraphics Centurion XVI version 16.1.07.01. All the results are expressed as mean ± s.d. After testing for normal distribution, the Student’s 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. A P value of <0.05 was considered statistically significant.

**Results**

The mean age and height were similar in both groups. BMI and mean lean mass were significantly decreased in the hyperthyroidism group. Also in this group, BMD was diminished at several skeletal sites (Table 1) while the prevalence of reduced BMD and osteoporosis as well as the prevalence of fractures was increased (Table 2). In the hyperthyroidism group, fractures were detected in nine cases by VFA but not by X-ray and in six cases by both techniques (in three cases there was no concordance).

In terms of the grade of fractures, only mild and moderate degrees were detected, while regarding the type of fractures only wedge and crush types were found in both groups. BMD qualification of the seven men with fractures was as follows: control group – normal in one; and hyperthyroidism group – reduced BMD in three, and osteoporosis in three (Table 3). The Z-scores of patients with fractures in the hyperthyroidism group are given in Table 4.

In the control group, fractures were localized in the lumbar spine, whereas in hyperthyroidism group 2 had been localized in lumbar spine and 4 in thoracic spine.

**Discussion**

In adults, the excessive levels of thyroid hormones in blood cause bone loss. Histomorphometric analyses revealed increased osteoclasts number and resorbing surfaces with loss of trabecular bone volume (15). Although both bone resorption and formation are increased, the existence of natural balance disappears leading to a bone resorption phase exceeding the bone formation phase and consequently to an incomplete substitution with new bone cells and loss of mineralized bone. Histology shows an increased porosity of cortical bone. Histology shows an increased porosity of cortical bone.

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**Table 1** Means (± s.d.) of the anthropometric data, lean and fat masses, BMD, biochemical parameters and thyroid function in hyperthyroidism and control groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=24)</th>
<th>Hyperthyroidism (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.9 (±8.3)</td>
<td>37.6 (±7.0)</td>
<td>0.4652</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.9 (±13.9)</td>
<td>76.9 (±13.9)</td>
<td>0.0524</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74 (±0.05)</td>
<td>1.75 (±0.06)</td>
<td>0.5424</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0 (±5.0)</td>
<td>24.9 (±3.8)</td>
<td>0.0198</td>
</tr>
<tr>
<td>Lean (kg)</td>
<td>60.5 (±6.2)</td>
<td>55.6 (±8.1)</td>
<td>0.0244</td>
</tr>
<tr>
<td>Fat (kg)</td>
<td>24.7 (±15.7)</td>
<td>18.6 (±6.7)</td>
<td>0.0885</td>
</tr>
<tr>
<td>BMD L1–L4 (g/cm²)</td>
<td>1.072 (±0.15)</td>
<td>0.988 (±0.11)</td>
<td>0.0367</td>
</tr>
<tr>
<td>BMD femoral neck (g/cm²)</td>
<td>0.964 (±0.16)</td>
<td>0.862 (±0.16)</td>
<td>0.0374</td>
</tr>
<tr>
<td>BMD total hip (g/cm²)</td>
<td>1.090 (±0.14)</td>
<td>0.979 (±0.14)</td>
<td>0.0096</td>
</tr>
<tr>
<td>BMD distal radius (33%) (g/cm²)</td>
<td>0.801 (±0.05)</td>
<td>0.781 (±0.06)</td>
<td>0.1494</td>
</tr>
<tr>
<td>BMD whole body (g/cm²)</td>
<td>1.277 (±0.13)</td>
<td>1.168 (±0.09)</td>
<td>0.0018</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>1.65 (±0.64)</td>
<td>0.01 (±0.01)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Free T3 (pg/ml)</td>
<td>3.61 (±0.49)</td>
<td>11.65 (±6.68)</td>
<td>0.0144</td>
</tr>
<tr>
<td>Free T4 (ng/dl)</td>
<td>1.16 (±0.15)</td>
<td>3.8 (±2.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.5 (±0.4)</td>
<td>3.6 (±0.9)</td>
<td>0.7244</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.2 (±1.1)</td>
<td>9.7 (±0.5)</td>
<td>0.1120</td>
</tr>
</tbody>
</table>
bone (16). This progressively leads to a reduced BMD and osteoporosis development, reduced bone strength and consequently to a higher osteoporotic fracture risk (17).

Clinical studies investigating the bone consequences of hyperthyroidism (both overt and subclinical), namely BMD and fragility fractures, are relatively scarce in the male population. The importance of our study is due to the fact that it was done in a population of men, aged up to 50, with noniatrogenic overt hyperthyroidism and we have found a significant decrease in BMD in all skeletal sites except the distal radius. The distal radius also called as 33% and 1/3 radius is a 1/3 radius measurement and is a skeletal region at which cortical bone predominates (about 95%) and can be used for the diagnosis of osteoporosis, mainly when hip and/or spine cannot be measured or interpreted, in hyperparathyroidism and in very obese patients (14).

The finding of reduced BMD in all skeletal sites except the distal radius could be explained by the small number of patients.

In studies not investigating specifically the male population, the negative effects of thyroid hormones on bone have been described in all skeletons (both axial and appendicular); however, the effects are more pronounced in areas consisting mainly of cortical bone such as the femoral neck and the distal radius (18, 19, 20).

A study reported by El Hadidy et al. (21) in a male population with hyperthyroidism at the age of 23–65 years shows that there was a significant decrease in BMD of the ‘lower half radius’, which was related with both severity and duration of the hyperthyroidism; nevertheless, no other skeletal regions were studied. In our patients with hyperthyroidism, all skeletal regions were studied and BMD was significantly lower in all of them, except at distal radius.

Also, in a male population studied for the etiology of osteoporosis, it was found that 5% of the patients had a previous history of hyperthyroidism (22).

Regarding the etiology of hyperthyroidism, our patients had Graves’ disease and toxic multinodular goiter. Despite the absence of studies in men, at least in females these etiologies do not seem to influence the impact on BMD, but there is an increase in the prevalence of osteoporosis (23, 24).

Another study evaluating BMD at both lumbar spine and femoral neck 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 (25).

Some studies, especially in women, suggest that reduced TSH alone, with normal free T3 and free T4 serum levels (the so-called subclinical hyperthyroidism), is associated with reduced BMD and even fractures. Even low-normal TSH levels can already be associated with low BMD and increased risk of osteoporosis in healthy postmenopausal women (4, 5, 26).

A meta-analysis by Heemstra et al. (27) suggested that men and premenopausal women with iatrogenic subclinical hyperthyroidism do not seem to have a higher risk of bone loss (decreased BMD), while postmenopausal women do.

The significant decreases observed in both total body lean mass and BMI in the hyperthyroidism group can be explained by weight loss and gastrointestinal changes (increased gut motility and consequent malabsorption of proteins, minerals, and vitamins) associated with hyperthyroidism. On the other hand, the weight reduction trend, which is associated with a low bone mass, could also contribute to the BMD decrease in the hyperthyroidism group, but it is not securely the only explanation for such a finding because we did not find significant differences in both weight and total body fat mass in both groups; however, there was a tendency for

### Table 2

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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control (n=24)</th>
<th>Hyperthyroidism (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD qualification n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>15 (62.5)</td>
<td>7 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Reduced BMD and osteoporosis</td>
<td>9 (37.5)</td>
<td>17 (70.8)</td>
<td>0.041</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>1 (4.2%)</td>
<td>6 (25%)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

### Table 3

Grade and type of vertebral fractures and BMD qualification in men with fractures in the control and hyperthyroidism groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fractures (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Moderate</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Type</td>
<td>Wedge</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Crush</td>
<td>0</td>
</tr>
<tr>
<td>BMD qualification (n)</td>
<td>1 – normal</td>
<td>3 – osteoporosis</td>
</tr>
</tbody>
</table>
smaller values of weight and total body fat in the hyperthyroidism group.

The Rotterdam study carried out 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 (28).

In the hyperthyroidism group, we found six vertebral fractures, from mild to moderate degrees, and patients had a BMD qualification of osteoporosis and reduced BMD. So, the decreases in both bone and total lean masses were probably the most important factors leading to the increase in fracture risk observed in this population.

Despite the absence of data about osteoporotic fractures risk in a specifically young male population in literature, some studies such as 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 and decreased to normal afterwards (29).

Several studies carried out in patients with iatrogenic hyperthyroidism showed that the risk for fracture was higher in older men and mainly in women with a very low TSH level (30, 31, 32). However, it is not totally clear that iatrogenic hyperthyroidism does affect bone in a totally similar way as hyperthyroidism due to toxic goiter or autoimmune diseases.

Vertebral fractures may not always be due to osteoporosis, even in the elderly. Jiang et al. (33) studied whether the failure load and BMD of cadaveric vertebral specimens that were induced to fracture by mechanical testing varied according to whether the fracture appearances on radiographs were classified as traumatic or as osteoporotic; they found that the failure load was proportional to BMD and traumatic fracture specimens had higher BMD.

Past history of traumatic and pathological fracture in hyperthyroidism group was absolutely excluded. Also, none of them had symptoms related to bone especially at vertebral spine. Moreover, a reliable differentiation by imagiology can often be achieved because a vertebral body weakened by osteoporosis or metastasis collapses differently than a normal vertebral body and such radiological semiotics are usually clear cut.

One possible limitation of our study was the difficulty of visualization of vertebral spine above D7 by VFA in some cases; however, to overcome that, all patients had thoraco-lumbar spine X-ray, which was reviewed by two radiologists and only the proven vertebral fractures were included.

The strength of our study was the fact it was carried out in a relatively young population of men and also because no patient had previously been treated for hyperthyroidism, osteoporosis, or low bone mass and already had vertebral fractures. However, future studies with bigger male populations and also evaluating the effects of anti-thyroid treatment will be important to better understand the bone disease of hyperthyroidism.

Conclusions

In this controlled study of young men with hyperthyroidism, we found a significant decrease in BMD as well as in total lean body mass. Also, there was a trend for an increased prevalence of osteoporosis and osteoporotic vertebral fractures in the hyperthyroidism group.

The results of this study using VFA technology (confirmed by X-ray) suggest that BMD changes in young men with nontreated hyperthyroidism may lead to the development of osteoporosis and fragility vertebral fractures. These data support the pertinence of using VFA in the routine assessment of osteoporosis to detect silent fractures precociously and consider early treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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