Osteoporosis in patients with subclinical hypothyroidism treated with thyroid hormone

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Summary

Objective: **to estimate the prevalence of osteoporosis in patients being treated with thyroid hormone.**
Method: **cross-sectional retrospective study of primary care patients.**
Experimental Group: **patients diagnosed with subclinical hypothyroidism receiving thyroid hormone replacement therapy.**
Control Group: **patients not receiving replacement therapy.**
Once the sample was selected its members were summoned to complete a clinical questionnaire and undergo a bone density scan with a validated measuring device.
The description of qualitative data was done in absolute frequencies and percentages and that of the quantitative data as mean standard deviation, median.
In the comparison of qualitative data between groups we used the Chi-square test and contingency tables by rearranging the percentages of several variables.
Results: **182 patients were studied (112 experimental and 70 control), diagnosed with subclinical hypothyroidism. The average age at diagnosis was 42.5 and 41.2 years, respectively. 32.7% and 33.2% were smokers. In the experimental group the coexistence of two or more cardiovascular risk factors was detected in 5.7% of the patients. Mean TSH was 6.67 mU/L, mean freeT_4 1,04 ng/dl.**
67% of the patients studied had some level of bone loss: 87% osteopenia and 14% osteoporosis. 56% of those suffering from bone less were women. With regard to the size of the thyroid hormone treatment, only 12% received 150 µg/day or more. 61% had received treatment for between 5 and 10 years and 19.5% for more than 10 years.
Conclusions: **there is a high prevalence of bone loss in patients with subclinical hypothyroidism treated with exogenous thyroxin.**

KEY WORDS: osteoporosis; hypothyroidism; hormones thyroids.

Introduction

Osteoporosis (OP) is a skeletal disease characterized by reduced bone strength which predisposes to an increased risk of fracture. Bone strength is primarily a function of bone density and quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and the amount of bone loss. Bone quality refers to macro- and micro-architecture, bone turnover, size, accumulated damage (e.g. microfractures) and mineralization (1-3).
The definition of osteoporosis (OP) by the World Health Organization (WHO) is densitometric and non-clinical and is based on the measurement of bone mass with the DEXA method in the spine or hip. It establishes four categories: normal, osteopenia, osteoporosis and established osteoporosis. The presence of pathological low bone mass, osteopenia or osteoporosis, is the best indicator of fracture risk for the region where the bone mass is measured, hence its interest, since bone loss is asymptomatic until it produces its natural consequence: the osteoporotic fracture (OF) (4-6).
OP is a health issue with important implications for individuals, families and the community. Untreated OP results in unnecessary pain, restriction of function (disability), decreased quality of life, altered body image with low self-esteem, increased mortality and serious economic consequences (7, 8).
In Spain it is estimated that osteoporosis causes 500,000 fractures a year and is responsible for 80,000 hospital stays. The annual incidence of hip fracture in patients over 50 ranges between 2 and 3 per 1000, with a male/female ratio of 2 or 3:5. These are the injuries with the most serious social and health consequence with acute phase mortality in hospitalized patients ranging from 5% to 8%, a figure that rises to between 20% and 30% in the first year. It is estimated that among survivors only a third return to their independent status prior to the fracture, while one third will require home care, and the remaining third will depend on a chronic care center (9-11).
Moreover, one in five women over the age of 50 has a spinal fracture and although some are asymptomatic and related mortality is low, some produce chronic pain, height loss, respiratory problems, constipation and abdominal pain, which limit the activity

and quality of life of patients who suffer these symptoms (12-14). The high prevalence and easy deployment of the available therapeutic arsenal and the characteristics of primary care (PC) relating to patient accessibility, early diagnosis and treatment compliance make PC the optimum stage of care for the prevention, diagnosis and care of the osteoporotic patient, a view confirmed by organizations as prestigious as the National Osteoporosis Foundation (NOF) (14). There exist criteria for referral for cases that require the patient to be referred to other levels of care. These criteria will be addressed in this paper.

Subclinical hypothyroidism is defined by experts as a condition of mild thyroid failure characterized by normal levels of T_3 and T_4 with moderately elevated serum TSH between 5 and 10 mU/L (15, 16). Increased access to serological tests for TSH have resulted in an increase in the number of patients with abnormal thyroid function, but not necessarily symptomatic. This has led to a series of disputes among experts regarding the management and diagnosis of these patients (17, 18) . Subclinical hypothyroidism is a common condition, especially in middle aged and older adults. Its reported prevalence is between 3.9 and 6.5% in foreign studies (19, 20) and 5.6% in Chile (21). It is twice as frequent among women as men and 3 times more frequent among white people (20). Various studies have shown that 30% of patients with subclinical hypothyroidism developed hypothyroidism within 10 years and only 4% of patients with subclinical hypothyroidism normalized their TSH values. Factors influencing the progress of hypothyroidism are levels of TSH and the presence of antimicrosomal antibodies (21). There are no studies showing a reduction in mortality in patients with subclinical hypothyroidism treated with thyroid hormone. With regard to the general symptoms of hypothyroidism, cohort studies have shown no significant difference in the presence of constipation, fatigue or lack of energy in patients with subclinical hypothyroidism and euthyroid patients (22).

Some authors have suggested that treatment with levothyroxine may cause long-term osteoporosis, but there is no evidence to support this theory, and studies have shown no difference in bone density or fracture risk in those patients treated (23). A century ago Von Recklinghausen described the bone condition thyrotoxicosis. Hyperthyroidism is one of the endocrine diseases classically associated with osteoporosis. The effect of hyperthyroidism on bone remodeling and metabolism has been thoroughly described. Mundy and his collaborators demonstrated in 1975 that T_4 and T_3 can directly stimulate bone resorption *in vitro*. In addition, the normal bone remodeling cycle is reduced from 200 to 113 days, mainly at the expense of the formation period with a failure to replenish the bone. Both the formation markers of bone resorption may be elevated (24, 25).

Patients with endogenous hyperthyroidism have reduced BMD compared with euthyroid controls. It has been shown that the treatment produced a significant increase in trabecular BMD (26).

Exogenous administration of suppressive doses of thyroxin may have a negative effect on BMD. Diamond and his collaborators found a decrease in femoral neck BMD in pre-and post-menopausal women with thyroid carcinoma treated with suppressive doses of thyroxin; the reduction in lumbar spine BMD was significant only in post-menopausal women. Other controlled studies show no changes in BMD with suppressive therapy (27).

For all these reasons we decided to estimate the prevalence of osteoporosis in patients treated with thyroid hormone, considering such factors as the dose of thyroxin and thyrotropin levels, as well as the treatment time.

Method

This is a retrospective cross-sectional study of primary care patients.

Patients: a sample of 112 patients was drawn up, collected randomly and consecutively with an assumed confidence rate of 95%. The prerequisites for belonging to the sample were to be over 14 and have a TSH level of 4.5 mU/L and free T_4 levels in the normal range (0.8-1.2 ng/dl) and to be being treated with thyroid hormone replacement for the experimental group and not to be receiving such treatment for the control group.

Experimental group: patients diagnosed with subclinical hypothyroidism receiving thyroid hormone replacement therapy in the period June 2005 to January 2006. Control Group: patients with subclinical hypothyroidism not receiving replacement therapy. In all cases the following variables were analyzed: anthropometric, family and personal history, CBC and biochemical analysis, thyroid hormones, being diagnosed with subclinical hypothyroidism and receiving thyroid hormone replacement therapy. Once the sample was selected its members were summoned to complete a clinical questionnaire and undergo a bone density scan with a validated measuring device.

The description of qualitative data was done in absolute frequencies and percentages and the quantitative data as mean standard deviation, median, minimum and maximum.

In the comparison of qualitative data between groups we used the Chi-square test and contingency tables by rearranging the percentages of several variables (TSH, total cholesterol, HDL-C, LDL-c).

Results

182 patients were studied (112 experimental and 70 control), all diagnosed with subclinical hypothyroidism in the age range between 14 and 65 inclusive (Table 1).

As has already been mentioned, if it is estimated that there were 1040 consultations in this period it suggests that there would be an incidence of about 5% of new cases over a period of 6 months. Patients presented with the following symptoms, which eventually led to diagnosis:

- ► Weight change (3.8%)
- ► Gynecological reasons (11.5%)
- ► Symptoms of depression (5.8%)
- ► Alopecia (5.8%)
- ► Musculoskeletal pains (11.5%)
- ► Non-specific fatigue-dizziness (30.8%)

Among the subjects studied 32.7% of the experimental group and 33.2% of the control group were smokers.

Table 1 - General data.

Variables	Experimental	Control
Age	42.5	41.2
Sex	88.5% women	81.5% women
Smokers	32.7%	33.2%
No cardiovascular risk factors	81.2%	80.3%
Diabetes	2.8%	2.5%
Hypertension	5.7%	5.1%
Variables	experimental	control
Lipid disorders	1.9%	1.5%
Body Mass Index	25.67	24.76
Systolic arterial pressure	119.75	115
Dystolic arterial pressure	71.86	70.5
Glycemia	87.71	90
Total cholesterol	193.92	195
TSH	6.67	5.95
T4	1.09	0.98
CVR score	<5%	<5%

The association obtained between sex and TSH is close to being statistically significant in both groups with p= 0.08. For this reason we may assume that sex is a variable which may be dependent on TSH. In fact, when we look at the data obtained we can see that TSH is not distributed equally between the sexes but rather is predominant among women, regardless of the TSH range with which we are concerned. It remains the case, however, that 88.5% of the participants in the study were women.
With regard to the association between TSH and age a result close to statistical significance was obtained; p = 0,005 (p < 0,05). We may thus assume that TSH is a variable dependent on age. It must be remembered, however, that the subjects of this study were relatively young, with an average age of 42.4 years.
No statistically significant associations were found between TSH and the Body Mass Index (BMI), and the majority of patients had a normal BMI (up to 25), independently of the TSH values found.
With regard to the association between TSH and cholesterol (estimated for two ranges, one to 220 mg/dl and another >20 mg/dl) a figure close to statistical significance was found in both groups; p = 0.056.
It should be pointed out that a relationship close to statistical significance, p = 0.08, was found between high TSH and a raised level of LDL and triglycerides.
With regard to the association between TSH and fasting glucose, a predominance of unaltered fasting glucoses (up to 110) was found, regardless of the TSH range and there was no statistically significant relationship found.
A statistically significant relationship was found between TSH and mean free T_4: p=0.04 (p>0.05), thus verifying feedback mechanism that regulates thyroid physiology.
Regarding diastolic blood pressure levels; it was found to be less than 90mmHg in most patient ranges with their being a statistically significant relationship between altered TSH and normal diastolic blood pressure levels (p<0.05). A similar result was produced in the case of systolic blood pressure with the bulk of patients having a lower level than 140 mmHg, compared with those with higher values.
With regard to bone parameters it can be seen that there is a clearly significant difference in the experimental group both in terms of degree of bone mass loss, significantly related to sex (p>0.05), and years of treatment for hypothyroidism (p>0.039) and in terms of osteopenia and osteoporosis. Nevertheless there is no relationship with the dose of thyroid hormone being taken nor with levels of TSH or T_4 (Table 2).
A statistically significant relationship was observed between bone mass grade and Z score which suggests that the latter is a good variable to use for diagnosis (Table 3).

Table 2 - Treatment data.

Variables	Experimental	Control
Dose	72% 100 µg or more	0
Years of treatment	61,1% 5-10 years	0

Table 3 - Bone metabolims data.

Variables	Experimental	Control	
Bone mass loss	67%	35%	p: 0.002
Osteopenia	86%	54%	p: 0.001
Osteoporosis	14%	5%	p: 0.001

Discussion

Subclinical hypothyroidism is defined by experts as a condition of mild thyroid failure characterized by normal levels of T_3 and T_4 with moderately elevated serum TSH of between 5 and 10 mU/L (1-4).
Analyzing the results we can see that the “symptoms” of this condition include weight changes, various gynecological issues (changes in the duration and amount of the cycle, infertility), depressive symptoms, alopecia, musculoskeletal pain and nonspecific fatigue and dizziness. These are the reasons for which patients present themselves and which lead to a request for TSH to be measured.
The prevalence of subclinical hypothyroidism in our 5%, is consistent with other studies (5-11).
Although at an appropriate dose thyroxin is a very safe medicine, before treatment begins a number of possible side effects must be considered including restoration of euthyroidism, the exacerbation of ischemic heart disease and the production of acute adrenal insufficiency. Care must be taken to get the dose right, since an excess can lead to decreased bone mineral density, the onset of atrial arrhythmias and the precipitation of angina pectoris. Although there have been no descriptions of such complications arising, patients with coronary artery disease should initially receive a lower dose of levothyroxine, usually 12.5 to 25 µg per day, with this does being reassessed in 4 to 6 weeks depending on successive determinations of TSH and the clinical assessment. This is not the case with elevated TSH and normal T_4 as the adverse effects of thyroxin outweigh the benefits in patients with subclinical hypothyroidism scheduled for urgent or semi-elective surgery or invasive methods. Such procedures should not be delayed because there is no evidence of increased risk of complications or mortality, even in cases of established hypothyroidism (12-14).
The relationship between bone mass and thyroid functional status is an issue of utmost importance and currently controversial. Thyroid hormones are essential for growth and development during childhood and for the maintenance of bone in adulthood. In children with hypothyroidism one sees stunted growth with epiphyseal dysgenesis and delayed skeletal maturation while in adults the phases of bone renewal are prolonged with reduced osteoblast activity and increased cortical bone thickness. However, the most pronounced effects of thyroid hormones on bone in adults are seen in hyperthyroidism. Hyperthyroidism is a common pathology, with a prevalence of 2% in women and 0.2% in men. Despite treatment, in the long term, the mortality rate increases in this latter population to 2.9% as a result of the aftermath of femoral neck fractures (20). In a review of the impact of hyperthyroidism on bone, it was noted that 8% of patients had symptomatic bone disease, all women, mostly postmenopausal, of whom 65% had severe bone pain or evidence of fractures and up to 75% had been thyrotoxic for less than 1 year (28-32).
The pathogenic mechanism affecting the bone in hyperthyroidism is based on the increase both in the number and turnover rate of bone turnover units and thus an increase in osteoclast and osteoblast activity, with remodeling cycle time reduced by 50% and increased frequency of activation of units. These changes lead to an uncoupling between resorption and formation, with the net result of loss of mineralized bone in varying amounts depending on factors such as sex, menstrual function, thyroid disease severity and sum of other risk factors for osteoporosis (31-34).
At present there is little doubt about the deleterious effect of hyperthyroidism on bone, but controversy persists in two situations we will discuss in more detail because of their frequency and clinical implications: subclinical hyperthyroidism and chronic treatment with thyroid hormones.
Technical improvements have allowed more and more sensitive measurements of the levels of the hormone thyrotropin (TSH), which are a reliable indicator of the tissue activity of the thyroid hor-

mone (TH), so that if its levels are suppressed, even with HT still remain within normal limits, we can say that there exists a degree of tissue hyperthyroidism, a clinical condition known as subclinical hyperthyroidism, with a prevalence of 1%, progressing to frank hyperthyroidism in approximately 5% of cases each year. Given that the loss of bone mass resulting from hyperthyroidism, is only partially reversible, it seems logical that we should treat this condition situation as soon as possible, if it is shown that it is altering the bone metabolism. The controversy persists because early work showed that there was an increase of bone turnover in subclinical hyperthyroidism, but a recent study, which examined the correlations of TSH with bone mineral density during follow-up periods of 4 to 6 years, failed to demonstrate any difference between the groups with suppressed, normal or high TSH (31-34). However, in another study it has been confirmed that patients treated to maintain the euthyroid preserved bone density in the spine and hip, compared to untreated patients who suffered a 2% annual decline (19). Despite the controversy, the most prevalent trend today is to treat subclinical hyperthyroidism early, not only due to its potential impact on the bone, but also because of the cardiovascular risks it brings with it, such as the increased incidence of atrial fibrillation arrhythmias (24, 25).

Chronic treatment with thyroid hormones and its relationship to osteoporosis, the objective of this study, is one of the areas in which most work has been done in recent years. Here we must focus on two clearly different therapeutic objectives: suppressive treatment with thyroid hormones (with the objective of suppressing TSH levels, for example the treatment used after surgery and radioiodine in differentiated thyroid carcinomas) and replacement therapy (with the goal of normalizing TSH levels, such as that used in the primary autoimmune hypothyroidism). With suppressive therapy the patient is maintained in a state of subclinical hyperthyroidism, showing in most studies an increased bone turnover. A recent meta-analysis which included 1,250 patients from 41 studies, stratifying patients according to sex, menopausal status, dose of HT and anatomical site in which densitometry was carried out, and excluding those who had previous hyperthyroidism, concluded that suppressive treatment caused a significant loss of bone mass in the lumbar spine and hip in postmenopausal women only, with a more pronounced effect in the cortical bone. The loss was less than 1 standard deviation on average: 7% in lumbar spine, 5% in femoral neck, 9% in Ward's triangle and 7% in the distal portion of the radius (29). These results should be regarded with caution and confirmed with controlled studies to look at both bone density and the incidence of fractures.

In the case of HT replacement therapy no deleterious effect on bone has been shown, so it is necessary to properly monitor TSH levels during the long-term suppression of TSH only in those cases where it is absolutely necessary (high risk follicular thyroid carcinomas) and decide on the balance between the risks and benefits of treatment of thyroid nodular disease with suppressive doses of l-T (4,12,14). Exogenous administration of suppressive doses of thyroxine may have a negative effect on BMD. Diamond and colleagues found a decrease in femoral neck BMD in pre-and postmenopausal women with thyroid carcinoma treated with suppressive doses of thyroxin, reduction in lumbar spine BMD was significant only in postmenopausal women. Exogenous administration of suppressive doses of thyroxin may have a negative effect on BMD. Diamond and his collaborators found a decrease in femoral neck BMD in pre- and postmenopausal women with thyroid carcinoma treated with suppressive doses of thyroxin, the reduction in lumbar spine BMD was significant only in postmenopausal women (34).

Other controlled studies show no changes in BMD with suppressive therapy. Such factors as the dose of thyroxine and level of thyrotropin should be considered when it comes to analyzing these studies with conflicting results, while also taking into account issues related to the research design (1-3).

In our study we observed a high prevalence of bone loss in patients treated with thyroxin, which although not related to the dose they are taking was related to the number of years for which they had been taking it. This clearly leads to the decision that we must be cautious in starting treatment and although subclinical hypothyroidism occurs in young people they should only be treated when it is really necessary to do so.

Currently, no clinical practice guidelines recommend the use of treatments for osteoporosis in patients initiating treatment with exogenous thyroxin, but considering the results of this present study consideration should at least be given to periodic BMD studies to establish the earliest possible treatment.

In the light of all this there is a need for deeper study of subclinical hypothyroidism in future later studies, to determine its relationship with other conditions and to determine whether patients would benefit from early treatment, not only in the field of cardiovascular risk, but other areas, such as the prevention of osteoporosis or possible mood disorders.

Given its association with lipid abnormalities, it would be interesting to more accurately determine a possible association with the likelihood of suffering a cardiovascular event and try to check over the long term if the starting of treatment decreases the incidence of such events by comparison with a control population and if it does to establish it as prevention measure.

To treat or not to treat

At the end of the first decade of the third millennium, the controversy continues over the need to treat mild hypothyroidism, known as subclinical hypothyroidism (SCH). Those who treat with substitution therapy claim that it can deal with some symptoms that may be due to thyroid failure, prevent the condition advancing to overt hyperthyroidism and produce cardiovascular benefits. Although theoretically treatment may prevent progression to overt hypothyroidism, improve lipid profile (and hence cardiovascular mortality) and improve symptoms, no studies of sufficient quality to prove this exists.

Once the diagnosis is made an individual evaluation of the patient must be made. A reasonable framework for action is the following:

Substitution treatment is indicated for:

- Depression. Especially severe depression or depression that resists treatment.
- Pregnancy. Due to the adverse effects of hypothyroidism on fetal neurodevelopment, survival of the fetus and its association with toxemia and gestational hypertension.
- Children. So as not to interfere with their growth and development.
- Hyperthyroidism with certain causes: auto-immune, post-I_{131}, post external radiotherapy, post partial thyroidectomy.
  - TSH >10 mU/l.
- Goiter.
- Symptoms (fatigue or cognitive deficits) or dyslipidemia. Perform test treatment for 3-6 months.

Doubts exist about the benefits of treatment in cases of:

- Ischemic heart disease. For some authors, the doses used are not contraindicated.
- Arrhythmias.
- Osteoporosis.
- Patients over 60 years, especially those over 85 years, in which subclinical hypothyroidism are associated with longevity.

Some authors (31-34) have suggested that treatment with levothyroxine may cause long-term osteoporosis, but there is no evidence to support this theory, and studies have shown no difference in bone density or fracture risk in patients undergoing treatment. In our study we were able to see that there is a significant loss of

bone mass a loss which increases with age, which leads us to reflect that it seems replacement therapy is necessary but it must start when hypothyroidism is confirmed and once it has begun both the thyroid hormone and the loss of bone mass must be monitored, so treatment impede bone loss can be begun if necessary. Therefore, the multiplicity and the possible improvement of subclinical hypothyroidism associated with cardiovascular abnormalities suggest that the decision to treat a patient should depend on the presence of risk factors, rather than a threshold related to the determination of TSH.

Furthermore, replacement therapy with levothyroxine may be suspended if there is no clear benefit and is generally safe as long as excessive administration is avoided. This can be monitored by serum levels of TSH.

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