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# Osteoporosis in Patients with Subclinical Hypothyroidism Treated with Thyroid Hormone Replacement

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***Abstract*. 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: 112 patients diagnosed with subclinical hypothyroidism receiving thyroid hormone replacement therapy. Control Group: 70 subclinical hypothyroid patients not receiving thyroid replacement therapy. Once the sample was selected its members completed a clinical questionnaire and underwent a bone density scan with a validated measuring device. **Results**: Among the 182 patients studied, respectively, the experimental groups' mean age at diagnosis was 42.5 and the control patients' was 41.2 years; 32.7% were smokers as opposed to 33.2%; the coexistence of two or more cardiovascular risk factors were detected in 5.7% of experimental patients as opposed to ?% of control patients; mean TSH was 6.67 mU/L and mean free T4 was 1.04 ng/dL, compared to 5.95 mU/L and 0.98 ng/dL. The experimental and control groups significantly differed in percentage of reduced bone mineral density: respectively, 67% vs 35% lost bone mass, 86% vs 54% osteopenia, and 14% vas 5% osteoporosis. Fifty-six percentage of patients with bone loss were women. Control patients use no thyroid therapy for any time; in contrast, 72% of experimental patients used 100 or more mcg of $T_4$ and 12% use 150 mcg/day or more. Duration of $T_4$ treatment was 1-to-10 years for 61.1% of the patients and 10 years or more for 19.5%. **Conclusions**: The data used in this study indicate a high prevalence of bone loss in patients with subclinical hypothyroidism treated with exogenous thyroxine.

**Keywords** • Bone mass loss • Osteopenia • Osteoporosis • Subclinical hypothyroidism • Thyroxine replacement

## Introduction

Osteoporosis 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.[10-15]

The definition of osteoporosis 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.

Osteoporosis is a health issue with important implications for individuals, families, and the community. Untreated Osteoporosis 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.[10-16]

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 years of age ranges between 2 and 3 per 1000, with a male/female ratio of 0:2 or 3:5. These are the injuries with the most serious social and health consequence. Acute phase mortality in hospitalized patients ranges 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. One third will require home care, and the remaining third will depend on chronic care centers.[12-18]

Moreover, 1-to-5 five women over the age of 50 have a spinal fracture. Some fractures are asymptomatic and related mortality is low, but some fractures produce chronic pain, height loss, respiratory problems, constipation, and abdominal pain. These symptoms limit the activity and quality of life of the patients.[12-21]

Primary care is the optimum mode of care for the prevention, diagnosis, and care of the osteoporotic patient. This view has been confirmed by organizations as prestigious as the National Osteoporosis Foundation.[16] Primary care is optimum for several reasons: the high prevalence and easy deployment of the available therapeutic arsenal and the characteristics of primary care relating to patient accessibility, and early diagnosis and treatment compliance. There exists, of course, criteria for referral of cases that require the patient to have other levels of care. These criteria will be addressed in this paper.

The generally-accepted definition of subclinical hypothyroidism is a condition of mild thyroid failure characterized by reference range levels of $T_3$ and $T_4$ and moderately elevated serum TSH. Although what constitutes an elevated TSH level is debated and varies from country-to-country, the upper limit of the TSH range we used in this study is between 5 and 10 mU/L.[1,2]

Increased access to serological tests for TSH have resulted in an increase in the number of patients as having abnormal thyroid function, although some patients are free from symptoms of the abnormality. This has led to a series of disputes among experts regarding the management and diagnosis of these patients.[3]

Subclinical hypothyroidism is a common condition, especially in middle aged and older adults. Its reported prevalence is between 3.9% and 6.5% in studies conducted in the United States[4,5] and 5.6% in Chile.[6] It is twice as frequent among women as men and three times more frequent among white people.[6]

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 that influence the progress of hypothyroidism are levels of TSH and the presence of antimicrosomal (thyroperoxidase) antibodies.[7] No studies we are aware of have shown a reduction in mortality among patients with subclinical hypothyroidism who were 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 euthyroid patients and subclinical hypothyroid patients.[9]

Some authors have suggested that treatment of subclinical hypothyroidism with levothyroxine (thyroxine or $T_4$) may cause long-term osteoporosis. However, there is no evidence to support this theory, and studies have shown no difference in bone density or fracture risk in treated patients.[18,19]

A century ago, Von Recklinghausen described the thyrotoxicosis of bone due to hyperthyroidism. Hyperthyroidism is one of the endocrine diseases classically associated with osteoporosis.[36] The effect of hyperthyroidism on bone remodeling and metabolism has been thoroughly described. Mundy and his collaborators[37] found in 1977 that $T_4$ and $T_3$ can directly stimulate bone resorption *in vitro*. In addition, the normal bone remodeling cycle was reduced from 200 to 113 days. The remodeling was mainly at the expense of the formation period with a failure to replenish sufficient bone. Both formation markers of bone resorption may be elevated.

Patients with endogenous hyperthyroidism have reduced bone mineral density compared with euthyroid controls. It has been shown that treatment with exogenous thyroid hormone produced a significant increase in trabecular bone mineral density.[15]

Exogenous administration of suppressive doses

of thyroxine may have a negative effect on bone mineral density. Diamond et al. found a decrease in femoral neck bone mineral density in pre- and post-menopausal women with thyroid carcinoma treated with suppressive doses of thyroxine; the reduction in lumbar spine bone mineral density was significant only in post-menopausal women.[5,8] Other controlled studies show no changes in bone mineral density with suppressive therapy.[15,19]

Based on the studies we described above, we decided to estimate the prevalence of osteoporosis in patients treated with thyroid hormone, considering such factors as doses of thyroxine and TSH levels. We also considered the time length of treatment.

## Methods

This study was a retrospective cross-sectional evaluation of primary care patients. Patients were collected randomly and consecutively with an assumed confidence rate of 95%. The study sample consisted of a total 182 patients, 112 in the experimental group and 70 in the control group. The range was 14 to 65 years. All patients had to meet the laboratory criteria for subclinical hypothyroidism: They had to have a TSH level of at least 4.5 mU/mL and a free $T_4$ level within the reference range (0.8-1.2 ng/dL). Patients who were being treated with thyroxine replacement from June 2005 to January 2006 were included in the experimental group, and those who had not been treated with thyroid hormone were included in the control group.

Patients were analyzed for anthropometric variables, family and personal history, CBC, biochemistry, thyroid status, and treatment or non-treatment with thyroid hormone. Once the patient sample was selected, its members were summoned to complete a clinical questionnaire and undergo a bone density scan with a validated measuring device.

Of the 182 patients included, respectively, the experimental groups' mean age at diagnosis was 42.5 and the control patients' was 41.2 years. Among the experimental patients, 32.7% were smokers; 33.2% of control patients were smokers. Experimental and control patients had the coexistence of two or more cardiovascular risk factors. The mean TSH of experimental patients was 6.67 mU/L, and that of control patient was 5.95 mU/L. The mean free $T_4$ of experimental patients was 1.04 ng/dL and that of control patients was 0.98 ng/dL.

**Statical Analysis**. The description of qualitative data was done in absolute frequencies and percentages, and the quantitative data as means, standard deviations, median, minimum, and maximum.

**Table 1.** General Data

| Variables | Experimental | Control |
|---|---|---|
| Age | 42.5 | 41.2 |
| Sex | 88.5% women | 81.5% women |
| Smokers | 32.70% | 33.20% |
| No cardiovascular risk factors | 81.20% | 80.30% |
| Diabetes | 2.80% | 2.50% |
| Hypertension | 5.70% | 5.10% |
| Variables | experimental | control |
| Lipid disorders | 1.90% | 1.50% |
| Variables | experimental | control |
| 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 |
| $T_4$ | 1.09 | 0.98 |
| CVR score | < 5% | < 5% |

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

The experimental and control groups significantly differed in their mean percentages of reduced bone mineral density: respectively, lost bone mass (67% vs 35%), osteopenia (86% vs 54%), and osteoporosis (14% vs 5%). Among those with bone loss, 56% were women.

Control patients used no thyroid hormone therapy for any time; in contrast, 72% of experimental patients used 100 mcg/day or more mcg of $T_4$ and 12% used 150 mcg/day or more. Duration of the use of $T_4$ therapy was 1-to-10 years for 61.1% of the patients and 10 years or more for 19.5%.

**Table 2.** Treatment data.

| Variables | Experimental | Control |
|---|---|---|
| Dose | 72% 100 mg or more | 0 |
| Years of treatment | 61.1% = 5-to-10 | 0 |

No statistically significant associations were found between TSH and the body mass index (BMI). The majority of patients had a normal BMIs (up to 25), independently of their TSH values.

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.

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, statistical significance was obtained ($p = 0.005$). 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.

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 glucose (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 $T_4$ ($p = 0.04$), thus verifying feedback mechanism that regulates thyroid physiology.

**Table 3.** Bone metabolism data.

| Variables | Experimental | Control | *p* value |
|---|---|---|---|
| Bone mass loss | 67% | 35% | $p = 0.002$ |
| Osteopenia | 86% | 54% | $p = 0.001$ |
| Osteoporosis | 14% | 5% | $p = 0.001$ |

Regarding diastolic blood pressure levels; it was found to be less than 90 mm Hg 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 mm Hg, compared with those with higher values.

In regard to osteopenia and osteoporosis, there was 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 ($p < 0.039$). Nevertheless, we found no significant relationship between the dose of thyroid hormone being taken and the levels of TSH or $T_4$.

A statistically significant relationship was observed between bone mass grade and Z score. This suggests that the latter is a good variable to use for diagnosis.

## Discussion

Subclinical hypothyroidism is defined by experts as a condition of mild thyroid failure. The failure is characterized by $T_3$ and $T_4$ within their respective reference ranges, with moderately elevated serum TSH, such as 5-to-10 mU/L.[11,15]

In the US, in 2002, the American Academy of Clinical Biochemistry lowered the preferred upper end of the TSH to 2.5; in 2003, the American Association of Clinical Endocrinology lowered the upper limit to 3.03. Because the upper level of the reference range various in different countries, may be add to the end of the last sentence of your paragraph above the following? "The failure is characterized by reference range of $T_3$ and $T_4$ with moderately elevated serum TSH of between 5 and 10 mU/L,[11,15] although in other countries, the upper limit of the TSH reference range is lower.[35]

In analyzing our results, we see that among out study patients, "symptoms" of subclinical hypothyroidism may include weight changes, various gynecological issues (infertility and changes in the duration and amount of the cycle), depression, alopecia, musculoskeletal pain, nonspecific fatigue, and dizziness. Such symptoms provided the motivation for patients to present to our health centre requesting that we measure their TSH levels.

The prevalence of subclinical hypothyroidism among patients in our health zone is 5%. This percentage is consistent with the incidence reported in other studies.

At an appropriate dose, levothyroxine is a safe medicine and can restore euthyroidism. However, before treatment begins, a number of possible side effects must be considered. These include exacerbation of ischemic heart disease and production of acute adrenal insufficiency. Care must be taken to determine the appropriate dose for the individual patient, as an excess of levothyroxine may lead to decreased bone mineral density, the onset of atrial arrhythmias, and the precipitation of angina pectoris. No descriptions of such complications have arisen. However, for precautionary purposes, patients with coronary artery disease should initially receive a lower dose of levothyroxine, usually 12.5-to-25 mg per day. This dose should be reassessed in 4-to-6 weeks, depending on both successive clinical assessments and determinations of TSH.

For patients with subclinical hypothyroidism (elevated TSH and in-range $T_4$) who have coronary artery disease, urgent or semi-elective surgery or invasive methods should not be delayed. The reason is that there is no evidence of increased risk of complications or mortality, even in cases of established hypothyroidism.[16-18]

The relationship between bone mass and thyroid functional status is an issue of utmost importance and current controversy. Thyroid hormones are essential for growth and development during childhood and for the maintenance of bone in adulthood. In hypothyroid children, physicians are likely to stunted growth with epiphyseal dysgenesis and delayed skeletal maturation. In adults, the phases of bone renewal are prolonged with reduced osteoblast activity and increased cortical bone thickness.[38]

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 the female 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 of these patients were women and most were postmenopausal. Of these patients, 65% had severe bone pain or evidence of fractures, and up to 75% had been thyrotoxic for less than 1 year.[18,31]

The pathogenic mechanism that affects bone in hyperthyroidism is the increase both in the number and rate of bone turnover units. Thus, there is an increase in osteoclast and osteoblast activity. This reduces the remodeling cycle time by 50% and increases the frequency of activation of turnover units. These changes lead to an uncoupling between resorption and formation. The net result of the uncoupling is a loss of mineralized bone in varying amounts depending on factors such as sex, menstrual function, thyroid disease severity, and the sum of other risk factors for osteoporosis.[31-35]

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 hormone.

Technical improvements have allowed progressively more sensitive measurements of the levels of TSH. Arguably, the TSH level is a reliable indicator of the tissue activity of the thyroid hormone. If so, and TSH levels are suppressed, even with thyroid hormone levels within their reference ranges, we can say that

there exists a degree of tissue hyperthyroidism, a clinical condition known as subclinical hyperthyroidism. The condition has a prevalence of 1%, progressing to frank hyperthyroidism in approximately 5% of cases each year.

The loss of bone mass resulting from hyperthyroidism is only partially reversible.[32] Because of this, it seems logical that we should treat the condition as soon as possible, if it is shown that the condition is altering the bone metabolism. The controversy persists because early work showed that there was an increase of bone turnover in subclinical hyperthyroidism. In a recent study, however, tests run for correlations between TSH and bone mineral density were performed during follow-up periods of 4 to 6 years. These tests failed to demonstrate any difference between the groups with suppressed, normal, or high TSH levels.[31-35] In another study, patients who were treated to maintain euthyroidism had preserved bone density in the spine and hip, whereas untreated patients suffered a 2% annual decline in bone density.[35]

Despite the controversy, the most prevalent trend today is to treat subclinical hyperthyroidism early. Early treatment is warranted due to the possible potential impact of subclinical hyperthyroidism on bone, but also because of the cardiovascular risks it brings, such as an increased incidence of atrial fibrillation arrhythmias.[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, in the treatment after surgery and radioiodine in differentiated thyroid carcinomas) and replacement therapy (with the goal of maintaining in-range TSH levels, used in 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 included 1,250 patients from 41 studies. Study patients were stratified according to sex, menopausal status, dose of thyroid hormone, and anatomical sites in which densitometry was carried out, and exclusion of 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 an 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.

It has been shown that replacement therapy for Hashimoto's thyroiditis has no deleterious effects on bone. However, during long-term TSH-suppressive therapy, it is necessary to properly monitor TSH levels when it is absolutely necessary, as in high risk follicular thyroid carcinomas. The risks and benefits should be carefully considered in patients treated with suppressive doses of thyroxine therapy for thyroid nodular disease.[34,35] Exogenous administration of suppressive doses of thyroxine may have a negative effect on bone mineral density. Diamond and colleagues found a decrease in femoral neck bone mineral density in pre-and postmenopausal women with thyroid carcinoma treated with suppressive doses of thyroxine. However, reduction in lumbar spine bone mineral density was statistically significant only in postmenopausal women.[35]

Other controlled studies show no significant changes in bone mineral density with suppressive therapy. Such factors as the dose of thyroxine and level of TSH should be considered in analyzing these studies with conflicting results, while also taking into account issues related to the research design.[11,15]

In our study we observed a high prevalence of bone loss in patients treated with thyroxine. The bone loss was not related to the number of years the patients had been taking the hormone. This clearly leads to the decision that we must be cautious in starting treatment of a particular patient. Although subclinical hypothyroidism occurs in young people, we believe they should be treated only when it is necessary to do so.

Currently, no clinical practice guidelines recommend the use of exogenous thyroid hormone as a treatment for osteoporosis. In view of the results of the present study, consideration should be given to periodic bone mineral density testing to determine safe dosage levels for subclinical hypothyroid patients.

In the light of the widely variable study results we have cited, there is obviously a future need for more extensive study of subclinical hypothyroidism. Further studies are needed to determine the relationships of subclinical hypothyroidism to with other conditions. The studies are also important to determine whether patients would benefit from early treatment, not only in related to cardiovascular risk, but also to the prevention of osteoporosis and mood

disorders.

Given the association of subclinical hypothyroidism with lipid abnormalities, other research considerations are also important. We need to more accurately assess the likelihood of an association with the probability of cardiovascular events. It may be, for example, that starting thyroid hormone therapy decreases the incidence of such events compared to untreated patients. If early treatment turns out to decrease the incidents of such events, it may eventually be established as a standard preventive 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. 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 a patient's 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 of certain causes, including autoimmunity, post-$I^{131}$, post external radiotherapy, and post partial thyroidectomy.
- TSH > 10 mU/L.
- Goiter
- Symptoms, such as fatigue or cognitive deficits, and test results such as dyslipidemia, with testing performed 3-to-6 months.

Doubts exist about the benefits of treatment in cases of:

- Ischemic heart disease, although 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[25-34] have suggested that treatment with levothyroxine may cause long-term osteoporosis, but there is no evidence to support this theory. Moreover, studies have shown no reduction in bone density or increased fracture risk in patients undergoing treatment.

In our study we saw that there a significant loss of bone mass that occurred with age. This leads us to four probable conclusions: (1) replacement therapy seems necessary, but (2) must start when hypothyroidism is confirmed, and (3) once treatment has begun, both the thyroid hormone and the loss of bone mass must be monitored so that treatment to impede bone loss can be begun if necessary. Therefore, (4) the multiplicity and the possible improvement of cardiovascular abnormalities associated with subclinical hypothyroidism suggest that the decision to treat a patient should depend on the presence of risk factors, rather than a threshold TSH level. Furthermore, (5) replacement therapy is with levothyroxine generally safe if excessive administration is avoided, and the treatment can be suspended if there is no clear benefit from its use. Treatment decisions can be made based on monitoring by serum levels of TSH.

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