Clinical Study

Bone Demineralization in Postmenopausal Women: Role of Anamnestic Risk Factors

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This study evaluated the effects of L T4 administration on the bone mineral density (BMD) in physiological postmenopausal women after two years of continuative treatment. 110 postmenopausal women with nodular goiter aged between 50 and 55 years were examined before and after 2 years of therapy with a fixed dose of LT4 (1.6 mcg/kg/die) for the treatment of nodular thyroid disease. The results showed that the patients on treatment with LT4 have a slight, but significant reduction of the BMD after 2 years of treatment, associated with increased serum levels of alkaline phosphatase and urinary excretion of hydroxyproline, confirming our data conducted on the same group after one year of therapy. Comparison between patients receiving LT4 (group A) or not (group B) showed that group A patients had significantly lower BMD. We demonstrated the statistically significant influence of the following risk factors on BMD: (1) body mass index < 19 kg/m²; (2) the onset of menarche after the age of 15 years; (3) positive history for period of amenorrhoea; (4) nulliparity.

1. Introduction

Bioavailable 17β-estradiol correlates with the bone mineral density (BMD). On the contrary, an estrogenic lack determines a condition characterized by the prevalence of bone reabsorption phase over the bone formation phase. Osteoporosis in postmenopause recognizes also low serum 1,25(OH)₂D levels and a reduced intestinal transport of calcium, always due to the estrogenic lack. The reabsorption markers increase up to two times the values seen in premenopause, while values of bone formation markers increase only by 50% [1]. The biochemical indicators of increased osteoblastic activity are represented by the serum levels of osteocalcin and of alkaline phosphatase, while the urinary levels of hydroxyproline are expression of an increased osteoclastic activity. In presence of an accelerated bone replacement, osteocalcin and alkaline phosphatase serum levels and urinary hydroxyproline excretion are increased. The diagnosis of osteopenia and/or osteoporosis is conventionally made by measuring bone densitometry. There is a wide debate concerning the effects of the treatment with L-thyroxin (LT4) on BMD. Thyroid hormones certainly determine an increase of both osteoblastic and osteoclastic activities over both cortical and trabecular bones [2, 3]. However, the data about the real impact that LT4 therapy exerts on BMD of women subjected to prolonged periods of treatment appear contrasting. In particular, an approach built on the preventive determination of the anamnestic profile considered at risk for bone demineralization in women undergoing LT4 use is lacking. Hyperthyroidism has been associated with bone demineralization [3–7]. Studies in vitro suggest that thyroid hormones increase more the re-absorption than bone formation, hence determining a loss of bone mass [8, 9]. It has also been reported how thyrotoxicosis increases the fracture risk in post-menopause women and in patients with low bone mass peak. Fractures are more frequent in those parts of the skeleton in which predominates the cortical bone, such as the hip and the distal part of the arm [10]. A recent study has also shown that endogenous subclinical hyperthyroidism
might be considered an additional risk factor for osteoporosis in postmenopausal women, especially for cortical bone, whereas exogenous subclinical hyperthyroidism has no effect on BMD [11]. Post-menopausal women with nodular thyroid disease often undergo continuous and prolonged treatment with LT4 administered at suppressive dosages. Nodular thyroid disease and osteoporosis share common factors: (a) both are present with an elevated frequency in the general population; (b) they are more prevalent in the female sex; (c) the incidence increases with age. Since increased levels of thyroid hormones may contribute to bone demineralization.

The aim of this study was to evaluate the effects of treatment with a fixed dose of LT4 on BMD in physiological post-menopausal women with normofunctioning nodular thyroid disease, compared to women, the same average age, who did not receive LT4.

2. Patients and Methods

2.1. Patient Selection. To examine the effects of the treatment with LT4 on BMD, 110 (range 50–55 years, average age 53), natural post-menopausal patients with normofunctioning uninodeular or multinodular benign thyroid disease were enrolled, after informed consent, if they:

(i) had last regular menstruation less than 5 years before;
(ii) had a normal T-score (≥1 SD);
(iii) did not have secondary causes of bone demineralization (genetic, endocrine-metabolic, osteoarticular, hematologic, neoplastic, gastrointestinal, drug administration, and/or prolonged immobilization);
(iv) did not receive LT4 treatment in the previous two years;
(v) did not have a history positive for vertebral fracture.

Following preliminary evaluation, all patients were prescribed LT4 at the fixed dose of 1.6 μg/kg/die.

Exclusion Criteria. Surgical menopause, hormone replacement therapy in the last two years and autoimmune thyroid disorders.

2.2. Control Group. Fifty women of the same average age (range 50–55 yrs, average age 53.5), having their last menstruation less than 5 years before (last referred menstruation), with normal T-score (≥1 SD) and not receiving LT4. None of the patients assumed any drugs.

2.3. Instrumental and Laboratory Evaluation. All patients underwent evaluation of BMD by dual X-ray absorptiometry of the lumbar vertebrae (Bone Densitomites Gammadensit X-ray, I’ACN Scientific Laboratories; Cerro Maggiore (MI), Italy) before LT4 treatment was begun (T0) and 2 years after treatment (group A) and/or followup (group B) (T2).

The serum levels of TSH (ECLIA, Roche Diagnostics, Monza (MI), Italy), FT4, FT3 (ECLIA, Roche Diagnostics, Monza (MI), Italy), AbTG and AbTPO (ECLIA, Roche Diagnostics, Monza (MI), Italy), were evaluated at T0 and at T2. All the patients enrolled underwent measurements of calcium serum levels (colorimetric method; Roche Diagnostics, Monza (MI), Italy), 24 h urinary calcium concentration (colorimetric method, Roche Diagnostics, Monza (MI), Italy), serum alkaline phosphatase (AP) bone isoenzyme levels (enzymatic method; Metra TM BAP EIA) and 24 h urine hydroxyproline concentration (colorimetric method; LTA; Bussero (MI), Italy) at T0 and T2.

2.4. Statistical Analysis. The results are reported as mean ± SEM throughout the study. According to LT4 therapy, patients were divided into 2 groups: a group which received LT4 therapy (group A) and group which did not receive any treatment (group B). The statistical analysis was performed using the Student t-test for paired or unpaired data, as suitable. The odd’s ratios of the risk factors in relationship to bone mineralization loss were determined. The statistical

### Table 1: Bone mineral density (BMD), TSH and markers of osteoblastic and osteoclastic activities before (T0) and two years (T2) after treatment with L-thyroxin in 110 postmenopausal patients with nodular thyroid disease.

|             | T0        | T1        |
|-------------|-----------|-----------|
| BMD (T-score) | −0.22 ± 0.07 | −1.02 ± 0.10* |
| TSH (μU/mL)  | 1.3 ± 0.1  | 0.8 ± 0.07*  |
| Serum calcium concentration (mg/dL) | 8.9 ± 0.02 | 8.8 ± 0.03 |
| Urinary calcium excretion (mg/24 h) | 183.2 ± 3.1 | 190.4 ± 3.3 |
| Alkaline phosphatase (UI/L) | 169.7 ± 2.5 | 188.6 ± 2.3* |
| Urinary hydroxyproline excretion (mg/m²/24 h) | 12.8 ± 0.6 | 15.7 ± 0.4* |

*P < 0.001 versus T0.

Normal values: TSH: 0.49–4.67 μU/L; serum calcium concentration: 8.2–10.5 mg/dl; urinary calcium excretion: 50–250 mg/24 h; alkaline phosphatase: 98–279 UI/L; urinary hydroxyproline excretion (22–65 yrs): 6–22 mg/m²/24 h.

### Table 2: Bone mineral density (BMD), TSH and markers of osteoblastic and osteoclastic activities before (T0) and two years (T2) after followup in 50 postmenopausal patients did not receive any therapy (control group).

|             | T0        | T1        |
|-------------|-----------|-----------|
| BMD (T-score) | −0.27 ± 0.02 | −0.30 ± 0.07 |
| TSH (μU/mL)  | 1.4 ± 0.2  | 1.5 ± 0.04 |
| Serum calcium concentration (mg/dL) | 9.1 ± 0.06 | 9.28 ± 0.01 |
| Urinary calcium excretion (mg/24 h) | 144.2 ± 2.1 | 146.5 ± 2.2 |
| Alkaline phosphatase (UI/L) | 160.7 ± 1.5 | 160.9 ± 1.2 |
| Urinary hydroxyproline excretion (mg/m²/24 h) | 13.1 ± 0.6 | 13.0 ± 0.1 |

*P < 0.001 versus T0.

Normal values: TSH: 0.49–4.67 μU/L; serum calcium concentration: 8.2–10.5 mg/dl; urinary calcium excretion: 50–250 mg/24 h; alkaline phosphatase: 98–279 UI/L; urinary hydroxyproline excretion (22–65 yrs): 6–22 mg/m²/24 h.
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amenorrhea; (4) nulliparity.

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of treatment. Forty-one out of 110 women (37.3%) had
but highly significant reduction of the BMD after two years
thyroid disease treated with a fixed dose of L T4 have a slight,

The results of this study showed that patients with nodular

4. Discussion

The patients enrolled had a mean age of 53.4 years (range
50–55 yrs). As expected, the treatment with L T4 caused a
significant reduction of TSH serum levels (P < 0.0001) at T2.
At T0, the group A patients had a mean T-score of −0.22 ±
0.07 which decreased significantly to −1.02 ± 0.10 at T2 (P
< 0.0001). The total calcium concentration in serum and 24
h urine after treatment with L T4 did not change significantly
in comparison to the pretreatment values (Tables 1 and 2).
The serum levels of AP and the amount of hydroxyproline
excreted with the 24 h urine increased significantly (P
< 0.0001) at T2. The total calcium concentration in serum and 24
h urine after treatment with L T4 did not change significantly
in comparison to the pretreatment values (Tables 1 and 2). The
impact of some risk factors for osteoporosis was evaluated
on the BMD of the patients treated with L T4. The results
of this analysis are shown in Table 3. A positive history for
osteoporosis, smoking habit, and length of menopause did
d not give a significant odd ratio. In contrast, the following risk
factors turned out to influence in a statistically significant
manner the BMD: BMI < 19 kg/m², the onset of menarche
after the age of 15 years, a positive history for periods of
prolonged amenorrhea, nulliparity.

4. Discussion

The results of this study showed that patients with nodular
thyroid disease treated with a fixed dose of LT4 have a slight,
but highly significant reduction of the BMD after two years
of treatment. Forty-one out of 110 women (37.3%) had
osteopenia at T2 (tra −1 e T-score −2.5 SD); in the control
group osteopenia at T2 occurred in 6% of patients. The loss
of BMD appeared mainly related to the following factors: (1)
BMI < 19 kg/m²; (2) menarche onset after the 15th year of
age; (3) a clinical history positive for periods of secondary
amenorrhea; (4) nulliparity.

In parallel with the modifications of the BMD after two
years of LT4 treatment, it was also observed an increase
in 24 h urinary hydroxyproline concentration, suggestive of
increased osteoclastic activity, and increased serum AP levels,
an index of increased osteoblastic activity. Altogether there-
fore these data suggest that LT4 treatment increases bone
metabolic turnover, with prevalence of the re-absorption
phase. The results of this study, therefore, favor the hypoth-
thesis that the treatment with suppressive dosages of LT4,
frequent in the clinical practice of women in menopause with
nodular thyroid disease, is a risk factor for the progression
of bone demineralization. In particular, women with the fol-
lowing predisposing risk factors: thinness, delayed menarche,
periods of secondary amenorrhea during the reproductive
age, nulliparity, are likely to undergo a more profound neg-
ative impact of LT4 treatment on BMD.

Contrasting results have been published about the role
played by LT4 treatment on the BMD. The discrepancies
between the various studies are determined by methodolog-
ic bias, such as (a) progressive reduction of the LT4 dosage
prescribed to women which by itself may justify a reduced
risk for bone loss; (b) inclusion of patients with a clinical
history positive for hypo- or hyper-thyroidism which has
been reported to impair BMD [25]; (c) differences in the
duration of the treatment; (d) heterogeneous methods and
site of BMD evaluation; (e) lack of data collection relative
to the role of other possible interfering factors; (f) inclusion
of pre-menopausal women; (g) unmatched controls (for
body weight, age at menarche and at menopause, calcium
dietary intake, smoking habits, alcohol intake, exercise, etc.).
A meta-analysis study, published in 1996, reviewed 41 con-
trolled cross-sectional studies, including about 1250 patients,
concerning the impact of thyroid hormone therapy on BMD.
Suppressive LT4 therapy was associated with significant bone
loss in postmenopausal women (but not in premenopausal
women), whereas, conversely, replacement therapy was asso-
ciated with bone loss in premenopausal women (spine and
hip), but not in postmenopausal women. The detrimental
effect of thyroid hormones appeared more marked on
cortical bone than on trabecular bone [26]. We will briefly
review the major studies appeared in literature afterwards

Table 3: Odd’s ratio of each risk factor.

| Risk factors         | n   | T score < −1 | T score > −1 < −2.5 | Odd’s ratio | 95% confidence interval | Chi square (P value) |
|----------------------|-----|--------------|---------------------|-------------|-------------------------|---------------------|
| Familiarity +        | 48  | 26           | 16                  | 1.0         | 0.45–2.4                | NS                  |
| Familiarity −        | 62  | 36           | 21                  |             |                         |                     |
| BMI < 19 kg/m²       | 41  | 11           | 24                  | 8.6         | 3.55–21.87              | <0.0005             |
| BMI ≥ 19 kg/m²       | 69  | 51           | 13                  |             |                         |                     |
| Menarche > 15 years  | 50  | 20           | 24                  | 3.9         | 1.64–9.16               | <0.0005             |
| Menarche < 15 years  | 60  | 42           | 13                  |             |                         |                     |
| Amenorrhoea +        | 52  | 15           | 26                  | 7.4         | 2.97–18.47              | <0.0005             |
| Amenorrhoea −        | 58  | 47           | 11                  |             |                         |                     |
| Nulliparity +        | 48  | 12           | 25                  | 8.7         | 3.41–22.07              | <0.0005             |
| Nulliparity −        | 62  | 50           | 12                  |             |                         |                     |
| Smoking +            | 40  | 17           | 16                  | 2.0         | 0.86–4.75               | NS                  |
| Smoking −            | 70  | 45           | 21                  |             |                         |                     |

NS: not statistically significant.
which can be divided into those showing a detrimental effect of LT4 on BMD and those showing no such an effect [12–24]. A summary of the main features of these studies is reported in Table 4.

A careful selection of a group of post-menopausal women with thyroid nodular disease under treatment with a fixed doses of LT4 allowed us to show that this treatment causes a slight but significant reduction of BMD. In addition, BMD reduction was associated with the following osteoporosis risk factors: BMI < 19 kg/m², the onset of menarche after the age of 15 years, history positive for period of amenorrhea, and nulliparity. In consideration that LT4 treatment is effective in a low percentage of patients with benign thyroid nodules, estimated to be 10–20% [27], a careful benefit/risk evaluation has to be taken into account before LT4 treatment is prescribed, particularly when other risk factors for bone demineralization are present. The present study confirms comments from our previous article, conducted on 99 post-menopausal women [28], all of them receiving LT4, prospectively evaluated after one-year treatment. In addition, to previous data, the present study considered an homogeneous control group, for average age and clinical features, including only physiological menopause limited to 5-year history (last menstruation). It also increase to two-year observation length of women receiving therapy, allowing a better understanding of the phenomenon. Moreover, this study excludes conditioning anamnestic factors such as: surgical menopause, HRT, and autoimmune thyroid disorders.

### Table 4: Summary of the principal characteristics of the main studies exploring the effects of the treatment with L-thyroxin on the bone mineral density (BMD).

| Authors                  | Thyroid disease          | Number of patients | Type of treatment | Length of treatment (years) | Menopausal status | Effect on BMD                               |
|--------------------------|--------------------------|--------------------|-------------------|----------------------------|-------------------|--------------------------------------------|
| Affinitio et al., 1996   | Hypothyroidism           | 54                 | Suppressive       | Various                    | After             | Decreased                                  |
| Baldini et al., 2002     | Nontoxic goiter          | 43                 | Suppressive       | ≥2                         | Before and after  | Unchanged                                  |
| Chen et al., 2004        | Cancer (thyroidectomy)   | 69                 | Suppressive       | 7.3 ± 3                    | 44 before 25      | Decreased                                  |
| Foldes et al., 1993      | Subclinical hyperthyroidism | 37              | None              | NA                         | Before and after  | None                                       |
| Gorres et al., 1996      | Cancer (thyroidectomy)   | 65                 | Suppressive       | 15 before 2 after 18 men   | Unchanged         |
| Hadji et al., 2000       | Nontoxic goiter and hypothyroidism | 156        | Substitutive      | >5                         | Before and after  | Slightly decreased                        |
| Hejckmann et al., 2005   | Cancer                   | 59                 | Suppressive       | >6                         | Unchanged         |
| Kung and Yeung, 1996     | Cancer (thyroidectomy)   | 46                 | Suppressive       | 2                          | After             | Decreased                                  |
| Larijani et al., 2004    | Thyroid nodules          | 41                 | Substitutive      | >1                         | Before            | Unchanged                                  |
| Mikosch et al., 2001     | Cancer                   | 98                 | Suppressive       | NA                         | Before            | Unchanged                                  |
| Nuzzo et al., 1998       | Nontoxic goiter          | 40                 | Suppressive       | 1.5–14                     | Before            | Decreased                                  |
| Sijanovic and Karner, 2001 | Cancer (thyroidectomy)   | 19                 | Suppressive       | 9                          | Before            | Decreased                                  |
| Toivonen et al., 1998    | Cancer (thyroidectomy)   | 29                 | Suppressive       | 9–11                       | 25 women          | Decreased                                  |

NA: not applicable.

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