Influence of thyroid hormones on bone density

Alden Begić1, Amela Begić2, Ajla Arnautović-Halimić2

1Department for Angiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, 2Clinic for Nuclear Medicine and Endocrinology; Clinical Centre of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To investigate the relations between hormonal status of the thyroid gland and mineral bone density in women in menopause with or without osteoporosis.

Methods The study included 120 postmenopausal women, who were divided into two groups. Group I included postmenopausal patients with osteoporosis, of whom 30 were in the early stages of postmenopause, and 30 of them where in the late postmenopausal phase. The second group included patients with preserved bone mass, of which 30 were in the early stage of postmenopause, and 30 were in the late postmenopausal phase. Bone densitometry (DEXA) was performed for all patients, along with analysis of the level of follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3).

Results A statistically significant correlation between TSH level and mineral bone density in the lumbar spine level (r=0.27) was found in early postmenopausal women (r <0.05), TSH and T-score at the level of the lumbar spine (r=0.31) (p<0.05), as well as between TSH and mineral content of the femur bone (r=0.29; <0.05). There was statistically significant independent association between thyroxine and mineral bone density at the lumbar spine level in the late postmenopausal women (b=0.29; p=0.025).

Conclusion In the early postmenopausal phase, TSH was associated with mineral bone density in the lumbar spine and in the area of the femur.

Key words: densitometry, thyroid gland, osteoporosis
INTRODUCTION

A healthy bone constantly undergoes processes of degradation and synthesis, and this process is called bone remodelling (1). In the younger age, the process of synthesis predominates over the degradation process. After menopause, the loss of bone mass increases up to 3% (1). By definition, osteoporosis is a systemic disease of the skeleton characterized by reduced bone mass and disorder of bone mineral microarchitecture, causing bone weakness and increased risk of fractures (1). The most frequent is postmenopausal osteoporosis, therefore female sex is an important risk for osteoporosis, although one third of patients with osteoporosis are men. The disease is usually asymptomatic, and when symptoms occur, they are usually symptoms of an advanced disease or a consequence of a fracture (2). The advancement of technology enabled the early detection of osteoporosis, before the onset of symptoms and complications of the disease (2).

Bone densitometry (DEXA) is the most important diagnostic tool for the detection of bone mass loss. It is considered to be the “gold standard” for assessing bone mineral density (BMD) (3). Classical radiological tests are not reliable enough to estimate the bone mass, because bone loss less than 30% cannot be detected. The control of hormonal disbalance in the period pre and postmenopausal is of great importance due to the prevention of comorbidity and acute conditions (primarily venous thromboembolism) (3). It is believed that more osteoporotic fractures occur in women annually than a combination of heart attack, stroke, and breast cancer. Early detection of osteoporosis prevents complications, but also reduces the costs of the treatment (1). One in five women aged over 70 years die during the first year after a hip fracture due to complications as a result of heart or lung disease, and one in four women needs long-lasting home care after the hip fractures (4). In the world, many studies are conducted to identify a link between factors that would indicate in advance the existence of a predisposition to the emergence of osteoporosis or to the disease itself, while it is still not clinically manifested, which could be preventive (4). It would be most effective to recognize risk factors in order to influence them on time, and to alleviate and slow down the disease and prevent the consequences of osteoporosis (3,4). The link between thyroid gland hormones within physiological limits and bone density are controversial (2,5). In our institution there was no similar research.

The aim of this study was to investigate the correlation between hormonal status of the thyroid gland and mineral bone density in women in menopause with or without osteoporosis. The importance of the article is to put the focus on significance of thyroid gland hormones disorders for the osteoporosis development, which could be of importance for the prevention of osteoporosis and its complications.

PATIENTS AND METHODS

Examinees and study design

This prospective, observational, cross-sectional, controlled study involved 120 postmenopausal patients who visited the Clinic for Nuclear Medicine and Endocrinology of the Clinical Centre of the University of Sarajevo (CCUS) in the period September 2011 - December 2013. The women were divided into two groups. Group I included postmenopausal women with osteoporosis, of whom 30 were in the early stage of postmenopause, and 30 were in the late postmenopausal phase. Osteoporosis was confirmed with bone densitometry with values of bone density - 2.5 standard deviation (SD) and lower than the average of bone mineral density (BMD) value in young healthy women of the same gender (between 20 and 40 years) at the level of the lumbar spine and/or hip.

The second (control) group included women with preserved bone mass, of which 30 were in the early stage of postmenopause and 30 were in the late postmenopausal phase (values of bone density were ±1 SD in comparison to the average BMD value in young healthy women of the same gender (between 20 and 40 years) at the level of the lumbar spine and/or hip. Patients from the control group were in accordance to age and degree of physical constitution of patients with osteoporosis.

Exclusion criteria were women with endocrine disorders: hypercorticism, hyperparathyroidism, hyperthyroidism, hypopituitarism, hyperprolactinemia, diabetes mellitus type I, hypercalciuria), rheumatoid arthritis, connective tissue diseases, digestive tract diseases, processes involving the bone marrow, receiving drugs that affect the bone
resorption and absorption (vitamin D, calcitonin, bisphosphonates, corticosteroids, heparin, anti-
convulsants, methotrexate, lithium, cyclosporine A, gonadotropin-releasing hormone agonist.
The research was approved by the Ethics Com-
mittee of the CCUS. A written informed consent
was obtained from patients.

Methods
DEXA was performed for all patients, along with
the level of follicle-stimulating hormone (FSH),
thyroid-stimulating hormone (TSH), free thyroxi-
e (FT4), and free triiodothyronine (FT3). Blo-
d samples for laboratory analysis were taken
from the cubital vein in gel tubes according to the
standard procedure, in the morning. The analysis
of thyroid hormones was performed on CO-
BAS analyser e411 (Roche, Basel, Switzerland).
Electrochemiluminescence method was used
with reference values of TSH of 0.3-4.2 mU/L,
FT4 of 12.0-22.0 pmol/L, FT3 of 3.1-6.8 pmol/L.
The deviation of the obtained value from the me-
dian bone density of a young, healthy person of
the same sex (between 20 and 40 years old) was
expressed in percent and SD (T score), and it re-
presented diagnostic criterion for postmenopausal
osteoporosis. The deviation of the obtained value
from the expected in half and year expressed in
percentages (%) and standard deviations (SD) (Z
score). Measurement was most commonly perfor-
med on the lumbar spine, segment L2-L4 in the
anteroposterior (AP) position with folded and rai-
sed knees in order to reduce physiological lumbar
lordosis and increase the intervertebral spacing. T
score within 1 SD indicated a normal finding if it
was between -1 and -2.5 for osteopenia, and below
2.5 SD for osteoporosis.

Statistical analysis
The results were analysed by a t-test for compari-
son among the examined groups where the condi-
tions for their application were fulfilled, i.e. corre-
spanding non-parametric tests (Mann-Whitney test)
if irregular distribution of variables was detected.
The degree of correlation was tested using the Pe-
ason or Spearman correlation coefficient.
The thyroid gland hormone values were com-
pared with bone marrow parameters: body mass
index (BMI), bone mineral content (BMC)). A
part of the locomotor system (lumbar spine, hip,
femur) was taken in account along with body
mass index (BMI) values. The p<0.05 was consi-
dered statistically significant.

RESULTS
The mean age of the group of women with osteo-
porosis was 58.70±1.0, while in the control group
it was 57.76±1.0 (p=0.12).
The mean BMI was lower in the group of wo-
men with osteoporosis (26.9±0.5 kg/m²) compa-
red to the group of women in the control group
(30.0±0.5 kg/m²) (p<0.001) (Table 1). The mean
BMI was 28.6±0.38 kg/m² in postmenopausal
women and according to BMI categories it was
within the range of excessive body weight.
The mean duration of the postmenopausal period
was statistically significantly higher in the group
of women with osteoporosis (11.4±1.1 g) compa-
red to the group of women in the control group
(8.5±0.9 g) (p=0.043) (Table 1).

The average values of bone mineral density and
mineral content of the bone in the lumbar spine
and hip level were statistically significantly higher
in the group of women with osteoporosis than in
the control group of women (Table 2). There was
no statistically significant difference in bone mass
parameters in postmenopausal women in the late
compared to early postmenopause.

<table>
<thead>
<tr>
<th>Characteristic (mean + SD)</th>
<th>Osteoporosis group (N=60)</th>
<th>Control group (N=60)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>26.9±0.5</td>
<td>30.0±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of last menstrual period</td>
<td>47.2±0.73</td>
<td>47.2±0.57</td>
<td>NS</td>
</tr>
<tr>
<td>Length of menopause</td>
<td>11.4±1.1</td>
<td>8.5±0.9</td>
<td>0.043</td>
</tr>
<tr>
<td>Length of reproductive period</td>
<td>33.1±0.73</td>
<td>33.6±0.54</td>
<td>NS</td>
</tr>
<tr>
<td>FSH</td>
<td>54.0±2.6</td>
<td>43.2±2.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

BMI, body mass index; FSH, follicle-stimulating hormone; NS, non-significant

<table>
<thead>
<tr>
<th>Spine level (mean+SD)</th>
<th>Osteoporosis group (N=60)</th>
<th>Control group (N=60)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine level (L1-L4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>0.77±0.11</td>
<td>1.02±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMC</td>
<td>46.9±0.9</td>
<td>63.2±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-score</td>
<td>-2.6±0.09</td>
<td>-0.28±1.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Z-score</td>
<td>-1.3±1.1</td>
<td>0.9±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>0.7±0.01</td>
<td>0.8±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMC</td>
<td>3.8±0.06</td>
<td>4.8±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-score</td>
<td>-1.4±0.1</td>
<td>0.03±0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Z-score</td>
<td>-0.47±0.1</td>
<td>0.92±0.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; BMC, bone mineral content;
Analysing the ratio of thyroid hormone ratio to values of mineral content and mineral bone density in postmenopausal women compared to the presence of osteoporosis, statistically significant correlations between thyroid hormone levels and mineral density and bone mineral content were noticed in both the group of women with osteoporosis and in the group of women with preserved bone mass (Table 3 and Table 4). Analysing the hormone ratio of thyroid gland hormone with mineral bone density in postmenopausal women in relation to the duration of menopause, a statistically significant correlation between TSH level, and mineral bone density at the lumbar spine level \(r=0.27\) was found in early postmenopausal women. \(r<0.05\), TSH and T-score at the level of the lumbar spine \(r=0.31\) \(p<0.05\), as well as between TSH and mineral content of the femur bone \(r=0.29; p<0.05\).

Table 3. Correlation coefficients between thyroid hormone and bone marrow parameters in postmenopausal women with osteoporosis

<table>
<thead>
<tr>
<th>Bone marrow parameter</th>
<th>Osteoporosis group ((N=60))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH</td>
</tr>
<tr>
<td>BMD (L1-L4)</td>
<td>(r=0.13)</td>
</tr>
<tr>
<td>BMC (L1-L4)</td>
<td>(r=0.01)</td>
</tr>
<tr>
<td>T-score (L1-L4)</td>
<td>(r=0.25)</td>
</tr>
<tr>
<td>BMD (Femur)</td>
<td>(r=0.13)</td>
</tr>
<tr>
<td>BMC (Femur)</td>
<td>(r=0.08)</td>
</tr>
<tr>
<td>T-score (Femur)</td>
<td>(r=0.14)</td>
</tr>
</tbody>
</table>

\(r\), correlation coefficient; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; BMD, bone mineral density; BMC, bone mineral content;

Table 4. Correlation coefficients between thyroid gland hormone and bone marrow parameters in postmenopausal women with preserved bone mass

<table>
<thead>
<tr>
<th>Bone marrow parameter</th>
<th>Control group ((N=60))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH</td>
</tr>
<tr>
<td>BMD (L1-L4)</td>
<td>(r=0.1)</td>
</tr>
<tr>
<td>BMC (L1-L4)</td>
<td>(r=0.03)</td>
</tr>
<tr>
<td>T-score (L1-L4)</td>
<td>(r=0.03)</td>
</tr>
<tr>
<td>BMD (Femur)</td>
<td>(r=0.06)</td>
</tr>
<tr>
<td>BMC (Femur)</td>
<td>(r=0.15)</td>
</tr>
<tr>
<td>T-score (Femur)</td>
<td>(r=0.1)</td>
</tr>
</tbody>
</table>

\(r\), correlation coefficient; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; BMD, bone mineral density; BMC, bone mineral content;

Table 5. Independent predictors of bone mineral density in the lumbar spine part of postmenopausal women in late-stage postmenopause (dependent variable - mineral bone density at the level of the lumbar spine)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta ((\beta))</th>
<th>t - test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>0.037</td>
<td>0.283</td>
<td>0.778</td>
</tr>
<tr>
<td>Age</td>
<td>0.163</td>
<td>1.318</td>
<td>0.194</td>
</tr>
<tr>
<td>BMI</td>
<td>0.39</td>
<td>3.014</td>
<td>0.004</td>
</tr>
<tr>
<td>FT4</td>
<td>0.286</td>
<td>2.315</td>
<td>0.025</td>
</tr>
</tbody>
</table>

FSH, follicle-stimulating hormone; BMI, body mass index; FT4, free thyroxine;

DISCUSSION

Analysing the ratio of thyroid hormone and mineral content in women with osteoporosis compared to the control group in our study no statistically significant correlation was found between thyroid hormone levels and BMD. This results are in line with the research of Pater et al. founding no evidence between variations in TSH values in euthyroid postmenopausal women and an impact on BMD and fracture risk (7). Also, the results of Marwah et al. showed that TSH had no effect on the mineral bone density in euthyroid women (8). Murphy et al. found the link between thyroid gland hormones in normal but borderline values (at the upper limit) and an association of physiological variations of the thyroid hormone with BMD and non-vertebral fractures (5). Kim et al. have proven that lower but normal TSH values are associated with low mineral bone density in healthy euthyroid women (6).

However, when comparing the thyroid hormone values and bone mass parameters relative to the duration of postmenopause, we obtained a statistically positive correlation in the early postmenopausal phase between TSH and BMD at the lumbar spine level, as well as TSH and the mineral content of the bone femur. In contrast to the lumbar spine area, in our study, we have not demonstrated the correlation between TSH and the mineral content of the bone at the hip level, which is a somewhat different result compared to the study conducted by Bauer et al. (9). In their study authors have shown a link between low TSH and fecundity values in older women (over 65) (9). They proved that women with low serum TSH values show signs of hyperthyroidism and...
have an increased risk of fractures in the area of the hip and spinal column (9). A positive correlation between FT4 and mineral bone density in the lumbar spine was observed in our study in the late postmenopausal phase, and an independent positive association of BMI and mineral bone density in the lumbar spine region was determined. Similar results were achieved by Pirro et al. as well as Garnero et al. (10,11). By examining the effect of TSH and FT4 on mineral bone density Van der Deure et al. showed that serum FT4 had a much higher bone effect than TSH (12). However, Zovkova and Hill did not demonstrate the effect of FT4 on bone remodelling parameters (13). A practical question in the research is whether subclinical forms of hypothyroidism and/or hyperthyroidism affect mineral bone density. Lee et al. came to the conclusion that in these conditions the bone mass in the area of the neck of the femur was reduced (14). There is evidence that TSH has a direct effect on both components of bone metabolism, construction (through osteoblasts) and degradation (via osteoclasts) (15-18). The practical application of epidemiological results in clinical practice is the setting of a cut-off value of the hormone status of the thyroid gland, i.e. thyroid hormone (FT4, FT3), and especially serum TSH, which is a risk factor for bone loss (19). Thyroid hormones are essential for the development of skeleton (20,21). TSH plays a major role in the preventive monitoring of bone mass after menopause (14). All postmenopausal women with serum TSH values of less than 2.0 mIU/L are treated in terms of osteoporosis because this value of TSH indicates a high risk of osteoporosis confirmation and osteoporotic fractures (4,18). Bone loss is greater and faster in the first years after menopause (early postmenopausal phase), and some authors even believe that bone loss begins before menopause, especially in the spinal column (17) suggesting that initial therapy should begin as early as possible after menopause (17). On the other hand, there are initial studies that discuss the role of TSH and its receptors in the skeletal rebuilding as well as possible future medicines (18), which also opens up opportunities for new research in this field.

In conclusion, a relation between the hormonal status of the thyroid gland and bone mineral density exists especially in the early stages of bone loss. Bone loss is greater and faster in the first years after menopause (early postmenopausal phase).

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**TRANSPARENCY DECLARATION**

Competing interests: None to declare.

**REFERENCES**


