ORIGINAL ARTICLE

Influence of thyroid hormones on bone density

Alden Begić[1], Amela Begić[2], Ajla Arnautović-Halimić[2]

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

Corresponding author:

Amela Begić

Clinic for Nuclear Medicine and
Endocrinology, Clinical Centre of the
University of Sarajevo Sarajevo,
Bosnia and Herzegovina

Bolnička 25, 71000 Sarajevo,
Bosnia and Herzegovina

Phone: +387 33 298 310;
Fax: +387 33 298 330;

E-mail: amelab709@gmail.com

ORCID ID: https://orcid.org/0000-0001-
7112-9694

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 postmeno-pausal 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 (ß=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 con-

sequences 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 densytometry 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 values in young healthy women between 20 and 40 years of the same gender 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, anticonvulsants, methotrexate, lithium, cyclosporine A, gonadotropin-releasing hormone agonist.

The research was approved by the Ethics Committee 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 thyroxine (FT4), and free triiodothyronine (FT3). Blood 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 median 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 represented 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 performed on the lumbar spine, segment L2-L4 in the anteroposterior (AP) position with folded and raised 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 comparison among the examined groups where the conditions for their application were fulfilled, i.e. corresponding non-parametric tests (Mann-Whitney test) if irregular distribution of variables was detected. The degree of correlation was tested using the Pearson or Spearman correlation coefficient.

The thyroid gland hormone values were compared with bone marrow parameters: body mass index (BMD), 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 considered statistically significant.

RESULTS

The mean age of the group of women with osteoporosis 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 women with osteoporosis (26.9±0.5 kg/m²) compared 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) compared to the group of women in the control group (8.5±0.9 g) (p=0.043) (Table 1).

Table 1. The characteristics of postmenopausal women and control group of women

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

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

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 2. Mineral density and mineral content of bones in the group of women with osteoporosis and in the control group

Spine level (mean+SD)	Osteoporosis group (N=60)	Control group (N=60)	p
Lumbar spine level (L1-L4)			
BMD	0.77±0.11	1.02±1.5	<0.001
BMC	46.9±0.9	63.2±1.5	<0.001
T-score	-2.6±0.09	-0.28±1.56	<0.001
Z-score	-1.3±1.1	0.9±1.7	<0.001
Hip level			
BMD	0.7±0.01	0.84±0.02	<0.001
BMC	3.8±0.06	4.8±0.16	<0.001
T-score	-1.44±0.1	0.03±0.11	<0.001
Z-score	-0.47±0.11	0.92±0.12	<0.001

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

Bone marrow parameter	Osteoporosis group (N=60)		
	TSH	FT4	FT3
BMD (L1-L4)	r=0.13	r=-0.01	r=-0.04
BMC (L1-L4)	r=0.01	r=-0.16	r=-0.1
T-score (L1-L4)	r=0.25	r=-0.1	r=-0.15
BMD (Femur)	r=0.13	r=-0.1	r=0.05
BMC (Femur)	r=0.08	r=-0.27	r=-0.14
T-score (Femur)	r=0.14	r=-0.12	r=0.0

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

Bone marrow parameter	Control group (N=60)		
	TSH	FT4	FT3
BMD (L1-L4)	r=-0.1	r=0.05	r=-0.15
BMC (L1-L4)	r=-0.03	r=-0.11	r=-0.17
T-score (L1-L4)	r=0.03	r=0.03	r=-0.1
BMD (Femur)	r=0.06	r=-0.03	r=-0.02
BMC (Femur)	r=0.15	r=-0.05	r=-0.18
T-score (Femur)	r=0.1	r=-0.02	r=-0.05

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

Triiodothyronine and thyroxine level was not statistically significantly related to the bone mass parameters at the lumbar spine or hip level. In a multi-linear regression model, a statistically significant independent correlation between thyroxine and mineral bone density at the lumbar spine level in postmenopausal women was verified (ß=0.29;

p=0.025) (Table 5). In addition to thyroxine, the independent positive association and BMI with mineral bone density at the lumbar spine level was verified (ß=0.39; p=0.004) (Table 5).

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)

Variable	Beta (ß)	t - test	p
FSH	0.037	0.283	0.778
Age	0.163	1.318	0.194
BMI	0.39	3.014	0.004
FT4	0.286	2.315	0.025

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).

FUNDING

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Clarke BL, Khosla S. Physiology of bone loss. Radiol Clin North Am 2010; 48:483–95.
2. Lunenfeld B, Stratton P. The clinical consequences of an ageing world and preventive strategies. Best Pract Res Clin Obstet Gynaecol 2013; 27:643–59.
3. Dalal PK, Agarwal M. Postmenopausal syndrome. Indian J Psychiatry 2015; 57:S222–32.
4. Carpintero P, Caeiro JR, Carpintero R, Morales A, Silva S, Mesa M. Complications of hip fractures: A review. World J Orthop 2014; 5:402–11.
5. Murphy E, Glüer CC, Reid DM, Felsenberg D, Roux C, Eastell R, Williams GR. Thyroid function within the upper normal range is associated with reduced bone mineral density and increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. J Clin Endocrinol Metab 2010; 95:3173-81.
6. Kim DJ, Khang YH, Koh JM, Shong YK, Kim GS. Low normal TSH levels are associated with low bone mineral density in healthy postmenopausal women. Clin Endocrinol (Oxf) 2006; 64:86-90.
7. Pater A, Nowacki W, Sypniewska G. Thyroid-stimulating hormone within normal range does not affect bone turnover in euthyroid postmenopausal women with osteoporotic fracture - a preliminary report. EJIFCC 2011; 22:113–7.
8. Marwaha RK, Garg MK, Tandon N, Kanwar R, Narang A, Sastry A, Bhadra K. Thyroid function and bone mineral density among Indian subjects. Indian J Endocrinol Metab 2012; 16:575-9.
9. Bauer DC, Ettinger B, Nevitt MC, Stone KL; Study of Osteoporotic Fractures Research Group. Risk for fracture in women with low serum levels of thyroid- stimulating hormone. Ann Intern Med 2001; 134:561-8.
10. Pirro M, Manfredelli MR, Scarponi AM, Lupattelli G, Bagaglia F, Melis F, Mannarino E.Association between thyroid hormone levels, the number of circulating osteoprogenitor cells, and bone mineral density in euthyroid postmenopausal women. Metabolism 2012; 61:569-76.

11. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res 1996; 11:337-49.

12. van der Deure WM, Uitterlinden AG, Hofman A, Rivadeneira F, Pols HA, Peeters RP, Visser TJ. Effects of serum TSH and FT4 levels and the TSHR-Asp727Glu polymorphism on bone: the Rotterdam Study. Clin Endocrinol (Oxf) 2008; 68:175-81.

13. Zovkova I, Hill M. Biochemical markers of bone remodeling correlate negatively with circulating TSH in postmenopausal women. Endocr Regul 2008; 42:12-7

14. Lee WY. Relationship between subclinical thyroid dysfunction and femoral neck bone mineral density in women. Arch Med Res 2006; 37:511-6

15. Murphy E, Williams GR. T3 rather than TSH mediates the effects of altered thyroid status on bone turnover in man. Endocrine Abstracts 2007; 13:P328.

16. Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y, Iqbal J, Eldeiry L, Rajendren G, Blair HC, Davies TF, Zaidi M. TSH is a negative regulator of skeletal remodeling. Cell 2003; 115:151-62.

17. Pouilles JM, Tremollieres F, Ribot C. Effects of menopuseon femoral and vertebral bone loss. J Bone Miner Res 1995; 10:1531-6.

18. Sampath KT, Šimic P, Sendak R, Draca N, Schiavi S, McPherson J, Giljevic Z, Vukicevic S. Thyroid stimulating hormone (TSH) may serve as a novel bone anabolic agent for postmenopausal osteoporosis. Calcif Tissue Int 2006; 78:S35.

19. Tuchendler D, Bolanowski M. The influence of thyroid dysfunction on bone metabolism. Thyroid Res 2014; 7:12.

20. Williams GR, Bassett JHD. Thyroid diseases and bone health. J Endocrinol Invest 2018; 41:99–109

21. Bassett JH, Williams GR. Role of thyroid hormones in skeletal development and bone maintenance. Endocr Rev 2016; 37:135–187.