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The Fracture Risk Assessment Tool (FRAX® score) in subclinical hyperthyroidism

Indeks za određivanje rizika od preloma kostiju (FRAX® skor) u supkliničkom hipertireoidizmu

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Abstract

Background/Aim. The Fracture Risk Assessment Tool (FRAX® score) is the 10-year estimated risk calculation tool for bone fracture that includes clinical data and hip bone mineral density measured by dual-energy x-ray absorptiometry (DXA). The aim of this cross-sectional study was to elucidate the ability of the FRAX® score in discriminating between bone fracture positive and negative pre- and postmenopausal women with subclinical hyperthyroidism. **Methods.** The bone mineral density (by DXA), thyroid stimulating hormone (TSH) level, free thyroxine (fT4) level, thyroid peroxidase antibodies (TPOAb) titre, osteocalcin and beta-cross-laps were measured in 27 pre- and postmenopausal women with newly discovered subclinical hyperthyroidism [age 58.85 ± 7.83 years, body mass index (BMI) 27.89 ± 3.46 kg/m^2, menopause onset in 46.88 ± 10.21 years] and 51 matched euthyroid controls (age 59.69 ± 5.72 years, BMI 27.68 ± 4.66 kg/m^2, menopause onset in 48.53 ± 4.58 years). The etiology of subclinical hyperthyroisims was autoimmune thyroid disease or toxic goiter. FRAX® score calculation was performed in both groups. **Results.** In the group with subclinical hyperthyroidism the main FRAX® score was significantly higher than in the controls (6.50 ± 1.58 *vs* 4.35 ± 1.56 respectively; $p = 0.015$). The FRAX® score for hip was also higher in the evaluated group than in the controls (1.33 ± 3.92 *vs* 0.50 ± 0.46 respectively; $p = 0.022$). There was no correlations between low TSH and fracture risk ($p > 0.05$). The ability of the FRAX® score in discriminating between bone fracture positive and negative pre- and postmenopausal female subjects ($p < 0.001$) is presented by the area under the curve (AUC) plotted *via* ROC analysis. The determined FRAX score cut-off value by this analysis was 6%, with estimated sensitivity and specificity of 95% and 75.9%, respectively. **Conclusion.** Pre- and postmenopausal women with subclinical hyperthyroidism have higher FRAX® scores and thus greater risk for low-trauma hip fracture than euthyroid premenopausal women. Our results point to the use of FRAX® calculator in monitoring pre- and postmenopausal women with subclinical hyperthyroidism to detect subjects with high fracture risk in order to prevent further fractures.

Key words:
hip fractures; risk assessment; questionnaires; postmenopause; hyperthyroidism.

Apstrakt

Uvod/Cilj. Alat za određivanje rizika od preloma kostiju (FRAX® skor) je matematički model za izračunavanje pretpostavljenog desetogodišnjeg rizika od preloma kostiju koji uključuje kliničke podatke i gustinu koštane mase u predelu vrata i butne kosti izmerene osteodenzitometrijom (*dual-energy x-ray absorptiometry* – DXA). Cilj ove studije preseka bio je da se proceni primenljivost skora FRAX® u prepoznavanju osoba sa povećanim rizikom od preloma kostiju i utvrdi da li supklinički hipertireoidizam nosi veći rizik od preloma kosti u odnosu na eutireoidno stanje. **Metode.** Mineralna koštana gustina merena DXA metodom, tireostimulišući hormon (TSH), slobodni tiroksin (fT4), antitela na tireoperoksidazu (TPOAt), osteokalcin i beta *cross-laps* mereni su kod 27 žena sa nedavno dijagnostikovanim supkliničkim hipertireoidizmom (58,85 ± 7.83 godina, indeks telesne mase (ITM) 27,89 ± 3,46 kg/m^2, nastanak menopauze u 46,88 ± 10,21 godini) i 51 žene uporedivih osobina (59,69 ± 5,72 god, ITM 27,68 ± 4,66 kg/m^2, nastanak menopauze u 48,53 ± 4,58 godini). FRAX® skor je upotrebljen za procenu rizika od preloma kostiju u obe grupe. **Rezultati.** Ukupni skor FRAX® (6,50 ± 1,58 *vs* 4,35 ± 1,56, $p = 0,015$) i skor FRAX® za prelom kuka (1,33 ± 3,92 *vs*

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0,50 ± 0,46, p= 0,022) bio je značajno veći u grupi sa supkliničkim hipertireoidizmom u odnosu na kontrolnu grupu. Nije bilo korelacije između nivoa TSH i rizika od frakture ($p > 0,05$). Kompetentnost skora FRAX® u razlikovanju pre-i postmenopauzalnih žena sa rizikom od frakture i bez rizika ($p < 0.001$) je prikazana površinom ispod krive (AUC) pomoću ROC analize. *Cut-off* vrednost skora FRAX® bila je u ovoj analizi 6%, sa pretpostavljenom senzitivnošću i specifičnošću od 95% i 75,9%. **Zaključak.** Pre- i postmenopauzalne žene sa supkliničkim hipertireoidizmom imaju veći skor FRAX® i time veći rizik od preloma kuka na malu traumu nego eutireoidne žene. Naši rezultati ukazuju na to da primena FRAX® kalkulatora u grupi pre- i postmenopauzalnih žena sa supkliničkim hipertireoidizmom doprinosi prepoznavanju osoba sa povećanim rizikom od preloma kostiju.

Ključne reči:
kuk, prelomi; rizik, procena; upitnici; postmenopauza; hipertireoidizam.

Introduction

Thyroid hormones are essential for bone development in children and acquisition of peak bone mass and bone turnover in adults [1–3]. In adults, thyroid hormones play important role as homeostatic regulators that maintain bone mass. Thyroid stimulating hormone (TSH) affects bone metabolism in direct pathway *via* specific receptors on the bone, although thyroid hormones exert catabolic effect on bone tissue by stimulating osteoclast activity [4, 5]. It is well known that overt hyperthyroidism and hypothyroidism increased the risk for bone fractures. Hyperthyroidism affects bone turnover by increasing bone resorption. Hypothyroidism suppresses bone formation and bone turnover, but underlying mechanism between hypothyroidism and fracture risk is not clear [6]. Some studies suggest that even mild or moderate thyroid disease is a respective risk factor for osteoporotic fractures, especially in postmenopausal women [7, 8]. Bone mineral density (BMD) is traditionally a predictive factor for osteoporotic fractures. The Fracture Risk Assessment Tool (FRAX® score) was recommended by the World Health Organization (WHO) [9]. This tool enabling a 10-year prediction for possible fractures, incorporates BMD measured by dual-energy-X-ray-absorptiometry (DXA) on the femoral neck, and a few of independent risk factors for fractures on low trauma like: age, previous fractures, parental hip fracture, body mass index (BMI), current smoking, usage of drugs which could affect bone density, alcohol abuse and poor health [10–15].

The aim of this cross-sectional study was to elucidate the ability of the FRAX® score in discrimination between bone fracture positive and negative pre- and postmenopausal women with subclinical hyperthyroidism in order to identify individuals at high risk for future osteoporotic fractures.

Methods

FRAX® score calculation (10-year estimated risk for bone fracture) and measurement of thyroid peroxydase antibodies (TPOAb), bone markers, osteocalcin and beta-cross-laps (β-cross-laps) were performed in the group of 27 peri- and postmenopausal women with newly discovered subclinical hyperthyroidism [age 58.85 ± 7.83 years, body mass index (BMI) 27.89 ± 3.46 kg/m^2, menopause onset in 46.88 ± 10.21 years] and 51 matched euthyroid controls (age 59.69 ± 5.72 years, BMI 27.68 ± 4.66 kg/m^2, menopause onset in 48.53 ± 4.58 years). The etiology of subclinical hyperthyroidism was autoimmune thyroid disease or toxic goiter.

The inclusion criteria for studied group were: women, 40–70 years of age, with the TSH level lower than 0.3 mIU/L and free thyroxin (fT4) level within the normal range. Additional including criteria were: no previous history of thyroid disease, no bowel disease with malabsorption and no steroid therapy longer than 6 months during the life. The studied and the control group were assessed via a questionnaire about independent risk factors for osteoporosis, such as previous fractures, current cigarette smoking, alcohol consumption, parental fractures and onset of menopause.

TSH and fT4 leveles measured by chemiluminescent microparticle immunoassay (CMIA) (Abbott, ARCHITECT ci8200). Reference ranges for TSH were 0.35–4.94 mIU/mL with analytical sensitivity of ≤ 0.1 μIU/mL and for fT4 9.0–19.1 pmol/L with analytical sensitivity of ≤ 0.4 ng/dL. The TPOAb was measured by CMIA for the quantitative determination of the IgG class of TPOAb in human serum and plasma (Abbott, ARCHITECT *i* system,). Reference values were < 5.61 IU/mL. Osteocalcin and β-cross-laps were determined by electrochemiluminescence immunoassay (ECLIA) (Roche, Cobas e601). The reference range for osteocalcin was 15–46 ng/mL, and for β-cross-laps 104–1008 pg/mL. The bone mineral density was measured by dual energy X-ray bone densitometer Lunar DPX. Measuring was performed on the lumbar spine and left femoral neck. BMD was expressed as standard deviation (SD) in T-score. The fracture risk was calculated by the FRAX® score assessment for Turkey [16, 17].

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS for Windows, release 20.0, SPSS, Chicago, IL). Data were expressed as mean values with SD or as absolute numbers with percentages. Numeric variables were analysed using Student's *t*-test or the Mann-Whitney *U*-test (for skewed data), while categorical data were analyzed using a χ^2 test and Fisher's exact test, as appropriate. Odds ratios (ORs) for vertebral and hip fracture in relation to thyroid function were determined using unadjusted and adjusted logistic regression (adjusted for age, BMI and BMD, expressed as T-score). Stepwise adjusted regression analysis of relationships between thyroid status and BMD, bone turnover and FRAX® scores was performed after adjustment for age, BMI and smoking. The ability of the FRAX® score and TSH in discriminating between bone fracture positive and negative perimenopausal women with subclinical hyperthyroidism was described by

the Receiver Operating Characteristic (ROC) curve method. The curves were drawn by plotting the sensitivity against the false positive rate (1-specificity), for varying the cut-off of the FRAX® score and TSH levels. The area under the curve (AUC) represents a quantitative measure of predictive value of TSH and FRAX® score for bone fracture. In all tests, *p* value < 0.05 was considered to be statistically significant.

The study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the institutional Ethics Board of the Faculty of Medicine, University of Belgrade, Serbia.

Results

The anthropometric, biochemical, BMD and personal history data of both examined groups are presented in Table 1.

There were no significant differences in mean values of the evaluated descriptive parameters including parents' fractures, current smoking, type 2 diabetes mellitus, as well as treatment with corticosteroids. Also, there were no significant differences between groups concerning age, BMI and fat mass.

The TSH level was significantly lower in subjects with subclinical hyperthyroidism in comparison with the control group (0.0730 ± 0.05 *vs* 2.23 ± 0.94 mIU/mL, respectively; *p* < 0.001). The fT4 level significantly higher in the examined group than in the healthy subjects (15.88 ± 2.21 *vs* 13.82 ± 1.31 pmol/L, respectively; *p* < 0.001). TPOabs were more prevalent in subclinical hyperthyroid women than in the healthy women (44.4% *vs* 3.9%, respectively; *p* < 0.001).

BMD in the lumbar spine was not significantly lower in the studied than in the control (-1.24 ± 1.10 *vs* -1.13 ± 1.59, respectively; *p* = 0.73). The hip T-score was lower in the examined group than in the controls (-1.34 ± 0.73 *vs* -0.68 ± 0.90, respectively; *p* = 0.002). There was no significant difference in bone markers – osteocalcin (25.99 ± 12.74 *vs* 21.79 ± 5.34 ng/mL, respectively; *p* = 0.22) and β-cross-laps (374.97 ± 180.68 *vs* 306.88 ± 110.73, pg/mL respectively; *p* = 0.18) between the two groups.

The main fracture risk, main FRAX® score, was higher in the examined than in the control group (6.50 ± 1.58 *vs* 4.35 ± 1.56 respectively; *p* = 0.015) and fracture risk for hip was also higher in the group with subclinical hyperthyroidism (1.33 ± 3.92 *vs* 0.50 ± 0.46 respectively; *p* = 0.022) (Table 1).

Unadjusted and adjusted (for age, BMI and lumbar spine T-score) logistic regression analysis indicated that the parameter of thyroid function and bone markers in subclinical hyperthyroid women were not related to fracture (*p* > 0.05) (Table 2).

Table 1

Characteristics of the subclinical hyperthyroid and healthy women

Parameter	Subclinical hyperthyroidism	Healthy women	*p*
Subjects, n	27	51	
Age (years), x̄ ± SD	58.85 ± 7.83	59.69 ± 5.72	0.593
BMI (kg/m^2), x̄ ± SD	27.91 ± 4.57	27.68 ± 4.66	0.830
Fat mass, (%) x̄ ± SD	42.15 ± 10.21	43.41 ± 5.79	0.530
Menopause (years), x̄ ± SD	46.88 ± 10.21	48.53 ± 4.58	0.343
Current smoking, n (%)	6 (22.2%)	10 (19.6%)	0.786
Diabetes mellitus, n (%)	1 (3.7%)	2 (3.9%)	0.960
Parental fractures, n (%)	3 (11.1%)	5 (9.8%)	0.856
TSH (mU/L), x̄ ± SD	0.0730 ± 0.05	2.23 ± 0,94	< 0.001
FT4 (mU/L), x̄ ± SD	15.88 ± 2.21	13.82 ± 1.31	< 0.001
TPOAb, n (%)	12 (44.4%)	2 (3.9%)	< 0.001
T score (L1-L4), x̄ ± SD	-1.24 ± 1.10	-1.13 ± 1.59	0.738
T score hyp, x̄ ± SD	-1.34 ± 0 .73	-0.68 ± 0 .90	0.002
Osteocalcin, x̄ ± SD	25.99 ± 12.74	21.79 ± 5.34	0.225
β-Cross-laps, x̄ ± SD	374.97 ± 180.68	306.88 ± 110.73	0.188
FRAX® (main), x̄ ± SD	6.50 ± 1,58	4.35 ± 1.56	0.015
FRAX® (femoral neck), x̄ ± SD	1.33 ± 3.92	0.50 ± 0.46	0.022
Previous fractures, n (%)	3 (11.1%)	1 (2.0%)	0.081

BMI – body mass index; TSH – thyroid stimulating hormone; FT4 – free thyroxine; TPOAb – thyroid peroxydase antibodies; FRAX – the Fracture Risk Assessment Tool score.

Table 2

Relationship between thyroid function tests and fracture

Parameter	Unadjusted logistic regression model			Adjusted* logistic regression model		
	OR *per* unit			OR *per* unit		
	p	change	95% CI for OR	*p*	change	95% CI for OR
TSH	0.320	0.618	1.240–1.594	0.343	0.628	0.240–1.643
FT4	0.251	1.334	0.816–2.180	0.402	1.266	0.729–2.198
TPOAb	0.999	0.000	0.000	0.998	0.000	0.000
OC	0.445	0.946	0.822–1.090	0.895	1.009	0.880–1.158
BCL	0.483	0.997	0.989–1.005	0.871	1.001	0.991–1.011
BMI	0.579	1.061	0.860–1.310			

***Adjusted for age, BMI and T score for L1-L4; OR – odds ratio; CI – confidence level; TSH – thyroid stimulating hormone; fT4 – free thyroxine level; TPOAb – thyroid peroxydase antibodies; OC – osteocalcin; BCL – beta-cross-laps; BMI – body mass index.**

The ability of the TSH and FRAX® score in discriminating between bone fracture positive and negative pre- and postmenopausal female subjects is presented by AUC plotted in ROC analysis (Table 3, Figure 1).

Table 3
ROC analysis of the association between TSH and FRAX® score

Parameters	Area	SE	*p*	95% CI for SE
TSH	0.644	0.162	0.336	0.326–0.961
Main FRAX® score	0.998	0.003	0.001	0.992–1.005
Hip FRAX® score	0.750	0.192	0.094	0.373–1.127

TSH – thyroid stimulating hormone; FRAX® – Fracture Risk Assessment Tool; ROC – receiver operating characteristics; SE – standard error; CI – confindence interval.

The determined FRAX® score cut-off value by this analysis is 6%, with estimated sensitivity and specificity of 95% and 75.9%, respectively (Figure 1).

The association was found between TSH and the main FRAX® score (p = 0.001). The relationship between thyroid function tests, T-score, markers of bone turnover and FRAX® scores after adjustment for age or age, BMI and smoking is presented in Table 4.

A significant association was found between serum TSH ($p < 0.001$), fT4 ($p = 0.02$) and femoral neck BMD (Table 4).

TSH was in association with hip FRAX® score and that was statistically significant ($p = 0.046$) (Figure 2).

The association ($p = 0.008$) between fT4 and main FRAX® score was also found as well as between fT4 and hip FRAX® score ($p = 0.014$) (Figures 3 and 4)

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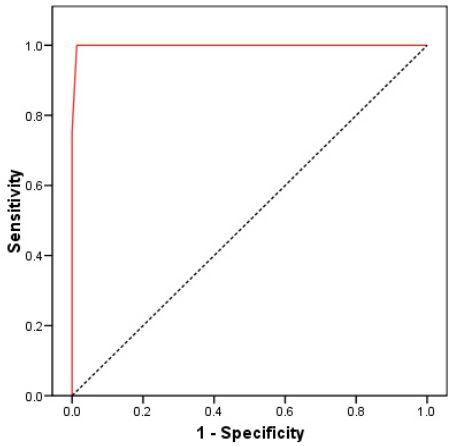

Fig. 1 – The ability of TSH in discriminating between bone fracture positive and negative pre- and postmenopausal female subjects.
TSH – thyroid stimulating hormone.

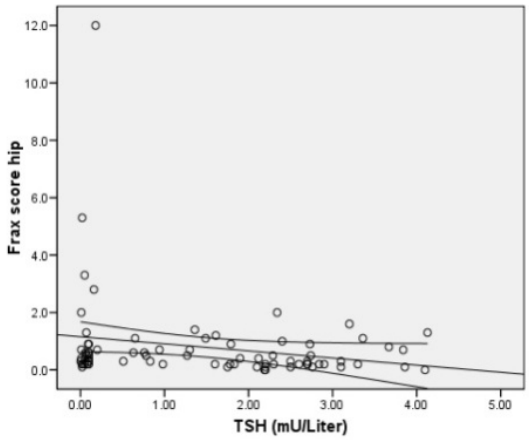

Fig. 2 – The hip FRAX® and TSH.
TSH – thyroid stimulating hormone; FRAX® – Fracture Risk Assessment Tool.

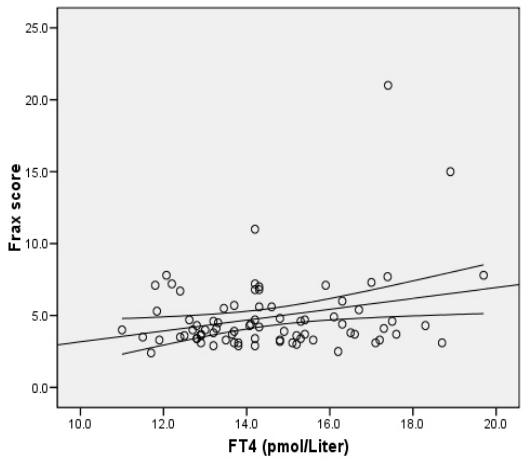

Fig. 3 – The main FRAX® score and FT4.
FRAX® – Fracture Risk Assessment Tool; fT4 – free thyroxine.

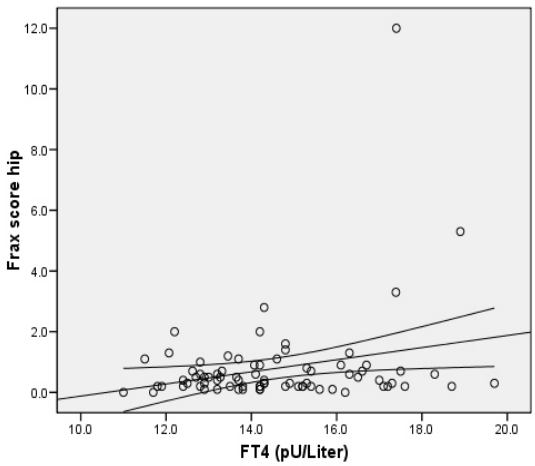

Fig. 4 – The hip FRAX® score and FT4.
FRAX® – Fracture Risk Assessment Tool; fT4 – free thyroxine.

Table 4

Relationship between thyroid function tests, T-score, markers of bone turnover and FRAX® scores

Parameters	TSH (mU/L) Adjusted linear regressive model			FT4 (mU/liter) Adjusted linear regressive model			TPOAb Adjusted linear regressive model	
	Model R^2	β coefficient (95% CI)	*p*	Model R^2	β coefficient (95% CI)	*p*	OR (95% CI for OR)	*p*
T skor								
L1–L4	0.040	0.157 (-0.059–0.374)	0.151	0.013	-0.094 (-0.426–0.238)	0.573	1.093 (0.707–1.690)	0.653
Hip	0.181	0.621 (0.304–0.939)	< 0.001	0.077	-0.602 (-1.113–0.092)	0.021	0.763 (0.366–1.590)	0.470
Bone marker								
OC	0.105	-0.025 (-0.071–0.020)	0.258	0.069	-0.036 (-0.110–0.038)	0.327	1.105 (1.010–1.209)	0.029
BCL	0.102	-0.002 (-0.005–0.001)	0.282	0.046	0.001 (-0.004–0.006)	0.655	1.009 (1.002–1.016)	0.012
FRAX® score								
Main	0.063	-0.110 (-0.220–0.000)	0.050	0.100	0.225 (0.062–0.389)	0.008	0.905 (0.651–1.258)	0.553
Hip	0.066	-0.208 (-0.413–0.004)	0.046	0.087	0.384 (0.081–0.687)	0.014	0.862 (0.426–1.743)	0.679

TSH – thyroid stimulating hormone; FT4 – free thyroxine; TPOAb – tyroid peroxydase antibodies; OC – osteocalcin; BCL – beta cross laps; BMI – body mass index; FRAX® – Fracture Risk Assessment Tool; CI – confidence interval; OR – odds ratio.

Discussion

The 10-year fracture risk in pre- and postmenopausal women with subclinical hyperthyroidism was compared with fracture risk in euthyroid women matched by age, BMI, age of menopause onset and percentage of fat mass. Some studies show that even a small variation in thyroid hormones level may affect bone quality [18]. First fracture appeared earlier in women with hyperthyroidism or thyroid cancer than in women without thyroid disease [19]. A meta analyse demonstrate that alkaline phosphatase activity may be decreased in femoral bone marrow cell cultures but not in vertebral bone marrow cells due to the excess of T3 [20]. Similar results were found in a study on animal model. That study shows that gene expression markers for osteoblast and osteoclast in levothyroxine (L-T4) treated rats are increased in the femoral bone but not in the lumbar spine [21]. A recent study indicates that the combination of L-T4 and levothyronine (L-T3) in the treatment of hypothyroidism causes a higher rate of bone resorption [22]. The level fT4 in the upper normal reference range but not low TSH level was independently related to decreased BMD in the lumbar spine in perimenopausal women [23]. Increased risk for fractures around the time of diagnosis has been reported in older men with subclinical hyper-or hypothyroidism [24]. The effect of thyroid hormones on bone metabolism is site specific. That was shown in a study on subclinical thyroid dysfunctional group (subclinical hyperthyroidism and hypothyroidism), compared with euthyroid controls [18]. Our results demonstrate that BMD in the lumbar spine was not lower in the group with subclinical hyperthyroidism than in the controls (-1.24 ± 1.10 *vs* -1.13 ± 1.59 respectively; $p = 0.73$) while the hip T-score was significantly lower in the examined group than in the controls (-1.34 ± 0 .73 *vs* -0.68 ± 0 .90 respectively; $p = 0.002$).

Excess of thyroid hormone, endogenous or due to overdose in thyroid replacement therapy even in asymptomatic persons, may be associated with elevated biochemical bone markers and poor bone mass [25–29]. In our study a significant association between serum TSH ($p < 0.001$), fT4 ($p = 0.02$) and femoral neck BMD was established. There was no association between TSH and fT4 and lumbar or hip BMD regarding bone markers. BMD is valuable but still not enough sensitive predictive fracture risk factor in population of postmenopausal women [30]. Some studies suggest that more than 50% of women with vertebral fractures have normal BMD and they do not meet criteria for osteoporosis; on the contrary, some premenopausal women with low BMI have relatively low fracture rates [31]. After surgical treatment of overt hyperthyroidism BMD and fracture risk decreased [32].

Considering BMD limitation to predict fractures, new fracture assessment tools were established in order to improve the prediction of osteoporotic fractures. One of them is the FRAX® score, as a computer-based algorithm for calculation 10-year hip or other bone fracture probability, obtained clinical risk factors, habits and hip BMD [15, 30, 33–36]. In our study, ROC analysis showed association between FRAX® score and TSH. The ability of TSH and FRAX® score in discriminating between bone fracture positive and negative pre- and postmenopausal female subjects is presented by the AUC plotted in ROC analysis. TSH was in association with hip FRAX® score ($p = 0.046$). The association between fT4 and the main FRAX® score was found ($p = 0.008$) as well as between fT4 and hip FRAX® score ($p = 0.014$).

The results regarding the contribution of bone markers in fracture risk were inconsistent [37–39]. Some studies did not find any difference among bone markers between patients with subclinical hyper- or hypothyroidism and healthy controls. Other studies reported the increase in bone markers in

perimenopausal women with hypothyroidism, whereas other investigators did not find any changes in bone markers in a similar study [40, 41]. We, also, did not find a difference in the levels of osteocalcin and β-cross-laps between the two groups ($p > 0.05$) as well as the association between bone markers and TSH or fT4 and FRAX® score.

The group with subclinical hypothyroidism had more prevalence of TPOAb than the control group ($p < 0.001$). The association was found between TPOAb and osteocalcin ($p = 0.029$) and cross-laps-levels ($p = 0.012$) but there was no association between TPOAt and fracture risk. Previously, was suggested that autoimmune thyroid disease in subclinical hypothyroid women increased hip fracture risk [42]. The influence of autoimmune disease on bone is complex and it is manifested as immunoregulatory imbalance. Alterations in homeostatic mechanisms might explain an imbalance of osteoblastic activity [43]. Osteopenia could be a consequence of chronic inflammatory autoimmune disorders with alteration osteclastic activity in new bone formation. The major regulators of bone destructions in autoimmune disorders are divided into two groups: proosteoclastogenic inflammatory cytokines (RANKL L) and antiosteclastogenic ones (OPG, IFN γ and IL 4). The influence of inflammation on bone is determinated with the duration of autoimmune disorders [44]. The association between TPOAb and osteocalcin in our study indicates that TPOAb (or inflammatory cytokines included in inflammatory response) may stimulate bone resorption. Short duration of autoimmune thyroid disease may be the explanation for missing association between TPOAb and FRAX® score.

The limitation of our study was that we did not know the duration of subclinical hyperthyroidism before the diagnosis was established.

Conclusion

Pre- and postmenopausal women with subclinical hyperthyroidism have higher FRAX® scores and, thus, greater risk for low-trauma hip fracture than euthyroid pre- and postmenopausal women. The results obtained in this study point out the use of FRAX® calculator in monitoring pre-and postmenopausal women with subclinical hyperthyroidism to detect subjects with high fracture risk and prevent future osteoporotic fractures.

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