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Fracture Risk in Obese Middle-Age Women with Autoimmune Thyroid Disease: Serbian Experience

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ABSTRACT

Introduction: The association between obesity, thyroid autoimmunity and bone health is still unclear. Autoimmune thyroid disease with or without thyroid dysfunction has a significant impact on the quality of life and bone quality. It is known that menopause is u turning point at which bone density is reduced, and in this period the prevalence of thyroid disease and obesity is higher. The aim of the study was to investigate whether overweightness or obesity might play a protective role in bone mineral density and fragility fracture risk in euthyroid women with autoimmune thyroid disease.

Material and methods: We have investigated 82 euthyroid, Thyroid Peroxidase Antibody (TPOAb) positive middle age women divided into two groups: obese with body mass index (BMI) 36.5 ± 5.9kg/m2, n=23, and control, non-obese women (BMI 25.6 ± 2.6kg/m2, n=59), without commorbidities with possible influence on bone mineral density (BMD). BMD was measured by means of Dual-X-ray Absorptiometry (DXA). Fracture risk was calculated by FRAX® score.

Results: BMD expressed as a T score was significantly lower at both sites (lumbar spine and femoral neck) in the control, non-obese women ($p<0.001$). The FRAX® score for major osteoporotic fractures was higher in the control group. The difference was close to the conventional level of statistical significance ($p=0.084$). The hip FRAX® was significantly higher in the control group ($p=0.002$). There was a positive, significant correlation between BMI and spine BMD ($r=0.470$, $p<0.001$) and hip BMD ($r=0.501$, $p<0.001$) in the whole group (n=82). There was a negative correlation between BMI and the FRAX® score for major osteoporotic fractures ($r=-0.196$; $p=0.084$) and the FRAX® hip score ($r=-0.191$; $p=0.086$) in the obese women, which was close to the conventional level of significance. Higher BMI even with higher TPOAb level was associated with higher BMD. After adjusting for age, menopause onset and smoking habits, BMI was a significant predictor both for the LS T-score and the hip T-score ($p<0.001$).

Conclusion: Moderate obesity in the middle age women with autoimmune thyroid disease is associated with higher bone mineral density and lower risk of fragility fractures, but also, obesity is the cause of many metabolic diseases, and it is

necessary to define a turning point at which obesity has a positive impact on bone quality, and when this effect gives way to the negative consequences of obesity.

INTRODUCTION

Thyroid hormones have a significant impact on the skeleton development, growth and remodelling of bones which is crucial for bone quality [1]. Some authors shown that autoimmune thyroid disease in euthyroid patients, separately from thyroid hormone levels, is associated with poor bone quality and thus increased fracture risk the relationship between fat mass and bone is complex and not fully understood. Obesity is associated with low fracture risk, but, on the other hand, investigations have shown that some specific factors that are released from adipocytes from peripheral fat tissue may affect bone quality and increase fracture risk. There is some evidence that the local interaction between fat and bone within the bone marrow could play an important role in the pathogenesis of age-related bone loss [2]. The protective effect of obesity may be explained by an increased mechanical load and the activation of osteocytes which act as "mechanostats" [3], as well as an increased synthesis of estrogen and leptin by fat cells. The higher bone mineral density (BMD) is attributed to multiple factors. An increased strain on bones imposed by higher body mass may lead to an improved structural integrity of bones [4]. Some investigators have shown that hepatic fat accumulation independently of adiposity is associated with decreased BMD [5]. After correcting for the mechanical loading effect of body weight in healthy adults, greater fat mass negatively correlates with BMD [6]. Some studies have shown that autoimmune thyroid disease in euthyroid patients, separately from thyroid hormone levels, is associated with poor bone quality and thus increased fracture risk [7-9]. It is also known that menopause is a turning point at which bone density is reduced, and in this period the prevalence of thyroid disease, particularly the autoimmune ones is higher, as well as weight gain [10]. The interrelations between obesity, thyroid autoimmunity and bone health in middle-age women is still unclear, so we wanted to find out whether moderate excess of fat mass, despite numerous negative metabolic effects, has a protective impact on bone mineral quality and possible lower fragility fracture risk in euthyroid middle-age women with autoimmune thyroid disease.

MATERIAL AND METHODS

A prospective study was performed in 82 consecutive thyroid peroxidase antibody (TPOAb) positive women who gave written consent at Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade. Women were divided into subgroups according to the their body mass index (BMI) (<30 kg/m2 and ≥30 kg/m2): obese (n=23) and control, non-obese (n=59).

Inclusion criteria were: postmenopausal women from 45 to 65 years of age, fT4 within normal range and TSH within normal range or slightly elevated. The exclusion criteria were: the history of previous thyroid dysfunction, steroid therapy lasting for more than 6 months, a systemic inflammatory disease and an inflammatory bowel disease, a vitamin D level lower than 50 nmol/L, a high level of parathyroid hormone, alkaline phosphatase or serum calcium out of the reference range.

Thyroid Stimulate Hormone (TSH) and free thyroxine (fT4) were measured by employing the CMIA (chemiluminescent microparticle immunoassay) method by Abbott, on ARCHITECT ci8200. The reference range for TSH was 0.35-4.94 mIU/mL, with the analytical sensitivity of ≤0.1 μIU/mL. The thyroid peoxydase antibodies (TPOAb) were measured by employing the CMIA (chemiluminescent microparticle immunoassay) method by Abbott for the quantitative determination of the IgG class of thyroid peroxidase autoantibodies in human plasma and serum on the ARCHITECT i system. The normal values were <5.61 IU/mL. The cut-off for TPO"+" was ≥10IU/ml. BMD was measured on the left femoral neck and lumbar spine by the Hologic dual energy X-ray bone densitometer. The BMD data were presented as a Standard Deviation (SD) in a T-score. All participants voluntarily filled out a questionnaire about their previous fractures, parental fractures, the onset of menopause and current cigarette smoking status. For assessing the risk of fragility fractures, the FRAX® score calculator was used. The fracture risk was calculated by the FRAX® score assessment for Turkey on the World Health Organization (WHO) recommendation to use a surrogate country calculation tool, based on country-specific mortality rates [11,12]. The study protocol was approved by the Ethics Committee of the Clinical Center of Serbia, Belgrade. All subjects gave their written informed consent in accordance with the Declaration of Helsinki.

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STATISTICAL ANALYSIS

Categorical data were presented as frequencies with percentages and analyzed using a chi-square test and Fisher's exact test. Numerical data are presented as mean values with standard deviations (mean ± SD) or median (25th-75th percentile) as appropriate. Normality of distribution was tested by mathematical and graphical methods. All data were normally distributed, except the TPOAb, FRAX® score and TSH level. Numeric variables were analyzed using Student's t-test or the Mann-Whitney U-test (for skewed data). Linear regression, unadjusted and adjusted (age, menopausal status and smoking habit) with LS T-score and hip score as depended variables was performed. SPSS 21.0 (SPSS Inc., Chicago, Illinois) was used to perform statistical analyses. The level of statistical significance was set at $P < 0.05$.

Table 1: Characteristics of obese and control, non-obese middle-age women.

	Obese N=23	Control, non-obese N= 59	p
Age, mean±sd	54.6±11.1	56.7 ± 8.2	0.407
BMI, mean±sd	36.5 ± 5.9	25.6 ± 2.6	**<0.001**
Menopause onset, mean±sd	50.0 ± 3.2	47.8 ± 4.2	0.108
Previous fractures, n (%)	2 (8.7)	7 (11.9)	0.680
Smoking, n (%)	3 (13.0	17 (28.8)	0.135
Diabetes mellitus, n (%)	2 (8.7)	1 (1.7)	0.189
Parent fractures, n (%)	5 (21.7)	10 (16.9)	0.614
TSH, mean±sd	5.2 ± 3.8	6.3 ± 4.1	0.496
TPOAb, median (25 th -75 th percentile)	478.0 (245.0-659.0)	274.0 (154.0-497.0)	0.048
FT4, mean±sd	13.1 ± 2.3	12.9 ± 2.7	0.729
LS T-score, mean±sd	-0.1 ± 1.2	-1.4 ± 0.9	**<0.001**
Normal BMD n (%)	16 (69.6)	22 (37.3)	**0.028**
Osteopenia, n (%)	6 (27.3)	28 (49.1)	
Osteoporosis, n (%)	1 (4.5)	9 (15.8)	
Femoral neck T- score, mean±sd	-0.3 ± 1	-1.1 ± 0.8	**<0.001**
FRAX® score for major osteop. Fr, median (25 th -75 th percentile)	4.3 (2.9-6.4)	4.6 (3.7-7.0)	0.084
FRAX® hip, median (25 th -75 th percentile)	0.3 (0.1-0.6)	0.5 (0.3-1.1)	**0.002**
FRAX® hip>3%	1 (4.3)	5 (8.5)	**0.519**

RESULTS

Clinical characteristics of investigated women are presented in Table 1. There were no significant differences regarding age, status and onset age of menopause between the groups. Previous fractures were present in 2 (8.7%) in obese and in 7 (11.9%) women in control group (p=0.680). Differences in smoking habits and prevalence of diabetes mellitus and parental fractures were not statistically different between the groups. Levels of TSH and fT4 were similar between obese and control, non-obese women. Level of TPOAb was statistically higher in obese women. Bone mineral density expressed as T score was significantly lower at both sites (lumbar spine and femoral neck) in control, non-obese women. Percent of women with osteopenia and osteoporosis were statistically higher in control, non-obese women. The FRAX® score for major osteoporotic fractures was higher in control, non-obese women, difference was close to conventional level of statistical significance (p=0.084). None of women had major FRAX score >20%. Hip FRAX® was significantly higher in control, non-obese women. Rates of women with FRAX® hip>3% were similar between groups.

The correlation of BMI with BMD and the FRAX® score in the whole group

There was positive statistically significant correlation between BMI and spine BMD (r=0.470, p<0.001), and hip (r=0.501, p<0.001), in whole group (n=82). There was negative correlation between BMI and FRAX® score for major osteoporotic fractures (r=-0.196; p=0.084) and FRAX® hip score (r=-0.191; p=0.086) in obese women, which was close to conventional level of significance.

In order to examine relationship between of LS T-score and body mass index, linear regression with LS T-score as depended variables was performed. Higher BMI was significant determinant of LS T-score (B=0.092, 95% CI=0.053-0.131, p<0.001). After adjusting for age, menopause onset and smoking habit, BMI was significant predictor for LS T-score (B=0.077, 95% CI=0.037-0.118, p<0.001).

In order to examine relationship between hip score and body mass index, linear regression with hip score as depended variables was performed. Higher BMI was significant determinant of hip score (B=0.077, 95% CI=0.047-0.106, p<0.001). After adjusting for age, menopause onset and smoking habit, BMI was significant predictor for hip score (B=0.063, 95% CI=0.032-0.093, p<0.001).

Correlation of spine and hip BMD and thyroid parameters in whole group

There was statistically significant correlation between level of TPOAb and spine BMD (r=0.243, p=0.048), and hip (r=0.243,

p=0.044), in whole group (n=82). There was no statistical significant correlation between TSH and spine (r=-0.14, p=0.900) and hip BMD (r=0.011, p=924). There was no statistical significant correlation between fT4 and spine (r=0.017, p=0.885) and hip BMD (r=-0.025, p=822). Higher BMI even with higher TPOAb level was associated with higher BMD (Figure 1).

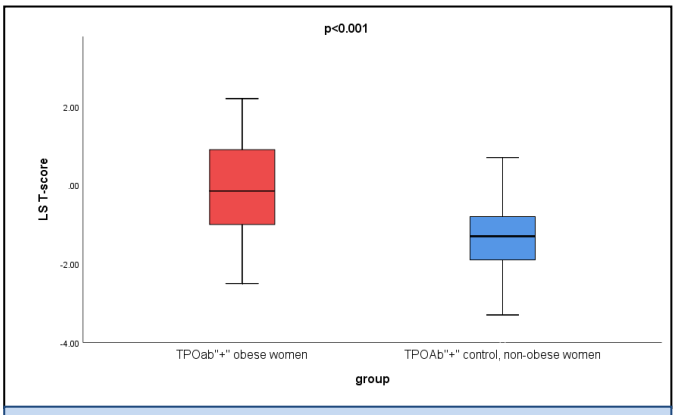

Figure 1: LS T-score in obese and control, non-obese women.

DISCUSSION

The endocrine system has a crucial impact on skeletal development and bone quality. Thyroid hormones and TSH influence longitudinal bone growth during childhood, and bone resorption as well as bone formation in adulthood [12,13]. Thyroid dysfunction is accompanied by changes in bone quality by a higher rate of bone resorption than bone formation in the case of hyperthyroidism, or by a lower rate of bone resorption in patients with hypothyroidism. Bone remodeling cycle is reduced in patients with hyperthyroidism from 200 to 100 days, and prolonged in patients with hypothyroidism up to 700 days. The lower bone mineral density in hyperthyroidism is associated with increased fracture risk, although the risk of fractures is increased in hypothyroidism due to increased stiffness of the bone [14-16]. In some studies, the presence of TPOAb in amount that meet the criteria for autoimmune thyroid disease, i.e. twice the upper limit of the reference range, is associated with an increased risk of future fractures in postmenopausal women [1,7,17].

In this study we have investigated the bone quality in obese or non-obese middle-age women with autoimmune thyroid disease which were not differ on onset of menopause, previous fractures, smoking habits and prevalence of diabetes mellitus. All women have vitamin D, serum calcium, phosphorus and fT4 within reference range and TSH in euthyroid range or slightly elevated, but groups differ in TPOAb level which was almost twise higher among obese than in non-obese women (478.0 vs. 274.0IU/ml). Average BMI in investigated group was 36.5 ± 5.9kg/m2, which means the second level of obesity with a moderate amount of excessive fat mass and with a moderate possible impact of joined factors of obesity on bone quality. The mean BMI in the control group was 25.6 ± 2.6 kg/m2, which was the borderline BMI between normal and overweight. In order to investigate the impact of BMI on bone quality and a risk of fragility fractures in women with autoimmune thyroid disease, we measured BMD on lumbar spine and on the hip. We found, after adjusting for age, menopause onset and smoking habit that a higher BMI was associated with higher BMD on lumbar spine and hip, as shown the other studies [18,19]. Some studies have shown that not only overt forms of thyroid dysfunction, but also subclinical hyper- or hypothyroidism may affect a bone remodeling process and less activate a bone formation [14,15,20]. TSH in the low-normal range is associated with a high risk of vertebral fractures, independently of age, the body mass index and levels of thyroid hormones [12,21]. TSH outside the reference range was recognized as an independent factor in fragility fractures [22]. In both investigated groups, in our study, TSH was slightly elevated, with no statisticaly significance between groups and with no significant correlation between TSH and spine and hip BMD. We did not find significant correlation between fT4 and spine and hip BMD which is comparable with previous studies. Investigations regarding impact of thyroid autoimmunity on bone, shown that a low TSH level, with thyroid hormones within the reference range and the presence of positive anti-thyroid antibodies was associated with elevated fracture risk [1,12]. Thyroid autoimmunity might has an impact on OPG/RANKL levels, independently of thyroid function [23]. Although the association between thyroid autoimmunity and bone health is still unclear, the possible underlying mechanism of the way autoimmunity acts on bone mass varies from an activation of interleukins to a change in bone turnover marker balances [24]. Previous studies shown that higher BMI was associated with higher bone mineral density until it goes into extreme obesity, when the bone quality decreases due to chronic inflammation caused by adipokines [18,19]. Among our investigated group

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with BMI >30kg/m2, the level of TPOAb was statistically higher (p=0.048) that implicate possible sinergistic impact of inflamation generate by fat mass and by autoimmunity. In order to define an association between obesity and the risk of hip fracture in adults, one meta-analysis has shown that many obese individuals have relatively high BMD, and that bone strength correlates with the amount of fat mass. This includes higher serum levels of adipokines associated with obesity, which are influencing factors for bone mass in obesity. Increased gluteofemoral adipose tissue has a protective mechanical effect on fragility fractures in women with obesity, which reduces impact of force on bone when they fall [4].

Obesity is a complex multifactorial metabolic disease with a substantial impact on the whole body, including the skeleton and bone quality. Moderate obesity increases BMD due to local adaptation to bone load [3,25,26]. The link between osteoblasts and adipocytes is the common precursor Mesenchymal Stem Cell (MSC). Excessive fat mass accumulation, insulin resistance and low level of vitamin D which is common in obese subjects, are a very important factors which influence BMD by the activation of proinflammatory cytokines, impair insulin signaling in osteoblasts, decrease osteocalcin levels and support bone degradation [27,28]. Elevated systemic inflammation status with abnormal circulating levels of inflammatory cytokines, might affect osteoclast differentiation and bone resorption in obesity, but also in menopausal women [29].

The BMD reduction due to estrogen deprivation is the common skeletal metabolic disorder in postmenopausal period which involves microarchitectural deterioration [30]. In the postmenopausal period, mild or moderate ectopic fat accumulation is an adaptive mechanism for protecting the skeleton and blood vessels from estrogen deficiency. Estrone produced by aromatase from androstenedione in white adipose tissue suppresses osteoclastic activity and stimulates bone formation by induced osteoblasts in obese postmenopausal women compared with non-obese age-matched controls [31]. Plasma leptin levels correlate with the amount of fat mass. Leptin may have an influence on bone remodeling by the induction of osteoblastogenesis, with the exception of premenopausal women [32]. One study has demonstrated that obesity induces an improvement in BMD which is modulated by the severity of obesity, bone site location, age and gender. The combination of accentuation of peak bone mass and the reduction of bone loss rate with ageing may explain a lower prevalence of osteoporosis in obese population [33].

Considering BMD's limited ability to predict osteoporotic fractures, we used a FRAX® score in order to assess fragility fracture risk in euthyroid obese and non-obese women with TPOAb. The FRAX® score, a computer-based algorithm for calculating bone fracture probability in the next 10 years, obtains hip BMD, clinical risk factors and smoking habits. The clinical value of this mathematical model is recommended for the initiation of an osteoporosis therapy if the FRAX® score for a hip is > 3%, or the total FRAX® score is > 20%, although BMD is below the recommended level for an osteoporosis therapy [34,35]. In our study, the FRAX® score for major osteoporotic fractures was higher in the non-obese women than in the obese women. Also, the FRAX® for the risk of hip fractures was significantly higher in the control, non-obese women. There were no statistically significant differences between the groups in terms of the number of previous fractures, parental fractures, smoking habits, menopause onset and diabetes mellitus presence. This result has shown that moderate obesity is associated with a lower fracture risk in the next 10 years, even if thyroid autoimmunity was present. This result is comparable in term of influence of higher BMI on BMD with study conducted by Fan et al, which correlate efficacy of FRAX® and higher BMI in assessment of fracture risk in postmenopausal women [36] and with the pilot study provided by Ang et al. who find that BMI was equivalent to the FRAX® and some other fracture assessment tools [37].

With this study we have shown that bone quality is better and the fracture risk is lower in moderately obese middle age euthyroid women with autoimmune thyroid disease than in normal-weight euthyroid women with autoimmune thyroid disease. This result suggests that moderate obesity has a greater positive impact on bone quality compared to the negative impact that auto-imune thyroid disease has.

The weakness of our study lies in the fact that we did not measure bone markers which are relevant for bone remodeling and cytokines that could provide a clue as to the impact of the amount of accumulated fat mass on bone quality and we have

no answer where is the border between a positive and a negative effect of obesity on bone quality.

Higher BMI has a positive effect on bone mineral density and on bone quality expressed by a lower risk of fragility fractures in the middle age euthyroid women with autoimmune thyroid disease. From a clinical point of view, the study shows that routine measurement of BMD is not necessary in middle-aged moderately obese women with autoimmune thyroid disease, due to the low risk of osteoporosis and thus a low risk of fragility fractures. The development of risk chart for clinicians, to identify subjects for a DXA could be useful to avoid unnecessary over diagnosis.

Hoverer, obesity is the cause of many metabolic diseases, and it is necessary to define a turning point at which obesity has a positive impact on bone quality, and when this effect gives way to the negative consequences of obesity. Skeletal loading is a known mechanism for increasing BMD, but for a more precise explanation of the mechanism by which obesity and autoimmune diseases affect bone quality and to determine a border between a positive and a negative effect of obesity on bone quality, further tests on different stages of obesity are required.

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