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The Effects of Thyroid Hormones on The Bone Density in Postmenopausal Women

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Abstract:
Objectives: *Osteoporosis has become an important public health problem that has to be assessed in parallel with the prolonged life expectancy in recent years. Management of bone health condition and prevention of fractures requires evaluation of the risk factors for osteoporosis, especially thyroid functions, in postmenopausal women. The study was conducted to determine the effects of bone mineral density (BMD) on changes in thyroid function in postmenopausal women.*
Methods: *The study sample included a total of 240 postmenopausal women. Data were collected using thyroid hormone results and BMD measurement results. Data were analyzed using statistical analysis methods. The results were evaluated at a 95% confidence interval and a significance level of p <0.05.*
Results: *While there was no statistical significance between TSH blood biochemistry and bone mineral density, a significant negative correlation was found between T4 blood biochemistry value and femoral neck bone mineral density.*
Conclusions: *In terms of osteoporosis of the femur neck, thyroid dysfunctions in postmenopausal women may be an important problem that can go unnoticed. Therefore, assessment of thyroid hormones will be effective in preventing postmenopausal osteoporotic.*
Keywords:*Osteoporosis, Postmenopausal, Thyroid Hormones, Bone Mineral Density (BMD).*

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I. Introduction

Osteoporosis is a systemic disease characterized by low bone mass, deterioration of microstructure of bone tissue, increased bone fragility and increased fracture probability[1,2,3]. Due to the increase in the lifespan of humans, the prevalence of osteoporosis has recently increased, and 200 million people have been diagnosed with osteoporosis worldwide[4]. In addition, economic costs associated with increased morbidity, mortality and fractures have significant effects on all countries. The incidence of osteoporotic fractures is increasing with an ageing population, and it is generally accepted that fractures of the vertebrae, radius and femur are high[2,5]. In a community-based study in Turkey, a total of 24.000 hip fractures were detected and 73% of these hip fractures occurred in women. It is estimated that this number will be 64.000 by 2035. Women have less bone mass than men and lose bone rapidly during the first ten years of menopause[6]. Osteoporosis is multifactorial in etiology and is influenced by genetic, hormonal, nutritional and lifestyle factors. For this reason, the effect of hyperthyroidism on bone loss and long-term outcomes varies depending on the nature and severity of thyroid disease, as well as on individual bone health and presence of other risk factors for osteoporosis[5,7]. Thyroid hormones play an important role in skeletal development, bone mass and bone formation process. Clinical-epidemiological studies conducted in recent years show that the deficiency and excess of thyroid hormones are associated with a risk of fracture[8]. In cases where the thyroid hormones are produced too much (hyperthyroidism), absorption of calcium in the gut is reduced[9]. Symptoms of thyroid disease may resemble postmenopausal complaints and it can be difficult to determine clinical differences[10].

Hip, wrist and pelvic fractures are among the most common osteoporotic fractures affecting hundreds of millions of people all over the world. Due to the aging of industrialized societies, osteoporosis and osteopenia-related fractures are estimated to increase in the coming years[5,11]. Therefore, it is necessary to assess the risk factors for osteoporosis, especially thyroid functions, in postmenopausal women to manage bone health and prevent fractures. This study was conducted to determine the effects of thyroid functions on bone density in postmenopausal women.

II. Material And Methods

This study was conducted as a cross-sectional descriptive research with a total of 240 postmenopausal women admitted to the gynecology and obstetrics unit of a research and training hospital in Turkey.

Subjects & selection method: The study sample was selected from postmenopausal women who were admitted to the gynecology and obstetrics services for a Pap smear test and general check-up during a three-month period. Those with a history of cancer, thyroid disease, pregnancy, genetic disease and drug and substance dependence were not included in the study.

Procedure methodology

Institutional permissions were obtained prior to the research. During the sampling, no pressure was given to women to participate in the study and written and verbal consent was taken from all the participants. Those included in the study were referred to the hospital's Nuclear Medicine Center for BMD (Bone Mineral Density) measurement. The BMD measurements were made in the hospital's Nuclear Medicine Center, in an area used solely for BMD measurements with DEXA (Dual Energy X-ray Absorptiometry). The World Health Organization (WHO) recommends that osteoporosis be diagnosed with BMD measurements[12]. The TSH, T3, T4, FT3 and FT4 values of the study sample were measured in the laboratory. A questionnaire form and a socio-demographic information form prepared by the researchers were filled in during that time. Also, the women's bone mineral density was measured with DEXA. Thus, the necessary data for our research were transferred to a computer database. Statistical analyzes of the data were carried out using the IBM SPSS software. Data were analyzed using descriptive statistical methods (e.g. mean, standard deviation, frequency and percentage distributions). In order to compare quantitative data, one-way Anova test was used for comparing parameters displaying normal distribution between groups and Tukey HDS test was used to determine the group that caused the difference. Also, Kruskal Wallis test was used for the comparison of the parameters without normal distribution between groups and Mann Whitney U test was used to determine the group causing the difference. Finally, inter-parameter relations were evaluated using Pearson and Spearman's correlation analysis. The results were evaluated at a 95% confidence interval and a significance level of $p<0.05$.

III. Result

According to the data on the women's demographic characteristics, their age range varied between 44 and 69 and the mean age was 55.67±5.56.

Table no 1: Distribution of Demographic Characteristics

Demographic Characteristics		n	%
Age	45-49	46	*19.2*
	50-54	**80**	***33.3***
	55-59	48	*20.0*
	60-64	38	*15.8*
	65-69	28	*11.7*
Education level	Literate	12	*5.0*
	Primary School	**143**	***59.6***
	High school	24	*10.0*
	Higher education	37	*15.4*
	Illiterate	24	*10.0*
Occupation	**Housewife**	**182**	***75.8***
	Civil servant	4	*1.7*
	Retired	54	*22.5*
Financial status	Good	108	*45.0*
	Moderate	**131**	***54.6***
	Bad	1	*0.4*
Marital Status	**Married**	**205**	***85.4***
	Single	2	*0.8*
	Widow	33	*13.8*
Total		**240**	***100.0***

According to the gyneco-obstetric characteristics of the women, the average age of menarche was 13.88±3.27 years, the average age of menopause was 46.18±5.07 years and the average duration of menopause was 9.25±7.19 years.

Table no 2: Means of Gyneco-Obstetric Characteristics

Gyneco-obstetric characteristics	Mean ± SD
Menarche age	13.88 ± 3.27
Menopause age	46.18 ± 5.07
Menopause duration (years)	9.25 ± 7.19
Number of pregnancies	4.17 ± 2.22
Number of births given	2.91 ± 1.43
Number of living children	2.57 ± 1.10
Breastfeeding duration (months)	12.71 ± 6.22

According to distribution of BMD measurements and vertebral measurements, 32.1% of the women had osteoporosis, 43.3% had osteopenia and 24.6% were normal. According to the femur measurements, 16.3% had osteoporosis, 53.8% had osteopenia and 30.0% were normal.

Table no 3: Distribution of Bone Mineral Density Measurements

BMD Score Assessment		N	%
Vertebra L_2L_4	**Osteoporosis**	77	***32.1***
	Osteopenia	104	***43.3***
	Normal	59	***24.6***
Femur neck	**Osteoporosis**	39	***16.3***
	Osteopenia	129	***53.8***
	Normal	72	***30.0***
Total		240	***100.0***

There was a highly significant and positive correlation between the participants' body mass indexes, vertebral T-scores, Z-scores and BMD scores ($p<0.01$). Also, there was a moderate and positive correlation between the femur Z-scores and body mass indexes ($p<0.05$). However, no statistically significant relationship was found between the women's body mass indexes and femur T-scores and BMD scores ($p>0.05$).

Table no 4: Correlation Between Body Mass Index and BMD Measurements

	r	p
Vertebra T Score	0.318	***0.000*** **
Vertebra Z Score	0.376	***0.000*** **
Vertebra BMD Score	0.308	***0.000*** **
Femur T Score	0.119	*0.066*
Femur Z Score	0.184	***0.004*** **
Femur BMD Score	0.111	*0.087*

** p<0.01 (Pearson correlation analysis)

We found a statistically significant positive correlation between the vertebral Z-scores and menopausal ages ($p<0.01$). However, there was no statistically significant relationship between the vertebral T and BMD scores and the menopause ages ($p>0.05$), and between the femur T-scores, Z-scores and BMD scores and the menopause ages ($p>0.05$). On the other hand, there was a statistically significant negative correlation between the vertebral T-scores and the durations of menopause ($p<0.01$). While there was no significant correlation between the vertebral Z-scores and the durations of menopause, there was a highly significant negative correlation between the vertebral BMD scores and the durations of menopause ($p<0.01$). There was also a highly significant negative correlation between the femur T-scores and BMD scores and the durations of menopause ($p<0.01$). There was a negative correlation with femur Z-scores at a significance level of $p<0.05$.

Table no 5: Correlation Between Menopause Age, Menopause Duration and Number of Births and BMD Measurements

	Menopause Age		Menopause Duration		Number Of Births	
	r	p	r	p	r	p
Vertebra T Score	0.097	*0.135*	-0.215	***0.001****	-0.117	*0.069*
Vertebra Z Score	0.183	***0.004****	-0.022	*0.735*	-0.023	*0.728*
Vertebra BMD	0.092	*0.154*	-0.226	***0.0001****	-0.131*	***0.042****
Femur T Score	-0.035	*0.588*	-0.391	***0.0001****	-0.129*	***0.046****
Femur Z Score	0.051	*0.429*	-0.154	***0.017****	-0.019	*0.765*
Femur BMD	-0.012	*0.853*	-0.393	***0.0001****	-0.111	***0.087***

** p<0.01 * p<0.05 (Pearson correlation analysis)

There was no statistically significant correlation between the vertebral T-scores and Z-scores and the number of births among the participants (p>0.05), but there was a statistically significant negative correlation between the vertebral BMD scores and the number of births among the participants (p<0.05). There was also a significant negative correlation between the femur T-scores and the number of births (p <0.05). However, there was no statistically significant relationship between the femur Z and BMD scores and the number of births (p>0.05).

Table no 6: Comparison of Thyroid Hormone Levels and Vertebra and Femur, T and BMD Score Values

	VERTEBRA				**FEMUR**			
	T Score		**BMD score**		**T Score**		**BMD score**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***
FT3	0.092	*0.154*	0.110	*0.089*	0.028	*0.668*	0.023	*0.721*
FT4	0.105	*0.105*	0.086	*0.185*	-0.067	*0.304*	-0.051	*0.433*
TT3	0.028	*0.668*	0.052	*0.419*	-0.027	*0.675*	-0.034	*0.596*
TT4	0.004	*0.947*	0.023	*0.718*	-0.155	***0.016****	-0.147	***0.023****
TSH	-0.044	*0.502*	-0.040	*0.536*	0.079	*0.222*	0.064	*0.324*

*p<0.05 (Pearson and Spearman's correlation analysis)

Finally, in our study, there was no significant correlation between the vertebral T-scores and BMD scores and the FT3, FT4, TT3, TT4 and TSH values (p>0.05). While there was no significant correlation between the femur T-scores and BMD scores and the FT3, FT4, TT3 and TSH values (p>0.05), there was a statistically significant negative correlation between the femur T-scores and BMD scores and the TT4 values (p<0.05).

IV. Discussion

Osteoporosis has become an important public health problem that has to be assessed in parallel with the prolonged life expectancy in recent years[4]. In particular, the increase in the rate of bone destruction due to the decrease in estrogen level accelerates the development of osteoporosis in menopause. Thus, the decrease in bone mass can trigger self-destruction without trauma[3].

In our study, which examined the effect of thyroid functions on bone mineral density in postmenopausal women, the participants' ages ranged from 44 to 69 years with an average age of 55.67±5.56 years. According to 2013 data from Turkey Demographic and Health Surveys (DHS), about 49 percent of women ages 48 and 49 in our country are menopausal[13]. According to the definition of the WHO, the 6-8-year period after menopause is called postmenopausal period. While menopause is seen in later ages in developed countries such as the USA and some European countries, it is seen in earlier ages in underdeveloped and developing countries including some Middle Eastern countries[14,15].

According to the gyneco-obstetric characteristics of our participants, the average age of menarche was 13.88±3.27 years and the average age of menopause was 46.18±5.07 years. In another study conducted in Turkey, the menarche age was 13.64±1.33 and the average age of menopause was 46.44±4.96[16]. The average menarche and menopausal ages in a study conducted to determine hip fracture and risk factors in Europe by the WHO, the European Osteoporosis and Bone Disease Foundation and Sandoz Switzerland under the title Mediterranean Osteoporosis Study (MEDOS) were comparable to those in our study[17].

The WHO recommends that osteoporosis be diagnosed with bone mineral density tests. Osteoporosis is diagnosed if the detected bone mineral density values are lower than the standard deviation (SD) of 2.5 (-2.5 and below) compared to the reference bone mineral density values obtained from healthy and young adults. Cases with values between -1 and -2.5 are classified as "osteopenia"[12]. In our study, the BMD assessments were performed in accordance with the WHO definitions. According to the measurements of vertebral L2L4 bone mineral densities, 32% of the women had osteoporosis, 43% had osteopenia, 16% had osteoporosis and 54% had osteopenia according to femur neck measurements. In a study of 7.532 women over the age of 50 in the USA, the rate of osteoporosis was 29% according to the vertebral L2L4 T score measurements[18]. In different regions of Italy between 2012-2014, the prevalence of osteoporosis in 3.247 postmenopausal women over 50 years of age was found to be 36.6%[19]. In a study of 4.946 women over the age of 50 in Korea, 35.5% of the women were found to have osteoporosis and 46.7% were found to have osteopenia[20]. Differences in population, socioeconomic status and ethnic backgrounds in various geographical areas of the world can be leading to differences in osteoporosis rates[21].

The relationship between obesity and osteoporosis is still a controversial issue. The cross-correlation between bone tissue and fat tissue plays a key role in determining the effect of obesity on BMD. This may be due to the relationship between estrogen and obesity. In some studies, menopausal women who were obese were shown to have higher blood estrogen concentrations than others[22,23,24]. There was a positive correlation between body mass index and BMD in our study. In India, Kumar et al. found consistent results with our data[25]. In a study conducted in China with 6.477 people by calculating the mechanical loading effects of total body weight

on bone mass, an inverse relationship was found between bone mass and fat mass. According to that study, increased fat mass may not have a beneficial effect on bone mass[22].

Bone loss in postmenopausal women is actually due to estrogen deficiency, which affects the balance between osteoblast resorption and bone formation controlled by osteoblasts[26]. In our study, while there was a positive significant correlation between menopausal age and BMD, there was a significant negative correlation between menopause duration and BMD. In the MEDOS study, late menarche or early menopause was associated with an increase in fracture risk in each country[17]. Early menopause, especially before 45 years of age, is a significant risk factor for osteoporosis[26]. In a study by Corina et al., BMD in postmenopausal women was lower than premenopausal women, regardless of body weight. Estradiol and estrone show positive correlation with bone mass in premenopausal women[27]. Similarly, according to our results, prolonged release of estrogen in the body seems to be protective in osteoporosis.

In our study, while there was no significant correlation between thyroid hormones and vertebral T and BMD scores, T4 value was found to be significantly correlated with femur neck T and BMD score negatively. According to our results, there was a decrease in bone mineral density as the amount of T4 in blood increased.

Poul et al. reported that excessive T4 led to a dilution of 12.8% in the femur neck but it did not affect the lumbar vertebrae[28]. In a controlled study conducted with 9.704 women by Bauer et al., the frequency of hyperthyroidism was found to be higher in women who previously had hip fractures. In the same study, it was found that women with thyroid hormone excess (T4 excess) were at high risk for new hip and vertebral fractures. The effect reported in that study was independent of factors such as age, past hyperthyroidism, individual health status, use of thyroid and estrogen[9].

According to morphological studies, with advancing age, thyroid is affected by degenerative processes leading to epithelial flattening, thyroid follicles diminish in size, and fibrous connective tissue and lymphoid tissue increase. The ability of the thyroid gland to absorb iodine is 40% lower in people over 80 years of age than people under 30 years of age. Especially T4, which we call the main thyroid hormone, is influenced more by this situation[29,30]. A study of 403 elderly individuals by Van den Beld found that high T4 and T3 concentrations negatively affected physical activity. That study also determined that low serum T4 ratio increased life span[31].

Interactions between thyroid hormones and bone are complex and still not fully understood. During development, the thyroid hormone is necessary for bone cells to grow and mature. Lack of thyroid hormone in pregnancy and newborn causes skeletal defects. In later life, hypothyroidism causes a decrease in bone turnover. Since the activity of osteoclasts predominates over the activity of osteoblasts, thyroid hormone in excess induces increased activity of osteoblasts and osteoclasts leading to high bone turnover and loss of osteoclasts[24,32]. In a study of 30 premenopausal and 27 postmenopausal Graves patients by Ercolano et al., significant bone remodeling was observed in the postmenopausal group compared to the premenopausal group[33]. Symptoms of thyroid diseases are similar to those of postmenopausal complaints, so it is difficult to differentiate clinically[8,10]. Some studies and meta-analyzes found that particularly T4 therapy does not have a significant effect on BMD in men or pre-menopausal women, but it reduces BMD in menopausal women by 5% to 7%[33].

In a similar study of 152 postmenopausal women conducted by Pala et al. in 2006, bone mineral density was assessed only by TSH and no significant relationship was found[34]. In parallel with our results, it is thought that TSH value is not a good marker to show bone mineral density. Recent studies have frequently examined negative effects of thyroid dysfunctions on heart and bone[35]. Research findings on the relationship between thyroid dysfunctions and bone mineral density are controversial, but recent research focus on an important metabolic disease such as osteoporosis in postmenopausal women implies that it is a serious problem.

V. Conclusion

The most serious consequence of osteoporosis is femur fractures with a mortality rate of 15-20%[36]. In terms of osteoporosis of the femur neck, thyroid dysfunctions in postmenopausal women may be an important problem that can go unnoticed. However, there is some controversy in new studies about the fact that the parameters of thyroid functions cannot accurately describe thyroid diseases.

In our study, a statistically significant negative relationship was found only between TT4 and femur neck bone mineral density among thyroid functions. It was determined that T4 level is higher in the participants with decreasing levels of femur neck bone mineral density.

This was a single-center cross-sectional, it did not have a control group (healthy premenopausal women or healthy men), it was based solely on BMD data, and it did not address the risk of fracture or other bone turnover markers, which affect the generalizability of our findings. For this reason, further research and meta-analyzes of the subject are needed.

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