DOI: 10.5152/etd.2018.0065

Manuscript Type: Original Article

Title: Treatment Outcomes of Postmenopausal Osteoporosis in Patıents with Stable Hypothyroidism: A 5 Year Follow Up Retrospective Study

Running Head: Efficacy of Hypothyroidism on Osteoporosis

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Cite this article as: Yılmaz V, Umay E, Gündoğdu İ, Tezel N. Treatment Outcomes of Postmenopausal Osteoporosis in Patıents with Stable Hypothyroidism: A 5 Year Follow Up Retrospective Study. Erciyes Med J 2018; DOI: 10.5152/etd.2018.0065

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ABSTRACT

Objective: The aim of this study is to evaluate the efficacy of hypothyroidism on the treatment outcomes of postmenopausal osteoporosis (PMOP) treatment.

Materials and Methods: 50 patients with hypothyroidism and also diagnosed as PMOP according to lumbar and femur neck bone mass density (BMD) evaluation with dual X-ray absorptiometry (DXA) who did not receive any treatment for PMOP including calcium and vitamin D were included for the study. Control group was constituted by 47 patients with PMOP but have no comorbidity. Demographic features including age, height, weight, occupation, level of education, menarche and menopause age, clothing style, daily calcium intake, tobacco and/or alcohol consumption, daily physical activity level, personal history of fragility fracture or in mother and duration of hypothyroidism were recorded. Biochemical parameters including BMD scores, calcium, phosphate, alkaline phosphatase, parathormone, calcidiol, osteocalcine, urine calcium, phosphate levels and creatinine clearance were also recorded. Patients were treated with bisphosphonate, calcium and vitamin D and same parameters were evaluated at the end of first and fifth year.

Results: The average age of all individuals was 58.25±8.89 years and the average duration of hypothyroidism diagnosis was 4.00 years. The demographic features and biochemical parameters before PMOP treatment were not different between patient and control groups (p>0,005). BMD scores of both groups were significantly improved at the end of first and fifth years of treatment (p<0,005) but the variation of the scores were not different.

Conclusions: Hypothyroidism with stable or unstable thyroid functions does not effect PMOP treatment prognısis in Turkish population.

Keywords: Hypothyroidism, postmenopausal, osteoporosis, bone, quality

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INTRODUCTION

Thyroid hormones and vitamin D are endocrine molecules which have multipl functions in metabolism and act through their nuclear receptor signalling pathways (1). Most of the metabolic effects of thyroid hormones are mediated by triiodothyronine (T3) which is producted from a prohormone thyroxine (T4) (2). T4 has complex effects on bone metabolism including both stimulation of bone formation and resorption (3). Primary hypothyroidism is characterized by increased thyroid stimulating hormone (TSH) and decreased T3 levels (4). According to the National Health and Nutrition Examination Survey (NHANES III) the prevalence of hypothyroidism in United States is found 0,5% (5).

As T3 and T4 act in several metabolic pathways, their dysfunction is associated with broad range of metabolic disorders including osteoporosis, hypercholesterolemia, obesity and cardiovascular disease (6-8). Osteoporosis and increased risk of fracture are common in patients with hypothyroidism (9). Even subclinical hypothyroidism is reported to be in association with insufficient bone mineralization and decreased bone strength (10). However, the results of the studies about the association between TSH levels and bone mineral density (BMD) scores are controversial. Marhawa et al. (11) have found no correlation between TSH levels and T scores in Indian population. Like their study, Loida et al. (12) have found no difference in T scores, prevalence of vertebral and non-vertebral fractures in Puerto Rico population. On the other hand in contrast with these results, Kim et al. (13) suggested that lower TSH concentrations are associated with lower T scores in Korean male population.

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Except the study of Kısakol et al. (10), the relationship between hypothyroidism and osteoporosis in Turkish population was not examined previously. The aim of the present study is to evaluate the effect of hypothyroidism on prognosis of osteoporosis treatment in long term.

MATERIALS and METHODS

Study Design

The study was set as a retrospective cohort which evaluated 97 patients who were followed up by our outpatient clinic between January 2010-2015 and met WHO osteoporosis criteria.

50 patients who were diagnosed as postmenopausal osteoporosis (PMOP) with lomber and/or femur neck BMD screening but have no history of PMOP treatment including calcium and vitamin D, have comorbid hypothyroidism and treated with levothyroxine at least a year were conducted for patient group. Control group was constituted with 47 patients with PMOP at same age but have no comorbidity. Patients who had additional comorbidity except hypothyroidism or diagnosed with any comorbid disease during follow up, had taken PMOP treatment irregularly, under 50 years and had secondary osteoporosis or premature menopause were excluded.

Patients were informed about the study and their written consents were obtained before the study. The study was approved by the local Ethical Board (S.B Diskapi Yildirim Beyazit Education and Research Hospital Medical Research and Experimental Studies Ethical Board 26.01.2015 19/14) and was performed in accordance with the principles of the Declaration of Helsinki.

Demographics and Disease Characteristics

Demographic features of patients including age, height, weight, body mass index (BMI=weight/height^2, kg/m^2), educational level, number of pregnancy, age of menarche and

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menopause, daily calcium, coffee and tea consumption, smoking, daily exercise level, clothing style, maternal history of fracture and duration of hypothyroidism were recorded. Educational level was determined as “not reader and/or writer”, “only reader and/or writer”, “primary school degree” (5 years of formal education), “junior high school degree” (8 years of formal education), “high school degree” (11 years of formal education) or “university degree” (over 11 years of formal education). Clothing style was determined as “closed clothing” which refers to clothes that cover the body completely, “traditional clothing” which refers to clothes that cover arms and legs and “modern clothing” which refers to clothes that do not cover arms and legs. Daily calcium consumption was interrogated by questioning “everday”, “at least twice a week” or “never” usage of a 250 mililiters of milk, 30 grams of cheese or a 200 grams of yoghurt which consists 150 miligrams of calcium. Tea, coffee and alchol consumption was considered as “overuse” if it is over 150 miligrams/day and “normal” if it is under. Individuals who walk at least 30 minutes a day were accepted as “normal physically active” and if not accepted as “physically inactive”.

Measurements of BMD were done by using a DXA (Norland XR-46 system, Coopersurgical, Fort Atchinson, WI, USA). The BMDs of the lumbar spine (L1 to L4) and the hip region (total hip and femoral neck) were measured according to standard protocols and T- scores of the measurements were assessed. Biochemical parameters for all subjects were including serum calcium (Ca), phosphor (P), alkaline phosphatase (ALP), parathormone (PTH), TSH, calcidiol (25(OH)D3), osteocalcine (OC) and urine Ca and P levels.

Treatment

All individuals were instructed for daily PMOP exercises (range of motion, stretching and isokinetic exercises) and daily activities. Range of motion (ROM) exercises include shoulder, elbow, wrist, hip

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and ankle joints with 5 repetition twice a day and stretching exercises include muscles associated with these joints. Isokinetic exercises include non-weight bearing exercises with low force (e.g: low load high repetition exercises). For daily activities patients were allowed to choose one or more dynamic weight bearing exercises with low or high force like walking, jogging, jumping or running. 70 miligrams of alendronate weekly, 2500 miligrams of calcium carbonate (equivalent to 1000 miligrams of calcium ion) and 880 international units (IU) of vitamin D3 daily were prescribed for all subjects. All subjects were followed up during 5 years with same BMD values and biochemical measurements.

Comparisons

BMD values and biochemical parameters were compared in and between patient and control groups before treatment, one year and five years after treatment.

Sample size

A power analysis was performed using G Power 3.1.8. We determined that a sample size of 42 (for each group) would be a sufficient number of patients to provide an 80% power with a significance of 0.05, given an effect size of 0.3. The effect size was calculated to determine a 10% difference in DXA screening recommendation with a standard deviation of 10%.

Statistical Analysis

Data analyses were performed by Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) for Windows. The continuous variables were evaluated with the Kolmonorow-Smirnow test to determine if they were different from normal distribution and descriptive statistics were described as mean ± standard deviation and median (1^{st}-3^{rd} quartile) for

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continuous variables and frequencies and percentages (%) for nominal variables using Pearson chi-square test. Statistically significant differences in repeated measurements within the group were evaluated with the Wilcoxon Signed Rank test. In group comparisons, Bonferroni correction was performed to avoid estimated type 1 error and $p<0.017$ values were accepted as statistically significant. Parameters were compared in and between groups before treatment, one year and five years after treatment with Mann Whitney U test and $p<0.05$ scores were accepted as significant.

RESULTS

All the individuals were female and the average age of patient group was 59.10±8.70 years while average age of control group was 57.36±9.10 years. Most of the individuals had primary school degree (n=44, 45.4%) and housewife (n=87, 89.7%). The demographic features, BMD values and the biochemical parameters before treatment of the patient and control groups are given in Table 1 and Table 2.

Demographic features were not different between patient and control groups ($p>0.005$). Mean BMD score for total lumbar (L1-4) region was -2.63±1.02 while for femur neck was -2.42±1.03. In patients group, mean TSH level was 3.18±1.12 mIU/L (normal: 0.4-4.5 mIU/L), mean FT3 level was 2.48±1.27 pg/mL (normal: 2-4.4 pg/mL) and mean FT4 level was 1.13±0.72 pg/mL (normal: 0.7-2 pg/mL). In control group, mean TSH level was 3.21±1.08 mIU/L, mean FT3 level was 2.47±1.41pg/mL and mean FT4 level was 1.13±0.72 pg/mL. TSH, FT3 and FT4 levels were not significantly different between patient and control groups ($p=0.338$, $p=0.182$ and $p=0.114$ respectively). Biochemical parameters and BMD values were not different between patient and control groups.

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The biochemical parameters and BMD values of the subjects at first and fifth year of treatment are given in Table 3 and Table 4.

Biochemical parameters of the individuals at first and fifth years of the treatment were not different ($p>0.005$).

In group analysis, significant increase in total lumbar (L1-4) and femur neck T scores between the baseline and fifth year of treatment were found in patient ($p=0.001$ for each) and control group ($p=0.001$ for each). At fifth year of treatment, same parameters were found significantly improved compared to the first year both in patient ($p=0.003$ and $p=0.004$ respectively) and control group ($p=0.008$ and $p=0.002$ respectively).

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DISCUSSION

Osteoporosis is one of the major complications of thyroid dysfunction. Despite obvious increase of fracture risk, hypothyroidism is known to be associated with higher T scores compared to healty subjects (14). The counterregulation between thyroid hormones and PTH may be the potential mechanism for decreased bone turnover in patients with hypothyroidism (15). In the present study, PTH, calcidiol and osteocalcine levels were not significantly different between patient and control groups. We found slightly increased PTH and osteocalcine and decreased calcidiol levels in both groups due to osteoporosis of all conducted subjects. Increased PTH levels both in patient and control groups are related with poor calcium intake in both groups. However, we found daily calcium excretion in urine decreased due to the same cause.

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It has been proposed that both osteoblasts and osteoclasts have TSH receptors and thyroid dysfunction is related with both bone formation and resorption (16). Several studies indicate the correlation between hypothyroidism and increased risk fracture (17). But this issue is controversial. Some studies report an association between duration of hypothyroid period and subsequent risk of osteoporotic fractures in young and middle aged men but not in women (18) because of pronounced effects of hypothyroidism on gonadal steroids and low levels of testosterone (19). On the other hand, there is a general consensus suggesting that over treatment of hypothyroidism with levothyroxine may lead to excessive bone loss and increased risk of osteoporotic fractures (20). In our study we did not find any difference between the lumbar and femur neck T scores of the patient and control groups. Current study was conducted with female patients recieving levothyroxine treatment at least one year and in euthyroid stage. Further expert studies including men and patients who are not in euthyroid state may have different results.

Another controversial issue about the effect of hypothyroidism on PMOP treatment is the effect of levothyroxine treatment. Most of the previous studies about the effect of hypothyroidism on PMOP and bone metabolism had conducted with patients when they were in hypothyroid period (10,18). Patients with thyroid dysfunction who recieve levothyroxine treatment can not be classified as “hypothroid”, however it has been proposed that although levothyroxine theraphy compansed the metabolic dysfunction, underlying thyroid metabolism disorder might influence the metabolic processes including bone metabolism (21). Vestergaard et al. (22) noted an increased risk of fracture limited to forearms in patients with hypothyroidism who are over 50 years old. In another study of the same author, it was reported that there was an increase in the risk of any fracture within the first 10 years after the diagnosis of hypothyroidism regardless from levothyroxine treatment (10). Lee et al. concluded that the risk of hip fracture is increased in men over 65 years old with subclinical

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hypothyroidism but the effect of thyroxine treatment is unknown (23). In the present study, we evaluated patients with hypothyroidism in “euthyroid” period and our results are in association with recent data. We found no significant difference in lumbar BMD values between patient and control group suggesting that levothyroxine treatment have no effect on PMOP in Turkish population.

There are some limitations for the present study. We conducted the study with limited participants. We evaluated the patients in “euthyroid” period. Studies with larger patient population which evaluates the patients both in “hypothyroid” and “euthyroid” period may evaluate the exact effect of thyroid dysfunction on bone metabolism in patients with hypothyroidism.

In conclusion, hypothyroidism can be seen as a comorbid problem in Turkish postmenopausal patients with osteoporosis. The effects of subclinically hypothyroidism on PMOP before (10) but to our best knowledge this is the first study which evaluates the effect of thyroid dysfunction on PMOP in long term follow up in Turkish population. According to our results, we found no difference between BMD scores of the patients with PMOP and PMOP comorbid hypothyroidism. In long term, hypothyroidism has no significant effect on PMOP treatment with an antiresorptive agent, calcium and vitamin D.

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Table 1. Demographic features of the patient and control groups

Parameters	Patient Grup (n=50) mean±SD n (%)	Control group (n=47) mean±SD n (%)	p
Age (years)	59.10±8.70	57.36±9.10	0.339
BMI (kg/m²)	29.72±5.67	30.11±5.22	0.172
Educational level			
not reader and/or writer	0	1 (2.1)	0.122
only reader and/or writer	6 (12)	13 (27.7)	
primary school degree	13 (26)	18 (38.3)	
junior high school degree	26 (52)	7 (14.9)	
high school degree	2 (4)	4 (8.5)	
university degree	3 (6)	4 (8.5)	
Number of pregnancies	3.44±2.20	3.19±2.22	0.813
Menarche age (years)	14.04±1.47	14.34±1.80	0.974
Menopause age (years)	54.72±6.31	54.68±6.02	0.821
Fragility fracture before menopause	6 (12)	8 (17)	0.724
Daily Ca Intake			
Everyday	3(6)	4 (8.5)	0.218
At least twice a week	26 (52)	31 (66.0)	
Never	21 (42)	12 (25.5)	
Tea, coffee and alcohol consumption			
Overuse	12 (24)	8 (17)	0.137
Normal	38 (76)	39 (83)	
Clothing Style			
Closed clothing	1 (2)	3 (6.4)	0.131
Traditional clothing	42 (84)	34 (72.3)	
Modern clothing	7 (14)	10 (21.3)	
Physical Activity			
Normal physically inactive	38 (76)	33 (70.2)	0.163
Physically inactive	12 (24)	14 (29.8)	
Maternal history of fragility fracture	10 (20)	9 (19.1)	0.882

Values are expressed as mean±standard deviation, median (1st-3rd quartiles) or n(%). BMI: body mass index; Ca: calcium

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Table 2. BMD scores and biochemical parameters of patient and control groups before treatment

Parameters	Patient Grup (n=50) Median (1st-3rd quartile) n (%)	Control Grup (n=47) Median (1st-3rd quartile) n (%)	p
Total lumbar (L1-4) T score	-2.50 (-3.20_-1.42)	-2.60 (-2.82_-2.00)	0.094
Total femur neck T score	-2.60 (-3.30_-1.90)	-2.75 (-3.27_-2.06)	0.612
Serum Ca (9-11 mg/dl)*	7.90 (7.70-8.12)	7.80 (7.70-8.00)	0.725
Serum P (3-4.5 mg/dl) *	3.60 (2.90-4.10)	3.30 (3.00-3.90)	0.317
Serum ALP (30-120 U/l) *	58.50 (21.25-92.10)	41.50 (28.12-98.20)	0.521
Serum PTH (12-65 ng/L) *	54.10 (41.80-64.40)	48.50 (26.20-68.33)	0.823
Serum Calcidiol (20-40 ng/mL) *	11.03 (8.20-16.90)	13.40 (8.27-19.35)	0.331
Serum osteocalcine (3-13µg/L) *	12.60 (6.62-20.82)	14.25 (7.71-19.74)	0.178
24 hours urine Ca (50-150 mg/day)*	41.20 (24.61-69.30)	40.60 (18.50-61.68)	0.106
24 hours urine P (0.4-1.3 gr/day) *	0.82 (0.46-1.16)	1.07 (0.70-1.48)	0.158

Values are expressed as mean±standard deviation, median (1st-3rd quartiles) or n(%), Ca: calcium; P: phosphate; ALP: alkaline phosphatase; PTH: parathormone

Table 3. BMD scores and biochemical parameters of the subjects at first year of the treatment

Parameters	Patient Grup (n=50) Median (1st-3rd quartile), n (%)	Control Grup (n=47) Median (1st-3rd quartile), n (%)	P
Total lumbar (L1-4) T score	-1.90 (-3.32_-1.12)	-2.20 (-3.03_-1.18)	0.853
Total femur neck T score	-2.55 (-3.30_-1.72)	-2.50 (-2.97_-2.06)	0.918
Serum Ca (9-11 mg/dl)*	8.90 (8.65-12.45)	9.90 (9.72-10.05)	0.351
Serum P (3-4.5 mg/dl) *	3.60 (3.15-4.20)	3.50 (3.15-4.10)	0.721
Serum ALP (30-120 U/l) *	66.50 (29.25-137.21)	72.02 (37.12-136.40)	0.684
Serum PTH (12-65 ng/L) *	38.20 (20.70-60.87)	30.50 (23.95-66.28)	0.472
Serum Calcidiol (20-40 ng/mL) *	19.85(11.54-30.80)	18.50 (11.60-25.40)	0.261
Serum osteocalcine (3-13µg/L) *	17.68 (12.76-21.25)	19.75 (14.42-20.90)	0.918
24 hours urine Ca (50-150 mg/day)*	48.56 (41.15-62.28)	49.42 (40.19-59.27)	0.832
24 hours urine P (0.4-1.3 gr/day) *	0.51 (0.35-1.34)	0.47 (0.40-1.05)	0.083

Values are expressed as mean±standard deviation, median (1st-3rd quartiles) or n(%), Ca: calcium; P: phosphate; ALP: alkaline phosphatase; PTH: parathormone

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Table 4. BMD scores and biochemical parameters of the subjects at fifth year of the treatment

Parameters	Patient Grup (n=50) Median (1^{st}-3^{rd} quartile), n (%)	Control Grup (n=47) Median (1^{st}-3^{rd} quartile), n (%)	P
Total lumbar (L1-4) T score	-1.30 (-2.05_-0.60)	-1.21 (-2.40_-0.75)	0.147
Total femur neck T score	-1.40 (-2.30_-0.52)	-1.30 (-2.43_-0.92)	0.231
Serum Ca (9-11 mg/dl)*	9.20 (8.80-11.28)	9.18 (8.80-13.90)	0.845
Serum P (3-4.5 mg/dl) *	3.10 (2.70-4.15)	3.80 (3.20-3.95)	0.344
Serum ALP (30-120 U/l) *	68.12 (41.18-95.62)	59.08 (35.10-87.11)	0.193
Serum PTH (12-65 ng/L) *	44.58 (26.31-66.57)	42.60 (11.40-72.30)	0.261
Serum Calcidiol (20-40 ng/mL) *	20.45 (12.57-29.80)	26.50 (15.10-31.60)	0.658
Serum osteocalcine (3-13µg/L) *	13.09 (7.30-18.65)	14.02 (12.11-18.05)	0.586
24 hours urine Ca (50-150 mg/day)*	58.20 (52.14-75.17)	55.96 (42.41- 68.24)	0.712
24 hours urine P (0.4-1.3 gr/day) *	0.72 (0.34-1.08)	0.61 (0.47-0.82)	0.335

Values are expressed as mean±standard deviation, median (1st-3rd quartiles) or n (%), Ca: calcium; P: phosphate; ALP: alkaline phosphatase; PTH: parathormone

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