Osteoporosis Frequency in Hyperthyroidism, Assessment of Osteoporosis Therapy Schemes in Hyperthyroid Osteoporotic Patients

Hipertiroidide Osteoporoz Sıklığı, Hipertiroidisi Olan Osteoporotik Hastalarda Osteoporoz Tedavi Şemalarının Değerlendirilmesi

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Abstract
Objective: Hyperthyroidism causes secondary osteoporosis. The aims of our study were to asses how frequent osteoporosis is seen in hyperthyroidism, can euthyroidism reverse bone loss in hyperthyroid osteoporotic patients, do anti resorptive agents provide additional benefit when added to antithyroid drugs and if so which one is most beneficial.
Material and Methods: This study was performed retrospectively in hyperthyroid patients who were diagnosed between 1999 and 2003 in Eskişehir Osmangazi University Faculty of Medicine Endocrinology Department. All patients were still hyperthyroid despite antithyroid therapy at the time of first bone mineral densitometry. Second bone mineral densitometry was performed after at least 8 months of therapy for osteoporosis (calcitriol, biphosphonates or calcitonin plus 500 g/day calcium). The bone mineral densities were measured with dual energy X ray absorptiometry. 61 patients (48 females and 13 men) met the criteria. There was also 38 healthy controls (24 females and 14 men).
Results: In this retrospective study we found that osteoporosis frequency in hyperthyrodism is 72,13 % and adding anti resorptive agents to anti thyroid therapy is beneficial. This benefit seems more apparent with calcitriol and biphosphonates.
Conclusion: Ostetoporosis is still frequent in hyperthyrodism. Adding anti resorptives to anti thyroid therapy, especially calcitriol or biphosphonates, can be recommended.*Turk Jem 2007; 11: 37-43*
Key words: Hyperthyroidism, osteoporosis, frequency, therapy

Özet
Amaç: Hipertiroidi sekonder osteoporoza neden olan bir durumdur. Çalımamızın amaçları hipertiroidide osteoporoz sıklığını, hipertiroidisi olan osteoporotik hastalarda ötiroidizm sağlanmasının kemik kaybını geri döndürüp döndüremeyeceğini, anti rezorptif ajanların anti tiroid ilaçlara eklenmesinin ilave yarar sağlayıp sağlamayacağını ve eğer sağlıyorsa hangisinin daha yararlı olduğunu değerlendirmektir.
Gereç ve Yöntemler: Bu çalışma 1999-2003 yılları arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde tanı alan hipertiroidili hastalarda retrospektif olarak gerçekleştirilmiştir.İlk kemik mineral dansitometrisi sırasında tüm hastalar antitiroid tedaviye rağmen hipertiroiddi. İkinci kemik mineral dansitometrisi en az 8 aylık osteoporoz tedavisi (kalsitriol, bifosfonat ya da kalsitonine ilave 500 mg/gün kalsiyum) sonrası elde edildi. Kemik mineral yoğunluğu dual enerjili X ışını absorpsiyometrisi ile ölçüldü. Altmış bir hasta (48 kadın ve 13 erkek) kriterleri karşıladı. Otuz sekiz sağlıklı kontrol (24 kadın ve 14 erkek) de alındı.
Bulgular: Biz bu retrospektif çalışmada hipertiroidide osteoporoz sıklığını %72.13 oranında ve anti tiroid tedaviye anti rezorptif ajanlar eklenmesini yararlı olarak bulduk. Bu yararlı etki kalsitriol ve bifosfonatlarla daha belirgin görülmektedir.
Sonuç: Hipertiroidide osteoporoz sıklığı hala fazladır. Anti tiroid tedaviye anti rezorptif ajanalrın, özellikle kalsitriol ve bifosfonatların, eklenmesi tavsiye edilebilir. *Turk Jem 2007; 11: 37-43*
Anahtar kelimeler: Hipertiroidi, osteoporoz, sıklık, tedavi

Introduction

Osteoporosis (OP) is a skeletal disorder characterized by low bone mass and micro-architectural deterioriation of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). Secondary OP refers to osteoporosis in which an underlying cause or factor other than those attributable to postmenopausal state or aging can be identified. It is important to look for secondary causes and aggravating factors because these can be reversible (2).

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There is no doubt that untreated hyperthyroidism has an adverse effect on the skeleton causing high turn-over osteoporosis and fractures. Recently hyperthyroidism is diagnosed earlier and treated more effectively. Although severe skeletal complications are rarely seen, there is evidence for reduced bone mineral density in patients with thyrotoxicosis (3).
The aims of our study were to asses how frequent osteoporosis is seen in hyperthyroidism, can euthyroidism reverse bone loss in hyperthyroid osteoporotic patients, do anti resorptive agents provide additional benefit when added to antithyroid drugs and if so which one is most beneficial.

Material and Methods

This study was performed retrospectively in hyperthyroid patients who were diagnosed between 1999 and 2003 in Eskişehir Osmangazi University Medical Faculty Endocrinology Department.
Diagnosis of hyperthyroidism (Basedow-Graves, toxic adenoma or toxic multinodular goitre) was made by physical examination, thyroid function tests and radioactive iodine uptake added to thyroid scintigraphy. First bone density measurements were made in hyperthyroid period. Patients were given therapy for osteoporosis and used their medications at least for 8 months. Group 1 received 0.50 microgram / day calcitriol peroral (po) and included 13 patients. Group 2 received 400 mg/day cyclic etidronate po or 10 mg/day or 70 mg/week alendronate po and included 23 patients. Two biphosphonates are included in the same group because there were only 8 patients in etidronate group. Group 3 received 200 IU/day salmon calcitonin intranasally and included 11 patients. Five hundred mg/day calcium (Ca) po were given to all groups. Bone density measurements were repeated after therapy. There was also a group of patients with two bone density measurements repeated after at least 12 months but without therapy for osteoporosis (Group 0). This group included 14 patients. Total number of patients was 61 (48 female, 13 male). All patients continued anti-thyroid therapy (propylthiouracil or metimazole) and β-blocker (propranolol) during this period. The control group included a total of 38 (24 female, 14 male) healthy persons.
Exclusion criteria were as follows: 1) Age under 30 years 2) Type 2 diabetes mellitus 3) Therapy for any type of malignancy 4) Connective tissue diseases 5) Pancreas or biliary system operations, intestinal malabsorption 6)Lactation or pregnancy in last 1 year 7) Using hormone, diuretic, anticonvulsant, anti-acid drugs 8) Glucocorticoid therapy for ophtalmopathy or other reasons 9) Alcohol abuse 10) Osteoporosis diagnosed before hyperthyroidism 11) High levels of serum creatinine 12) Bone density measurements made in different centers or by different devices.
Daily calcium excretion (calciuria) is measured by Modular Roche auto-analyser from urine collected during 24 hours and expressed as mg/day. For 24 hour urine collection patients were told to empty their bladder and discard the urine into toilet. All urine in the next 24 hour period were passed into clean bottles. Exactly 24 hours after starting the collection bladder was emptied into the bottle this time. Calcium (Ca) and phosphorus (P) are measured as mg/dl, albumine is measured as g/dl and alkaline phophatase (ALP) is measured as uIU/ml by Modular Roche auto-analyser. TSH (thyrotropin) (uIU/ml) , Free T3 (FT3) (pg/ml) and Free T4 (FT4) (ng/dl) are measured by E-170 Roche auto-analyser. Parathyroid hormone (PTH) (pg/ml) is measured by Immulite 2000 DPC auto-analyser. Ca is expressed as corrected Ca calculated by formula of Corrected Ca= (4 - albumine) + serum Ca.
DXA by Hologic-QDR 4500 W fan beam X ray bone densitometer is used for bone mineral density measurements and results are expressed as g / cm^2. Measurements are obtained from both spine (L_1, L_2, L_3, L_4, L_{1-4}) and hip (trochanteric, intertrochanteric , Ward's triangle, total).

Statistics

Results are given as mean ± standard error (S.E) for homogenously distributed parameters and as median for non- homogenously

Table 1. Comparison of patient and control groups according to clinical characteristics and initial laboratory parameters

Sex (Female)	Patient (n=48) % 78.6 (48 / 61)	Control (n=24) % 63.1 (24 / 38)	ns
Menopause	Patient (n=26) % 54.1 (26 / 48)	Control (n=8) % 33.3 (8 / 24)	ns
Age (year) Mean ± S.E.	Patient (n=61) 47.34 ± 1.50	Control (n=38) 44.68 ± 1.39	ns
BMI (kg / m^2) Mean ± S.E.	Patient (n=61) 25.66 ± 0.60	Control (n=37) 27.70 ± 0.90	ns
Ca (mg / dl) Mean ± S.E.	Patient (n=61) 9.51 ± 0.09	Control (n=38) 9.47 ± 0.08	ns
P (mg / dl) Mean ± S.E.	Patient (n=61) 3.80 ± 0.06	Control (n=37) 3.41 ± 0.06	***
Calciuria (mg / day) Mean ± S.E.	Patient (n=51) 153.41 ± 15.77	Control (n=32) 180.70 ± 17.93	ns
ALP (U / L) Median	Patient (n=60) 277.50	Control (n=38) 176.50	***
PTH (pg / ml) Median	Patient (n=49) 49.60	Control (n=37) 34.60	**

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

distributed parameters. Student-t test , Pearson, ANOVA, Tukey and Dunnett tests are used for parametric variables. Wilcoxon Signed Ranks test, Spearman, Mann-Whitney, Kruskal Wallis and Ki-square tests are used for non-parametric variables.

Results

Table 1 shows the clinical features and initial laboratory parameters of patient and control groups. Bone mineral densities of patients before therapy for osteoporosis were lower than control group (Table 2). Osteoporosis was defined as a value for BMD >2.5 SD lower than young adult mean and 44 of 61 hyperthyroid patients had osteoporosis at least in one of the regions measured (72.13%). Thirteen of 44 patients had osteoporosis only in one region (29.54%).
When we compared clinical features of each group (Group 0,1,2,3) the oldest group was group 3 ($p<0.05$ for group 0, $p<0.01$ for group 1 and $p<0.05$ for group 2). Body mass index (BMI) and duration of hyperthyroidism were similar in all groups ($p>0.05$) (Table 3). When we compared clinical features of each group with healthy controls only calcitonin group was found older ($p<0.01$).

Table 2. Comparison of bone densities with control group before therapy

Variables	Mean ± S.E.		
	Patient (n=61)	Control (n=38)	Significance
L1 (g / cm^2)	0.698± 0.018	0.848 ± 0.022	***
L2 (g / cm^2)	0.775 ± 0.021	0.931 ± 0.022	***
L3 (g / cm^2)	0.822 ± 0.016	0.931 ± 0.023	***
L4 (g / cm^2)	0.849 ± 0.015	0.969 ± 0.024	***
L1-4 (g / cm^2)	0.795 ± 0.015	0.930 ± 0.020	***
Femur neck (g / cm^2)	0.681 ± 0.013	0.752 ± 0.028	*
Trochanter (g / cm^2)	0.572 ± 0.013	0.696 ± 0.016	***
İntertrochanter (g / cm^2)	0.878 ± 0.019	1.060 ± 0.028	***
Ward's triangle (g / cm^2)	0.545 ± 0.019	0.673 ± 0.025	***
Total (g / cm^2)	0.754 ± 0.016	0.890 ± 0.020	***

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

Table 3. Comparison of clinical features of each group

Variables	Mean ± S.E.			
	Group 0 (n=14)	Group 1 (n=13)	Group 2 (n=23)	Group 3 (n=11)
Age (year)	45.92 ± 2.67	41.61 ± 2.99	46.43 ± 2.34	57.81 ± 3.15
BMI (kg/m^2)	26.97 ± 1.06	23.84 ± 1.07	25.39 ± 0.91	26.69 ± 2.05
Duration of hyperthyroidism (month)	26.57 ± 8.57	23.69 ± 6.48	13.00 ± 2.75	43.36 ±19.50

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

Table 4. Comparison of bone densities with control group after therapy

Variables	Mean ± S.E.		
	Patient (n=61)	Control (n=38)	Significance
L1 (g / cm^2)	0.734 ± 0.020	0.848 ± 0.022	***
L2 (g / cm^2)	0.819 ± 0.018	0.931 ± 0.022	***
L3 (g / cm^2)	0.847 ± 0.017	0.931 ± 0.023	**
L4 (g / cm^2)	0.882 ± 0.016	0.969 ± 0.024	**
L1-4 (g / cm^2)	0.825 ± 0.017	0.930 ± 0.020	***
Femur neck (g / cm^2)	0.708 ± 0.017	0.752 ± 0.028	ns
Trochanter (g / cm^2)	0.607 ± 0.013	0.696 ± 0.016	***
İntertrochanter (g / cm^2)	0.930 ± 0.018	1.060 ± 0.028	***
Ward's triangle (g / cm^2)	0.561 ± 0.022	0.673 ± 0.025	**
Total (g / cm^2)	0.795 ± 0.016	0.890 ± 0.020	**

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

When we compared bone mineral densities obtained after osteoporosis therapy, the results were still lower than control group except femur neck. (Table 4).

Table 5 shows bone mineral densities before and after therapy for each group. Statistically significant increases are also mentioned as % values.

When we compared the patients according to being euthyroid or not at the time of second bone mineral densitometry there was no statistically significant difference between bone densities before and after osteoporosis therapy both in euthyroid and still hyperthyroid patients in group 0. In group 1 there was statistically significant difference only in total region in still hyperthyroid patients and both in L1 and total regions in euthyroid patients. Statistically significant differences in still hyperthyroid group 2 were observed in trochanter

Table 5. Comparison of bone densities for each group before and after therapy

Variables	Group	n	Mean ± S.E.		Significance	% increment
			Before	After		
L1 (g / cm²)	0	14	0.773 ± 0.033	0.788 ± 0.040		
	1	13	0.769 ± 0.025	0.825 ± 0.033	*	7.28
	2	23	0.671 ± 0.027	0.721 ± 0.023	**	7.45
	3	11	0.579 ± 0.048	0.582 ± 0.053		
L2 (g / cm²)	0	14	0.878 ± 0.027	0.888 ± 0.034		
	1	13	0.789 ± 0.070	0.877 ± 0.042		
	2	23	0.755 ± 0.023	0.806 ± 0.023	**	6.75
	3	11	0.670 ± 0.046	0.689 ± 0.045		
L3 (g / cm²)	0	14	0.935 ± 0.028	0.932 ± 0.036		
	1	13	0.857 ± 0.023	0.891 ± 0.041		
	2	23	0.792 ± 0.020	0.825 ± 0.020	*	4.16
	3	11	0.701 ± 0.037	0.729 ± 0.035		
L4 (g / cm²)	0	14	0.955 ± 0.026	0.962 ± 0.032		
	1	13	0.890 ± 0.025	0.931 ± 0.038		
	2	23	0.816 ± 0.021	0.865 ± 0.021	**	6.00
	3	11	0.735 ± 0.031	0.758 ± 0.029		
L1-4 (g / cm²)	0	14	0.891 ± 0.025	0.897 ± 0.031		
	1	13	0.847 ± 0.021	0.885 ± 0.035		
	2	23	0.764 ± 0.021	0.809 ± 0.020	**	5.89
	3	11	0.676 ± 0.037	0.695 ± 0.038		
Feur neck (g / cm²)	0	14	0.730 ± 0.025	0.752 ± 0.030		
	1	13	0.720 ± 0.030	0.789 ± 0.041	*	9.58
	2	23	0.683 ± 0.016	0.714 ± 0.021	*	4.53
	3	11	0.565 ± 0.029	0.543 ± 0.021		
Trochanter (g / cm²)	0	14	0.630 ± 0.026	0.645 ± 0.023		
	1	13	0.619± 0.028	0.672 ± 0.023	**	8.56
	2	23	0.570 ± 0.013	0.613 ± 0.016	***	7.54
	3	11	0.448 ± 0.029	0.467 ± 0.023		
Intertrochanter (g / cm²)	0	14	0.958 ± 0.036	0.988 ± 0.030		
	1	13	0.927 ± 0.045	1.005 ± 0.034	*	8.41
	2	23	0.864 ± 0.025	0.923 ± 0.025	***	6.82
	3	11	0.745 ± 0.040	0.784 ± 0.038	*	5.23
Total (g / cm²)	0	14	0.818 ± 0.031	0.832 ± 0.027		
	1	13	0.803 ± 0.032	0.879 ± 0.034	**	9.46
	2	23	0.750 ± 0.020	0.797 ± 0.022	***	6.26
	3	11	0.626 ± 0.036	0.644 ± 0.032		
Ward's triangle (g / cm²)	0	14	0.584 ± 0.032	0.579 ± 0.038		
	1	13	0.633 ± 0.044	0.680 ± 0.053		
	2	23	0.550 ± 0.023	0.579 ± 0.026		
	3	11	0.378 ± 0.033	0.361 ± 0.029		

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

Table 6. Comparison of euthyroid and still hyperthyroid patients at the time of second bone mineral densitometry

			Hyperthyroid				Euthyroiod		
		n	Before	After	p	n	Before	After	p
			Mean ± S.E.				Mean ± S.E.		
Group 0	L 1	7	0.773 ± 0.063	0.752 ± 0.066	ns	7	0.773 ± 0.028	0.824 ± 0.048	ns
	L 2		0.881 ± 0.053	0.860 ± 0.046	ns		0.875 ± 0.022	0.915 ± 0.053	ns
	L 3		0.911 ± 0.047	0.890 ± 0.045	ns		0.958 ± 0.031	0.975 ± 0.054	ns
	L 4		0.904 ± 0.039	0.929 ± 0.044	ns		1.005 ± 0.024	0.996 ± 0.045	ns
	L 1-4		0.871 ± 0.047	0.864 ± 0.047	ns		0.911 ± 0.019	0.931 ± 0.042	ns
	Neck		0.720 ± 0.038	0.729 ± 0.044	ns		0.740 ± 0.037	0.776 ± 0.042	ns
	Troch		0.646 ± 0.036	0.628 ± 0.030	ns		0.614 ± 0.039	0.662 ± 0.036	ns
	Int		0.970 ± 0.057	0.957 ± 0.045	ns		0.947 ± 0.049	1.019 ± 0.040	ns
	Tot		0.822 ± 0.045	0.815 ± 0.040	ns		0.815 ± 0.046	0.849 ± 0.038	ns
	Wd's		0.556 ± 0.042	0.522 ± 0.047	ns		0.612 ± 0.051	0.636 ± 0.054	ns
Group 1	L 1	5	0.795 ± 0.057	0.802 ± 0.069	ns	8	0.752 ± 0.022	0.840 ± 0.037	*
	L 2		0.842 ± 0.045	0.833 ± 0.041	ns		0.755 ± 0.112	0.905 ± 0.064	ns
	L 3		0.838 ± 0.033	0.846 ± 0.027	ns		0.870 ± 0.032	0.919 ± 0.064	ns
	L 4		0.867 ± 0.040	0.884 ± 0.024	ns		0.905 ± 0.034	0.960 ± 0.059	ns
	L 1-4		0.838 ± 0.032	0.844 ± 0.030	ns		0.852 ± 0.030	0.910 ± 0.053	ns
	Neck		0.733 ± 0.067	0.807 ± 0.086	ns		0.712 ± 0.031	0.778 ± 0.046	ns
	Troch		0.646 ± 0.067	0.685 ± 0.055	ns		0.602 ± 0.022	0.665 ± 0.020	*
	Int		0.912 ± 0.113	0.998 ± 0.073	ns		0.936 ± 0.033	1.010 ± 0.037	ns
	Tot		0.803 ± 0.081	0.889 ± 0.074	*		0.802 ± 0.023	0.874 ± 0.035	ns
	Wd's		0.661 ± 0.082	0.705 ± 0.096	ns		0.616 ± 0.054	0.665 ± 0.066	ns
Group 2	L 1	10	0.709 ± 0.017	0.745 ± 0.026	ns	13	0.641 ± 0.046	0.702 ± 0.037	*
	L 2		0.775 ± 0.016	0.818 ± 0.032	ns		0.740 ± 0.040	0.797 ± 0.034	**
	L 3		0.832 ± 0.016	0.841 ± 0.023	ns		0.762 ± 0.032	0.813 ± 0.032	*
	L 4		0.856 ± 0.017	0.886 ± 0.028	ns		0.785 ± 0.033	0.848 ± 0.031	**
	L 1-4		0.799 ± 0.013	0.827 ± 0.026	ns		0.736 ± 0.036	0.796 ± 0.031	**
	Neck		0.697 ± 0.008	0.717 ± 0.017	ns		0.673 ± 0.029	0.712 ± 0.035	*
	Troch		0.572 ± 0.015	0.617 ± 0.010	**		0.569 ± 0.022	0.611 ± 0.027	**
	Int		0.855 ± 0.027	0.911 ± 0.019	ns		0.870 ± 0.040	0.933 ± 0.043	**
	Tot		0.739 ± 0.015	0.789 ± 0.017	**		0.758 ± 0.034	0.804 ± 0.038	**
	Wd's		0.583 ± 0.026	0.610 ± 0.022	ns		0.525 ± 0.034	0.554 ± 0.042	ns
Group 3	L 1		-	-		8	0.558 ± 0.063	0.564 ± 0.066	ns
	L 2		-	-			0.653 ± 0.060	0.674 ± 0.056	ns
	L 3		-	-			0.678 ± 0.048	0.711 ± 0.043	ns
	L 4		-	-			0.721 ± 0.042	0.749 ± 0.039	ns
	L 1-4		-	-			0.657 ± 0.049	0.680 ± 0.048	ns
	Neck		-	-			0.553 ± 0.034	0.539 ± 0.022	ns
	Troch		-	-			0.429 ± 0.036	0.456 ± 0.029	ns
	Int		-	-			0.743 ± 0.054	0.783 ± 0.049	*
	Tot		-	-			0.624 ± 0.048	0.651 ± 0.039	ns
	Wd's		-	-			0.350 ± 0.035	0.344 ± 0.035	ns

*- p<0.05; **- p<0.01; ***- p<0.001; ns- p>0.05; SE- standart error

and total regions but in all regions except ward's triangle in euthyroid group 2. We could not compare still hyperthyroid group 3 patients before and after osteoporosis therapy because of the few number of patients in this group. In euthyroid group 3 patients statistically significant difference was observed only in intertrochanteric region (Table 6).

There was 10.7% increase in still hyperthyroid group 1.The increases were 11.7% for L1 and 10.46% for trochanter in euthyroid group. The increases in hyperthyroid group 2 were 7.86% for trochanter and 6.76% for total. The increases were 9.51% for L_1, 7.70% for L_2, 6.69 % for L_3 , 8.02% for L_4 , 8.15% for L_{1-4} , 5.79% for femur neck, 7.38% for trochanter, 7.24% for intertrochanter and 6.06% for total in euthyroid group.

Although the increases were not statistically significant, bone densities were also increased in other euthyroid groups. However bone densities continued to decrease in hyerthyroid group without osteoporosis therapy and also increased in groups receiving osteoporosis therapy despite hyperthyroidism.

In Table 7 female patients are compared according to being in pre or postmenopausal period. However this comparison was not possible for each group because of the few number of patients.

Discussion

In the present study we examined osteoporosis frequency and effects of hyperthyroidism on bone in our hyperthyroid outpatients. There has been no general agreement on the incidence of osteopenia in hyperthyroidism or the recovery of the mineral loss after treatment of hyperthyroidism (4).

In a retrospective study involving a total of 1015 female patients, osteoporosis was detected in 384 (38%) when patients with spine bone mineral density 2.5 standard deviation below a reference range established using data obtained from a Turkish population of normal healthy women using dual energy X-ray absorptiometry (T score less than -2.5) accepted as having osteoporosis. A secondary cause has been found in 33 (8.6%) of the 384 osteoporotic patients thyrotoxicosis (n=10), parathyroid adenoma (n=10) and glucocorticoid administration (n=7) constituted 82% of the causes of osteoporosis (5).

Osteoporosis frequency is found 72.13% in our study according to the definition of osteoporosis 'A value for BMD or BMC >2.5 SD lower than young adult mean' (6). When compared with healthy controls bone densities of hyperthyroid patients were found lower both in spine and hip. Acotto et al compared BMD in women with untreated hyperthyroidism and age-matched controls in a cross-sectional study. BMD of lumbar spine, femoral neck and total skeleton were lower in hyperthyroid patients (7).

Thyrotoxicosis increases bone turnover. This accentuation of the normal remodelling sequence increases the number of osteoclasts and resorption sites, and alters the ratio of resorptive to formative bone surfaces. One result of this increase in bone resorption is hypercalcemia which has been reported to occur in approximately 20% of patients with thyrotoxicosis. Hypercalciuria is also common in patients with thyrotoxicosis (8).

Ca and calciuria of our patients were found similar with control group. We think performing measurements under anti-thyroid therapy and propranolol have prevented hypercalcemia. Because treatment with antithyroid drugs usually normalizes serum Ca within a few weeks (9,10,17) and it has been reported that propranolol improves the hypercalcemia in some patients (11).

Hyperphosphatemia and hyperphosphaturia is also common in hyperthyroidism (12). Total ALP increases in approximately 30% (13) and bone specific ALP increases in approximately 60-70 % (14) of patients. ALP and P levels were higher in our patient group as also reported in literature . We did not measure ALP isoenzymes but liver damage was excluded by normal levels of other liver enzymes, abdominal ultrasonography and viral markers.

PTH levels were higher in our patient group although usually reported as supressed in hyperthyroidism (8) . However a rise in plasma PTH from a supressed low normal level during the thyrotoxic status to high normal during anti-thyroid therapy is also reported (12). Since thyroid hormones can increase tissue respon-

Table 7. Comparison of female patients according to being pre or postmenopausal

	Mean ± S.E. Before Therapy			Mean ± S.E. After Therapy		
	Premenopausal (n=22)	Postmenopausal (n=26)	p	Premenopausal (n=22)	Postmenopausal (n=26)	p
L_1 (g / cm^2)	0.732 ± 0,018	0.607 ± 0.028	**	0.793 ± 0.022	0.618 ± 0.028	***
L_2 (g / cm^2)	0.782 ± 0.042	0.717 ± 0.028	ns	0.867 ± 0.027	0.727 ± 0.027	**
L_3 (g / cm^2)	0.864 ± 0.020	0.761 ± 0.028	**	0.889 ± 0.029	0.774 ± 0.026	**
L_4 (g / cm^2)	0.877 ± 0.020	0.800 ± 0.029	*	0.927 ± 0.027	0.823 ± 0.027	*
L_{1-4} (g / cm^2)	0.828 ± 0.018	0.728 ± 0.027	**	0.873 ± 0.024	0.743 ± 0.025	**
Femur neck (g / cm^2)	0.692 ± 0.015	0.626 ± 0.020	*	0.726 ± 0.021	0.638 ± 0.026	*
Trochanter (g / cm^2)	0.571 ± 0.013	0.528 ± 0.020	ns	0.623 ± 0.016	0.548 ± 0.018	**
İntertrochanter (g / cm^2)	0.858 ± 0.023	0.836 ± 0.029	ns	0.951 ± 0.027	0.864 ± 0.026	*
Total (g / cm^2)	0.750 ± 0.019	0.710 ± 0.024	ns	0.811 ± 0.024	0.733 ± 0.024	*
Ward's triangle (g / cm^2)	0.592 ± 0.024	0.457 ± 0.025	***	0.636 ± 0.030	0.452 ± 0.027	***

*- $p<0.05$; **- $p<0.01$; ***- $p<0.001$; ns- $p>0.05$; SE- standart error

siveness to catecholamines and catecholamines can stimulate PTH secretion the elevated levels of PTH can also be secondary to thyrotoxicosis (15).

Some studies suggest that euthyrodism may improve thyrotoxic bone disease (16-18). In our study bone densities also increased in Group 0 despite still hyperthyroid patients.However the increments were not statistically significant probably because of the few number of patients. Moreover longer euthyroidism period could make the results statistically significant.

Bone densities of patients after osteoporosis therapy added to antithyroid therapy were found still lower than control group. In several studies it has been shown that bone density does not return to normal after anti-thyroid therapy (19,21) . However there are studies showing normalization of bone density after anti-thyroid therapy also (21,22). The result in our study may be due to the short duration of osteoporosis therapy.

When we compared bone densities with control group after osteoporosis therapy results were found similiar with healthy controls in Group 1, but Group 1 had the highest bone densities before therapy also. Bone densities of Group 3 were lower than healthy controls almost in all regions. We think this is probably due to oldest mean age, most number of menopausal women, longest hyperthyroidism period and lowest bone densities before therapy .

Patients in Group 2 received etidronate and alendronate but we assessed them together because of the few number of patients in two groups. The increments in biphosphonate group were found lower than calcitriol group probably due to lower bone densities before therapy and higher number of post menopausal women. Additionally Group 1 had the shortest hyperthyroidism period. Lower increments in Group 3 is again probably due to the group characteristics mentioned above.

When we compared female patients according to being pre or postmenopausal bone densitites before and after therapy were found lower in postmenopausal group. Jodar et el also found the effects of hyperthyroidism on bone is more apparent in postmenopausal group (23).

One of the aims of our study was to evaluate which osteoporosis therapy was most beneficial in hyperthyroid osteoporotic patients. Since this was a retrospective study number of patients decraesed after excluding who do not meet the criteria. Most of the patients were hyperthyroid women with Basedow Graves. As a result using steroid for ophtalmopathy was the most frequent exclusion criteria. There was a group who have already been receiving therapy for postmenopausal osteoporosis and were also excluded.

According to our present data we found that adding anti resorptive agents to anti thyroid therapy is beneficial in osteoporosis seen in hyperthyroid patients. This benefit seems more apparent with calcitriol and biphophonates. More detailed data can be obtained by larger prospective studies.

References

1. Dennison E, Cooper C. Osteoporosis. In Bertagna XY, Fischer JA, Groop L, Schoemaker J, Serio M, Wass JAH (Eds) Endocrinology and Metabolism Mc Graw-Hill International (UK) Ltd. 2001, 271-82.
2. Taxel P, Kenny A. Differantial diagnosis and secondary causes of osteoporosis. Clin Cornerstone 2000; 2: 11-21.
3. Allain TJ, McGregor AM. Thyroid hormones and bone. J Endocrinol 1993; 139: 9-18.
4. Toh SH, Claunch BC, Brown PH. Effect of hyperthyroidism and its treatment on bone mineral content.Arch Intern Med 1985; 145: 883-6.
5. Çakır B, Odabaşı E, Turan M, Güler S, Kutlu M. Secondary osteoporosis in women : A retrospective analysis. Archiv Gynecol Obstet 2002; 226: 214-7.
6. Raisz LG, Kream BE, Lorenzo JA. Metabolic Bone Disease. In Wilson JD, Foster DW, Kronenberg HM, Larsen PR (Eds) Williams Textbook of Endocrinology. 9 th Edition. W.B.Saunders Company. 1998, 1211-29.
7. Gomez Acotto C, Schott AM, Hans D, et al. Hyperthyroidism influences ultrasound bone measurement of os calcis. Osteoporosis Int 1998; 8: 455-9.
8. Baran DT, Braverman LE. Thyroid hormones and bone mass. J Clin Endocrinol Metab 1991; 72: 1182-3.
9. Bijlsma JWJ, Durumsa SA, Roelofs JMM, der Kinderen PJ. Thyroid function and bone turnover. Acta Endocrinol 1983; 104: 4249.
10. Mosekilde L, Christiansen MS, Melsen F, Sorensen NS. Effect of antithyroid treatment on serum calcium-phosphorus metabolism in hyperthyroidism. I: Chemical quantities in serum and urine. Acta Endocrinol 1978; 87: 743-50.
11. Feely J. Propranolol and the hypercalcemia of thyrotoxicosis.Acta Endocrinol 1981; 98: 528-32.
12. Pantazi H, Papapetrou PD. Changes in parameters of bone and mineral metabolism during therapy for hyperthyroidism. J Clin Endocrinol Metab 2000; 85: 1099-106.
13. Siddiqi A, Burrin JM, Noonan K, James I, Wood DF, Price CP, Monson JP. A longitudinal study of markers of bone turnover in Grave's disease and their value in predicting bone mineral density. J Clin Endocrinol Metab 1997; 82: 753-9.
14. Tibi L, Patrick AW, Leslie P,Toft AD, Smith AF. Alkaline phosphatase isoenzymes in plasma in hyperthyroidism. Clin Chem 1989; 35: 1427-30.
15. Barsotti MM, Targovnik JH, Verso TA. Thyrotoxicosis, hypercalcemia and secondary hyperparathyroidism. Arch Intern Med 1979; 139: 661.
16. Rosen CJ, Adler RA. Longitudinal changes in lumbar bone density among thyrotoxic patients after attainment of euthyroidism. J Clin Endocrinol Metab 1992; 75: 1531-4.
17. Langdahl BL, Loft AG, Eriksen EF, et al. Bone mass, bone turnover, calcium homeostasis and body composition in surgically and radioiodine treated former hyperthyroid patients. Thyroid 1996; 6: 169-75.
18. Diamond T, Vine J, Smart R, Butler P. Thyrotoxic bone disease in women: A potentially reversible disorder. Ann Intern Med 1994; 120: 8-11.
19. Krolner B, Jorgensen JV, Nielsen SP. Spinal bone mineral content in myxoedema and thyrotoxicosis effect of thyroid hormone(s) and antithyroid treatment. Clin Endocrinol (oxf) 1983; 18: 439-46.
20. Jodar E, Monoz-Torres M, Escobar-Jimenez F, et al. Antiresorptive therapy in hyperthyroid patients : Longitudinal changes in bone and mineral metabolism. J Clin Endocrinol Metab 1997; 82: 1989-94.
21. Rosen CJ, Adler RA. Longitudinal changes in lumbar bone density among thyrotoxic patients after attainment of euthyroidism. J Clin Endocrinol Metab 1992; 75: 1531-4.
22. Nielsen HE, Mosekilde L, Charles P. Bone mineral content in hyperthyroid patients after combined medical and surgical treatment. Acta Radiol Oncol Radiat Phys Biol 1979; 18: 122-8.
23. Jodar E, Monoz-Torres M, Escobar-Jimenez F, Quesada-Charneco M, Lund del Castillo JD. Bone loss in hyperthyroid patients and in former hyperthyroid patients controlled on medical therapy: influence of aetiology and menopause. Clin Endocrinol (Oxf) 1997; 47: 279-85.