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Bone Markers Status in Graves' disease before and after Treatment

P Tofighi, P Shoushtarizadeh, A Hossein-nezhad, V Haghpanah, B Rajabi-pour, Kh Adabi, S Sharghi, *B Larijani

Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Iran

Abstract

Background: Bone turnover is reported to increase in favor of resorption in overt hyperthyroidism and the rate of resorption is associated with the levels of thyroid hormones. As persistent increase in bone turn over is responsible for accelerated bone loss, patients with Graves' disease may have increased risk for osteoporosis. The aim of this study was to determine relationship between Graves' disease and bone markers.

Methods: The subjects of our study were 31 consecutive untreated GD patients and 37 normal volunteers who were matched on sex proportion and age ranging was diagnosed by suppressed levels of TSH and elevated level of free T3 and free T4 and positive thyroid receptor antibody. Through a clinical trial study executed in endocrinology and metabolism research center, we investigated the relationship between serum osteocalcin & cross-laps with Graves' disease and then kinds of treatment with PTU and methimazole after 8 weeks follow up.

Results: No significant differences in age and sex between patients and controls were found. Significant differences in serum bone markers and thyroid hormones were detected between patients and controls before therapy ($p< 0.001$). After treatment we found a significant improvement and returning to normal range in all serum lab tests. There were not any differences in the effect of treatment on thyroid hormones and bone markers between two groups.

Conclusion: We found close relationship between Graves' disease and bone markers. So that treatment of Graves' disease can improve bone turn over. These findings indicated that early diagnosis and management of Graves' disease can be effective for osteoporosis prevention in these patients.

Keywords: *Graves' disease, Bone Turnover, Hyperthyroidism, Osteoporosis*

Introduction

Graves' disease (GD) is an autoimmune thyroid disease in which anti-TSH receptor autoantibodies cause hyperthyroidism (1-3).

The annual incidence in women over a 20 yr period is around 0.5 per 1000 (4) It is the most prevalent autoimmune disorder in the United States (4) with the highest risk of onset between the ages of 40 and 60 yr. Graves' disease is about 5- to 10-fold common in women compared to men (5). Approximately 90% of patients who are younger than 50 yr old have a firm, diffuse goiter of variable size, as compared with about 75% of older patients (6).

Those with a history of thyrotoxicosis extended more than a year may have severe and premature osteoporosis. A metaanalysis of 289 published studies on the effect of hyperthyroidism on bone fragility found that hyperthyroid patients had decreased bone mineral density and increased risk of fracture (5). In addition, it was reported that bone collagen breakdown is increased in thyrotoxicosis (7, 8). The thyroid hormones affect bone cells by mechanism, which is not well known. It seems that the osteoclast response to T3 is mediated by osteoblast (9, 10). The effect of T3 on bone is proposed to be through some soluble mediators secreted by osteoblasts (11).

There is no curative therapy for Grave's disease. Current treatment is to reduce the thyroid's hormone production (12). They consist of antithyroid drugs, radioactive iodine, and surgery (4). Carbimazole, its active metabolite methimazole, and propylthiouracil all inhibit thyroid peroxidase and thus the synthesis of thyroid hormone. Propylthiouracil also blocks the ex-

***Corresponding author:** Tel: +98 21 84902476, Fax: +98 21 88220037, E-mail: emrc@sina.tums.ac.ir

trathyroidal deiodination of thyroxine to triiodothyronine, which may lead to a more rapid initial reduction in serum triiodothyronine concentrations and possibly to a more rapid resolution of symptoms of hyperthyroidism, as compared with the other drugs.

In practice, this action is of value only in patients with severe hyperthyroidism or thyrotoxic crisis, and carbimazole and methimazole offer the advantages that fewer tablets are needed for initial treatment and that once-daily doses are effective at the start of treatment in patients with mild hyperthyroidism and after the first three to four weeks of treatment in those with more severe hyperthyroidism (5). Approximately 30 to 40 percent of patients who are treated with an antithyroid drug remain euthyroid 10 yr after the discontinuation of antithyroid drug therapy, which means that the Graves' disease has remitted (5).

There is not much study on the relationship between Graves' disease and osteoporosis. In addition, there are limited studies on effectiveness of treatment on the improvement of bone metabolism with treatment. The aim of our study was to evaluate the relationship between Graves's disease and osteoporosis, and the efficiency of its treatment on bone markers.

Material and Methods

This clinical trial study was conducted in the out patients clinic of Endocrine & Metabolism Research Center (EMRC) of Tehran University. The case group consists of 32 newly diagnosed Graves disease that had not started the treatment. They were compared with 37 healthy volunteer age, sex and BMI matched controls.

The diagnosis of the Graves disease was based on the level of thyroid hormones, antithyroid antibodies, physical exams, and endocrinologists' clinical diagnosis.

Exclusion criteria include pregnancy, diabetes, non-cooperation, and treatment for Graves' disease. For all participants inform consent was taken and a questionnaire including their general characteristics, past medical history, and primary examination completed. In each person, 10 ml of venous blood was drained from the left arm. Second blood samples were drained after 8 wk of treatments. The concentrations of TSH receptor, T4, T3, T3up, osteocalcin, crosslaps, FT3, and FT4 were measured. ELISA kits were used to measure osteocalcin and crosslaps (Nordic Bioscience, Denmark) and RIA was used for thyroid function tests (Kavoshyar Co.) The patients were divided randomly in two treatment groups based on received PTU and metimazole. Both groups underwent treatment and followed for 8 wk. The primary dose of PTU (Iran Hormone) was 300 mg/kg 3 times a day and metimazole (Loghman) 30 mg/day 3 times a day for about 4 wk.

After the second appointment, the secondary dose was adjusted in relation with the response to the therapy. The secondary dose of PTU was 100 mg/day two times a week and of metimazole 10 mg/day two times a day.

The data were entered to the SPSS software (Ver. 11.5) and analyzed. The student T-Test was used to compare the mean values.

In case where parametric tests were not able to show the differences or the sample did not have normal distribution, we used Mann-Whitney U test. Chi square was used to compare the frequency of variables and if not possible, Exact Fisher Test was used. *P* less than 0.05 were considered significant.

Results

Over all 31 people were entered in the case group and 37 people in the control group. The mean values of age in the case and control groups were 39.39±15.68 and 34.44±12.62 yr respectively. There were not significant differences between the mean values of age in two groups. Body Mass Index (BMI) in the case and control groups were 23.62±4.29 kg/m^2 and 23.8 ±3.91 kg/m^2 before the treatment respectively, which did not show significant differences. 64.5% in the case and 67.6% in the control groups were

women that mean that there were not significant differences in sex distribution between the two groups. The amount of thyroid hormones in case and control group is compared in table 1.Significant differences was detected in serum content before the treatment in two groups. In the case group there were 14 patients (45.2%) received Methimazole and 17 patients received PTU. There were not significant differences in age, sex, serum thyroid hormones, and BMI distribution between two groups (Table 2). Significant differences in thyroid hormones were detected after completion of treatment in two groups with the first result. But in terms of thyroid hormones change there were not significant differences between two groups. In the Methimazole group more changes were seen in the serum TSH. (P= 0.03) (Table 4). Serum bone markers showed decrease in bone turn over in both group (Methimazole and PTU).There were significant changes in serum osteocalcin and cross-laps in Methimazole group. Serum osteocalcin and cross-laps decreased 75.16% and 47.14% after treatment respectively. However, in the PTU group, only serums cross laps showed significant differences with 49.15% decrease (Table 3).
In comparison, there were not significant differences in bone marker changes in two groups.

Table 1: Characteristics of participants and chemical parameters concentrations in base line of study

Variables / Groups	Case Mean ±SD	Control Mean ±SD	*P*-value
Age (years)	39.39±15.68	34.44±12.62	0.12
Sex (female percent)	64.5%	67.6%	0.4
BMI (kg/m^2)	23.62±4.29	23.80±3.91	0.4
T_3(nmol/L)	551.58±217.77	148.68±26.43	0.000
T_4(nmol/L)	237.39±50.08	108.97±17.86	0.000
TSH(mIU/L)	0.12±0.10	1.70±1.42	0.000
Anti TPO Ab(IU/ml)	10764.23±14503.19	2306.96±7984.84	0.009
Anti TG Ab(IU/ml)	325.68±738.22	31.91±48.41	0.044
Free T_3(pnmol/L)	17.70±7.14	7.31±0.87	0.000
Free T_4(pnmol/L)	60.95±17.71	16.35±2.46	0.000
Thyroglobulin(mg/L)	60.00±148.15	8.66±11.97	0.078
Anti TSH receptor(IU/ml)	27.63±40.12	0.46±0.16	0.001

Table 2: Comparison of serum chemical parameters concentrations between two treatment groups before treatment

Variables / Groups	Methimazole Mean±SD	PTU Mean±SD	*P*-value
T_3(nmol/L)	590.43±253.59	519.59±185.09	0.376
T_4(nmol/L)	247.50±54.99	229.06±45.62	0.316
TSH(mIU/L)	0.12±0.13	0.13±0.08	0.788
Anti TPO Ab(IU/ml)	10824.36±14833.52	10714.71±14683.63	0.984
Anti TG Ab(IU/ml)	274.07±696.33	368.18±789.69	0.730
Free T_3(pnmol/L)	18.69±8.45	16.88±6.01	0.492
Free T_4(pnmol/L)	63.82±18.62	58.58±17.13	0.421
Thyroglobulin(mg/L)	59.94±159.27	60.05±143.33	0.998
Anti TSH receptor(IU/ml)	19.46±29.76	34.36±46.82	0.311

Table 3: Comparison of serum chemical parameters changes between two treatment groups after treatment

Group-Mean & SD Variables	Methimazole			Propyltiouracil		
	Before treatment Mean ±SD	After Treatment Mean ±SD	*P*	Before treatment Mean ±SD	After Treatment Mean ±SD	*P*
T_3(nmol/L)	584.92±274.58	205.33±82.66	0.000	512.81±188.97	273.38±122.31	0.000
T_4(nmol/L)	248.42±59.29	106.25±45.34	0.000	227.19±46.44	122.94±31.62	0.000
TSH(mIU/L)	0.12±0.13	4.46±7.57	0.074	0.12±0.08	0.11±0.13	0.810
Anti TPO Ab(IU/ml)	10127.08±14678.60	3005.03±8525.35	0.082	9509.38±14270.20	9649.0±14182.77	0.985
Anti TG Ab(IU/ml)	301.58±752.29	239.33±531.45	0.368	379.44±814.17	343.50±750.55	0.091
Free T_3(pnmol/L)	18.53±9.14	8.34±2.51	0.001	16.32±5.74	9.56±2.93	0.000
Free T_4(pnmol/L)	62.82±19.85	106.25±45.34	0.002	57.44±17.01	122.94±31.62	0.000
Thyroglobulin(mg/L)	69.74±171.01	24.62±33.33	0.30	63.06±147.47	45.30±120.49	0.038
Anti TSH receptor (IU/ml)	21.94±31.58	10.30±12.44	0.086	35.71±48.01	39.81±55.32	0.378
Osteocalcin(ng/ml)	39.54±16.21	29.72±16.07	0.042	29.66±12.58	30.15±10.37	0.880
Cross laps(IU/ml)	1.16±0.46	0.55±0.32	0.002	1.18±0.47	0.58±0.20	0.000

Table 4: Mean and standard deviation of hormones changes after the treatment in two groups of patients

Variables	Methimazole Mean±SD	PTU Mean±SD	*P*
T_3(nmol/L)	10.19±8.01	6.76±4.11	0.152
T_4(nmol/L)	45.03±15.06	37.23±14.74	0.182
TSH Ab(IU/ml)	11.63±21.34	4.10±18.06*	0.045
BMI(kg/m^2)	1.92±1.47*	1.27±1.61*	0.267
Osteocalcin(ng/ml)	9.81±14.76	0.48±12.69	0.058
Cross laps(ng/ml)	0.60±0.53	0.59±0.49	0.975

* The amounts have decreased

Discussion

Hyperthyroidism affects approximately 2% of women and 0.2% of men (12). The most common cause of hyperthyroidism is Graves' disease (12) with an annual incidence of around 0.5 per 1000 in women over a 20-year period (4). Graves' disease is 1⁄5 to 1⁄10 as common in men as in women (5) .In this study the number of women were more than men which was consistent with other studies .In our study we found elevated bone markers in hyperthyroid state, significantly higher than the control group, similar to other studies (13-15).

In this study the patients were divided into two treatment groups (Methimazole and Propylthiouracile). The results demonstrate that thyroid hormones and Graves disease parameter had improved in both groups in accordance with other studies done in this field .Also there were no significant differences in thyroid hormone changes in both treated groups. Duration of treatment was 8 wk which was consistent with other studies which showed that 4-8 wk is the optimal time for effects of these drugs (15, 16).

The side effects of Methimazole and PTU are little, and these drugs have lower side effects (1-5%) such as rashes, arthralgia, fever and leucopenia in comparison with other therapies (16). We encounter no side effect in our study.

Our results demonstrate decrease in bone turnover after 8 wk concomitant with improvement in thyroid hormones. In a similar study with PTU, they found elevated osteocalcin levels in

hyperthyroid state, significantly higher than the control group, and when these patients were in euthyroid state, serum levels decreased, still being higher than the control group (13). Our results were in agreement with their findings. In another study with Methimazole they found that hyperthyroidism due to Graves' disease causes an increase of serum levels of osteocalcin (14). In addition, there are some studies, which were done on thyrotoxicosis and hyperthyroidism, which shows bone marker decrease after treatment (15, 16).

Over all, Graves' treatment has positive effects on chemical parameters and changes in these parameters are in accordance with thyroid hormones. Most of the studies showed that Graves' treatment may cause improvements in bone markers after the euthyroid state. Some studies evaluated Osteocalcin as a bone formation marker after Graves' treatment (13-16). However, the limitation of these studies is that they did not measure bone resorption markers like crosslaps at the same time. Taken as a whole, there are not many studies that were demonstrated relationship between Graves' disease and bone markers. Accordingly, our study has originality, despite its limitation, to show this relationship.

In conclusion, Graves' disease is consistent with high bone turnover, which can lead to osteoporosis. Early detection and management of Graves' disease can be effective for osteoporosis prevention in these patients. Treatment of Graves' disease not only improves thyroid hormones and chemical parameters of the disease, but also decrease bone turnover in favor of bone resorption.

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