Advanced Age and Mild Thyrotoxicosis are Associated with Nodular Goiter in Graves Disease

Graves Hastalarında Tiroid Nodülü Varlığı İleri Yaş ve Ilımlı Tirotoksikoz ile İlişkilidir

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Abstract

Objective: The primary goal of this study is to evaluate predictors of nodular goiter in Graves Disease (GD).

Materials and Methods: A total of 202 consecutive patients (mean age: 45; 145 female, 57 male) were enrolled. All patients were treated with antithyroid drugs as initial therapy. TSH, FT3, FT4, TRAb, ATPO, and ATG were measured. Radioactive iodine uptake and thyroid ultrasonography were performed, and thyroid volume and nodule diameter were assessed. Ultrasound-guided fine needle aspiration was performed on thyroid nodules ≥ 8mm.

Results: Diffuse goiter was detected in 51% of patients. Solitary nodules were detected in 16%, and multi-nodular disease in 33%. Mean nodule diameter was 8.82 mm. Nodular disease was slightly more common in women (p=0.063). Patients with nodular GD were older (p=0.004), had lower levels of FT3 (p=0.016) and TRAB (p=0.002) when compared with subjects with diffuse GD. Age (OR:6.867) was the independent variable predicting nodular GD.

Conclusions: Increased prevalence of nodules was associated with advanced age and milder thyrotoxicosis. Apoptosis of thyroid follicular cells due to excess iodine might interfere with nodule formation, and lead to diffuse goiter in severe thyrotoxicosis. Because of increased rate if malignancy in GD, comprehensive evaluation of thyroid nodules of any size is mandatory. *Turk Jem 2009; 13: 1-4*

Key words: Thyroid nodule, Graves disease

Özet

Amaç: Bu çalışmanın birincil amacı Graves Hastalığı'ndaki (GH) nodüler guatr belirleyicilerinin ortaya konmasıdır.

Gereç ve Yöntemler: Çalışmaya 202 ardışık hasta dahil edildi (ortalama yaş: 45, 145 kadın). Tüm hastalara başlangıç tedavisi olarak antitiroid ilaçlar uygulandı. TSH, FT3, FT4, TRAb, ATPO ve ATG, radyoaktif iyot (I-131) uptake, tiroid ultrason değerlendirmeleri, nodül çapı ve tiroid hacmi ölçümleri yapıldı. Sekiz mm ve üzerinde çapa sahip tiroid nodüllerinden ince iğne aspirasyon yöntemi ile biyopsi alındı.

Bulgular: Hastaların %51'de difüz guatr mevcuttu. Hastaların %16'sında tek nodül, %33'ünde birden çok nodül saptandı. Ortalama nodül çapı 8.82 mm idi. Nodüler hastalık kadınlarda ılımlı olarak daha sık olarak saptandı (p=0.063). Nodüler guatr saptananan hastalar daha yaşlı (p=0.004), daha düşük FT3 (p=0.016) ve daha düşük TRAb düzeylerine (p=0.002) sahip idi. Yaş nodüler Graves Hastalığı ile ilişkili tek bağımsız belirleyici idi (OR:6.867).

Tartışma: Graves hastalarında nodül saptanma oranı yüksek ve ılımlı tirotoksikoz ve ileri yaş ile ilişkili olarak saptandı. Tirotoksikozu daha belirgin hastalardaki diffüz guatr, foliküler hücrelere tirotoksikozun derecesi ile doğru orantılı olarak girişi artan iyotun foliküler hücrelerde apopitoza neden olması ile açıklanabilir. Literatürde Graves hastalığı seyrinde tiroid kanseri gelişim riskinin arttığı gösterilmiştir. Bu nedenden ötürü nodüler Graves hastalığında nodül boyutundan bağımsız olarak ileri inceleme gerekliliği söz konusudur. *Turk Jem 2009; 13: 1-4*

Anahtar kelimeler: Tiroid nodülü, Graves hastalığı

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Introduction

Thyroid nodules are common in the general population; the prevalence of thyroid nodules detected by ultrasonography (US) is 20-76% (1). Aging, female gender, and ionizing radiation are the most common risk factors associated with increased prevalence of thyroid nodules. The association of hyperthyroidism and nodular thyroid disease is arousing interest because of the increased likelihood of developing thyroid cancer (2,3). In recent studies, the rate of thyroid malignancy in Graves Disease (GD) was shown to be between 8 and 17% in North America, whereas the risk of thyroid cancer is about 5% in all thyroid nodules regardless of their size (4-6).

In GD, factors associated with the presence of thyroid nodules have not been evaluated extensively. In one study, the rate of US-detected nodules larger than 8 mm was 33.6%. Furthermore, in the same study, half of the nodules developed during follow-up, suggesting a causative role of GD in nodule development (7). In a more recent study, the incidence of thyroid nodules was found to be 35% in GD (8). Several studies have evaluated the clinical characteristics of patients with or without nodules, and the effect of thyroid function and the degree of thyrotoxicosis on nodularity.

The aim of this study was to investigate the prevalence of nodular GD and the relationship of clinical characteristics and thyrotoxicosis and nodularity.

Materials and Methods

Two hundred and two consecutive patients with Graves' disease (mean age: 45 years; 145 female, 47 male) were enrolled into the study. Subjects were recruited from patients admitted to Dokuz Eylul University, Division of Endocrinology and Metabolism clinic for management of thyrotoxicosis. Diagnosis of GD was based on the presence of clinical and biochemical thyrotoxicosis [suppressed thyrotropin (TSH) and/or elevated free tri-iodothyronine (FT3) and/or free thyroxine (FT4) and positive TSH receptor antibody (TRAb)], diffuse or nodular goiter, and increased radioactive iodine (RAI) uptake.

All patients were treated with antithyroid drugs (ATD) as initial therapy. Thyroid US was performed using a real-time US scanner (HDI 5000, Advanced Technology Laboratories, Bothel, WA, USA) with 7- to 15-MHz linear transducers at the time of diagnosis. Thyroid and nodule dimensions, vascular pattern of thyroid parenchyma and nodules, and pathological lymphadenopathy were recorded. Thyroid volume was calculated with the following formula (height x width x depth x 0.524 for each lobe) (9). Nodule sizes were measured in 3 dimensions, and the greatest dimension was used in analysis. Nodule characteristics were reported, and nodule(s) of greater than 8 mm were evaluated by US-guided fine-needle aspiration (FNA). In cases where US was negative for nodules, but pathological examination of the thyroidectomy material revealed the presence of nodules, the diameter reported by the pathologist was used in the analysis.

The thyroid uptake study was performed 4 and 24 hours after the oral administration of 370 kBq I-131 using a specialized thyroid probe. The uptake percentage was calculated using the counts obtained from the thyroid bed and the mid thigh (as a background measurement). Normal values are; 5-15% at 4 hours, and 15-25% at 24 hours.

In 69 cases with nodular GD, ^{99m}Tc Scintigraphy was performed to evaluate nodule activity. The thyroid scintigraphy was obtained with a pinhole collimator 15 minutes after the injection of 185 MBq of Tc-99m pertechnetate. A 64x64 matrix and 200.000 counts were used for the imaging.

Patients were asked to have follow-up visits every six weeks to assess thyroid hormone levels, complete blood count, and liver enzymes. Patients who had childbearing potential, thyroid nodules, or ophthalmopathy were advised to have total thyroidectomy as the definitive treatment. Radioactive iodine therapy was recommended in case of diffuse goiter and low TRAb levels. Patients who refused either surgery or RAI therapy, or who were not eligible for surgery because of comorbidities or advanced age were followed with ATD for 12 to 18 months.

Neuro-ophthalmologic examination was performed at the initial diagnosis. In cases without ophthalmopathy, follow-up at 6-month intervals was suggested. Patients with thyroid ophthalmopathy were closely monitored.

Assays

Free T3 (normal range 1.8-4.2 pg/mL) and free T4 (normal range 0.8-1.9 ng/dL) levels were determined using immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, USA). Anti-thyroid peroxidase antibody (Anti TPO), anti-thyroglobulin antibody (Anti Tg), and serum TSH levels were measured using solid phase chemiluminescent immunometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, USA). TRAb (<9 U/L: negative for TRAb, 9-14 U/L: borderline and >14 U/L positive for TRAb) was measured with a radio-receptor assay (RIAZEN TSH-R-Ab, ZenTech, Belgium).

Statistical analysis

All data are shown as the mean±SD. Statistical analyses were performed using the SPSS (SPSS, Inc., Chicago, IL, USA) software. Continuous variables were compared by Independent Samples T-Test or One-way ANOVA. Categorical variables were compared by Chi-square statistics. Correlation analysis was performed by Pearson test. Determination of factors predicting the presence of nodules was performed by logistic regression analysis. The possible factors associated with nodule diameter were evaluated by linear regression analysis. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

The mean age of the patients was 45.3±13.5 years. There were 145 women and 57 men. At diagnosis, FT3 level was 9.43±6.14 pg/mL, FT4 level was 3.94±2.02 ng/dL, and TSH level was 0.02±0.07 mIU/mL. Thyroid volume was 21.19±16.64 cm^3. Radioactive iodine uptake at 4 and 24 hours was 39.78±20.00% and 54.47±17.58%, respectively. Ophthalmopathy was present in 22% of the patients (n=45). Definitive treatment was administered in 164 cases: [ATD 42% (n=69), RAI therapy 21% (n=35), total thyroidectomy 37% (n=60)]. Recurrent disease was observed in 5.4% of the patients (n=11).

Characteristics of nodular GD

In 51% of the patients (n=103), diffuse goiter was detected. Solitary or multiple thyroid nodules were detected in 49% of the patients (n=99). Solitary nodules were found in 16% (n=33), and multi-nodular disease was detected in 33% (n=66). Mean nodule diameter was 8.82±6.13 mm., Nodular goiter was found in 77 of 145 women with GD (53.1%). The rate of nodular GD in men was 38.5% (22/57) (p=0.063). $Tc^{99}m$ scintigraphy was performed in 46 of 99 patients with nodular GD. In 20 patients, nodule diameter was below the detection threshold. The nodules were hypoactive or normoactive in 16 patients. Hyperactive nodules were detected in five patients, and mixed nodular activity (hypoactive and hyperactive nodules) was detected in five patients.

When the patients were divided into two groups by the presence of nodules, it was demonstrated that patients with nodular GD were older (48.1 vs 42.6 years p=0.004), had milder elevations in FT3 (8.3 vs 10.4 pg/mL, p=0.016), TRAB (20.1 vs 42.8, p=0.002) and FT4 (3.6 vs 4.2 ng/dL, p=0.063) levels. Radioactive iodine uptake, TSH (0.022 vs 0.029, p=0.509), ATPO (345 vs 360, p 0.807), ATG (338 vs 349, p=0.888), thyroid volume (22.9 cm^3 vs 19.6 cm^3 p=0.185) and ophthalmopathy rate (23% vs 28% p=0.461) were not significantly different between patients with nodules and those without (Table 1).

The comparison of patients with solitary or multiple nodules showed that age (46.0 vs 49.2 p=0.268), FT4 (3.53 vs 3.72 ng/dL p=0.677), FT3 (7.87 vs 8.52 pg/mL p=0.609), TSH (0.035 vs 0.015 mIU/mL p=0.399), ATPO (382.5 vs 327.7 p=0.550), ATG (240.0 vs 384.3 p=0.271), and radioactive iodine uptake did not differ between groups. Patients with multiple nodules had higher TRAb levels (24.64 vs 11.49 p=0.008) and increased thyroid volume (25.86 cm^3 vs 16.65 cm^3 p=0.004).

In logistic regression analysis, adjusting for age, gender, FT4, FT3, TRAb, ATPO, ATG, thyroid volume, 4-hour and 24-hour RAI uptake, we demonstrated that age (OR:6.867, p=0.009) was the significant independent variable predicting nodular GD (Table 2). Nodule diameter was found to be correlated with 4-hour RAI uptake (r=0.226 p=0.033), TRAb (r=0.221 p=0.009), and thyroid volume (r=0.488 p=0.0001). Linear regression analysis, after adjusting for age, gender, free thyroid hormone levels, thyroid autoantibodies, thyroid volume, and radioactive iodine uptake, showed that thyroid volume is the sole independent variable associated with nodule diameter (beta=0.446 p=0.0001).

Malignancy

The rate of thyroid malignancy in cases evaluated with FNA cytology and/or thyroidectomy material (n=77) is 3.89% (n=3). All of the cancers were thyroid papillary carcinoma. There were two females and one male, with a mean age of 48.3±13.5 years. The mean diameter of the tumors was 4 mm. In one of the cases, preoperative US was negative for nodules, and in other two cases, FNA was benign.

Discussion

The prevalence of thyroid nodules and thyroid cancer has been reported to be increased in patients with GD. Dobyns et al. reported the prevalence of palpable nodules to be 15.8% in 36 050 patients treated for hyperthyroidism in a cooperative study (10). In GD, sonographic evaluation of the thyroid gland has led to the demonstration of increased prevalence of nodules (33.6% for nodules >8mm) (7). Prevalence of nodules in GD was found to be 49% in our study group.

In different studies, the reported prevalence of thyroid nodules varies between 10 and 31% (4,8,10-13). The relatively higher rate in our study may be associated with iodine deficiency in our region. Endemic goiter is an important public health problem in Turkey; legislation for mandatory iodization of household salt was passed in July 1999. The factors associated with increased nodularity in GD have not been clearly demonstrated. In our study, advanced age was the main predictor of nodular GD (odds ratio: 6.869, p=0.009). Similarly, Kim et al. showed that advanced age was the only significant variable predicting nodularity in GD (14).

We observed that nodule prevalence is higher in patients with lower levels of FT3, FT4, and TRAb, and to some extent, lower levels of RAI-uptake. Interestingly, Kim et al. demonstrated similar findings in their prospective study (14). The mechanism behind increased iodine-uptake-associated of diffuse goiter in GD is unknown, but several mechanisms could be involved. It was previously demonstra-

Table 1. Clinical characteristics of study participants

	Nodular GD (n=99)	Diffuse GD (n=103)	p value
Age	48.1±13.2	42.6±13.3	0.004
Gender (F/M)	77/22	68/35	0.063
FT3 (pg/ml)	8.3±5.5	10.4±6.4	0.016
FT4 (ng/dl)	3.6±1.9	4.2±2.0	0.063
TSH (μIU/ml)	0.029±0.070	0.022±0.077	0.498
ATPO (IU/ml)	345.8±421.3	360.0±394.8	0.807
ATG (IU/ml)	335.7±715.8	349.6±656.9	0.888
TRAb (U/l)	20.1±29.6	42.8±62.6	0.002
Thyroid volume (cm^3)	22.9±18.8	19.6±14.2	0.185
RAI uptake 4 hours (%)	36.1±18.4	42.8±21.0	0.067
RAI uptake 24 hours (%)	52.3±15.9	56.6±18.9	0.182
Nodule diameter (mm)	8.82±6.13	-	-
Definitive treatment* (ATD/RAI/TT)	32/18/31	37/17/29	0.701

TSH: thyrotropin, FT3: free tri-iodothyronine, FT4: free thyroxine (FT4), TRAb: TSH receptor antibody and RAI, radioactive iodine uptake. (* For 164 patients)

Table 2. Logistic regression analysis evaluating independent variables predicting nodular GD

	B	Odds ratio	p value
Age	0.049	6.867	0.009
Gender	0.222	0.177	0.674
FT3	-0.029	0.315	0.575
FT4	0.059	0.180	0.671
ATPO	-0.001	0.850	0.357
ATG	0.000	0.424	0.515
TRAb	-0.014	2.683	0.101
Thyroid volume	0.021	1.644	0.200
RAI uptake 4 hours	0.006	0.057	0.812
RAI uptake 24 hours	-0.025	1.021	0.312

FT3: free tri-iodothyronine, FT4: free thyroxine (FT4), Anti TPO: Anti-thyroid peroxidase antibody, Anti Tg: anti-thyroglobulin antibody, TRAb: TSH receptor antibody and RAI, radioactive iodine uptake

ted that excess iodine might lead to apoptosis of thyroid follicular cells in vitro (15). This effect may intercept with nodule formation. Furthermore, a negative association between higher TRAb levels and nodular disease is evidence against mediation of nodule formation by TSH receptor stimulation in the thyroid gland.

In our study, the sole variable related to nodule diameter was thyroid volume (size of goiter); however, we did not demonstrate thyroid volume to be a predictor of nodularity per se in GD. Mean nodule diameter in our cohort was 8.8 mm. This nodule size is below 10 mm, which the majority of the guidelines suggest as the lower limit for indication of FNA in patients without risk factors for thyroid cancer. Despite the variable rate of thyroid cancer among patients with GD, thyroid malignancy, especially papillary carcinoma, was reported to be more common in some studies (2,7,8,14,16). Furthermore, as TSH stimulates growth of metastatic differentiated thyroid cancer expressing the TSH receptor, it is possible to hypothesize that high levels of TRAb might stimulate thyroid cancer growth and early metastatic spread, thus negatively affecting prognosis. When all these data are taken into consideration, it can be suggested that the threshold for performing FNA should be lowered in patients with nodular GD.

The rate of thyroid cancer in cases evaluated with FNA material and/or a thyroidectomy specimen was found to be 3.89% in our cohort. That is quite similar to the results of a prospective study by Kim et al. (14), and not to be higher than that in euthyroid subjects. The reported frequency of histological diagnosis of thyroid cancer in patients with GD undergoing thyroidectomy is highly variable. Possible reasons for the discrepancy between results might include different genetic background and different environmental factors. The overall prevalence of malignancy in our study group was not evaluated because not every individual with a US detected nodule underwent FNA or thyroidectomy. Because of this limitation, the rate of detected malignancy may not reflect the true prevalence.

In conclusion, patients with GD should be evaluated comprehensively for the presence of nodules, because the prevalence is significantly higher than the prevalence derived from epidemiological data obtained from large cohort studies. The current guidelines advising FNA from thyroid nodules ≤10 mm in diameter could be inaccurate in patients with nodular GD because the majority of the nodules are < 10 mm. Early evaluation and pathological diagnosis is of vital importance because the exposure of thyroid malignancy to TRAb may stimulate tumor growth.

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