Original Article

Prediction of the recurrence risk of Graves' disease after antithyroid drug therapy

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Abstract

Objective: This study aimed at observing the prognostic factors for Graves' disease (GD) recurrence after treatment with antithyroid drugs.

Patients and Methods: Clinical data for 247 patients with primary GD hyperthyroidism diagnosed in the endocrinology department of our hospital between March 2014 and February 2017 were collected. Age, sex, thyroid size, thyroid hormone levels, thyrotropin receptor antibody (TRAb), thyroglobulin antibody, thyroid peroxidase antibody, urinary iodine, and other prognostic factors before and after treatment were analyzed and compared.

Results: After ATD treatment, 151 cases were in remission and 96 cases were not. The mean age at diagnosis was 37.3 ± 14.0 years in the remission group and 31.2 ± 12.2 years in the nonremission group ($P = 0.032$). The levels of free triiodothyronine (FT_3) in the nonremission group and remission group were 25.7 ± 8.4 and 18.3 ± 9.1 pmol/L, respectively. The proportion of patients with goiter and thyroid-associated orbitopathy was higher in the nonremission group than the remission group. Similarly, both the FT_3/FT_4 ratio (4.63 ± 1.08 and 3.72 ± 0.69, $P = 0.020$) and TRAb level (27.4 ± 10.7% and 18.1 ± 9.8%, $P = 0.001$) significantly increased. Logistic regression analysis indicated that high thyroid volume (odds ratio [OR] =9.647, $P = 0.003$), high free T_3/free T_4 ratio (OR = 1.541, $P = 0.019$), and TRAb level (OR = 1.317, $P = 0.002$) were independent factors influencing drug treatment failure and were associated with poor prognosis. After drug withdrawal, patients with distinctly enlarged thyroid glands, thyroid-associated eye disease, and low serum thyroid-stimulating hormone (sTSH) levels were higher in the nonremission group than in the remission group.

Conclusion: GD patients with goiter, high TRAb level and high FT3/FT4 ratio had poor poor response to drugs. The recurrence rate was high in patients with thyroid-related eye disease, and sTSH delayed recovery.

Keywords: Antithyroid agents, Graves' disease, remission

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Submitted: 07-Oct-2022, **Revised:** 11-Feb-2023, **Accepted:** 14-Feb-2023, **Published:** 30-Mar-2023

Access this article online	
Quick Response Code:	Website: www.environmentmed.org
	DOI: 10.4103/ed.ed_23_22

INTRODUCTION

Hyperthyroidism is an organ-specific autoimmune disease involving thyrotoxicosis caused by excessive production of thyroid hormone by the thyroid gland.

How to cite this article: Zhang Q, Fu Y. Prediction of the recurrence risk of Graves' disease after antithyroid drug therapy. Environ Dis 2023;8:7-12.

Graves' disease (GD) is the most common cause of hyperthyroidism. Most of them are caused by thyrotropin receptor antibody (TRAb) stimulation, thus leading to excessive secretion of thyroid hormone in thyroid follicular cells.[1] Studies have indicated that hyperthyroidism not only leads to metabolic disorders of various substances in the body but also affects the cardiovascular, nervous, digestive, and other systems, thereby causing severe physical and mental harm.[2] Antithyroid drugs (ATDs) are currently the first choice treatment for GD because of convenience and safety and that ATDs do not cause irreversible hypothyroidism. However, the drug treatment course is long, patients are prone to relapse after drug withdrawal, the overall recurrence rate is high,[3-7] and the low cure rate is low. Moreover, drug treatment carries a risk of serious adverse reactions. Therefore, clinical research has focused on finding therapeutic strategies to ensure treatment efficacy and prevent disease recurrence. The aim of this study was to observe the outcomes of ATD treatment in patients with GD and to evaluate the factors influencing hyperthyroidism recurrence.

PATIENTS AND METHODS

Study participants

The study was approved by the Luhe Hospital Ethics Committee (2018-LHKY-040-03). A total of 273 patients diagnosed with GD and hyperthyroidism in the endocrinology department of our hospital between March 2014 and February 2017 were selected, and 247 patients were finally enrolled in the study. Patients received regular methimazole therapy and no other therapy or combination therapy, except for those who were switched to another therapy because of adverse reactions during therapy. The patients comprised 65 men (26.3%) and 182 women (73.7%). The age at disease onset was 34 ± 13 years, and the age range was 21-65 years. No patients had strong emotional fluctuations or stress events such as trauma, surgery, or serious illness during the entire course of the disease. All patients met the diagnostic criteria for GD in the 2007 Chinese Guidelines for the Diagnosis and Treatment of thyroid diseases: (1) hypermetabolic symptoms of hyperthyroidism; (2) diffuse goiter; (3) elevated serum thyroid hormones (free triiodothyronine [FT3], FT4, T3, and T4) and diminished thyroid-stimulating hormone (TSH); (4) protruding eyes and other invasive eye signs; (5) pretibial mucinous edema; and (6) TRAb, thyroid peroxidase antibody (TPOAb), and anti-thyroglobulin antibody (TgAb) positivity. Among them, (1), (2), and (3) are essential conditions for diagnosis, and (4), (5), and (6) are auxiliary conditions. The exclusion criteria were as follows: (1) hyperthyroidism without goiter; (2) nodular goiter with hyperthyroidism or hyperthyroidism due to causes other than GD; (3) hyperthyroid heart disease or atrial fibrillation; (4) uncontrolled hypertension (or blood pressure >140/90 mmHg after antihypertensive treatment); (5) recurrent GD; (6) pregnancy or lactation in women; (7) malignant tumors; (8) psychosis, radiotherapy, chemotherapy, antidepressant therapy, or immunosuppressive therapy; (9) abnormal liver function and liver enzyme alanine aminotransferase >two times the upper limit of normal; (10) moderate-to-severe renal insufficiency; and (11) hyperthyroidism crisis or hyperthyroidism with myasthenia gravis.

The NOSPECS classification was used to grade the changes in eyes due to hyperthyroidism,[8] as absent (level 01) or present (level 26).

Study methods

Detection index

General data were collected for each group, including sex, age, height, weight, smoking history, family history of autoimmune diseases, thyroid function level (FT3, FT4, serum thyroid-stimulating hormone [sTSH], TPOAb, TgAb, and TRAb), urinary iodine, thyroid color ultrasound examination, and presence of hyperthyroidism. Thyroid enlargement was evaluated as follows: degree I: palpable thyroid, no clear enlargement visible to the naked eye; degree II: palpable and macroscopic enlargement, confined to the sternocleidomastoid muscles bilaterally; and degree III: enlargement beyond the outer margin of the sternocleidomastoid muscle. A 5 ml volume of fasting venous blood was collected in the morning, centrifuged, and stored at −20°C. TPOAb, TgAb, TRAB, FT4, FT3, and TSH were detected through electrochemiluminescence with a Roche E601 electrochemiluminescence analyzer and kit. Urine iodine was detected with an OTT-I-P series iodine automatic detector. Thyroid ultrasound was performed with a HITACHI HI VISION Preirus instrument.

Therapeutic method

The initial drug dose is MMI 30 mg/day, and monthly follow-up was conducted to monitor thyroid function, blood cell analysis, and liver function. Symptoms were relieved for 4–8 weeks after treatment, and ATD dose maintenance was adjusted according to the gradual decrease of TSH, FT3, and FT4 indicators (2.5–5.0 mg/day). The patients were followed up once per month for 6 months after drug withdrawal. Subsequently, the patients were followed up every 3 months for 1 year. One physician was responsible for the entire treatment and follow-up. The 247 patients had good compliance, taking the medicine as instructed. Drug dosages were adjusted, and relevant

tests were rechecked regularly during disease treatment and follow-up.

Discontinuation criteria

Treatment was discontinued if patients simultaneously had a treatment time ≥18 months, took methimazole ≤5 mg/day, maintained normal FT3, FT4, and TSH for ≥6 months, and showed a decrease in TRAb to normal levels.

Criteria for remission, nonremission, and relapse

The criteria for remission were normal clinical manifestations after ATD had been discontinued for more than 1 year and normal serum thyroid hormone and TSH levels. The criterion for no remission was an inability to stop drug treatment for more than 2 years. The criterion for relapse was hyperthyroidism recurring after ATD treatment discontinuation, that is, FT4 increased and TSH decreased at any time after ATD treatment was discontinued.

Statistical methods

SPSS 14.0 software (IBM Corp, Armonk, N.Y., USA) was used for statistical analysis. Measurement data are expressed as means $\bar{x} \pm S$, and enumerated data are expressed as percentages. The count data between the groups were analyzed with the test. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Comparison of baseline data between the groups

Among 247 patients with GD, 151 had remission (remission group, 61.1%) and 96 had no remission (nonresponse group, 38.9%). In the remission group, the duration of treatment was 18.4 ± 1.8 months, and thyroid function remained normal 1 year after drug withdrawal. In the nonremission group, 43 patients relapsed after drug withdrawal (relapse group), whereas 53 patients failed to stop drug withdrawal (nonwithdrawal group). In the nonremission group, the age of onset was lower ($P < 0.05$), the level of TRAb higher ($P < 0.05$), and the levels of TPOAb and TgAb increased but were not statistically significantly ($P = 0.058$ and $P = 0.078$). Compared with the remission group, the nonremission group had substantial goiter and thyroid eye signs, and the FT3 level and FT3/FT4 ratio were higher in the initial stage of the disease ($P < 0.05$). No significant differences were observed in sex ratio, family history, course of disease, smoking history, or urinary iodine between the groups [$P > 0.05$; Table 1].

Table 1: Comparison of baseline data between the antithyroid drug treatment response group and nonresponse group (x±S)

	Remission group (n=151)	Nonresponse group (n=96)	P
Age (years)	37.3±14.0	31.2±12.2	0.032
Gender (male/female)	39/112	26/70	0.713
Duration of disease (months)	3.9±2.6	4.2±2.9	0.841
Family history (yes/no)	28/123	17/79	0.694
Smoking (yes/no)	18/133	9/87	0.364
BMI (kg/m^2)	24.5±4.2	23.7±3.9	0.836
FT3 (pmol/L)	18.3±9.1	25.7±8.4	0.029
FT4 (pmol/L)	40.6±10.2	42.3±11.4	0.183
FT3/FT4	0.45	0.61	0.020
sTSH (mIU/L)	0.04±0.03	0.03±0.02	0.211
TRAb%	18.1±9.8	27.4±10.7	0.001
TPOAb%	19.3±11.7	23.1±10.3	0.058
TgAb%	17.2±10.1	19.6±9.7	0.078
Exophthalmos*, n (%)			
Yes	78 (51.7)	16 (16.7)	0.004
No	73 (48.3)	80 (83.3)	
Goiter, n (%)			
Degree I	124 (82.1)	28 (29.2)	0.007
Degree II and above	27 (17.9)	68 (70.8)	
Urine iodine	181±59.1	197±61.2	0.813

*NOSPECT score ≥2 was considered to indicate ocular signs. BMI: Body mass index, TRAb: Thyrotropin receptor antibody, TPOAb: Thyroid peroxidase antibody, sTSH: Serum thyroid-stimulating hormone, TgAb: Thyroglobulin antibody

Comparison of data at drug discontinuation between the remission group and the nonremission group

The treatment time for the 247 patients exceeded 18 months, and the treatment times for the failed drug withdrawal group and the relapse group were significantly longer than that of the remission group ($P < 0.05$). The percentage of patients with thyroid enlargement and thyroid-related ophthalmopathy in the relapsed group was much greater than that in the remission group (all $P < 0.05$). The proportion of patients with thyroid enlargement and/or thyroid-related ophthalmopathy after treatment in the failed drug withdrawal group was higher than that in the remission and relapsed groups (all $P < 0.05$). Significant differences were observed in the serum FT3 level, FT3/FT4 ratio, and sTSH level between the remission group and the relapsed group [all $P < 0.05$; Table 2].

Logistic regression analysis of predictors of drug treatment outcomes in patients with GD

Multivariate logistic regression analysis was performed with treatment outcome as the dependent variable and thyroid size at onset, eye signs, FT3 levels, FT3/FT4 ratio, TSH, TRAb, TPOAb, and TgAb urinary iodine levels as independent variables. The independent predictors of non-remission were thyroid size at disease onset (odds ratio [OR] =9.647, $P = 0.003$), TRAb level (OR = 1.317, $P = 0.002$), and FT3/FT4 ratio [OR = 1.541, $P = 0.019$; Table 3].

DISCUSSION

ATDs are currently the main treatment for hyperthyroidism, but the recurrence rate after drug withdrawal is high, and recurrence cannot be predicted before treatment. Therefore, predicting the therapeutic effect of ATD and

Table 2: Comparisons between the remission group after antithyroid drug treatment and the relapse and failure groups after drug withdrawal (x±S)

	Remission group (*n*=151)	Nonresponse group (*n*=96)		P1	P2
		Relapsed group	Failed drug withdrawal group		
Duration of treatment (months)	18.4±1.8	20.7±2.3	>24	0.031	-
FT3 (pmol/L)	3.61±0.92	4.03±0.74	4.49±0.83	0.079	0.147
FT4 (pmol/L)	13.41±1.61	14.23±1.59	14.72±1.84	0.523	0.615
sTSH (mIU/L)	2.054±1.126	1.893±0.992	0.364±0.096	0.617	0.003
TRAb%	9.43±3.71	10.91±2.83	-	0.068	-
Exophthalmos, *n* (%)					
Yes	14 (9.3)	12 (28.0)	23 (43.4)	0.011	0.037
No	13 (90.7)	31 (72.0)	30 (56.7)		
Goiter, *n* (%)					
Degree I	107 (70.9)	12 (27.9)	9 (17.0)	0.026	0.026
Degree II and above	44 (29)	31 (72.1)	44 (83)		

P1: Comparison of the relapsed group versus the remission group, P2: Comparison of the relapsed group versus the failure to discontinue group. TRAb: Thyrotropin receptor antibody, sTSH: Serum thyroid-stimulating hormone

Table 3: Multivariate logistic regression analysis of patients with Graves' disease recurrence

Independent variable	OR value	95% CI	*P*
Size of thyroid gland	9.647	3.104–26.381	0.003
FT3/FT4	1.541	1.263–1.724	0.019
TRAb	1.317	1.157–1.421	0.002

P<0.05 the risk factors entered into the regression model. TRAb: Thyrotropin receptor antibody, CI: Confidence interval, OR: Odds ratio

the recurrence of GD after treatment is important to decrease the recurrence rate and relapse-associated harm, and to adjust the treatment selection.

The results of multiple clinical trials using different clinical characteristics and treatment methods have indicated different recurrence rates.[9] In a retrospective Italian study in 306 patients with GD treated with MMI for 12–24 months, hyperthyroidism relapse occurred in 194 patients (63.4%) after drug withdrawal.[10] In a retrospective audit of 536 newly diagnosed patients with GD presenting to the Thyroid Clinic in Birmingham, UK, 314 received elective medical treatment for 18 months; this medical treatment failed in 198 (63.5%) patients.[11] In a systematic review and network meta-analysis of the comparative effectiveness of therapies, across eight studies in a total of 667 patients treated with ATDs, relapse of hyperthyroidism occurred in 352 patients (52.7%).[12] The results of our study showed that the recurrence rate of ATD treatment within 1 year was approximately 17.4%. The reason for this low recurrence rate might have been that in our study, remission was defined as maintenance of normal thyroid status for more than 1 year after withdrawal of ATD. Some cases may relapse after remission for 1 year, and this possibility cannot be ruled out. Therefore, given the short observation period of this study, we asked the patients to visit our hospital regularly for thyroid function review, and we will continue to perform follow-up for future studies.

The pathogenesis of GD is caused by the autoantibody TRAb directly indicated stimulating the TSH receptor on the surfaces of thyroid cells.[13] Approximately 95% of patients with newly diagnosed GD are TRAb positive, and high TRAb levels are indicative of severe immune disorders.[1,14-17] In recent years, many studies have indicated TRAb as a predictor of ATD treatment outcomes.[5,14-17] Patients with higher TRAb levels at the time of GD diagnosis have a significantly elevated risk of recurrence, whereas patients with low TRAb levels tend to have a better prognosis and maintain longer remission periods.[14,16] In addition, the stimulatory (TSAb) and blocking (TBAb) properties of TRAb can be distinguished through new detection techniques,[18] and the antibodies of patients with GD have been found to be mainly TSAb. In recent studies, TSAb has been shown to be a better predictor of recurrence risk than TRAb in ATD-treated patients with GD.[9,19,20] Our study indicated that lower TRAb levels in patients with initial hyperthyroidism were associated with better effects of antithyroid drug treatment and lower recurrence rates. Simultaneously, we measured TSAb levels, which may be tested in patients with initial hyperthyroidism in the future, to improve the significance of disease recurrence prediction. Previous studies have shown that the serum T3 level and FT3/FT4 ratio at the time of disease onset are independent factors predicting ATD treatment outcomes in patients with GD.[20-23] Patients with higher serum T3 levels and FT3/FT4 ratios have a greater risk of relapse and thus usually require higher initial doses and longer durations of treatment.[21-23] Our findings are consistent with the conclusions of previous studies. Compared with that in the remission group, the FT3/FT4 ratio in the nonremission group was significantly higher. Multiple logistic regression analysis indicated that the FT3/FT4 ratio was an independent factor predicting ATD outcomes in patients with GD. In addition, attention must be paid to serum TSH levels. Thyroid hormone is well known to decrease TSH levels through a negative feedback mechanism,[24] and TSH levels in some patients with GD continue to be diminished after ATD treatment and do not return to normal ranges after the normalization of thyroid hormone levels.[24,25] Previous studies have demonstrated

that inhibition of TSH after drug withdrawal is a predictor of GD recurrence.[20,25] These studies have suggested that patients with GD with delayed TSH recovery should continue ATD treatment until TSH levels reach a normal range. In this study, patients in the nonremission group showed delayed TSH recovery, whereas those in remission achieved normal thyroid function after ATD treatment. Therefore, patients with GD with TSH inhibition during ATD treatment may be more likely to relapse if drugs are stopped prematurely, and ATD treatment should be extended until TSH level returns to normal.

Goiter, Graves' ophthalmopathy, age of onset, and smoking are additional related factors affecting the recurrence of hyperthyroidism. After 5 years of follow-up, Laurberg has found that the long-term remission rate in patients with no or only mild thyroid enlargement before treatment is significantly higher than that in patients with moderate thyroid enlargement.[24] In addition, patients with GD with significantly decreased goiter after ATD treatment also have a higher remission rate.[9] In addition, we observed that thyroid size at disease onset was associated with the recurrence rate after drug withdrawal and that patients with substantial thyroid enlargement at the end of treatment had a higher rate of relapse after drug withdrawal. In the multivariate logistic regression analysis, goiter was a factor predicting the outcome of ATD treatment among patients with GD. Graves' ophthalmopathy was present in approximately 30% of diagnosed GD cases.[26,27] Regarding the effect of Graves' eye disease on recurrence of hyperthyroidism, Eckstein *et al.* have found that the remission rate among patients with GD with severe Graves' ophthalmopathy is only 7%.[28] After treatment, if no significant improvement was observed in patients with Graves' ophthalmopathy, the likelihood of recurrence was high. This study indicated that the proportion of patients in the recurrent group with Graves' ophthalmopathy was much higher than that in the remission group ($P < 0.05$), and the proportion of patients with Graves' ophthalmopathy in the continuing group was higher than those in the remission group and the relapse group ($P < 0.05$). Although ocular signs were not included in the regression equation, we inferred that patients with insignificant improvement in ocular signs after the end of treatment are more likely to relapse. The incidence of GD gradually increases with age, and young patients with GD are generally believed to have more serious immune abnormalities than older patients. The younger the age at onset of GD, the poorer the response to ATD and the prognosis, and the higher the risk of recurrence.[11,14,29] A study by Allahabadia *et al.* has found that patients with GD under 40 years of age have a higher recurrence rate than older patients.[11] In children and adolescents, two previous long-term follow-up studies[30,31] have shown remission rates of <25% after more than 2 years of ATD treatment. In this study, the age at disease onset was younger in the nonremission group, in agreement with findings in the literature. Simultaneously, after discontinuation of ATD therapy in patients with GD, smokers have been reported to have a higher risk of relapse than nonsmokers.[32,33] In this study, smoking history was not included in the regression equation, thus suggesting that this factor does not predict drug treatment effects. Owing to the high proportion of women and nonsmoking patients included in this study, no correlation between smoking and GD was observed, in contrast to the findings in several previous studies. Therefore, the relationship between smoking and GD must be further studied by expanding the sample size.

CONCLUSION

This study identified several risk factors predicting the recurrence of GD. These risk factors can be used together to develop a risk-scoring system. Prospective studies should assess the prognostic accuracy of such scores to guide treatment decisions. However, this study has several limitations. For example, compared with the durations of other clinical trials, the 1-year observation period was relatively short, the sample size must be further increased, and more accurate detection indicators are needed to support our conclusion.

Financial support and sponsorship

The study was financially supported by the Canal Project.

Conflicts of interest

There are no conflicts of interest.

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