

Original Research Article

Parameters affecting the period for being euthyroid in newly-diagnosed Graves' disease treated with antithyroid agent

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ABSTRACT

Background: There are limited data about the factors affecting the response time to medical treatment in Graves' disease (GD) although many studies examined the predictors of the relapse after drug withdrawal. The aim of the current study was to evaluate the time for becoming euthyroid under antithyroid drug (ATD) therapy and the parameters influencing this period in patients diagnosed as GD.

Methods: Patients with newly-diagnosed GD and decided to treat with ATD initially between March 2017 and September 2018 were retrieved retrospectively. Sociodemographic features as well as laboratory parameters like thyroid function tests and thyroid-stimulating hormone-receptor antibody (TRab) at the time of diagnosis were recorded.

Results: Out of 41 patients, 63.4% (n=26) were female. The mean age was 36.1±11.7 years and 43.9% (n=18) of them were smoking. The time between the initiation of treatment and the duration of becoming euthyroid was 2.4±1.8 months. No significant difference was noted between age, gender, and smoking status and the time to become euthyroid under ATD treatment. This period was significantly positively correlated with levels of free triiodothyronine, free thyroxine, and negatively correlated with thyroid-stimulating hormone. Response to ATD therapy was higher in patients with pre-treatment TRab levels <10 IU/l than TRab ≥10 IU/l (p=0.011).

Conclusions: Pretreatment thyroid function tests and TRab levels may be taken into consideration before deciding treatment in patients with newly diagnosed GD. It would be useful to design more comprehensive studies so that this proposal can find a response in clinical practice.

Keywords: Euthyroidism, Free thyroxine, Free triiodothyronine, Graves' disease, Thyroid-stimulating hormone, Thyroid-stimulating hormone-receptor antibody

INTRODUCTION

Thyrotoxicosis is a broad term that describes disorders due to the excess production of thyroid hormones, regardless of the source, whilst the term 'hyperthyroidism' is used if this thyrotoxicosis occurs as a result of increased hormone synthesis by the thyroid gland.¹ The most frequent cause of hyperthyroidism is Graves' disease (GD) unless its occurrence rate changes from 60% to 80% due to the iodine intake status. It is an

organ specific autoimmune thyroid disease that is manifested by hyperthyroidism clinic as a result of circulating antibodies against thyrotropin receptor. Its reported incidence is 20 to 30 cases/100000 per year and prevalence is approximately 0.5-1.5% with a varied female to male ratio from 4:1 to 7:1 even 10:1 in different studies.²⁻⁴ Although the cause of GD is still clearly unknown, it is thought to be the result of a complex interaction between genetic susceptibility that contributes 70-80% and environmental factor with an effect of 20-30%.⁵

Antithyroid drug (ATD), radioactive iodine (RAI) therapy, and surgery are the three options for the treatment of GD.^{1,2} It is clear that none of these three treatment modalities are perfect, and each of them have advantages, disadvantages, risks and benefits. The differences in treatment preferences of GD were examined according to different regions such as United States (US), Europe and Japan, 69% of respondents preferred RAI treatment in US, while 22% in Europe, and 11% in Japan. Medical treatment choice from much to less as follows; 88% in Japan, 77% in Europe, and 30.5% in US.⁶ However, it has been observed that these preferences have changed in the last 20 years. In a previous study with 696 respondents, ATD, RAI and surgical treatment preferences for uncomplicated GD were 53.9%, 45.0%, and 0.7%, respectively.⁷ When we compared with the study in 1991, ATD usage improved from 30.5% to 40.5% and RAI therapy decreased from 69% to 58.6% in North America and the rates for medical and RAI treatment were 85.7% instead of 77% and 13.3% instead of 22% in Europe.^{6,7} There was not much difference in rates of surgery choices over the past years. Many factors are thought to play a role in preference changes (e.g. worsening orbitopathy due to the RAI treatment).

After medical treatment discontinued, the rate of relapse is high and other treatment options are needed. Determining the parameters affecting ATD treatment will help to avoid potentially harmful side-effects and time loss. There are many studies researching the predictors related to relapse/recurrence in GD. However, very limited number of reports evaluated parameters between the initiation of treatment and becoming euthyroid with ATD. For this reason we decided to focus at this point based on insufficient data and necessity. The aim of the current study was to assess the response period to ATD therapy and the parameters affecting this period.

METHODS

Selection of participants

The medical records of patients with GD who applied to Internal Medicine and Endocrinology and Metabolism Unit of Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital (Istanbul, Turkey) between March 2017 and September 2018 were retrieved retrospectively. Patients aged between 18-65 years, who were newly-diagnosed and decided to treat with ATD initially, whose followed-up no longer than one month intervals until thyroid function tests (TFT) normalized were enrolled to the study. However, patients <18 or >65 years old, who were treated initially with other options such as RAI or surgery, known history of malignancy, malnutrition, chronic inflammatory disorders, have just been diagnosed with acute illness, followed-up in intensive care unit, whose pregnant or in postpartum period, having allergy or other side effects to the ATD, patients whose liver enzyme levels such as

alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were not suitable to start treatment, and using medications influencing TFT were excluded.

Data collection

Patients' gender, age, and smoking status were recorded. Laboratory parameters [free triiodothyronine (FT₃), free thyroxine (FT₄), thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), anti-thyroglobulin antibody (TgAb), thyroid-stimulating hormone-receptor antibody (TRab), ALT, AST, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)] of the patients at the time of diagnosis were evaluated.

The duration of the visit which the patients with GD was started to treat and became euthyroid determined and this time was calculated as months. Euthyroidism was accepted as normalizing thyroid function tests.

The side-effects of the drug was recorded for each patient. The patients were grouped with respect to the age (<40 and ≥40 years), gender, smoking status (smokers and non-smokers), ESR (<10 and ≥10 mm/hour), CRP (<5 and ≥5 mg/l), and TRab (<10 and ≥10 IU/l) levels and compared in terms of the time they became euthyroid. They were also divided into three groups according to their euthyroid duration which was expressed in months.

Statistical analysis

Analyses were performed using SPSS version for Windows 20.0 (IBM Corporation, Chicago, IL, USA). Shapiro Wilk test was performed to understand whether the variable was normally or abnormally distributed. Datas were reported as mean±standard deviation (SD), median (minimum-maximum) or percentage (%). Differences between groups were tested using the two sample T test for normally distributed or the Mann-Whitney U test for abnormally distributed data. Normally distributed independent continuous variables were compared with one way ANOVA test, whereas non-normally distributed independent continuous variables were compared with Kruskal-Wallis test among the groups. Spearman's correlation coefficient was used for the evaluation of relationships between parameters. A two-tailed p value of ≤0.05 was considered to be statistically significant.

RESULTS

Out of 41 patients, 63.4% (n=26) were female and 36.6% (n=15) were male. They were aged between 18 and 58 (36.1±11.7) years and 43.9% (n=18) of them were smoking. All the patients were treated with methimazole as an antithyroid agent. The time between the initiation of treatment and the duration of becoming euthyroid was 2.4±1.8 (1-8) months. Transaminase enzyme level

elevation was observed in 5 (12.2%) of the patients but was not a level which requires discontinuation of the therapy and regressed spontaneously. None of the

patients developed agranulocytosis or other side effects associated with methimazole. Laboratory parameters at the time of diagnosis are shown in Table 1.

Table 1: Laboratory parameters of the patients at the time of diagnosis.

Parameter	Mean±SD	Median (min-max)
Free triiodothyronine (pg/ml)	9.9±6.6	-
Free thyroxine (ng/dl)	3.0±1.8	2.58 (1.21-7.77)
FT3/FT4 ratio	3.1±0.7	3.07 (1.38-5.10)
Thyroid-stimulating hormone (uIU/ml)	0.06±0.3	0.005 (0.005-1.94)
Thyroid peroxidase antibody(IU/ml)	216.8±202.5	-
Anti-thyroglobulin antibody (IU/ml)	533.7±1060.9	137.5 (10-4.000)
TRab (IU/l)	7.95±10.0	3.54 (0.47-40)
Alanine aminotransferase (U/l)	21.8±9.0	20 (11-49)
Aspartate aminotransferase (U/l)	19.1±5.0	18 (12-34)
Erythrocyte sedimentation rate (mm/hour)	17.2±16.4	11 (1-60)
C-reactive protein (mg/l)	3.3±5.1	1.13 (0.23-22)

SD: Standard deviation, TRab: Thyroid-stimulating hormone-receptor antibody

Table 2: Comparison of various parameters in terms of becoming euthyroid under antithyroid drug treatment.

Parameter	Group	n	The period to become euthyroid (months)		P
			Mean±SD	Median (min-max)	
Gender	Female	26	2.5±2.0	2 (1-8)	0.582
	Male	15	2.4±1.4	2 (1-5)	
Age	<40 years	25	2.2±1.5	2 (1-6)	0.401
	≥40 years	16	2.8±2.1	2 (1-8)	
Smoking status	Smokers	18	2.8±1.9	2 (1-8)	0.197
	Non-smokers	23	2.2±1.6	2 (1-7)	
TRab	<10 IU/L	32	2.2±1.8	2 (1-8)	0.011
	≥10 IU/L	9	3.3±1.4	3 (2-8)	
ESR	<10 mm/hour	18	2.3±1.9	2 (1-8)	0.476
	≥10 mm/hour	23	2.5±1.7	2 (1-7)	
CRP	<5 mg/L	32	2.2±1.7	2 (1-8)	0.097
	≥5 mg/L	9	3.2±1.9	2 (1-7)	

n: number, SD: Standard deviation, TRab: Thyroid-stimulating hormone-receptor antibody, ESR: Erythrocyte Sedimentation rate, CRP: C-reactive protein

No significant difference was noted between sociodemographic data such as age, gender, and smoking status and the time to become euthyroid under ATD treatment. We did not find any association with respect to the ESR (<10 or ≥10 mm/hour) and CRP (<5 or ≥5 mg/l) levels. Response to ATD therapy was higher in patients with pre-treatment TRAB <10 IU/l compared to the TRAB levels ≥10 IU/l (p=0.011). Comparison of various parameters in terms of becoming euthyroid under ATD treatment were given in Table 2.

When the patients were divided into 3 groups according to the normalization of TFT tests in the first, 1-2, and ≥3 months, 26.7% of male participants become euthyroid within the first, 40.0% within 1-2, 33.3% within ≥3

months while these rates were 42.3%, 26.9%, and 30.8%, in female patients, respectively (Table 3). We observed that FT3, FT4, and TRAB levels increased whereas TSH level decreased as the euthyroidization period goes from the earliest to latest.

The time to become euthyroid was significantly positively correlated with FT3 (p=0.01, r=0.4), FT4 (p=0.005, r=0.43), TRAB (p<0.001, r=0.54) and negatively correlated with TSH (p=0.023, r=-0.35) in correlation analysis. No difference was detected with respect to age (p=0.644, r=0.07), FT3/FT4 ratio (p= 0.58, r=0.08), TPOAb (p=0.272, r=0.17), TgAb (p=0.884, r=0.02), ALT (p= 0.444, r=0.12), AST (p=0.233, r=0.19), ESR (p=0.235, r=0.19), and CRP (p=0.379, r=0.14).

Table 3: Comparison of patients by grouping according to the normalization of thyroid function tests as first, 1-2, and ≥3 months.

The period to become euthyroid (months)				
	<1 month (n=15)	1-2 months (n=13)	>2 months (n=13)	P value
Parameter	Mean±SD	Mean±SD	Mean±SD	
Age (years)	34.53±2.77	37.07±2.88	37.00±4.05	0.823
Male gender ratio (%)	26.7	46.2	38.5	0.557
FT3 (pg/ml)	6.38±0.89	9.91±1.69	14.10±2.14	0.011
Free thyroxine (ng/dl)	2.07±0.22	3.26±0.48	4.11±0.58	0.007
FT3/FT4 ratio	3.03±0.14	3.07±0.23	3.35±0.24	0.557
TSH (uIU/ml)	0.15±0.12	0.01±0.03	0.006±0.004	0.050
TPOAb (IU/ml)	152.1±37.23	227.64±66.67	280.79±58.81	0.585
TgAb (IU/ml)	385.60±196.47	738.84±377.33	499.45±297.60	0.835
TRab (IU/l)	0.22±0.28	10.93±3.38	11.59±3.01	<0.001
ALT (U/l)	20.66±2.09	20.53±2.45	24.46±2.83	0.456
AST (U/l)	17.93±0.74	17.53±1.18	22.15±1.80	0.082
ESR (mm/ hour)	13.33±3.61	20.15±5.52	18.76±4.37	0.428
C-reactive protein (mg/l)	2.46±1.13	3.71±1.70	4.05±1.47	0.380

n: number, SD: Standard deviation, FT3: Free triiodothyronine, TSH: Thyroid-stimulating hormone, TPOAb: Thyroid peroxidase antibody, TgAb: Anti-thyroglobulin antibody, TRab: Thyroid-stimulating hormone-receptor antibody, ALT: Alanine aminotransferase, AST: Aspartat aminotransferase, ESR: Erythrocyte sedimentation rate

DISCUSSION

We found that the period to become euthyroid was associated with FT3, FT4, TSH, and TRab levels in newly-diagnosed patients with GD. The patients' age, gender, smoking status, TPOAb, TgAb, and acute phase reactant levels did not affect this period. As far as we know, there are very few studies examining the response time to treatment. One of these was conducted by Choi et al. which is similar to our work but its methodology and findings were different in some aspects. They categorized the response in two groups as 'responding slowly and quickly' and evaluated this period based on various parameters.⁸ They revealed that patients with high levels of FT4 and TRab responded more quickly to treatment opposite to our results. On the other hand, there are many studies examining the factors influencing the relapse after medical treatment in patients with GD. We think that the predictors of relapse may also have an effect on the duration of becoming euthyroid in spite of lack of evidence to support this idea. For these purposes, probable parameters such as age, gender, goitre size, methimazole dose, presence of TRab, urinary iodide excretion, pretreatment thyroid hormone levels, T3/T4 ratio, smoking status, and presence of Graves' orbitopathy were examined. However, different outcomes were reported in different researches, these parameters have been shown to be efficacious on remission and/or recurrence.

Similar to other autoimmune diseases, GD is more common in females. Although the reason is not fully understood, estrogen is thought to have an effect but it is not possible to explain this high prevalence in favour of

females only with estrogen role. Gender is accurately known to influence prevalence besides its impact on response or relapse in patients with GD is contradictory. Some studies have stated that males respond the medical treatment poorer than the females while no gender difference was reported in others alike to our data.^{4,8-10} Likewise gender, the effect of age on relapse have conflicting results. For comparison this effect, 40 years of age were generally targeted as we did in our study. Relapse rate was delayed in patients who were below the age of 40 years in some reports and over the age of 40 in several of others.^{4,11} Opposite to these findings, no association was observed between age and response or relapse in various works is in agreement with the present study.^{8,10,12,13}

The relationship between smoking and GD as well as Graves orbitopathy is clearly known. It has been reported that this effect is dose-dependent, more obvious in females, and disappears after several years after quitting smoking.¹⁴ Besides, smoking has been shown to reduce the risk of Hashimoto disease, and lowers TPOAb and TgAb antibodies levels.^{5,14} We did not find any association between smoking status and response rate. No significant difference was detected in smokers compared to non-smokers with respect to relapse in a study comprised of 306 patients.¹⁵ In another large-scale analysis in Northern Sweden covering the years 2000-2010 and examining the medical records, no relationship was found due to current smoking. Interestingly, previous smoking was reported to have a protective effect against relapse unlike current literature.¹⁶ Although there are additional published data supporting our findings, there are also some defending the opposite.^{17,18}

We observed that patients with higher pre-treatment FT3 and FT4 levels achieved euthyroidism later than the patients with lower levels. Benker et al suggested a correlation between pre-treatment T3 levels and response to methimazole.¹⁹ Several studies reported that only high pre-treatment T4 levels were associated with early relapse. This is contrary to data of Choi et al where relapse rates were found to be lower in patients with high FT4 levels.⁸ Although various reports pointed out the effect versus no effect of FT3, FT4 levels and FT3/FT4 ratio individually, some of them examined their effects together.^{8,12,15,19-23} Hussein and his colleagues found that higher FT3 and FT4 levels were correlated with medical treatment failure in a study containing 659 patients which supports our results.¹² Additionally, it has been reported that both pre-treatment low TSH values and TSH suppression which reappear after drug withdrawal were associated with relapse.^{17,24} Negative correlation was found between TSH level and becoming euthyroid in our study. Response time increases as the TSH value suppresses which is in confirmation with past reports.

The level of TRAb has been subject of interest related to both response and relapse probably due to its role in pathogenesis. Pre- or post-treatment high TRAb levels reported to reduce remission success or delay the time entering remission.^{10,11,15,17,21,22,24-26} In the 'Remission induction and sustenance in Graves' disease' (RISG) study, the rate of remission was found to be 63% in patients with baseline TRAb levels below 10 IU/l instead of 39% above 10 IU/l.²⁷ Quadbeck et al showed that when the cut-off value for TRAb was taken as 1.5 IU/l or 10 IU/l, TRAb had positive predictive value of 49% or 83%, negative predictive value of 54% or 62%, and specificity of 14% or 92%.¹⁷ We took the cut-off value for TRAb as 10 IU/l and we observed in newly-diagnosed patients that the time to become euthyroid was shorter with TRAb<10IU/l compared to the TRAb levels ≥10IU/l. On the contrary, Choi et al revealed that patients with high levels of TRAb respond to treatment faster.⁸ Furthermore, Genna et al reported that rapid or gradual response to treatment was not affected by TRAb and TgAb levels.²⁸

The presence of TPOAb and TgAb antibodies which are known to be diagnostic markers of Hashimoto's thyroiditis, another autoimmune disease at the other end of the spectrum, are also exist in GD. These antibodies have not been investigated as intensely as TRAb or TSAb levels and their effect on relapse remain uncertain. Responsiveness to ATD therapy was not related to TPOAb and TgAb levels in our study. Liu et al and Lin et al reported that these antibodies have no effect on the course of the disease which is similar to our findings.^{15,24} In contrast, patients were divided into three groups as TPOAb (-) and TgAb (-), TPOAb (+) and TgAb (-), and both TPOAb and TgAb (+) in a study with 117 patients and relapse rates were found 39%, 27%, and 11%, respectively.²⁹ They concluded that relapse had been more frequent in the absence of these antibodies.

Some limitations for this research should be regarded. First one is the retrospective nature and relatively small size prevented us from making more detailed results. The second limitation is that the thyroid volumes were not measured even though the patients had ultrasonography findings because it is not a routine procedure in our center. In spite of these limitations, our findings are in line with a lot of data in published literature.

CONCLUSION

Our findings suggest that non-medical treatment options can be considered in newly-diagnosed patients with GD who have properties such as high FT3, FT4, TRAb and low TSH levels. It would be useful to design more comprehensive studies to confirm this hypothesis.

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REFERENCES

- De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906-18.
- Wiersinga WM. Graves' disease: can it be cured? *Endocrinol Metab.* 2019;34:29-38.
- Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol.* 1977;7:481-93.
- Allahabadi A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 2000;85:1038-42.
- Wiersinga WM. Clinical relevance of environmental factors in the pathogenesis of autoimmune thyroid disease. *Endocrinol Metab.* 2016;31:213-22.
- Wartofsky L, Glinioer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan and the United States. *Thyroid.* 1991;1:129-35.
- Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab.* 2012;97:4549-58.
- Choi HS, Yoo WS. Free thyroxine, anti-thyroid stimulating hormone receptor antibody titers, and absence of goiter were associated with responsiveness to methimazole in patients with new onset Graves' disease. *Endocrinol Metab.* 2017;32:281-7.
- Magri F, Zerbini F, Gaiti M, Capelli V, Ragni A, Rotondi M, et al. Gender influences the clinical presentation and long-term outcome of Graves' disease. *Endocr Pract.* 2016;22:1336-42.
- Cappelli C, Gandossi E, Castellano M, Pizzocaro C, Agosti B, Delbarba A, et al. Prognostic value of thyrotropin receptor antibodies (TRAb) in Graves'

- disease: a 120 months prospective study. *Endocr J.* 2007;54:713-20.
11. Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid.* 1997;7:369-75.
 12. Hussain YS, Hookham JC, Allahabadia A, Balasubramanian SP. Epidemiology, management and outcomes of Graves' disease- real life data. *Endocrine.* 2017;56:568-78.
 13. Bolaños F, González-Ortiz M, Durón H, Sánchez C. Remission of Graves' hyperthyroidism treated with methimazole. *Rev Invest Clin.* 2002;54:307-10.
 14. Wiersinga WM. Smoking and thyroid. *Clin Endocrinol.* 2013;79:145-51.
 15. Liu L, Lu H, Liu Y, Liu C, Xun C. Predicting relapse of Graves' disease following treatment with antithyroid drugs. *Exp Ther Med.* 2016;11:1453-58.
 16. Mohlin E, Nyström HF, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000-2010. *Eur J Endocrinol.* 2014;170:419-27.
 17. Quadbeck B, Hoermann R, Roggenbuck U, Hahn S, Mann K, Janssen OE. Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves' disease. *Thyroid.* 2005;15:1047-54.
 18. Glinoe D, de Nayer P, Bex M, Belgian Collaborative Study Group on Graves' disease. Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. *Eur J Endocrinol.* 2001;144:475-83.
 19. Benker G, Vitti P, Kahaly G, Raue F, Tegler L, Hirche H, et al. Response to methimazole in Graves' disease. The European Multicenter Study Group. *Clin Endocrinol.* 1995;43:257-63.
 20. Park S, Song E, Oh HS, Kim M, Jeon MJ, Kim WG, et al. When should antithyroid drug therapy to reduce the relapse rate of hyperthyroidism in Graves' disease be discontinued? *Endocrine.* 2019;65:348-56.
 21. Masiello E, Veronesi G, Gallo D, Premoli P, Bianconi E, Rosetti S, et al. Antithyroid drug treatment for Graves' disease: baseline predictive models of relapse after treatment for a patient-tailored management. *J Endocrinol Invest.* 2018;41:1425-32.
 22. Struja T, Kaeslin M, Boesiger F, Jutzi R, Imahorn N, Kutz A, et al. External validation of the GREAT score to predict relapse risk in Graves' disease: results from a multicenter, retrospective study with 741 patients. *Eur J Endocrinol.* 2017;176:413-9.
 23. Shi H, Sheng R, Hu Y, Liu X, Jiang L, Wang Z, et al. Risk factors for the relapse of Graves' disease treated with antithyroid drugs: a systematic review and meta-analysis. *Clin Ther.* 2020;42:662-75.e4.
 24. Liu X, Shi B, Li H. Valuable predictive features of relapse of Graves' disease after antithyroid drug treatment. *Ann Endocrinol.* 2015;76:679-83.
 25. Nedrebo BG, Holm PI, Uhlving S, Sorheim JI, Skeie S, Eide GE, et al. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. *Eur J Endocrinol.* 2002;147:583-9.
 26. Tun NN, Beckett G, Zammitt NN, Strachan MW, Seckl JR, Gibb FW. Thyrotropin receptor antibody levels at diagnosis and after thionamide course predict Graves' disease relapse. *Thyroid.* 2016;26:1004-9.
 27. Karmisholt J, Andersen SL, Bulow-Pedersen I, Carlé A, Krejbjerg A, Nygaard B. Predictors of initial and sustained remission in patients treated with antithyroid drugs for Graves' hyperthyroidism: the RISG study. *J Thyroid Res.* 2019;2019:5945178.
 28. Gemma R, Nakamura H, Mori T, Andoh S, Suzuki Y, Yoshimi T. The change in 123I-uptake between 3- and 24-hours is useful in predicting early response to methimazole in patients with Graves' disease. *Endocr J.* 1996;43:61-6.
 29. Takaichi Y, Tamai H, Honda K, Nagai K, Kuma K, Nakagawa T. The significance of antithyroglobulin and antithyroidal microsomal antibodies in patients with hyperthyroidism due to Graves' disease treated with antithyroidal drugs. *J Clin Endocrinol Metab.* 1989;68:1097-100.

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