

RESEARCH

Open Access



Efficacy of Anti-Thyroid Medications in Patients with Graves' Disease

Moeber Mohammed Mahzari^{1,2,3,8*}, Manal Muteb Alanazi^{3,4}, Yara Mohammed Alabdulkareem^{1,3}, Wesal Abdullah Alharbi^{1,3}, Aram Saeed Alzahrani^{1,3}, Norah Abdullah Alqahtani^{3,5}, Ibrahim Mahmoud Ajwah⁶ and Husam I. Ardah^{1,2,7,8}

Abstract

Introduction Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism due to increased thyroid-stimulating hormone receptor antibodies (TRAb). The treatment of GD often consists of radioactive iodine therapy, anti-thyroid drugs (ATD), or thyroidectomy. Since few studies have collected data on remission rates after treatment with ATD in Saudi Arabia, our study aimed to assess the efficacy and the clinical predictors of GD long-term remission with ATD use.

Method We conducted a retrospective chart review study of 189 patients with GD treated with ATD between July 2015 and December 2022 at the endocrine clinics in King Abdulaziz Medical City in Riyadh. All GD patients, adults, and adolescents aged 14 years and older who were treated with ATD during the study period and had at least 18 months of follow-up were included in the study. Patients with insufficient follow-up and those who underwent radioactive iodine (RAI) therapy or thyroidectomy as first-line therapy for GD were excluded from the study.

Results The study sample consisted of 189 patients, 72% of whom were female. The patients' median age was 38 years (33, 49). A total of 103 patients (54.5%) achieved remission. The median follow-up period for the patients was 22.0 months (9, 36). Patients who achieved remission had lower mean free T4 levels (25.8 pmol/l \pm 8.93 versus 28.8 pmol/l \pm 10.82) (P value = 0.038) and lower median TRAb titer (5.1 IU/l (2.9, 10.7)) versus (10.5 IU/l (4.2, 22.5)) (P value = 0.001) than patients who did not achieve remission. Thirty-five out of 103 patients who achieved remission (34%) relapsed after ATD discontinuation. The patients who relapsed showed higher median thyroid uptake on ^{99m}Tc-pertechnetate scan than patients who did not relapse: 10.3% (5.19, 16.81) versus 6.0% (3.09, 12.38), with a P value of 0.03. They also received ATD for a longer period, 40.0 months (29.00, 58.00) versus 25.0 months (19.00, 32.50), with a P value of < 0.0001.

Conclusion The remission of GD was achieved in approximately half of the patients treated with ATD; however, approximately one-third of them relapsed. Lower Free T4 and TRAb levels at diagnosis were associated with remission. Longer ATD use and higher thyroid uptake upon diagnosis were associated with relapse after ATD discontinuation. Future studies are necessary to ascertain the predictors of ATD success in patients with GD.

Keywords Graves' disease, Anti-thyroid medications, Remission, Relapse, Hyperthyroidism, TSH receptor antibodies

*Correspondence:

Moeber Mohammed Mahzari

Moeber@hotmail.com; MahzariM@ksau-hs.edu.sa

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Graves' disease (GD) is an autoimmune disease characterized by hyperthyroidism due to increased thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) [1]. TRAb mimic TSH and stimulate its receptors. TSH receptor stimulation via TRAb subsequently causes an excessive production of thyroid hormones (T3 and T4). These thyroid hormones circulate in the bloodstream and affect nearly every tissue system in the body, including the cardiac muscle and the nervous system. Patients with GD hyperthyroidism exhibit many symptoms, such as tremors, palpitations, weight loss, and diarrhea [2]. Graves' ophthalmopathy is a specific complication of GD that occurs due to TRAb-induced inflammation of the orbital structures. It manifests as swelling of the tissues around the eyes and the exophthalmos [3].

The prevalence of GD is estimated at 2–3% of the overall population worldwide. It usually affects more women than men at a ratio of 10:1. GD affects all age groups; however, it is more common in middle-aged individuals, with a peak incidence in the 40–60-year-old age group [4, 5]. In Saudi Arabia, there are limited epidemiological data on GD. The exact prevalence of GD in the Saudi population is unknown. However, Malabu et al. reported a female-to-male ratio of 2.9:1 and a mean age of 32 ± 0.9 years in a study conducted in Riyadh, Saudi Arabia [6].

GD treatment aims to restore euthyroidism to improve clinical symptoms and prevent long-term complications. Treatment varies depending on clinical characteristics and the patient's preferences [7, 8]. RAI, surgery, and anti-thyroid drugs (ATD) are approved options for treating GD [7–9]. RAI is widely considered safe and has a low morbidity rate [8]. Successful RAI therapy for GD can be accomplished in most patients (>90%) with a single dose [10]. Thyroidectomy is another treatment option for GD patients with large goiter or thyroid nodules [11]. The thyroid gland can either be totally removed with a lower incidence of recurrence or partially removed with an approximately 8% chance of recurrence [12]. Nevertheless, in Europe, Asia, and the USA, ATD, including propylthiouracil (PTU) and methimazole (MMI), are considered the first-line treatment for GD before RAI therapy or thyroidectomy [7]. MMI is often preferred over PTU due to its better safety profile [7, 8, 13]. Both PTU and MMI take around 18 months to induce a sustainable remission of GD, although a relapse rate of up to 50–60% has been reported [7, 8].

GD remission is defined as an euthyroid state for at least six months while off or on a small dose of ATD [13, 14]. Several studies have confirmed that ATD could result in long-term remission in up to 50% of patients [7, 8]. The predictors of ATD course outcomes have been examined in many studies. These predictors include TRAb level, goiter size, baseline free T4 level, and the degree of

ophthalmopathy [7, 8, 12, 14, 15]. In Saudi Arabia, only a few studies have collected data on the remission rates of GD after treatment with ATD [6]. Therefore, this study aimed to assess the efficacy of ATD in treating GD in the Saudi population and the clinical predictors of long-term remission. This study aids in managing patients with GD by delineating the factors associated with sustainable remission and relapse with ATD use.

Method

This retrospective chart review study was conducted in the endocrinology clinics at King Abdulaziz Medical City in Riyadh, Saudi Arabia. All GD patients, adults, and adolescents aged 14 years and older treated with ATD as first-line therapy at the discretion of the treating endocrinologist were included. The study period was from July 2015 to December 2022. All the patient had at least 18 months of follow-up. GD diagnosis was based on clinical presentation with symptoms of thyrotoxicosis with suppressed TSH, high levels of either free T4 or free T3, or both. The confirmation of GD diagnosis was achieved through either a high TRAb level, a high thyroid uptake on ^{99m}Tc -pertechnetate scan, or both. Patients with insufficient follow-up and those who had undergone RAI therapy or thyroidectomy as a first-line therapy for GD were excluded from the study.

The collected data included demographic variables, such as age, and gender. Clinical variables included TRAb levels, TSH, free T4 and T3 levels, ^{99m}Tc -pertechnetate scan uptake results, duration of ATD therapy, and Graves' ophthalmopathy severity. TSH, free T4, and free T3 were measured with a Chemiluminescent Microparticle Immunoassay (the Abbot Alinity i system). The reference range was 0.35–4.94 mIU/L for TSH, 9–19 pmol/L for free T4, and 2.9–4.9 pmol/L for free T3. TRAb levels were measured using an electrochemiluminescence immunoassay (Roche Cobas e411), and the normal reference value was <1.8 IU/l. The severity of ophthalmopathy was assessed and documented by the treating endocrinologist based on the grading system established by the European Group on Graves Orbitopathy (EUGOGO) [16].

Remission and relapse status was collected for all patients. Remission was defined in this study as a state of being clinically euthyroid, with normal levels of TSH and free T4 and T3 for any period off ATD. Patients who continued to require any dose of ATD after a minimum of 18 months of ATD use to maintain euthyroidism were considered to have persistent GD and did not achieve remission. Relapse was defined as a clinical recurrence of hyperthyroidism, with low TSH and high free T4 and T3 at any time after being off ATD.

Statistical analysis was conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous

variables were reported as mean and standard deviation (SD) if normally distributed, while abnormally distributed variables were reported as median and inter-quartile ranges (IQR) with appropriate statistical tests use. Categorical variables were reported as frequencies and percentages.

To determine the factors associated with remission and relapse, the study participants were divided into two groups based on remission and relapse status. The groups were compared using the Chi-square test or Fisher's exact test for categorical variables, and the T-test or the Kruskal–Wallis test for continuous variables, as appropriate. Then, a multivariate logistic regression analysis used to identify independent risk factors. All variables found to be associated with remission and relapse in the univariate analysis, as well as available variables previously associated with remission and relapse in the literature, such as age, gender, free T4 levels, and TRAb levels, were used in the multivariate analysis. Area under the curve (AUC) calculation was employed to study the receiver operating characteristic curve (ROC) to determine the free T4 and TRAb cut-off values to predict remission. Inferential statistical tests were considered significant if their P values were <0.05.

The study was approved by the Institution Review Board (IRB) at King Abdullah International Medical Research Center-Riyadh with Protocol Number: NRC22R/314/06 and approval number IRB/1431/22 with a waiver of the study subjects' consent per the institutional policy for retrospective studies.

Results

Study sample characteristics

Out of 227 patients diagnosed with GD during the study period, 189 patients met the study inclusion and exclusion criteria. The majority of the study sample (72%) was female, and the patients' ages ranged from 18 to 80 years old. Around 71.3% of the study sample had mild Graves' ophthalmopathy. The TRAb titer ranged from 0.9 to 36 IU/l. The median thyroid uptake on the ^{99m}Tc-pertechnetate scan was 10.0 (4.20, 16.69), consistent with GD diagnosis. The median follow-up period for the patients was 22.0 months (9, 36). All the patients except one were treated with methimazole with a median initial dose of 15 mg (10, 20) with gradual titration as per the treating endocrinologist. Table 1 shows the study sample's clinical characteristics.

Assessment of patients who achieved remission

A total of 103 out of 189 patients (54.5%) achieved GD remission. The free T4 level at the time of diagnosis was significantly lower in patients who achieved remission versus patients who did not, with a mean difference of 3.0 pmol/l ($P=0.038$). Similarly, the TRAb level at diagnosis was significantly lower in patients who achieved remission than in patients who did not, with a median difference of 5.4 IU/l ($P=0.001$). A significant proportion of the female patients (61.7%) achieved remission, while only 35% of the male patients achieved remission. The only two patients with severe ophthalmopathy and 67% of the patients with moderate ophthalmopathy did not achieve remission. A detailed comparison of

Table 1 Clinical characteristics of the study sample

Variable	Result
Age (years), Median (IQR), $n=189$	38.0 (33.00, 49.00)
BMI(kg/m ²), Mean(SD) $n=189$	29.1(6.11)
Gender, female, n (%)	136(72%)
*Free T4 upon diagnosis(pmol/l), Mean (SD), $n=189$	27.2 (9.93)
**Free T3 upon diagnosis(pmol/l), Median (IQR), $n=185$	9.7(6.80, 17.05)
[§] Thyroid uptake on ^{99m} Tc-pertechnetate scan (%),Median (IQR), $n=146$	10.0(4.20, 16.69)
^{§§} TSH receptor antibodies level up on diagnosis(IU/l), Median (IQR), $n=166$	6.7(3.40, 15.80)
Mild ophthalmopathy, n (%) , $n=181$	129 (71.3%)
Moderate ophthalmopathy, n (%) , $n=181$	50 (27.6%)
Severe ophthalmopathy, n (%) , $n=181$	2 (1.1%)
Remission rate, n (%) , $n=189$	103 (54.5%)
Relapse rate after remission, n (%) , $n=103$	35 (34.0%)
Duration of ATDs treatment before remission (months), Median (IQR), $n=103$	29.0(20.00, 42.00)
Time to relapse after remission (months), Median (IQR), $n=32$	14.0(7.00, 20.00)

IQR: interquartile range

SD: standard deviation

ATDs: anti-thyroid drugs

*Reference normal range free T4: 9–19 pmol/L

** Reference normal range free T3: 2.9–4.9 pmol/L

[§] Reference normal range Thyroid uptake on ^{99m}Tc-pertechnetate scan: 1–4%

^{§§} Reference normal value TSH receptor antibodies level: <1.8 IU/l

Table 2 Comparison of ATD-treated Graves' disease patients who achieved remission versus patients who did not achieve remission

Variable	Remission (n=103)	No remission (n=86)	P-value
Age (years), n, [Median (IQR)]	103,[39.0(34.00, 50.00)]	86,[38.0(31.00, 49.00)]	0.484 [^]
Free T3 upon diagnosis(pmol/l), n, [Median (IQR)]	103,[9.2(7.00, 15.80)]	82,[11.1(6.40, 23.60)]	0.177 [^]
Free T4 upon diagnosis(pmol/l), n, [Mean (SD)]	103,[25.8 (8.93)]	86,[28.8 (10.82)]	0.038 [*]
TSH receptor antibodies level up on diagnosis(IU/l), n, [Median (IQR)]	93,[5.1(2.90, 10.70)]	73,[10.5(4.20, 22.50)]	0.001 [^]
Thyroid uptake on 99mTc-pertechnetate scan (%),n, [Median (IQR)]	79,[7.8(3.77, 14.70)]	61,[10.5(4.77, 21.50)]	0.061 [^]
BMI (Kg/m2), n, Mean (SD)	103,[28.8 (5.88)]	86,[29.4 (6.40)]	0.485 [*]
Duration of ATDs treatment (months), n, [Median (IQR)]	103,[29.0(20.00, 42.00)]	86,[33.0(23.00, 53.00)]	0.154 [^]
Female patients, n (%)	84 (81.6)	52 (60.5)	0.001 ^{**}
Male patients, n (%)	19 (18.4)	34 (39.5)	0.001 ^{**}
Mild ophthalmopathy, n (%)	81 (84.4)	48 (56.5)	<0.0001 ^{**}
Moderate or severe ophthalmopathy, n (%)	15 (15.6)	37 [§] (43.5)	<0.0001 ^{**}

IQR: interquartile range

SD: standard deviation

ATDs: anti-thyroid drugs

* P value calculated using T -Test

[^] P value calculated using Wilcoxon rank sum test

^{**} P value calculated using Chi-square test

[§] This include 2 patients with severe ophthalmopathy and 35 patients with moderate ophthalmopathy

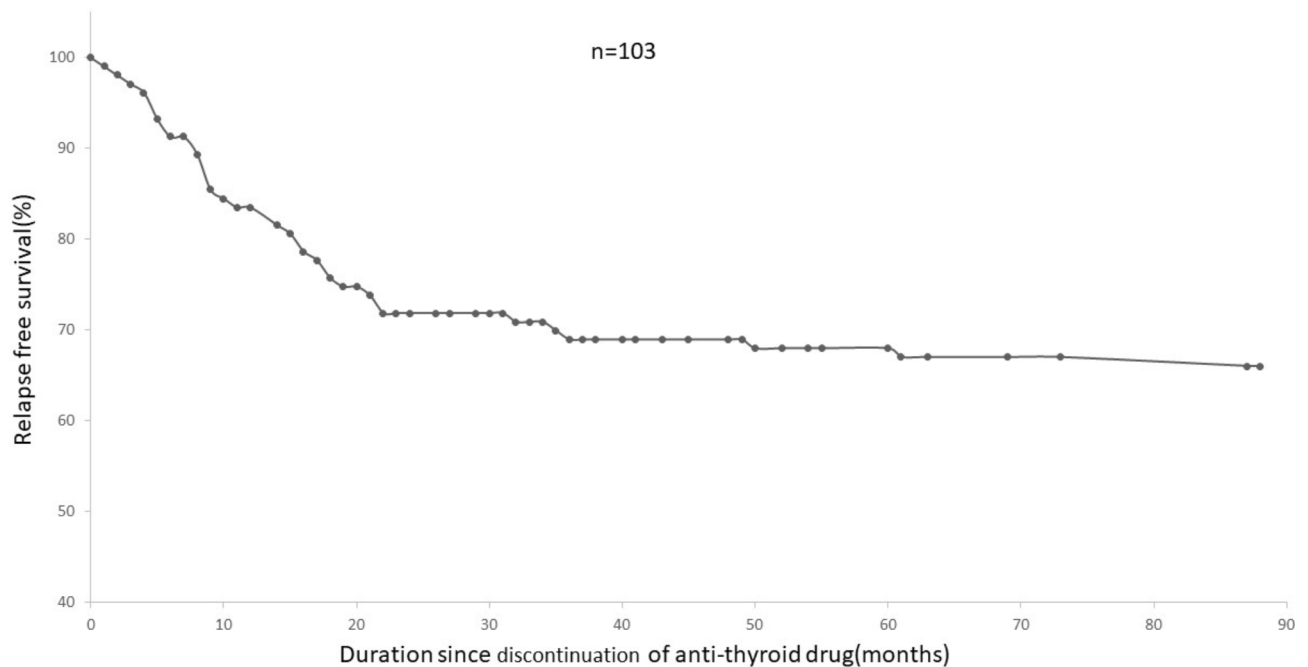


Fig. 1 Survival curve of patients who achieved remission

the patients who achieved remission versus those who did not is shown in Table 2. Of the patients who did not achieve remission, 22 patients underwent thyroidectomy, 17 patients received RAI, and 47 patients continued on ATD.

Assessment of patients who developed relapses

In terms of relapses, of the 103 patients who achieved remission, 35 (34%), 30 of whom were female, relapsed

after ATD discontinuation. The median time to relapse was 14 months (7, 20). Figure 1 shows the remission survival curve of the 103 patients with remission during follow-up. Patients who relapsed showed significantly higher thyroid uptake on 99mTc-pertechnetate scan at baseline than patients who did not relapse, with a median difference of 4.3% (P=0.03). Similarly, patients who relapsed were treated with ATD for a longer period than patients without relapse, with a median difference

Table 3 Comparison of Graves' disease patients who experienced relapse after ATDs discontinuation versus patients who did not experience relapse

Variable	Relapse (n = 35)	No relapse (n = 68)	P-value
Age (years), n, [Median (IQR)]	35,[38.0(33.00, 51.00)]	68,[39(34.00, 49.50)]	0.826 [^]
Free T3 upon diagnosis(pmol/l), n, [Median (IQR)]	35,[9.1(5.80, 15.70)]	68,[9.4(7.05, 16.60)]	0.526 [^]
Free T4 upon diagnosis(pmol/l), n, [Mean (SD)]	35,[26.7 (8.21)]	68,[25.4 (9.31)]	0.495 [*]
TSH receptor antibodies level up on diagnosis(IU/l), n, [Median (IQR)]	32,[5.0(3.70, 10.90)]	61,[5.1(2.50, 10.30)]	0.454 [^]
Thyroid uptake on 99mTc-pertechnetate scan (%),n, [Median (IQR)]	30,[10.3(5.19, 16.81)]	49,[6.0(3.09, 12.38)]	0.030 [^]
BMI (Kg/m2), n, Mean (SD)	35,[27.8 (6.38)]	68,[29.3 (5.58)]	0.215 [*]
Duration of ATDs treatment (months), n, [Median (IQR)]	35,[40.0(29.00, 58.00)]	68,[25.0(19.00, 32.50)]	< 0.0001 [^]
Female patients, n (%)	30 (85.7)	54 (79.4)	0.435 ^{**}
Male patients, n (%)	5 (14.3)	14 (20.6)	0.435 ^{**}
Mild ophthalmopathy, n (%)	29 (87.9)	52 (82.5)	0.494 ^{**}
Moderate ophthalmopathy, n (%)	4 (12.1)	11 (17.5)	0.494 ^{**}

IQR: interquartile range

SD: standard deviation

ATDs: anti-thyroid drugs

^{*} P value calculated using T -Test[^] P value calculated using Wilcoxon rank sum test^{**} P value calculated using Chi-square test**Table 4** Multivariate analysis for variables as predictors for remission

Effect	Beta	Standard Error	Odds Ratio	[95% Conf. Interval]	P-value
Free T4 upon diagnosis	0.0240	0.0252	1.024	(0.97, 1.08)	0.3406
TSH receptor antibodies level up on diagnosis	0.0550	0.0260	1.057	(1.00, 1.11)	0.0341
Thyroid scan and uptake up on diagnosis	0.0121	0.0137	1.012	(0.99, 1.04)	0.3783
Gender	-0.6922	0.4567	0.500	(0.20, 1.23)	0.1296
Ophthalmopathy severity(mild versus moderate and sever)	-1.4539	0.5337	0.234	(0.08, 0.67)	0.0064
Age	0.0212	0.0171	1.021	(0.99, 1.06)	0.2141
Duration of ATDs treatment	0.00110	0.00868	1.001	(0.98, 1.02)	0.8994

ATDs: anti-thyroid drugs

of 15 months ($P < 0.0001$). No significant differences in free T4 or TRAb levels were identified (Table 3). Of the patients who relapsed after the discontinuation of ATD, 10 received RAI, 2 underwent thyroidectomy, and the remaining 23 were restarted on a second course of ATD.

Predictors of remission

Available and previously reported variables associated with remission and the variables showed significance in the univariate analysis were incorporated in a multivariate analysis to assess the factors associated with remission. TSH receptor levels and ophthalmopathy severity were found to be significantly associated with remission (Table 4). The ROC curve, which determined the free T4 level cutoff to predict remission using Youden's J statistics, showed the best AUC of 0.5887, at the best cutoff value of 28.5 pmol/l, with a sensitivity of 52% and a specificity of 66% (Fig. 2). Similarly, the ROC curve, which determined the TRAb level cutoff to predict remission using Youden's J statistics, showed the best AUC of 0.6697 at the best cutoff value of 13.4 Iu/l, with a sensitivity of 47% and a specificity of 84% (Fig. 3).

Predictors of relapse

Available and previously reported variables associated with relapse and the variables that showed significance in the univariate analysis were incorporated into a multivariate analysis to assess the factors associated with relapse. Only the duration of ATD treatment was associated with relapse (Table 5).

Discussion

This retrospective cohort study evaluated the demographics of patients from Saudi Arabia with GD. The remission and relapse rates and the factors affecting both outcomes were also investigated. Like other autoimmune diseases, GD is more commonly diagnosed in middle-aged women [7, 17]. Accordingly, in this study, around two-thirds of the patients were female, and the median age at diagnosis was 38 years.

GD diagnosis is based on the documentation of thyrotoxicosis with suppressed TSH, with the elevation of free T4 and T3. GD is usually confirmed by the documentation of elevated TRAb or with high thyroid uptake on nuclear imaging [7, 8]. Thyroid I¹²³ is commonly used to

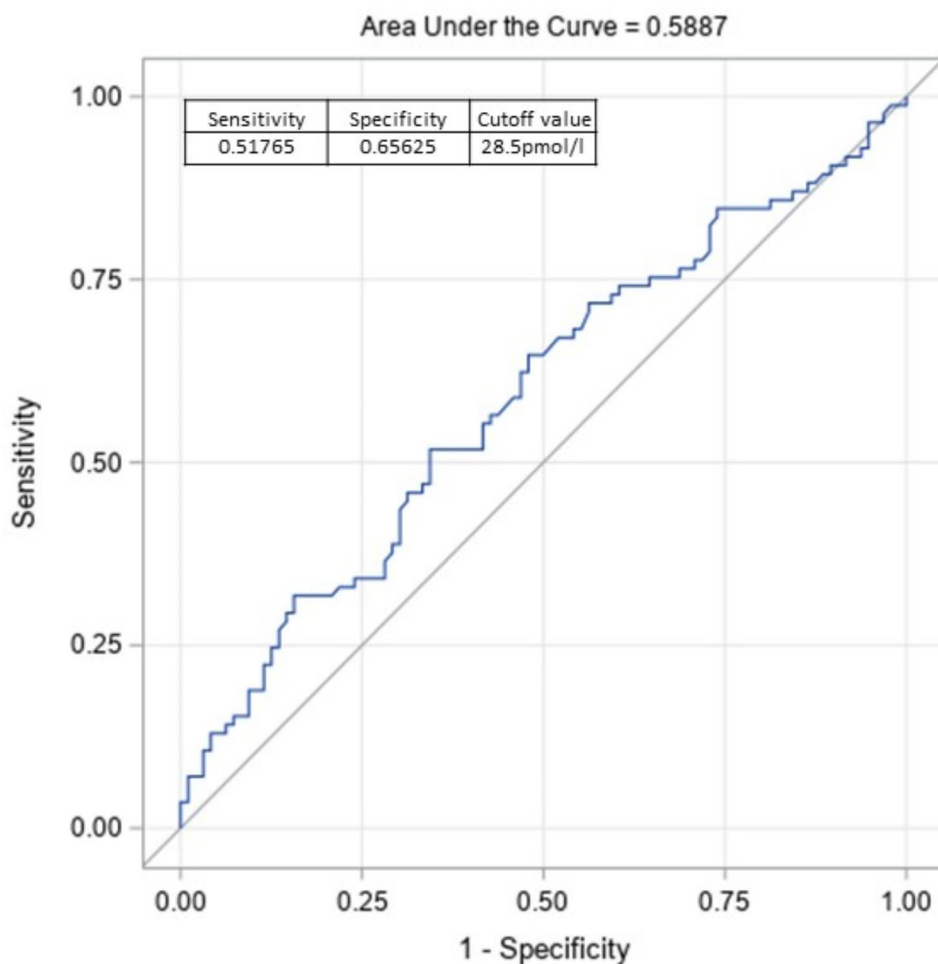


Fig. 2 Receiver operating characteristic curve of free T4 predicting remission

confirm GD; however, the ^{99m}Tc pertechnetate scan is also widely used due to its availability and the short time the scanning takes [7, 8]. In this study, TRAb and ^{99m}Tc -pertechnetate scans confirmed a GD diagnosis.

The management strategies for overt hyperthyroidism caused by GD are either the reduction of thyroid hormone production with ATD or reduction of thyroid tissue, leading to hypothyroidism through radioactive iodine ablation or thyroidectomy. The American Thyroid Association and the European Thyroid Association recommend the three treatment options as a first-line therapy for GD [7, 8]. ATDs are widely accepted as a first-line treatment given their safety and efficacy [18].

When considering ATDs as a treatment option for GD, the treating physician and the patient should be aware of the possibility of not achieving remission and of experiencing relapse after achieving remission. Studies have found an ATD-induced remission of GD in 30–70% of patients [7, 8, 19]. The current study's failure rate for achieving remission with ATDs was 45.4%, which is consistent with that of previous studies [13, 18].

TSH receptor antibodies level known to predict clinical and biochemical outcomes among GD patients treated with ATD. The American Thyroid Association and European Thyroid Association recommend measuring TRAb at the end of the treatment period and before stopping the ATD to guide the decision of whether to discontinue ATD, prolong low-dose ATD, or proceed with definitive therapy (RAI or surgery) [7, 8]. We found that the remission rate was inversely related to the initial TRAb level; thus, a lower TRAb level was observed in patients who achieved remission than in those who did not. In addition, we established that remission was achieved more often among females, patients with low baseline free T4, and patients with mild Graves's ophthalmopathy. These findings are, to an extent, consistent with previous studies. Karmisholt et al. determined that patients with higher free T4 and TRAb levels upon diagnosis were less likely to experience remission. However, there was no difference in the likelihood of remission based on gender or eye disease status [13]. In contrast, Song et al. found that only the free T4 level at diagnosis predicts remission [20].

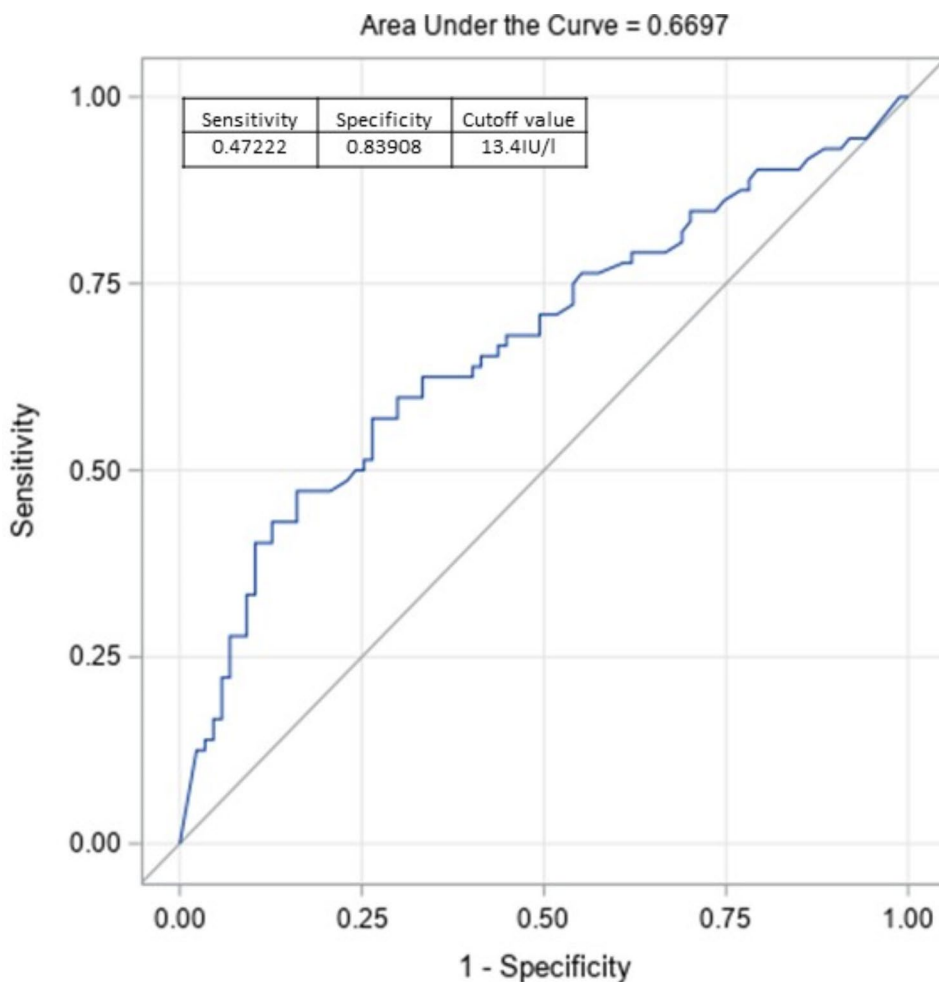


Fig. 3 Receiver operating characteristic curve of TRAb predicting remission

Table 5 Multivariate analysis for variables as predictors for relapse

Effect	Beta	Standard Error	Odds Ratio	[95% Conf. Interval]	P-value
Free T4 upon diagnosis	0.0429	0.0466	1.044	(0.95, 1.14)	0.3576
TSH receptor antibodies level up on diagnosis	-0.00888	0.0499	0.991	(0.90, 1.09)	0.8589
Thyroid scan and uptake up on diagnosis	-0.0823	0.0524	0.921	(0.83, 1.02)	0.1162
Gender	-0.7718	0.7911	0.462	(0.10, 2.18)	0.3293
Ophthalmopathy severity(mild versus moderate and sever)	-0.9819	1.1014	0.375	(0.04, 3.24)	0.3726
Age	0.000938	0.0242	1.001	(0.95, 1.05)	0.9691
Duration of ATDs treatment	-0.0612	0.0194	0.941	(0.91, 0.98)	0.0016

ATDs: anti-thyroid drugs

Zuhur et al. observed that females achieved sustained remission more often than males did [21]. Similar to this study, previous studies have associated Graves’s ophthalmopathy severity and remission rates with ATD [14, 22].

The evaluation of factors associated with remission has led to developing the Graves Recurrent Events After Therapy (GREAT) score. GREAT score variables include age, free T4 level, TRAb titer level, and thyroid goiter size. The lower the GREAT score, the more likely a patient with GD is to achieve remission [23]. However,

validation studies of the GREAT score have shown that only TRAb levels are consistent predictors of GD remission [24]. In line with that finding, the multivariate analysis in this study, incorporating most of the components of the GREAT score and the variables found to be significant in univariate analysis, showed that only higher TRAb levels upon the diagnosis of GD were significantly associated with the failure to achieve remission with ATD. The best cutoff value of 13.4 Iu/l for TRAb levels on the ROC curve to predict remission was correlated with an AUC of

0.6697, with a high specificity of 83% but a low sensitivity of 47%. Similar to this study's findings, Karmisholt et al. found that the best TRAb level cutoff value for predicting remission was 10 IU/l with 74% specificity and 57% sensitivity [13]. These cutoff values of TRAb to predict remission require further investigation to assess their utility in clinical practice. For free T4, the best cutoff value of 28.5 pmol/l on the ROC curve had a low AUC (0.5887), with a low sensitivity of 52% and a specificity of 66%, indicating that free T4 levels upon diagnosis exhibit a poor ability to predict remission. Further studies are necessary to determine the utility and cutoff values of TRAb and other biochemical variables to predict remission.

The relapse rate after remission in this study was 34%, which is comparable to previous studies that showed a 30–40% relapse rate in the first year and an overall relapse rate of GD after ATD discontinuation of up to 50–60% [7, 8, 15, 25, 26]. In this study, the median time to relapse was 14 months after ATD discontinuation, which is consistent with other studies reporting that relapse usually occurs in the first two years after ATD discontinuation [7, 23].

This study found that individuals with higher thyroid uptake on ^{99m}Tc-pertechnetate scans and who required a longer duration of treatment with ATD had an increased risk of relapse. However, after conducting a multivariate analysis, only the prolonged use of ATD was predictive of relapse. Other factors, such as gender, age, baseline free T4, TRAb level, and the presence of thyroid eye disease, did not significantly impact the risk of relapse. Similar to our findings, previous studies have established that a higher uptake on a ^{99m}Tc-pertechnetate scan is associated with more frequent relapses [27]. However, Azizi et al.'s systematic review contradicted our findings. They reported that a longer duration of ATD (>60 months) resulted in up to an 85% chance of sustained remission without relapse [28]. This systematic review supported the findings of a randomized clinical trial that found a 15% relapse rate after a long duration (95 +/- 22 months) of ATD use versus a 53% relapse rate in patients who received ATD for 19 +/- 3 months [29]. Park et al. also established that the relapse rate in relation to ATD treatment duration was 42.4% at one year, 38.5% at two years, 33.8% at three years, 31.7% at four years, 30.2% at five years, 27.8% at six years, and 19.1% at over six years [25]. However, other studies have indicated the opposite and were thus consistent with this study. For example, Park et al. determined that ATD use for more than six months is an independent predictor of relapse [24]. Similarly, Kim et al. reported that longer ATD and multiple courses of ATD were associated with persistent GD [30]. Therefore, it is unclear whether a longer duration of ATD results in sustainable remission or indicates the need for long-term ATD use to maintain remission.

This significant aspect of GD management requires further studies.

In terms of the relationships between TRAb titer, free T4 levels, and relapse rates, we found that baseline TRAb status and free T4 level did not affect the relapse rate, a finding similar to that of previous studies [15, 23]. This finding, however, contradicts those of other studies in which patients who relapsed had higher serum TRAb, free T4 levels, and larger goiter at baseline [31].

Our study was the first to report on ATD efficacy and predictors of remission and relapse of GD in the Middle-Eastern population. However, the study has limitations because it is a retrospective, single-center study missing important variables such as accurate thyroid volume and end-of-treatment TRAb levels. Future studies to evaluate the predictors of GD remission and relapse with ATD are necessary to improve first-line treatment selection for patients with GD. Moreover, studies to validate the GREAT score in different populations are needed to enhance its utility in clinical practice.

Conclusion

This study's findings demonstrated that a significant proportion of patients achieved remission with ATD. Patients with lower levels of free T4 and TRAb at diagnosis had higher remission rates. The female gender, mild ophthalmopathy, and shorter durations of thionamide treatment are factors associated with remission. Conversely, higher thyroid uptake on ^{99m}Tc-pertechnetate scan at baseline and longer ATD treatment duration were associated with an increased risk of relapse. These findings have implications for personalized treatment approaches and highlight the necessity of monitoring specific biomarkers and clinical characteristics to optimize treatment outcomes and long-term prognosis in GD patients.

Abbreviations

GD	Graves' disease
TRAb	Thyroid-stimulating hormone receptor antibodies
ATD	Anti-thyroid drugs
TSH	Thyroid-stimulating hormone
RAI	Radioactive iodine
PTU	Propylthiouracil
MMI	Methimazole
EUGOGO	European group on graves orbitopathy
SD	Standard deviation
IQR	Inter-quartile ranges
AUC	Area under the curve
ROC	Receiver operating characteristic curve
IRB	Institution review board

Acknowledgements

We acknowledge Mr. Yazeed Altaif from the Office of Research at King Saud bin Abdulaziz University for Health Sciences for his assistance during the copy-editing phase.

Author contributions

MM, MA, YA, WA, AA and NA designed the study. MM, MA, YA, WA, AA, NA and HA worked on the methodology. MM, MA, YA, WA, AA, NA and IA worked on

the data curation. HA, MM, MA, YA, WA, AA and NA did the statistical analysis. MM, MA, YA, WA, AA, NA and IA wrote the first draft. MM, MA, YA, WA, AA, NA, IA and HA revised the manuscript. MM did the study supervision. All authors contributed and approved the final version of the paper.

Funding

None.

Data availability

The data that support the findings of this study are not openly available due to institutional policy, but will be available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

The study approved by the Institution Review Board (IRB) at King Abdullah International Medical Research Center-Riyadh with Protocol Number: NRC22R/314/06 and approval number IRB/1431/22 with a waiver of the study subjects' consent as per the institutional policy for retrospective studies.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh 22490, Saudi Arabia

²Department of Medicine, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs, Riyadh 14611, Saudi Arabia

³King Abdullah International Medical Research Center, Riyadh 11481, Saudi Arabia

⁴College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh 14611, Saudi Arabia

⁵College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh 14611, Saudi Arabia

⁶Department of Internal Medicine, Ministry of Defense, King Salman Armed Forces Hospital, Tabuk, Saudi Arabia

⁷Department of Biostatistics and Bioinformatics, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

⁸King Saud bin Abdulaziz University for Health Sciences, Mail Code, P.O. Box 3660, Riyadh 3130, 11481, Kingdom of Saudi Arabia

Received: 29 April 2024 / Accepted: 26 August 2024

Published online: 06 September 2024

References

1. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, et al. Graves' disease. *Nat Reviews Disease Primers*. 2020;6(1):1–23.
2. Subekti I, Pramono LA. Current diagnosis and management of Graves' disease. *Acta Med Indones*. 2018;50(2):177–82.
3. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med*. 2016;375(16):1552–65.
4. Bartalena L. Diagnosis and management of Graves disease: a global overview. *Nat Rev Endocrinol*. 2013;9(12):724–34.
5. Dong YH, Fu DG. Autoimmune thyroid disease: mechanism, genetics and current knowledge. *Eur Rev Med Pharmacol Sci*. 2014;18(23):3611–8.
6. Malabu UH, Alfadda A, Sulimani RA, Al-Rubeaan KA, Al-Ruhaily AD, Fouda MA, et al. Graves' disease in Saudi Arabia: a ten-year hospital study. *J Pak Med Assoc*. 2008;58(6):302–4.
7. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. European Thyroid Association guideline for the management of Graves' hyperthyroidism. *Eur Thyroid J*. 2018;7(4):167–86.
8. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–421.
9. Burch HB, Cooper DS. Management of Graves disease: a review. *JAMA*. 2015;314(23):2544–54.
10. Wong KK, Shulkin BL, Gross MD, Avram AM. Efficacy of radioactive iodine treatment of graves'hyperthyroidism using a single calculated 1311 dose. *Clin Diabetes Endocrinol*. 2018;4(1):1–8.
11. Katzung BG, Dong BJ. *Thyroid & Antithyroid Drugs*. Basic & Clinical Pharmacology. New York: McGraw-Hill; 2018. pp. 687–702.
12. Liu J, Fu J, Xu Y, Wang G. Antithyroid drug therapy for Graves' disease and implications for recurrence. *International journal of endocrinology* 2017. 2017.
13. 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 RISGstudy. *J Thyroid Res*. 2019.
14. 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(4):1453–8.
15. 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(4):662–e754.
16. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol*. 2021;185(4):G43–67.
17. McLeod DSA, Caturegli P, Cooper DS, Matos PG, Hutfless S. Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. *JAMA*. 2014;311(15):1563–5.
18. Ma C, Xie J, Wang H, Li J, Chen S. Radioiodine therapy versus antithyroid medications for Graves' disease. *Cochrane Database Syst Reviews*. 2016(2).
19. Mohlin E, Filipsson Nyström H, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000–2010. *Eur J Endocrinol*. 2014;170(3):419–27.
20. Song A, Kim SJ, Kim M-S, Kim J, Kim I, Bae GY, et al. Long-term antithyroid drug treatment of graves' disease in children and adolescents: a 20-year single-center experience. *Front Endocrinol (Lausanne)*. 2021;12:687834.
21. Zuhur SS, Yildiz I, Altuntas Y, Bayraktaroglu T, Erol S, Sahin S et al. The effect of gender on response to antithyroid drugs and risk of relapse after discontinuation of the antithyroid drugs in patients with Graves' hyperthyroidism: a multicenter study. *Endokrynol Pol*. 2020.
22. Wang X, Li T, Li Y, Wang Q, Cai Y, Wang Z et al. Enhanced predictive validity of integrative models for refractory hyperthyroidism considering baseline and early therapy characteristics: a prospective cohort study. *J Translational Med*. 2024;22(1).
23. Vos XG, Ender E, Zwinderman AH, Tijssen JGP, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 2016;101(4):1381–9.
24. 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(4):413–9.
25. Park S, Song E, Oh H-S, 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(2):348–56.
26. Park SY, Kim BH, Kim M, Hong AR, Park J, Park H, et al. The longer the antithyroid drug is used, the lower the relapse rate in Graves' disease: a retrospective multicenter cohort study in Korea. *Endocrine*. 2021;74(1):120–7.
27. Singhal N, Praveen VP, Bhavani N, Menon A, Menon U, Abraham N, et al. Technetium uptake predicts remission and relapse in Grave's disease patients on antithyroid drugs for at least 1 year in south Indian subjects. *Indian J Endocrinol Metab*. 2016;20(2):157.
28. Azizi F, Abdi H, Mehran L, Amouzegar A. Appropriate duration of antithyroid drug treatment as a predictor for relapse of Graves' disease: a systematic scoping review. *J Endocrinol Invest*. 2022;45(6):1139–50.
29. Azizi F, Amouzegar A, Tohidi M, Hedayati M, Khalili D, Cheraghi L, et al. Increased remission rates after long-term methimazole therapy in patients with graves' disease: results of a randomized clinical trial. *Thyroid*. 2019;29(9):1192–200.
30. Kim YA, Cho SW, Choi HS, Moon S, Moon JH, Kim KW, et al. The second antithyroid drug treatment is effective in relapsed Graves' disease patients: a median 11-year follow-up study. *Thyroid*. 2017;27(4):491–6.

31. Bano A, Gan E, Addison C, Narayanan K, Weaver JU, Tsatlidis V, et al. Age may influence the impact of TRAbs on thyroid function and relapse-risk in patients with Graves disease. *J Clin Endocrinol Metab.* 2019;104(5):1378–85.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.