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Outcomes of Long-Term Follow-up of Patients Receiving Antithyroid Medication for Hyperthyroidism due to Graves' Disease

Marwa Mohy Eldin Abdelrahman Ahmed*

Department of Internal Medicine, Benha Faculty of Medicine, Benha University, Benha, Egypt.

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ABSTRACT

Background: Thyrotropin (also known as thyroid stimulating hormone (TSH)) receptors antibodies (TRAb) activate thyroid follicular cells in the autoimmune condition known as Graves' hyperthyroidism, which causes thyrotoxicosis and swelling of the thyroid gland.

Objective: Using a thorough retrospective cohort design, this research assessed the effectiveness of antithyroid drugs (ATDs) and risk variables linked to the recurrence of Graves' hyperthyroidism.

Methods: With enough follow-up data, we evaluated 2100 individuals who had just received a Graves' hyperthyroidism diagnosis. Evaluation of the treatment results of the subjects and risk factors for recurrence-free survival, particularly alterations in thyrotropin receptors antibodies.

Results: The participants' average age was 44.8 years, and 64% of them were females. After using ATD for a median of 22.9 months (interquartile range (IQR) 16.9-34.4), 1450 participants were given the option to discontinue the medication. Initial remission ratio was 56.6%. 95.24% of participants completed the second round of ATD therapy after the initial recurrence and the remission ratio was 56.6%. 7.14% of participants required surgery, and 10.9% received radioactive iodine treatment, throughout the course of a median follow-up duration of 67 months. About 29.7% of patients were still receiving ATD medication for chronic lower-dose maintained or recurring illness. Male gender, being younger (<45 years old), and fluctuating or smoldering of TRAb levels were all distinct risk indicators for the first recurrence following ATD therapy.

Conclusions: ATD therapy is a viable choice for both chronic condition and the first therapy of Graves' hyperthyroidism. The individual risk indicators of recurring must be determined to identify the effective therapeutic duration for ATD therapy.

Keywords: Antibody; Remission; Thyrotropin receptor; Antithyroid Drug; Graves' Hyperthyroidism.

* Corresponding author
Email: marwa.abdelrhman@fmed.bu.edu.eg

INTRODUCTION

Thyrotropin (also known as thyroid stimulating hormone (TSH)) receptors antibodies (TRAb) activates thyroid follicular cells in the autoimmune condition known as Graves' hyperthyroidism, which causes thyrotoxicosis and swelling of the thyroid glands [1, 2].

Individuals with Graves' hyperthyroidism can currently choose between operation, radioactive iodine treatments, and antithyroid drugs (ATDs) [3]. ATD is the favored first-line treatment in most places despite geographic differences because it is secure and easily accessible [4]. The main therapeutic concern with ATD remains the probability of recurring when medication is stopped, in contrast to RAI therapy or surgery, which are characterized by a somewhat more adjuvant treatment [5]. According to American and European recommendations, ATD should be maintained for 12 to 18 months, with remission frequencies of 50 to 55% [6]. Yet, other research, including a randomized clinical trial, claims that a lengthier therapy course, lasting up to 41–120 months, is linked to a survival benefit with remission frequencies of 57–85% [7]. This leads to the issue of whether all individuals with Graves' hyperthyroidism should get long-term ATD medication. Age, sex, goiter size, smoking status, and the existence of thyroid-associated ophthalmopathy (TAO) are among the numerous risk variables previously identified to be connected to illness prognosis [8].

So, instead of a fixed long-term duration, it might be acceptable to identify the individual risk of recurrence and select the effective therapeutic length. Owing to its integral part in the pathogenesis of the disease, TRAb concentration is also a major contributor to risk when considering personal characteristics. The American and European recommendations advise measuring TRAb before stopping ATD medication because it helps forecast the likelihood of recovery [9]. Together with age, goiter, and initial free T4 (fT4) value, the initial TRAb was also discovered to assist in predicting the illness recurring prior to ATD therapy [10]. Using a long-term randomized trial, Bandai *et al*. [5] hypothesized that in addition to TRAb at the beginning and conclusion of ATD, the trend of TRAb, defined as smooth disappearing, fluctuation form, and smoldering form, may aid in predicting the chronic presentation of Graves' hyperthyroidism [11].

This work provided the first insight into the significance of the dynamical alteration of TRAb, which required to be confirmed and emphasized. Individuals with chronically increased (smoldering) TRAb may opt to switch from long-term ATD management to definitive treatment such as RAI or thyroidectomy [5]. There is no known outcome in this condition, though a significant recurring frequency could be anticipated. Also, it can be difficult for therapists to decide whether to cease ATD when the TRAb is significantly changing. As a result, our goal was to use a complete cohort with a large size and long-term follow-up to determine the effectiveness of ATD in individuals with Graves' hyperthyroidism. In doing so, we aimed to discover risk variables, such as the alteration in TRAb throughout therapy for ATD that was related to outcome.

PATIENTS AND METHODS

Study design: This was a retrospective study, which was conducted at Jeddah hospital Hospitals during the period from 2018 to 2023.

Inclusion criteria: Both genders with Graves' hyperthyroidism, who had just received a fresh diagnosis and have adequate follow-up evidence.

Exclusion criteria: Patients having an ATD treatment for less than one year due to poor adherence, or with inadequate follow-up evidence (follow-up length below one year), were excluded from the study.

Ethical considerations: Review Board authorized this investigation, and because it was retrospective in nature, written permission was not required. The study was conducted in accordance with the declaration of Helsinki.

Diagnosis, treatment, and follow-up: According to laboratory results showing increased blood fT4 and TRAb values with suppressed TSH concentration, Graves' hyperthyroidism was identified. For the identification of Graves' hyperthyroidism, a higher absorption on a 99m-technetium (99m-Tc) thyroid scanning and the prevalence of thyrotoxicosis manifestations and symptoms were also taken into consideration. Methimazoles (MMI) (15–30 mg/day), carbimazoles (CAM, 20–40 mg/day), or propylthiouracils (PTU, 100–400 mg/day) were the initial medications administered to patients, and dosage titration was carried out as previously reported [12].

Once serum TSH and fT4 values returned to normal after an appropriate amount of exposure period, ATD discontinuation was taken into consideration. When TRAb was negative, ATD was typically terminated for participants. In the euthyroid condition, minimal preservation of therapy (MMI, 2.5 mg/day; CAM, 5 mg/day; and PTU, 25 mg/day) was also carried out, according to previous studies [13, 14]. Each 2-3 months while receiving ATD medication and every 3-6 months after stopping ATD, blood TSH, fT4, total T3, and TRAb were tested.

Laboratory measurements: The TSH-CTK-3 kits (radio-immunoassay (RIA); DiaSorin SpA, Saluggia, Italy) were used to detect the serum concentrations of TSH with a practical tolerance of 0.07 mIU/L (15). The blood overall T3 concentrations were determined by RIA using T3-CTK

(DiaSorin SpA), while the serum fT4 concentrations were determined using the fT4 RIA (Immunotech, Prague, Czech Republic). TSH, fT4, and overall T3 had reference ranges of 0.4–4.5 mIU/L, 0.80–1.90 ng/dL, and 151-277 ng/dL, correspondingly. Based on the package recommendations, the B-R-A-H-M-S TRAK human RIA (B-R-A-H-M-S GmbH, Hennigsdorf, Berlin, Germany) assessed TRAb using a selective TSH-binding inhibiting immunoglobulin (TBII) test [16]. With an experimental sensitivity of 0.3 IU/L and a functioning test sensitivity of 1.0 0.2 IU/L, TBII titers ≥ 1.5 IU/L were declared positive.

Definitions and outcomes: In accordance with the World Health Organization's goiter categorization, goiter was graded as follows: level 0, no goiter; level 1, thyroids palpable but not observable; and level 2, thyroids observable with the neck in a normally position [17]. Clinical activities and intensity were used to categorize TAO as mild, moderate, or severe [18]. Using all of the TRAbs obtainable throughout ATD therapy and divided into three groups, the increase of TRAb was evaluated. Smooth disappearing, smoldering type, and fluctuating type [5, 19]. Smoothly disappearing was described as the gradual decline of TRAb to a negative value prior to the termination of ATD. Once the tier of TRAb varied from positively to negatively during the ATD therapy phase, that is when the fluctuation type was identified. Whenever the titer of TRAb persistently remained positive over the period of therapy, the smoldering type was identified. After the conclusion of therapy, the TRAb patterns were evaluated. After stopping ATD, remission was considered to have occurred when the euthyroid state was sustained for more than one year [16, 20]. After stopping ATD, recurrence was described as continuously reduced TSH regardless of increasing fT4 throughout follow-up [16]. The possibility of transient thyrotoxicosis, including painless thyroiditis, besides a relapse of Graves' hyperthyroidism, was ruled out. Every therapist thought about using a second round of ATD treatment, RAI, or surgeries in the event of recurrence. The period of time between the end of ATD treatment and the start of the recurrence or the final follow-up was known as recurrence-free survivals (RFS).

Statistical analysis: The data was analyzed statistically using R version 3.4.4 (R Foundations for Statistical Computation; https://www.r-project.org/). Numbers were used to indicate categorical data (%) and the median and interquartile ranges (IQR) for continuous data. The chi-square and Wilcoxon rank-sum tests were employed to contrast the parameters. For the post-hoc assessment, Fisher's minimum substantial difference was utilized. The Kaplan-Meier methodology was employed to produce the survival curves, as well as the level of significance was assessed using the log-rank testing. Risk factors were assessed using the Cox-proportional hazards modeling and displayed as hazards ratios (HRs) and 95% confidence intervals (CIs). All P values were two-sided, and significance was determined by values lower than 0.05.

RESULTS

Fundamental features of Graves' hyperthyroidism individuals: Table 1 provides an overview of the prognostic factors' of 2100 individuals with Graves' hyperthyroidism. Participants' average age at initial diagnosis was 43.4 years, and 1630 (77.6%) of them were women. 250 individuals (11.9% of the overall) were former or present smokers. 910 (43.3%) and 346 (16.48%) of the participants had levels 1 and 2 goiters, respectively. 160 (7.6%) TAO participants required systematic steroids treatment due to moderate-to-severe illness. Upon assessment, the baseline titer of TRAb was 8.7 IU/L, and the median fT4 value was 2.4 ng/dL. Diagnostic progress and results for the entire cohort: A total of 150 individuals (7.14%) had surgery, while 230 (10.9%) received RAI medication. 29.7% of participants received ATD therapy as the starting treatment option. In the end, 1022 individuals (48.7%) had the option to stop taking ATD (Table2).

Following stopping the first ATD, remission of Graves' hyperthyroidism was found in 820 individuals (56.6%) (Figure 1). Moreover, recurring illness affected 630 (43.3%) individuals. The majority of the individuals (95.24%) with recurring Graves' hyperthyroidisms received the second ATD treatment, and 300 (50%) had a second opportunity to stop receiving ATD. 250 individuals were identified and managed of ATD medication after 50 individuals were excluded because their follow-up duration was lower than a year following ATD cessation. Following the second round of therapy, 115 individuals (46%) reported recurrent disease, and 135 individuals (54%) had experienced a second recovery. In 250 participants (Figure 1) who finished the second therapy cycle, we assessed the prognosis based on the thyroid's functions at the point in time of the first recurrence.

Clinical signs of recurrence and variations in TRAb values: We emphasized the 1450 individuals who stopped receiving ATD after receiving the initial ATD treatment (Table 3). Participants in the recurrence sample had a median age of 43.9 years, which is considerably younger than that of the treatment sample ($P < 0.001$). In the recurrence sample, there were more females and smokers than in the remission sample ($P = 0.03$ and $P = 0.01$, respectively). The recurring sample also frequently had clinically obvious TAO ($P = 0.03$). When the TRAb value in the remission sample was negative, a lot of individuals stopped using ATD ($P < 0.001$). Participants in the remission sample required considerably less treatment time (median 20.7 months) compared to the recurring sample (median 22.8 months, $P < 0.001$). The remission (4.9 months) and recurring samples needed substantially different amounts of time (4.7 months, $P = 0.01$) for the

blood TSH value to return to normal. Nevertheless, in participants with smooth disappearing and fluctuation form of TRAb, the time needed for the normalization of serum TRAb was not different depending on remission or recurrence (P = 0.53). There were no discernible differences between the uptake rates in the groups of patients in remission (7.7%) and those with recurrence (8.2%, P = 0.37).

Depending on TRAb trajectories, individuals were grouped into three categories: smoothly disappearing (n = 875, 60.34%), fluctuation (n = 290, 20%), and smouldering (n = 285, 19.6%) (Table 4). Participants in the smouldering cohort had a median age of 47.7 years, which was noticeably higher than the median ages of the other groupings (P = 0.001). Participants in the fluctuation group had ATD for 36.3 months, but those in the smouldering (24.7 months) and smoothly disappearing (18.4 months), (P< 0.001 and P< 0.001, respectively). The fluctuation group needed considerably more time (19.1 months) than the smoothly disappearing group (11.2 months, P <0.001) for the blood TRAb concentration to return to normal.

RFS following the initial ATD therapy: Diagnostic variables connected to individuals with Graves' hyperthyroidism's duration to recurrence (RFS) was assessed and distributed in Table 5. Participants were then separated into subgroups depending on the cutoff scores for age and fT4 that were established using the median scores of the entire patients' population. Younger ages (<45 years), males' sex, TAO, and smoking were statistically and negatively linked with RFS in multiple regression. Shorter RFS following first ATD medication was likewise associated with the elevated TRAb score at ATD discontinuation (HR = 1.80, 95% CI 1.59-2.16, P< 0.001) (Figure. 2 A). Considering the forms of TRAb alterations, lower RFS was similarly connected to fluctuation (HR = 1.64, 95% CI 1.31-2.06, P< 0.001) and smoldering kinds (HR = 2.15, 95% CI 1.74-2.65, P< 0.001) varieties in comparison to those with smoothly disappearing (Figure. 2B). Younger ages (45 years) and males (HR = 1.14, 95% CI 1.03-1.40, P = 0.01), as well as shifting TRAb characteristics (fluctuating group: HR = 1.50, 95% CI 1.17-2.12, P< 0.001; smouldering group: HR = 1.82, 95% CI 1.22-2.79, P <0.001), were independently linked potential risks for short RFS of Grave.

Table (1): General characteristics of all Graves' hyperthyroidism participants

Variable		Values
Total, *n*		2100
Sex, Female		1630 (77.6%)
Age (years)		43.4 (32.4–53.2)
Smoking	Current smoker	150 (7.1%)
	Previously smoker	100 (4.8%)
	Non-smoker	1850 (88.1%)
Initial ATD type[b]	Initial TRAb (IU/L)	8.7 (4.1–21.1)
	Initial total T3[c] (ng/dL)	227.0 (184.0–312.0)
	Initial free T4 (ng/dL)	2.4 (1.8–3.3)
	Initial TSH (μM/mL)	0.03 (0.03–0.03)
	Propylthiouracil	340 (16.2%)
	Carbimazole	640 (30.5%)
	Methimazole	1120 (53.3%)
TAO	Moderate to severe	160 (7.6%)
	Mild	140 (6.7%)
	Absent	1800 (85.7%)
Goiter[a]	Level 2	346 (16.48%)
	Level 1	910 (43.3%)
	Level 0	844 (40.2%)
Follow up duration (months)		67 (12.3-84.9)
Treatment duration (months)	Surgery	27.3 (15.9-51.7)
	RAI therapy	29.2 (17.59-49.8)
	Withdraw ATD after treatment	23 (17-35.5)
	Continue ATD treatment	55.4 (42.59-84.9)

[a] Level 0, no goiter; level 1, thyroids that may be felt but is not observable; level 2, thyroid that is noticeable with the neck in a correct position; [b] Without receiving ATD therapy, one subject has radioactive iodine ablations done; [c] 1346 individuals have accessible baseline T3 levels. TAO stands for thyroids-associated ophthalmopathy; TSH stands for thyroids-stimulating hormones; and TRAb stands for thyrotropin receptors antibodies.

Table (2): Final clinical outcome of the study participants

Variable	N (%)
Surgery	150 (7.14%)
RAI	230 (10.9%)
Lost follow-up after recurrence	75 (3.57%)
On ATD	623 (29.7%)
Off ATD	1022 (48.7%)

(ATD): Antithyroid drugs, (RAI): radioactive iodine.

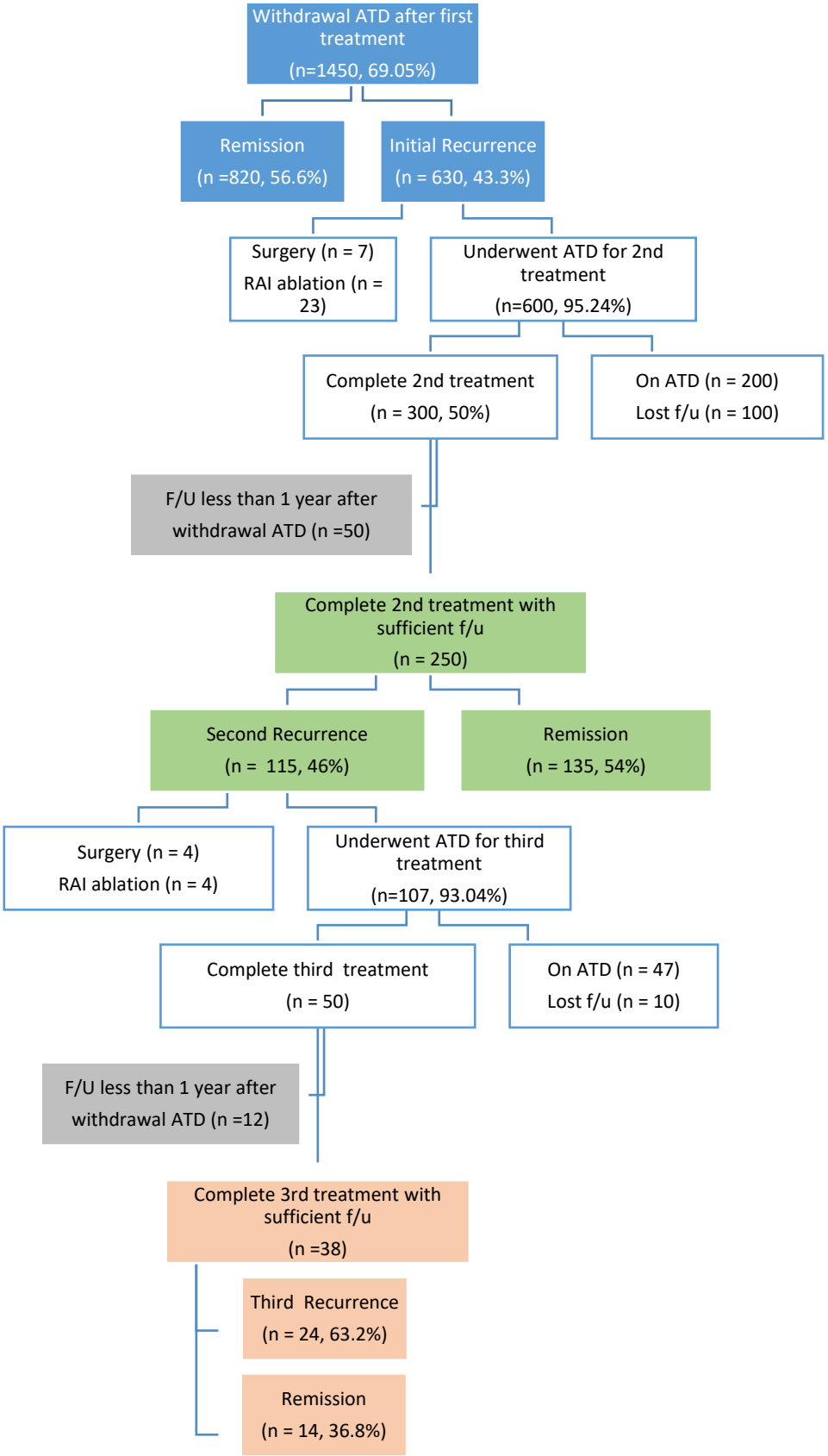

Figure (1): Clinical course and outcome of the patients treated with ATD, antithyroid drug; RAI, radioactive iodine; F/U, follow-up.

Table (3): Clinical characteristics of Graves' hyperthyroidism individuals in remission or recurrence following antithyroid medication therapy:

	Recurrence	Remission	Total	p-value
N	**630**	**820**	**1450**	
Age (years)	43.9 (31.6–52.4)	46.7 (36.9–54.3)	44.8 (34.1–54.9)	**<0.001**
Sex, female	427 (67.8%)	501 (61.09%)	928 (64%)	**0.03**
Smoking				0.01
Previous or current	47 (7.5%)	36 (4.4%)	71 (5.7%)	
No smoking	583 (92.5%)	784 (95.6%)	1367 (94.3%)	
ATD				0.23
PTU	57 (9.05%)	71 (8.7%)	128 (8.83%)	
CAM	213 (33.8%)	319 (38.9%)	532 (36.7%)	
MMI	360 (57.1%)	430 (52.4%)	790 (54.5%)	
TAO				**0.03**
Mild to severe	107 (16.98%)	107 (13.05%)	214 (14.8%)	
None	523 (83.02%)	713 (86.95%)	1236 (85.2%)	
Goiter[a]				0.42
Level 2	95 (15.08%)	86 (10.5%)	181 (12.5%)	
Level 1	269 (42.7%)	356 (43.4%)	625 (43.1%)	
Level 0	266 (42.2%)	378 (46.1%)	644 (44.4%)	
Thyroid scan uptake rate[d] **(%)**	8.2 (4.8–12.8)	7.7 (4.8–12.8)	8.9 (4.8–40.6)	0.37
TRAb normalization (months)[c]	13.0 (6.2–21.3)	12.0 (6.0–20.6)	12.4 (6.1–21.1)	0.53
TSH normalization (months)	4.7 (2.3–10.6)	4.9 (2.9–9.3)	4.2 (2.1–9.8)	**<0.01**
Duration of ATD (months)	22.8 (16.3–38.0)	20.7 (15.7–32.9)	22.9 (16.9–34.4)	**<0.001**
Duration of MMDT (months)	8.8 (5.9–13.5)	9.2 (5.2–14.5)	9.0 (5.1–14.1)	0.13
MMDT (yes)	510 (80.9%)	688 (83.9%)	1198 (82.6%)	0.06
TRAb level at withdraw (IU/L)	1.0 (0.6–1.4)	0.8 (0.5–1.3)	1.0 (0.5–1.5)	**<0.001**
TRAb at withdrawal (negative)	419 (66.5%)	657 (80.12%)	1076 (74.21%)	**<0.001**
Initial TRAb (IU/L)	7.7 (3.7–16.4)	7.8 (3.6–16.3)	7.8 (3.6–16.4)	0.87
Initial free T4 (ng/dL)	2.5 (2.1–3.5)	2.5 (1.8–3.4)	2.4 (2.0–3.3)	0.13
Initial dose of ATD (MMI, mg)[b]	12.2 (9.9–19.9)	12.2 (9.9–14.9)	12.2 (9.9–19.9)	0.11

Numbers (percentages) are used to denote categorical data and the medians (interquartile ranges) of continuous data. Statistically significant results are indicated in bold. [a] Level 0, no goiter; level 1, thyroid that may be felt but is not noticeable; level 2, thyroid that is noticeable with the neck in a correct position; [b] 5 mg MMI is equal to a dosage of 7.5 mg CAM and 100 mg PTU; [c] Participants in the fluctuation and individuals with smooth remission had their TRAb normalization time assessed; [d] 728 people have thyroids scans and uptakes with 99m-Tc. Antithyroid drugs (ATD), carbimazole (CAM), methimazole (MMI), propylthiouracil (PTU), thyroids-associated ophthalmopathy (TAO), thyrotropin receptors antibodies (TRAb), and thyroids-stimulating hormones (TSH), minimal maintenance dosage therapy (MMDT).

Table (4): Clinical features of Graves' hyperthyroidism patients based on TRAb development:

	Smoldering	Fluctuating	Smoothly disappearing	*P-value*
***n* (%)**	**285 (19.6%)**	**290 (20%)**	**875 (60.34%)**	
Sex, female	213 (74.7%)	191 (65.86%)	560 (64%)	0.58
Age (years)	47.7 (35.2–55.5)	42.0 (30.8–52.4)	45.9 (34.7–53.6)	**0.01**[bc]
Smoking				0.07
Previous or current	11 (3.86%)	23 (7.9%)	40 (4.6%)	
Non-smoker	274 (96.14%)	267 (92.1%)	835 (95.4%)	
Goiter[d]				0.82
Level 2	33 (11.6%)	34 (11.7%)	105 (12.0%)	
Level 1	125 (43.86%)	127 (43.8%)	411 (46.9%)	
Level 0	127 (44.6%)	129 (44.5%)	359 (41.03%)	
TAO				**0.01** [ab]
Moderate to severe	25 (8.8%)	28 (9.7%)	50 (5.7%)	
Mild	27 (9.5%)	22 (7.6%)	47 (5.4%)	
No	233 (81.8%)	240 (82.8%)	778 (88.9%)	
Initial ATD				0.07
PTU	25 (8.8%)	26 (8.97%)	52 (5.9%)	
CAM	99 (34.7%)	125 (43.1%)	310 (35.4%)	
MMI	161 (56.5%)	139 (47.9%)	513 (58.6%)	
First recurrence	179 (62.8%)	148 (51.03%)	315 (36%)	**<0.001**[abc]
MMDT (yes)	222 (77.9%)	235 (81.03%)	721 (82.4%)	0.19
Duration of ATD (months)	24.7 (16.8–43.7)	36.3 (23.2–56.1)	18.4 (15.0–26.2)	**<0.001**[abc]
TRAb normalization (months)[c]	-	19.1 (9.3–37.6)	11.2 (6.6–17.4)	**<0.001**[a]
TSH normalization (months)	5.7 (3.2–12.4)	6.0 (3.1–15.0)	5.1 (3.1–9.1)	**0.001**[abc]
TRAb at withdrawal (IU/L)	3.0 (2.3–4.7)	1.1 (0.7–15)	0.7 (0.4–1.1)	**<0.001**[abc]
Initial TRAb (IU/L)	11.5 (6.8–24.4)	8.8 (4.6–20.1)	7.7 (4.0–14.0)	**<0.001**[abc]
Initial free T4 (ng/dL)	2.4 (1.8–2.8)	2.5 (1.7–3.6)	2.5 (2.0–3.3)	0.10

Numbers (percentages) are used to denote categorical data and the medians (interquartile ranges) of continuous data. Statistically significant results are indicated in bold. [a] *P*< 0.05 between the fluctuation and smoothly disappearing sqmples; [b] *P*< 0.05 when comparing the groups for smoothly disappearing and smouldering; [c] *P* <0.05 between the groups fluctuating and smouldering; [d] Level 0, no goiter; level 1, thyroid that may be felt but is not noticeable; level 2, thyroid that is noticeable with the neck in a correct position. Antithyroid drugs (ATD), carbimazole (CAM), methimazole (MMI), propylthiouracil (PTU), thyroids-associated ophthalmopathy (TAO), thyrotropin receptors antibodies (TRAb), and thyroids-stimulating hormones (TSH), minimal maintenance dosage therapy (MMDT).

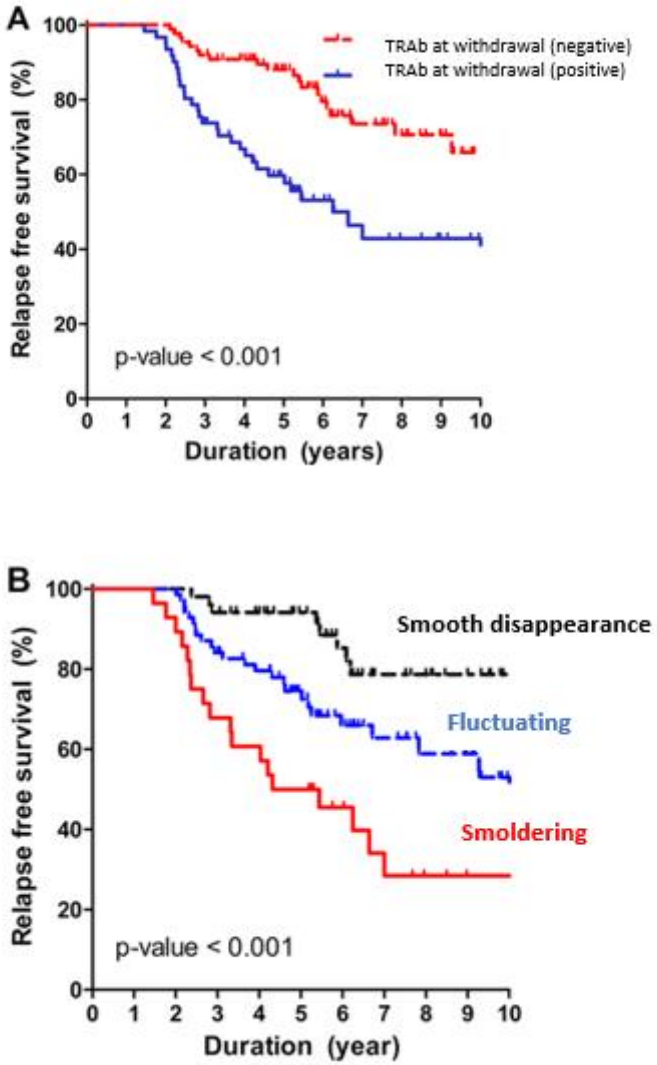

Figure (2): RFS of individuals with Graves' hyperthyroidism in a Kaplan-Meier graph. (A) RFS as of ATD removal as per TRAb. (B) RFS based on TRAb changes during ATD therapy. Recurrence-free survivals, thyroids-associated ophthalmopathy, and ATD Thyrotropin receptors antibodies, or TRAb.

Table (5): Medical elements linked to the return of Graves' hyperthyroidism following antithyroid medication therapy.

		Univariate analysis		Multivariate analysis	
	Reference	**HR (95% CI)**	***P-value***	**HR (95% CI)**	***P-value***
Male sex	Female	1.18 (1.07–1.43)	**0.003**	1.14 (1.03–1.40)	**0.01**
Age < 45 years	≥ 45	1.21 (1.22–1.45)	**0.001**	1.20 (1.22–1.45)	**0.001**
Smoking	Never smoke	1.50 (1.05–2.12)	**0.003**	1.23 (0.84–1.89)	0.08
Initial free T4	≤2.5 ng/dL	1.01 (0.75–1.10)	0.79	-	-
Goiter[a]	Level 0	1.07 (1.11–1.39)	0.04	-	-
TAO	No TAO	1.16 (1.02–1.50)	**0.03**	1.09 (0.76–1.28)	0.32
Initial TRAb (IU/L)					
>19.9		1.22 (0.77–1.39)	0.25		
6–19.9		1.08 (0.89–1.21)	0.26		
<6	-	-	-		
Positive TRAb at ATD withdrawal	Negative	1.80 (1.59–2.16)	**<0.001**	1.19 (0.75–1.56)	0.17
TRAb					
Smoldering		2.15 (1.74–2.65)	**<0.001**	**1.82 (1.22–2.79)**	**<0.001**
Fluctuating		1.64 (1.31–2.06)	**<0.001**	**1.50 (1.17–2.12)**	**<0.001**
Smooth disappearance	-	-	-	-	-

Variables that are statistically significant are bolded. [a] Level 0, no goiter; level 1, thyroid that may be felt but is not noticeable; level 2, thyroid that is noticeable with the neck in a correct position. Antithyroid drugs (ATD), carbimazole (CAM), methimazole (MMI), propylthiouracil (PTU), thyroids-associated ophthalmopathy (TAO), thyrotropin receptors antibodies (TRAb), and thyroids-stimulating hormones (TSH), minimal maintenance dosage therapy (MMDT).

DISCUSSION

In this substantial retrospective cohort analysis, we presented the clinical benefit of 2100 individuals who had recently received a Graves' hyperthyroidism diagnosis and had enough follow-up information. Following a median of 67 months of overall follow-up, 29.7% of participants were still receiving ATD treatment for recurrent disease and extended lower-dose maintenance, 18.04% of participants had undergone RAI or surgery, 3.57% lost follow-up after recurrence. 56.6% of participants in 1450 individuals who stopped receiving ATD after a median of 23 months of medication were in remission. The second round of ATD therapy had a remission ratio (54%) that was comparable to the first round (56.6%). The individualized risk of recurring is predicted by the changes of TRAb together with age and sex that could optimize the length of therapy.

The remission frequency of ATD is less compared to other ablative therapeutic interventions, such as thyroidectomy or RAI medication, since the primary mechanism of the disease is to block hormonal synthesis rather than control autoimmune etiology [21]. Many earlier investigations have found different remission rates after ATD therapy [22-26]. The lowest reported remission incidence was 20–30% [24], whereas disparities between ethnic groups and therapeutic regimens were frequently reported to be 50–60% [22, 23, 25].

Recent European research that examined the long-term therapy benefits of ATD in larger cohorts found that 45.3–47.3% of those suffering from autoimmune thyrotoxicosis experienced remission [11, 26].

Similar findings were also published in this research. In individuals who had the opportunity to stop using ATD for the first time, we discovered that the remission percentage was 56.6%. The median follow-up duration of 67 months revealed a total cumulative remission frequency of 54%. In terms of the general effectiveness of ATD, however, 48.7% of individuals who stopped taking it and 29.7% of those who kept taking it experienced long-lasting lower-dose maintenance advantages without experiencing any side effects from thyroidectomy or RAI treatment. There were a variety of optimum ATD treatment durations for individuals with Graves' hyperthyroidism. Whereas the current recommendations call for a duration of 12 to 18 months, several argue that a longer time frame is preferable [10, 27, 28].

According to a recent meta-analysis, 587 individuals who had ATD treatment for an average of 41 to 98 months experienced a 57% (95% CI 45–68%) remission rates [10].

In a prospective, randomized clinical trial involving 258 Graves' hyperthyroid individuals, those who received ATD for 95 ± 22 months and those who received it for 19 ± 23 months experienced recurrence ratios of 15% and 53%, respectively [27]. Yet, compared to the survey's longer experimental group, the shorter treatment group's participants were younger and had bigger goiters [27].

Based on the results of a recently multicenter retrospective sample research, the recurring rate declined dramatically with the length of ATD therapy, falling to 19.1% for more than 6 years and 42.4% for 1 year [28].

According to the findings of this research, individuals with Graves' hyperthyroidism can benefit from long-term ATD medication while remaining safe [10, 27, 28]. Therefore, establishing and recommending a standard and prolonged therapy term would not be acceptable given the varied associated symptoms of each participant. Those in our research who experienced a smooth disappearance of TRAb required less time for therapy, and the recurrence rate was lower (36%). Individuals with a fluctuating or smouldering type of TRAb, in comparison, required more time for therapy and experienced greater recurrence rates, which were 51.03% and 62.8%, respectively. Given that these individuals are anticipated to experience worse results, managing them for a longer duration makes sense. If patients received proper care, the length of therapy could be adapted to specific clinical circumstances.

Individuals with recurring Graves' hyperthyroidism who have received ATD are typically advised to seek definitive treatment, such as RAI surgery or medication [29, 30].

According to Sjölin and coworkers, the subsequent treatment's remission frequency was just 29.4% as opposed to the first treatment's incidence of 45.3% [11]. Yet, some research suggests that recurring Graves' hyperthyroidism can benefit from additional ATD **therapy** [31, 32]. In the USA, where RAI is favored, the latest trend is to restart ATD as a secondary therapy choice. 65% of individuals who had treatment failure following the first ATD therapy received the second ATD therapy, as reported by a large-scale population-based survey conducted in the USA [23].

There was no discernible change in the remission frequency between the first and second ATD medications in our research, which included most of the participants (95.24%) with recurring Graves' hyperthyroidism following the first ATD medication. As per our empirical findings, ATD is therefore a viable therapeutic choice for the initial and recurring Graves' hyperthyroidism.

It is simpler to measure TRAb titers prior to ATD termination than to measure TRAb trends. Even though the TRAb is negative, the outcome will vary depending on the TRAb development (fluctuating or smooth disappearance). Previous investigations showed the significance of TRAb declines that are smooth during the ATD therapy [5, 33], and our data confirms this. The tendency of TRAb will therefore

be more informative than the most recent TRAb at the removal of ATD. By creating the Graves' Recurrent Events after Treatment (GREAT) scoring using age, goiter, and the baseline fT4 levels, it was also discovered that the initial TRAb value could assist in predicting recurrence [34].

Rather than goiter and initial fT4, the new study indicated that male sex and increase in TRAb were crucial variables. The GREAT score research had the advantage of being a prospective multicenter experiment and developing a model that was capable of accurately predicting prognosis before ATD therapy. However, our work has the advantage of accurately capturing real-world outcomes, such as the dynamical variation of TRAb.

Limitations: There are a few restrictions on this research. Initially, because of its retroactive structure, there can be some bias. The length of medication was also continuously altered in accordance with the development of TRAb in this research, and the TRAb patterns might vary based on the duration of the medication. Secondly, there might have been variations in patient adherence, which might have affected the changes in TRAb. Nevertheless, by making sure the quantity of ATDs given met the date of the subsequent appointment, we attempted to reduce this issue. Finally, since it wasn't well documented in individuals with Graves' hyperthyroidism in the initial phases of the course of the study, we did not assess the negative effect of ATDs. Notwithstanding these drawbacks, this research presents real-world data from a sizable cohort of Graves' hyperthyroidism individuals who received enough ATD and had enough follow-up information.

Conclusions: Most of individuals with Graves' hyperthyroidism receive sufficient care and gain from ATD treatment. Younger ages and male gender were additional independent risk factors for RFS of Graves' hyperthyroidism, in addition to the changes in TRAb. Therefore, it might be appropriate to identify each patient's unique potential for recurrence and calculate the ideal therapy duration for Graves' hyperthyroidism individuals. ATD is also a highly viable choice for the initial management of Graves' hyperthyroidism and the therapy of recurring disease.

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