

# Predictors of Relapse in Graves' Hyperthyroidism after Treatment with Antithyroid Drugs

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## Abstract

**Background:** Choice of the treatment for patients with Graves' hyperthyroidism depends on local preference, the higher recurrence risk, comorbidities, and the patient's preferences. About half of the patients relapse after a course of a standard antithyroid drug (ATD) therapy for Graves' disease. **Objectives:** The objective of this study was to determine the clinical and biochemical features of Graves' hyperthyroidism that can predict the relapse of the disease after a standard course of ATD therapy. **Patients and Methods:** We conducted a retrospective 6-month study of 79 patients with Graves' hyperthyroidism who were treated with ATD (carbimazole) therapy for 12–18 months and went into remission for at least 1 year after ATD withdrawal. **Results:** The relapse rate in Graves' hyperthyroidism after 1 year in remission was 40.5%; patients with younger age (<40 years) and with severe biochemical disease correlated significantly with relapse. Gender, presence of a palpable goiter, orbitopathy, and smoking habits were not significant predictors of relapse, perhaps because of the small sample size. **Conclusions:** Forty percent of Graves' hyperthyroidism relapsed after 1 year of remission. Younger age and severe biochemical disease at diagnosis predicted relapse.

**Keywords:** Antithyroid drugs, Graves' disease, hyperthyroidism, relapse, remission

## INTRODUCTION

Graves' hyperthyroidism is the most common cause of hyperthyroidism.<sup>[1]</sup> Treatment options include antithyroid drugs (ATDs), radioactive iodine, or surgical resection, although none of these options target the mechanism of the disease, and there is no single treatment that can target both hyperthyroidism and the main extrathyroidal manifestation (orbitopathy).<sup>[2]</sup>

ATDs act by inhibiting thyroid hormone synthesis, but they have some immunosuppressive action. In Europe and Japan, ATDs are still the first-line treatment,<sup>[1]</sup> but in North America, radioactive-iodine is much preferred.<sup>[3,4]</sup> Endocrinologists in the Middle East and North Africa (MENA) seemed to practice in a hybrid fashion between these two groups depending on previous training and current affiliations.<sup>[5]</sup>

The major drawback of ATD is the high rate of relapse. Several studies have attempted to examine factors that can predict the relapse of the disease before the start of treatment which include some tests that are not routinely done in clinical practice; for example, human leukocyte antigen assessment, quantification of thyroid blood flow by Doppler sonography, thyrotropin-releasing hormone test, and thyroid-stimulating

hormone (TSH) receptor antibody titer. However, other predictors had been studied frequently including age, gender, thyroid size, smoking, and the severity of the biochemical hyperthyroidism at the time of diagnosis, but none of these risk factors have sufficient sensitivity and specificity to predict recurrence. Patients with these factors at the time of diagnosis tend to relapse earlier after ATD withdrawal; therefore, a low dose of methimazole (or carbimazole) for a longer duration may be advisable in these groups of patients with a higher risk of relapse.<sup>[6]</sup>

Choosing a treatment modality for a given patient with Graves' hyperthyroidism depends on multiple factors that include the local preference, a higher risk of relapse seen with ATD therapy, and a higher risk of hypothyroidism with radioactive-iodine and surgical resection; ATD therapy was the preferred treatment modality in the MENA region, although treatment plan can be shifted to a certain modality

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in the presence of Graves' orbitopathy (GO), large goiter, or pregnancy desire.<sup>[2,5,7,8]</sup>

Relapse rate after a course of ATD (for 12–24 months) varies across several studies from 30% to 70% which are described as follows:<sup>[1,2]</sup> Italy: 63.4%,<sup>[2,6]</sup> the UK: 63.5%,<sup>[2,7]</sup> Sweden: 43.5%,<sup>[2]</sup> and Japan: 34.2%.<sup>[8]</sup> Most of the relapses were in the 1<sup>st</sup> year after withdrawal of ATDs.<sup>[1,2,6,8]</sup>

## PATIENTS AND METHODS

We aimed to determine the clinical and biochemical features of Graves' hyperthyroidism that can predict the relapse of the disease after a standard course of ATD therapy in 79 Libyan patients with Graves' hyperthyroidism who were treated with ATD (carbimazole) therapy for 12–18 months and went into remission for at least 1 year after ATD withdrawal.

Patients diagnosed with Graves' hyperthyroidism between August 2010 and July 2012 were included. Diagnosis was based on clinical assessment, biochemical hyperthyroidism, and radiological examination (mainly ultrasound). Graves' hyperthyroidism was defined as the presence of biochemical hyperthyroidism (elevated T4 and undetectable TSH levels) with two of the following: diffuse goiter, significant peroxidase titer or thyroglobulin autoantibodies, and orbitopathy. Patients were recruited from six endocrine clinics in Benghazi Medical Center (a tertiary center) in Benghazi, Libya. Data were retrieved from medical charts. Inclusion criteria were adults (>18 years) diagnosed with Graves' hyperthyroidism who received ATD therapy for 12–18 months and went into remission for at least 1 year. Exclusion criteria were children and pregnant women. A total of 79 patients met these criteria. Baseline clinical parameters such as age, gender, goiter size (assessed clinically), smoking, and thyroid hormone status were recorded at the time of diagnosis. Goiter size and severity of orbitopathy could not be assessed accurately due to lack of documentation. However, the presence or absence of goiter and GO was based on the clinical assessment of the treating physician. Data were analyzed using the SPSS statistics version 18 (SPSS Inc., Chicago, IL, USA). The differences between the variables were explored using Chi-square test, and  $P < 0.05$  was considered to be statistically significant.

## RESULTS

A total of 79 patients diagnosed with Graves' hyperthyroidism between August 2010 and July 2012 were included in the study. Thirty-two patients (40.5%) had a recurrence of hyperthyroid state after remission for at least 1 year. The baseline factors are shown in Table 1. Younger patients had more relapse rate than the older age group (56.5% vs. 18.2%, respectively;  $P = 0.000$ ) [Figure 1]. Furthermore, patients who had a recurrence of hyperthyroidism had a biochemically more severe hyperthyroidism as evident by the higher T4 levels (>2 normal), but no significant difference was found for gender,

the presence of goiter, orbitopathy, or current smoking status at the time of diagnosis as predictors of recurrence.

## DISCUSSION

The outcome of therapy in Graves' disease varies between each patient, and choosing a treatment modality at the time of diagnosis has to be individualized, although identifying factors that could predict the relapse might be helpful.

Graves' hyperthyroidism is more common in adults, but it occurs in pediatrics. Winsa *et al.* found a higher relapse rate in younger age groups which occurred in 67% of patients aged <40 years and 52% of patients aged >40 years. Whereas, in other studies, results were similar with one exception when no significant correlation between age and relapse risk was detected.<sup>[10,11]</sup> In our study, the relapse rate was greater among people younger than 40 years of age.

The prevalence of Graves' hyperthyroidism is more in females than males (four to five times more common in females) as suggested by several studies, and the outcome after ATD therapy is less favorable in men. A higher relapse rate was demonstrated in males than females (80% vs. 60%) in a large prospective study.<sup>[7]</sup> However, no difference in relapse rate was noted between males and females in our patient groups, perhaps due to the smaller sample size in comparison with the study of Allahabadia *et al.* from the UK.<sup>[7]</sup> Two studies from Lithuania and China found no relation between the gender and the risk of relapse.<sup>[8,12,13]</sup>

The presence of a large goiter at the time of diagnosis was observed as a risk of relapse since the early 1950s;<sup>[14]</sup> since then, studies have shown an association between thyroid volume and relapse rate. Higher relapse rates were found with larger goiters;<sup>[15]</sup> while in our study, the exact size of goiter could not be retrieved because of lack of documentation, but the presence or absence of a palpable goiter does not affect the outcome.

About 20%–30% of patients with Graves' hyperthyroidism have associated orbitopathy. Our data showed that 24.1% of the patients had GO at the time of diagnosis, but this was not significantly associated with the risk of relapse ( $P = 0.078$ ). Previous studies regarding the relation between the relapse rate and the presence of GO were conflicting, but some studies have found a positive relation between GO and relapse rate.<sup>[16,17]</sup>

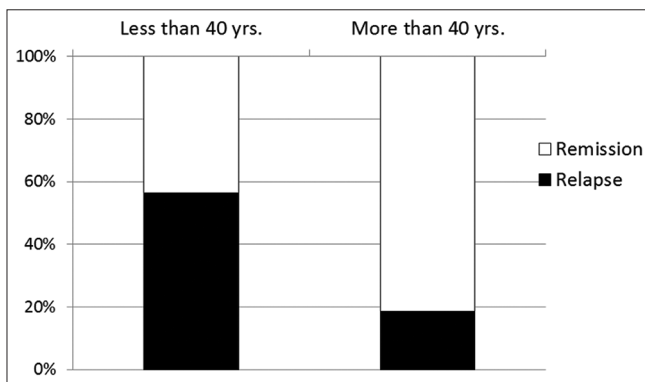
In the present study, severe biochemical hyperthyroidism was associated with a higher relapse rate ( $P = 0.001$ ). This is in agreement with previously reported concordant results demonstrating that severe biochemical disease at the time of diagnosis predicts increased risk of relapse.<sup>[7,9,10]</sup>

The risk of relapse in Graves' hyperthyroidism increases with smoking, and smoker's risk disappears few years after abstaining smoking.<sup>[16,17]</sup> The response to the medical therapy is less in smokers as the serum thyrotropin receptor antibody

**Table 1: Characteristics of patients in the whole group: Those who remained in remission and those who relapsed**

Patients' characteristics	Total, n (%)	Relapse, n (%)	Remission, n (%)	Statistical significance
Age <40 years	46 (58.2)	26 (56.5)	20 (43.5)	0.000
Age >40 years	33 (41.8)	6 (18.2)	27 (81.5)	
Males	12 (15.2)	5 (41.6)	7 (58.4)	0.930
Females	67 (84.8)	27 (40.3)	40 (59.7)	
Male current smokers	5 (41.7)	3 (60)	2 (40)	0.320
Male nonsmokers	7 (58.3)	2 (28.6)	5 (71.4)	
No palpable goiter	9 (11.4)	2 (22)	7 (78)	0.221
Palpable goiter	70 (88.6)	30 (42.8)	40 (57.2)	
No Graves' orbitopathy	60 (75.9)	21 (35)	39 (65)	0.078
Graves' orbitopathy present	19 (24.1)	11 (57.9)	8 (42.1)	
Total T4 >2 ULN	41 (51.9)	24 (58.5)	17 (41.5)	0.001
Total T4 <2 ULN	38 (48.1)	8 (20)	30 (80)	

Data are presented as n (%). ULN: Upper limit of normal



**Figure 1:** The percentage of remission and relapse in patients older and younger than 40 years of age

concentration decreases to a much slower rate in smokers than nonsmokers.<sup>[18]</sup> Glinoe *et al.* reported that relapse rate was 57% in smokers and 18% in nonsmokers with a significant risk for relapse;<sup>[19]</sup> while in this study, relapse rate in current male smokers was 60% compared with 28.6% in nonsmoker males ( $P = 0.320$ ).

## CONCLUSIONS

In the present study, relapse rate in Graves' hyperthyroidism after 1 year in remission was 40.5% in the younger age group and in those with severe biochemical disease at diagnosis. No significant association was detected with gender, the presence of goiter, orbitopathy, or smoking status, perhaps due to the smaller sample size or duration of the study. Further studies are needed with larger sample size.

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## Authors' contribution

SAL: study design, literature search, data acquisition, data analysis, statistical analysis, and manuscript preparation. HK: Study design, literature search, data acquisition, manuscript editing, and review. SEG: Study design, manuscript editing, and review. The final manuscript was reviewed and approved by all the authors prior to submission.

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## Conflicts of interest

There are no conflicts of interest.

## Compliance with ethical principles

This study was approved by the Research Ethical Committee at Benghazi Medical Center, Benghazi, Libya.

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