

Technetium uptake predicts remission and relapse in Grave's disease patients on antithyroid drugs for at least 1 year in South Indian subjects

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ABSTRACT

Context: Most of the information on remission related factors in Grave's disease are derived from Western literature. It is likely that there may be additional prognostic factors and differences in the postdrug treatment course of Grave's disease in India. **Aim:** To study factors which predict remission/relapse in Grave's disease patients from South India. Also to establish if technetium (Tc) uptake has a role in predicting remission. **Subjects and Methods:** Records of 174 patients with clinical, biochemical, and scintigraphic criteria consistent with Grave's disease, seen in our Institution between January 2006 and 2014 were analyzed. Patient factors, drug-related factors, Tc-99m uptake and other clinical factors were compared between the remission and nonremission groups. **Statistical Analysis Used:** Mann-Whitney U-test and Chi-square tests were used when appropriate to compare the groups. **Results:** Fifty-seven (32.7%) patients attained remission after at least 1 year of thionamide therapy. Of these, 11 (19.2%) patients relapsed within 1 year. Age, gender, goiter, and presence of extrathyroidal manifestations were not associated with remission. Higher values of Tc uptake were positively associated with remission ($P = 0.02$). Time to achievement of normal thyroid function and composite dose: Time scores were significantly associated with remission ($P = 0.05$ and $P = 0.01$, respectively). Patients with lower FT4 at presentation had a higher chance of remission ($P = 0.01$). The relapse rates were lower than previously reported in the literature. A higher Tc uptake was found to be significantly associated with relapse also ($P = 0.009$). **Conclusion:** The prognostic factors associated with remission in Graves's disease in this South Indian study are not the same as that reported in Western literature. Tc scintigraphy may have an additional role in identifying people who are likely to undergo remission and thus predict the outcome of Grave's disease.

Key words: Grave's disease, relapse, remission, technetium scintigraphy

INTRODUCTION

Parameters that help to predict the chance of remission and relapse in patients with Grave's disease on antithyroid drugs (ATDs), have been described from various parts of

the world.^[1-7] However, this may vary depending on factors like iodine status.^[8] The role of 99m-technetium (^{99m}Tc) pertechnetate uptake thyroid scintigraphy scan at presentation in predicting remission and relapse has not been well studied. Few studies done in early 90 s have shown a higher radioiodine uptake can be useful in predicting relapse, but its role in predicting remission still remains unclear.^[9]

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We also intended to confirm the previously described remission associated factors in our population.

SUBJECTS AND METHODS

Patient's data

Retrospective data of 174 patients with Grave's disease with near complete information who presented to our hospital in the period (2006–2014) were collected from electronic medical records. All the patients were treated with ATDs for 12–18 months at the end of which nonremitters were given the choice of radioiodine therapy, surgery or continuation of ATDs in small doses if that was sufficient.

The inclusion criteria were

- Patients diagnosed with Grave's disease after a physical examination, laboratory tests, and confirmed by Tc thyroid scintigraphy scan
- In remitters at least 1½ years follow-up after achieving remission
- Patients age more than 12 years.

Remission was defined as euthyroidism (normal thyroid function test [TFT]) for at least 5 months (with two documented normal thyroid functions 1–2 months apart) after stopping ATDs. Relapse was defined as biochemical documentation of thyrotoxicosis any time after satisfying remission criteria.

The following parameters were recorded for each patient from our database: Age, gender, smoking history, presence of goiter at time of presentation and 1 year after initiation of treatment, duration of treatment before undergoing Tc thyroid scintigraphy scan, uptake on Tc scan, free T4 level at time of diagnosis, total treatment duration, maximum dose of ATDs used, duration of maximum dose of ATD, time taken for normalization of TFT after ATD initiation, time to normalization of TFT multiplied by the dose used for same, time taken to reach the minimum dose of ATD, remission, relapse within 1 year, relapse after 1 year, radioiodine treatment, presence of ophthalmopathy and dermopathy.

TFT, which included thyroid stimulating hormone (TSH), free T4 was done at the time of diagnosis and at regular intervals as per the treating physician's discretion. Presence and size of goiter were examined by clinical examination. Ophthalmopathy was defined as the presence of eye signs. TSH, free T4 and were measured by chemiluminescent microparticle immunoassay.

Statistical analysis

Statistical analysis was performed with SPSS for Windows, Version 15.0. Chicago, SPSS Inc. Subjects who achieved remission were compared with those who did not achieve

remission. Relapsers were compared with nonrelapsers. Continuous variables were compared with Mann–Whitney U-test. Categorical variables were compared with Chi-square test.

Receiver operator curve (ROC) analysis was done to elucidate the value of Tc uptake cut-offs in predicting remission.

RESULTS

Of the 174 patients who met the inclusion criteria, 116 patients (66.6%) were females and 58 (33.3%) were males. Median age of the patients at the time of diagnosis was 44 years (12–78). Among the 174 patients, four patients were smokers (2.3%), while 126 patients (72.4%) were nonsmokers and smoking status of 44 patients (25.3%) was unknown. 135 patients (77.5%) had clinically detectable goiter at the time of diagnosis, out of which 82 patients had persistent goiter after 1 year of diagnosis.

All patients had undergone Tc thyroid scintigraphy scan at their first visit in our hospital. Out of total study patients, 79 were drug naive, i.e. they did not receive any ATD before undergoing thyroid scan. While, 95 patients out of 174 had received ATD before undergoing Tc thyroid scintigraphy scan. As per institutional protocol ATD were stopped for at least 7 days before undergoing Tc thyroid scintigraphy. Eye disease was present in 54 patients (31%), while Grave's dermopathy was found in six patients (3.4%). The median time taken for normalization of TFT was 7 months. The median for maximum dose of ATDs was 30 mg.

A composite variable of ATD dose with time score was included in this study. It was measured as a product of time taken for normalization of TFT multiplied by the dose of ATD used for same. The median score for same in our study patients was 180.

Median time taken to reach minimum dose in the study population was 12 months. Median T4 value at the time of diagnosis was 2.44 ng/dl.

In this study 57 patients (32.7%) had remission after initial ATD therapy. Only 38 (21.8%) patients had a duration of remission of at least 12 months. The comparison of various characteristics between remitters and nonremitters is given in Table 1.

Age, gender, and presence of goiter were not associated with remission. Smoking status and extrathyroidal manifestations had no bearing on remission.

Higher values of Tc uptake in thyroid scintigraphy scan were positively associated with remission ($P = 0.02$). Patient with lower FT4 at presentation had a higher chance of remission. Those who remitted had faster normalization of thyroid function. Furthermore, the composite variable that was a product of time taken for normalization of TFT and dose of ATD (time for normalization \times dose of ATD used) used for same, was found to be higher in the group who did not undergo remission. Neither the treatment duration nor the maximum dose of ATD used were found to be significant.

Out of the 57 patients (32.7%) who attained remission, 11 patients (19.2%) relapsed within 1 year. Comparison between relapsers and nonrelapsers is shown in Table 2.

The only factor that was found to be significant in this analysis was the Tc uptake. Patients with relapse (12.4% vs. 5.9%) had higher values of uptake ($P = 0.009$).

Table 1: Original

	Remission		P
	Yes	No	
<i>n</i>	57 (32.7)	117 (67.2)	
Gender (male:female)	19:38	39:78	0.56
Age	42	44	0.73
Free T4 (ng/dL)	2.03	2.18	0.01
Goiter at presentation (%)	41 (23.5)	94 (54.02)	0.14
Technetium uptake	6.4	7.9	0.02
Maximum dose (mg dose of carbimazole)	25	30	0.25
Duration of maximum dose	3	4	0.24
Treatment duration	19	17.5	0.40
Time to normalization of thyroid function (months)	5	7	0.05
Time to normalization \times maximum dose	100	140	0.01
Time to reach minimum dose (months)	6	8	0.67
Goiter at 1 year (%)	26 (14.9)	56 (32.1)	0.45
Dermopathy	1	5	0.35
Ophthalmopathy	18	36	0.52
Median values			

Table 2: Comparison of relapsers versus nonrelapsers

	Relapse		P
	Yes	No	
<i>n</i>	11	46	
Gender (male:female)	5:7	14:31	0.5
Age	40	42	0.6
Free T4 (ng/dL)	1.71	2.15	0.93
Goiter at presentation (%)	10 (83)	25 (70)	0.48
Technetium uptake	12.4	5.9	0.009
Maximum dose (mg dose of carbimazole)	25	30	0.51
Duration of maximum dose	3	4	0.16
Treatment duration	18	19	0.36
Time to normalization of thyroid function	3.5	5	0.21
Time to normalization \times maximum dose	95	107.5	0.89
Time to reach minimum dose	5	7	0.30
Goiter at 1 year (%)	7 (58)	22 (44)	0.52
Dermopathy (%)	1 (1.6)	6 (4.1)	0.95
Ophthalmopathy (%)	4 (33)	15 (30)	0.67

ROC analysis yielded an area under the curve (AUC) of 0.4 with significant P value (0.049). This was not pursued further as the sensitivity and specificity were low.

DISCUSSION

Studies evaluating remission factors in patients with Grave's disease in India have been very few^[10,11] and none from South India. Even in western literature, large studies evaluating factors associated with remission in Grave's disease are few. The current study looks into factors associated with remission in South Indian patients with Grave's disease. The main finding of this study has been the positive association of Tc uptake with remission.

The remission rate of 32.7% in the current study is slightly lower than that quoted in western literature.^[2,4,12] One year remission rate of 21.8% is lower than values quoted in most published literature. The criteria used to define remission varies from study to study. A study done in northern Swedish population reported a remission rate of 56.5%. There have been other studies as well which have also showed a higher remission rate, like one done by Ishtiaq *et al.*, which found remission rate of 41.9%,^[3] and 43.3% by Vitti *et al.*,^[4] 61% by Anagnostis *et al.*^[2] However in a study done in 1973, remission rate was found to be 13.6%,^[8] which was lower than the current study.

In the current study, age was not found to be associated with remission. A study by Allahabadia *et al.*^[13] found that patients aged <40 years had a lower remission rate than older patients. Also, in the same study, they found that males had a lower rate of remission when compared to females. Moreover, the presence of goiter was not found to be a predictor of remission in this study that was in contrast with results from another study^[14] which found that patients with small size goiter achieved early remission when compared with patients with large size goiters. However goiter volume related data were not available, and most of the patients in the current study had mild to moderate size goiters. The absence of association of both ophthalmopathy and dermatopathy with remission is in concordance with other studies.^[12,15,16] Nonsmoking status had a favourable effect on duration of remission in few studies, but no such association was found in the present study. However we acknowledge that we did not have complete information about smoking status of all the patients in the current study.

Tc uptake at initial presentation, as a potential factor in predicting remission, has not been much studied in the available literature. This study has been able to establish it as a factor which has been found to be positively associated

with remission in Grave's patient. Relapse of Grave's disease was also significantly related to the Tc uptake.

However, the absolute value of Tc uptake by itself did not have a high degree of predictive value as evidenced by the AUC of 0.4 ($P = 0.049$) for remission in drug-naïve patients.

Tc uptake after thionamide therapy and its relation to remission has been studied in the past. A study done in Japan in 1991 found that 86% of patients with Tc uptake of <4% after achieving euthyroid state with thionamide therapy, remained euthyroid on follow-up.^[17] An Indian study done in 1996 also established Tc uptake at the end of 18 months thionamide therapy as a significant predictor of outcome of Grave's disease.^[10] Another study done in early 90's concluded that a higher radioactive iodine uptake after thionamide therapy can predict relapse, while predicting remission is difficult.^[9] Contradictory results have been reported in a study in done in 1998 which did not find thyroid uptake useful in predicting the outcome (remission/relapse) in Grave's disease patients.^[16] Studies have also been conducted to study the association of Tc uptake with treatment success with a single dose of Iodine 131.^[11] They found that patients with high pretreatment $^{99m}\text{TcO}_4^-$ uptake are more likely to require repeated doses of ^{131}I to achieve complete remission.

The level of free T4 at the time of diagnosis was evaluated for all patients included in this study. It was found to be another predictor for remission and our data showed that a lower level of free T4 at presentation is associated with a greater chance of remission. The studies done so far which have evaluated free T4 levels with remission have also found similar results. A small study done in Pakistan showed that a lower free T4 level at presentation was associated with greater rate of remission. Similar data were provided by Anagnostis *et al.*,^[2] where lower free T4 levels after 6 months of treatment with ATDs were found to be associated with a longer duration of remission. Free T4 level was not found to have any predictive value for relapse in our study. This finding is supported by a 10 years long study done in a northern Swedish population^[12] which also found no association of free T4 with relapse.

A novel factor that was looked into in the current study was the time taken to normalize TFT with ATD treatment. This factor has not been evaluated so far, for its role in predicting remission. We found it to be significantly associated with remission. It was found that patients who underwent remission took lesser time for normalization of TFT after starting ATD. Also, the composite variable that was a product of time taken to normalize thyroid function and dose of ATD was also found to be higher in patients

who did not undergo remission. Hence, the patients who remitted took lesser time with ATD treatment to become euthyroid and thus had a lower value for the composite variable, when compared to ones who did not remit. These factors can thus help clinicians to predict patients who might undergo remission.

19.2% of the patients relapsed within 1 year in the current series, which was slightly lower when compared to the data from the western literature.^[5,12,16] A study conducted in northern Swedish population^[12] found goiter to be associated with relapse that was conflicting with our results, as we found no such association. Furthermore, they found smoking to have a protective impact on a relapse that was not found to have any significance in the current study. The findings from the current study were similar to a study conducted in Germany by Quadbeck *et al.*^[15] which had showed no association of relapse with age, goiter and extrathyroidal manifestations. Our study also found no association between relapse and time taken to normalize TFT. Relapsers and nonrelapsers had no significant difference in their time taken for normalization of TFT. A higher Tc uptake was found to be significantly associated with relapse in the present study. Similar result was also noted in a study done in early 90 s.^[9]

Limitation of this study is its retrospective nature and data collection from the available medical records. The absence of ultrasonographic data on thyroid size for all patients is also one of the limitations in analyzing goiter size as a predictor of remission. TSH receptor antibodies as a predictor for remission and relapse that has been established by various studies^[4,7,18,19] was not studied here.

CONCLUSION

Tc uptake scan at diagnosis has emerged as a novel factor in predicting remission and relapse in patients with Grave's disease. Though more studies are needed to establish further it as an important factor to predict remission and delineate long-term outcome. A lesser time taken for normalization of TFT has also been found to be positively associated with remission. Furthermore, the composite variable of the product of time taken for normalization of TFT and dose of ATD has emerged as a factor to predict remission. A lower value for the composite variable has shown a greater chance for remission. So, this is the first time that Graves' disease in South Indian population has been studied for factors predicting remission. It has clearly shown the role of Tc uptake scan as an additional factor in predicting remission as well as relapse in patients with Grave's disease.

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Conflicts of interest

There are no conflicts of interest.

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