ADDIS ABABA UNIVERSITY SCHOOL OF MEDICINE
COLLEGE OF HEALTH SCIENCES

Assessment of the diagnosis, follow-up and treatment outcomes in patients with hyperthyroidism at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia

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Abbreviations/Acronyms

AF	Atrial Fibrillation
ANC	Absolute Neutrophil Count
Anti Tg	Anti thyroglobulin Antibody
Anti TPO Ab	Anti thyroid peroxidase Antibody
ATD	Anti Thyroid Drug
CBC	Complete Blood Count
CFDS	Color Flow Doppler Sonography
FT3	Free T3
FT4	Free T4
GD	Graves' Disease
HF	Heart Failure
LFT	Liver Function Test
LT4	Levothyroxine
RAIU	Radio Active Iodine Uptake
TA	Toxic Adenoma
TFT	Thyroid Function Test
TKIs	Tyrosine Kinase Inhibitors
TMNG	Toxic Multi Nodular Goiter
TRAb	TSH Receptor Antibody
TSH	Thyroid Stimulating Hormone
TT3	Total T3
TT4	Total T4
ULN	Upper Limit of Normal

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Background

Hyperthyroidism is a disease condition characterized by increased synthesis and secretion of thyroid hormone by the thyroid gland. A diagnosis of hyperthyroidism is made based on clinical presentation and abnormality in TFT characterized by low level of TSH and elevated thyroid hormones. Diagnosing the different forms of hyperthyroidism based on clinical manifestations and TFT alone is challenging.

Objective

To assess the diagnosis, follow-up and treatment outcomes in patients with hyperthyroidism at Endocrine Clinic, TASH.

Methods

A retrospective follow-up study was employed to evaluate the diagnosis, follow-up and treatment outcomes of patients with hyperthyroidism at Endocrine Clinic, TASH. A census was performed to those patients who were aged 18 years and above, diagnosed to have hyperthyroidism on Antithyroid drug for more than 18 months on follow up from September 2009 to August 2012 E.C, excluding pregnant women. Patients' response to different treatment options were evaluated. Also, factors associated with treatment outcomes were identified. While descriptive statistics (mean, proportion, percentage and standard Deviations) were used to summarize the results, multivariate logistic regression and chi square test were used as appropriate to check the association between dependent and independent variables. Statistical significance was determined at a p value of < 0.05 and CI of 95%.

Results

In this study, a total of 230 patients with hyperthyroidism were involved, of which 208[90.4%] of them were female and 22[9.6%] were male. The female to male ratio was 9.4 to 1. The mean age of the participants was 44 years +/-13 SD. In about 60 % of patients the duration of diagnosis of hyperthyroidism was less than 04 years. The most common symptom and sign were palpitation and goiter accounting [89.6%] and [78.2%] respectively.

Significant association was found with therapy and duration of treatments. Those patients who had been following treatment for four years and above, were more likely to have improved outcome

compared to those who were following their treatment for less than four year (AOR=2.869, CI=1.173-7.0211, *p*=0.021). In addition, those patients who were on initial combination therapy (Beta adrenergic blocker + ATD) were 2.189 times highly likely to have improved outcomes compared to those who took single therapy (ATD or Beta-adrenergic blocker) (AOR=2.189, CI=1.144-4.187, *p*=0.018).

Conclusions

In this study, the most common cause of hyperthyroidism was TMNG and Treatment outcome was strongly associated with duration of hyperthyroidism and initial usage of combination therapy.

Key words: Hyperthyroidism, Toxic Multinodular Goiter, Graves' Disease, Toxic Adenoma

1. Background

1.1. Introduction

Hyperthyroidism is a disease condition characterized by increased synthesis and secretion of thyroid hormone by the thyroid gland. It is associated with comorbidities like Atrial fibrillation, stroke, lung disease and diabetes mellitus [1].

The global prevalence of overt hyperthyroidism in iodine replete areas ranges from 0.2% to 1.3% [2]. The prevalence of Hyperthyroidism in 376 patients with thyroid disorders done at TASH was 233 (61.7%) of this Toxic Multinodular Goiter (TMNG) occurred in 135 (35.9%), Toxic Nodules (TN) in 32 (8.5%) and Graves' disease (GD)in 65 (17.3%) [3]. Hyperthyroidism is more common in women than men in a ratio of 5:1[4].

The prevalence of Toxic nodular goiter increases with age and the presence of dietary iodine deficiency. This shows that compared to GD, the TMNG may be more common in older patients especially those who are residing in regions of iodine deficiency [5].

The common causes of endogenous hyperthyroidism are due to GD or nodular thyroid disease. Patients with hyperthyroidism may have symptoms that include anxiety, tremor, palpitations, heat intolerance, and weight loss. Goiter is commonly present and the size depends upon the cause of the hyperthyroidism. Exophthalmos is a common presentation of patients with Graves' disease.

A diagnosis of hyperthyroidism is made based on clinical presentation and abnormality in thyroid function test characterized by low level of TSH and elevated thyroid hormones. Ancillary investigations like Thyrotropin Receptor Antibodies (TRAb) and thyroid ultrasound are important for diagnosis and follow up of patients with hyperthyroidism. Diagnosing the different forms of hyperthyroidism based on clinical manifestations and TFT only is challenging.

Treatment of hyperthyroidism includes use of thionamides, radio ablation therapy and surgery depending the patient condition and preferences. Different diagnostic tools, follow-up measures and modalities of treatment needs to be employed for better patient care and improvement in treatment outcome.

1.2. Statement of the Problem

Hyperthyroidism is one of the common thyroid disorders reported in the National Endocrine Clinic of TASH. Diagnosing the different forms of hyperthyroidism based on clinical manifestations and TFT only could be challenging. However, due to limited availability of TFT test and consistency of test results forces physician to diagnose based on clinical manifestation only. In addition, the ratio of TT3 to TT4 is not usually applied in the diagnosis of the causes of hyperthyroidism despite it being a useful tool in differentiating GD from thyroiditis.

In the evaluation of patients with hyperthyroidism Color-Doppler Ultrasound is important diagnostic tool to differentiate GD from other conditions like thyroiditis based of increased flow in GD. CFDs are less exploited for diagnosis and follow up of patients with hyperthyroidism probably related to few trained man power, lack of the initiative to order the test and unavailability of the ultrasound [11].

The goal of therapy of hyperthyroidism is to render a patient euthyroid as quickly as possible but there is an observed delay in attainment of euthyroid state because of patient, physician and resource related factors.

Although there is regular appointment of patients with hyperthyroidism in the National Endocrine Clinic, periodic clinical and biochemical evaluation is not fully done because of giving less attention to basic follow up clinical evaluation from health care provider, resource unavailability and the remote residence of some of the patients.

There is an observed gap that Patients and physician discussion on hyperthyroidism follow-up and management not practiced as expected with focus on the side effects of ATDs and the need to notify if serious adverse events occur and on treatment options like surgery with its possible complication when indicated.

A patient is considered to be in remission if he/she has a normal serum TSH, free T4, and total T3 for 1 year after discontinuation of ATD therapy. To evaluate remission and chance of recurrence after completion of therapy determination of TRAb levels is important despite its being unavailable.

It is not uncommon to see some patients on high dose PTU treatment with signs and symptoms of hyperthyroidism which could be related to the efficacy of the drug where options of use of carbimazole or methimazole are not widely available.

One of the definitive treatment options include thyroid surgery which is usually delayed after the patient became euthyroid for patient and physician factors. Surgery is less often practiced in patients with TMNG who usually require a high dose of ATDs.

Therefore, there are observed deficiencies with regard to diagnostic workup, follow-up assessment and evaluation of treatment response of hyperthyroid patients at the National Endocrine Clinic.

1.3. Significance of the Study

From this study prevalence of different types of hyperthyroidism in patients who have follow up at national endocrine clinic of TASH could be obtained. The study will recommend that complete and serial availability of TFT for diagnosis, follow-up and assessing treatment response taking in to account the increasing number of patients with hyperthyroidism and the majority being unable to pay for these investigations.

Exploiting routinely Color flow doppler ultrasound as a diagnostic aid for our patients on follow up with hyperthyroidism is useful and the study will give stress for the use of doppler color flow ultrasound to be done by trained fellows with technical support from radiology unit.

There are patients with hyperthyroidism on high dose of PTU despite that they are not responding both clinically and biochemically probably related to PTU resistance. The study will recommend the introduction of first line drugs to the clinic like methimazole and carbimazole in the treatment of hyperthyroidism. The study also recommends the use of TRAb measurement as a diagnostic support to confirm for diagnostic challenges and check for the possibility of relapse of hyperthyroidism after completion of treatment.

From this study for proper diagnosis, follow up and treatment outcome assessment of patients with hyperthyroidism serial follow up using a structured follow-up chart will be proposed that includes different components like diagnosis, follow-up and treatment outcome which can be adaptable to electronic data recording system.

2. Literature Review

2.1. Diagnosis of Hyperthyroidism

Hyperthyroidism has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference.

When hyperthyroidism is suspected, the diagnosis should be confirmed by measurement of serum thyrotropin and total or free thyroxine, which are usually present in low and high concentrations respectively. If the thyrotropin level is low but the thyroxine level is normal, serum triiodothyronine should be measured, since the patient may have triiodothyronine toxicosis.
Clinical signs and symptoms are moderately correlated with elevation of thyroid hormones in younger patients and those with larger goiters [6]. In the elderly, the classic symptoms and signs of hyperthyroidism are less prevalent and thyroid function tests need to be performed for those presenting with atrial fibrillation, weight loss, or shortness of breath [7].

The utility of the ratio of total T3 to total T4 can also be used as it increases in thyrotoxicosis caused by GD whereas T4 is elevated more than T3 in thyrotoxicosis caused by thyroiditis, in one study the ratio of total T3 to total T4 (ng/lg) was >20 in GD and toxic nodular goiter. In unsettled diagnosis of hyperthyroidism caused by GD or thyroiditis use of the ratio of total T3/T4 could give supportive evidence for diagnosis [8].

Diagnostic tools aid in conditions where some of the patients lack distinctive clinical features and initial biochemical evaluation. This includes diagnostic testing with measurement of TRAb when indicated [9]. In addition to the usual thyroid function test, TRAb testing is of paramount importance in differentiating GD from thyroiditis when indicated.

In a study done by McKee et al. the use of TRAb measurements to diagnose GD compared to RAIU measurements reduced costs by 47% and resulted in a 46% quicker diagnosis. TRAb determination is more useful in the diagnosis and follow-up of treatment outcome in hyperthyroid patients who present with non-nodular thyroid enlargement with no definite orbitopathy [9].

As part of the diagnosis of causes of hyperthyroidism determination of the radioactive iodine uptake (RAIU) helps to differentiate the different forms of hyperthyroidism depending on their radioactive iodine uptake and radioactive iodine scan [10]. Diagnosis of hyperthyroidism could be

well supported by the use of thyroid ultrasonography for measurement of thyroidal blood flow which depends on resource and expertise availability. Color Flow Doppler Study (CFDs) could differentiate the untreated GD from the Hashimoto's thyroiditis, which had similar grayscale findings.

Hot nodules could also be differentiated from cold nodules with more prominent vascular patterns. As an inexpensive, fast, and noninvasive imaging procedure, CFDs could be helpful in the initial clinical evaluation and may avoid radioactive iodine scan in a substantial number of thyrotoxic patients [11].

2.2. Treatment of Hyperthyroidism

The treatment modalities for overt hyperthyroidism include Radioactive Iodine Therapy (RAI), Antithyroid drugs (ATDS), or thyroidectomy. The decision to the modality of treatment is chosen by the patient and physician.

Patients with symptomatic thyrotoxicosis are treated with beta-blockers with a special focus on the elderly individual with resting tachycardia or those with underlying cardiovascular disease. In one study patients taking B-adrenergic blockers with methimazole showed lower heart rates, less shortness of breath, and fatigue compared to those who took methimazole alone [12].

The preference of ATDs is for those patients with a high likelihood of remission (patients, especially women, with mild disease, small goiters, and negative or low-titer TRAb. ATDs are most widely used in the treatment of hyperthyroidism of this PTU is the main one. ATD therapy is targeted at achieving the euthyroid state as quickly and safely as possible. Patients with GD on ATDs could go to remission in about 12-18 months but about one-third of patients TSH-blocking antibodies may develop that leads to hypothyroidism [13].

Treatment with ATDs might have an immunosuppressive role that is beneficial to primarily decrease thyroid-specific autoimmunity and also the hyperthyroid state [14].

Surgery is chosen by some patients as a preferred mode of treatment emphasizing a relatively higher value on prompt and definitive control of hyperthyroidism, avoidance of radioactive iodine, and side effects of ATDs despite relative surgical risks and the need for lifelong thyroid hormone replacement. Treatment of TMNG (Plummer’s disease) with antithyroid medications, ethanol

ablation, Radioactive iodine ablation, or surgery must balance the goals of therapy, the durability of cure, relief of symptoms, risk of malignancy, and risk of complications [15].

2.3. Follow up of Hyperthyroid Patients

One of the common presentations of hyperthyroidism is weight loss and many patients gain considerable weight after treatment of their hyperthyroidism with radioiodine, a thionamide, or surgery. Therefore, weight measurement during follow-up of patients with hyperthyroidism should be done [16].

Nonadherence is the common cause of failure to achieve euthyroidism with ATDs [17]. A study done by CHAIN, et al described that checking for T3 levels is initially important as some patients will have persistently elevated Serum T3 levels after normalization of Serum T4 following ATDs therapy [18].

ATDs side effects include minor allergic side effects and rare but serious allergic/toxic events such as agranulocytosis, vasculitis, or hepatic damage. In a recent systematic review of eight studies between GD patients receiving MMI or PTU of this 13% of patients experienced adverse events [20]. ATD-associated agranulocytosis is uncommon but it is life-threatening.

PTU should be discontinued if patients have symptoms like jaundice, sore throat and fever and confirm that this information is communicated to the patient. Patterns of hepatotoxicity in PTU is hepatic necrosis whereas methimazole is associated with cholestasis [19].

When compared with methimazole, PTU at any dose appears to be more likely to cause agranulocytosis compared with low doses of MMI. In a large study of 754 cases of ATD induced agranulocytosis done in japan by Nakamura, H et al observed that agranulocytosis tends to occur abruptly within 3 months after initiation of ATD therapy, although it develops gradually in some patients [21].

A clear guide should be put in place that PTU should be discontinued if transaminase levels (found incidentally or measured as clinically indicated) reach >3 times the upper limit of normal or if levels elevated at the onset of therapy increase further and need to consider the cross-reactivity between ATDs [22].

2.4. Treatment Outcome of Hyperthyroidism

The assessment of the treatment outcome targeting remission varied because of some characteristics features like male gender, smoking and those with large goiters (80 g) have lower remission rate and prolonged therapy beyond 18 months. The majority of patients with GD gradually enter remission of TSH-receptor autoimmunity during medical or after surgical therapy, with no difference between the types of therapy. Remission of TSH-receptor autoimmunity after radioiodine therapy is less common [6].

In a retrospective study designed to evaluate the initial response to carbimazole in patients with Graves' disease (GD) and determinants of response, occurrence of adverse effect and the frequency of hypothyroidism showed GD younger patients might benefit from higher initial doses of carbimazole and patients with positive titres of Anti TPO Ab and Anti Tg Antibody, lower doses of 131I might prevent hypothyroidism [27].

In a study done by Allahabadia, A., et al entitled Age and gender predict the outcome of treatment for Graves' disease showed that factors postulated to predict outcome have not generally proved clinically useful, males and younger patients are more likely to fail to respond to medical treatment, and male patients are likewise less likely to respond to a single dose of radioiodine. It was suggested in the study that those groups with low remission rates should be offered definitive treatment with radioiodine or surgery soon after presentation [24].

In an article published on NEJM there long-term remission of Graves' hyperthyroidism during antithyroid-drug therapy was reported with rates ranging from 10 to 75 percent. Small goiter and recent onset of the hyperthyroidism were found to be associated with remission but there are no reliable tests for predicting relapse at the time that therapy is discontinued. The duration of treatment is also another factor that affects the likelihood of remission and relapse is most likely within the first six months after withdrawal of therapy but may occur years later [25].

The number of patients who underwent surgery and subsequent remission is one of the assessment tools in patients with hyperthyroidism. Total thyroidectomy has a nearly 0% risk of recurrence, whereas subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at 5 years [26].

3. Objective

3.1. General Objective

- To assess the diagnosis, follow-up and treatment outcomes in patients with hyperthyroidism at Endocrine Clinic, TASH.

3.2. Specific Objectives

- To evaluate the diagnostic methods of hyperthyroidism at Endocrine Clinic of TASH.
- To describe the follow-up visits of hyperthyroid patients in Endocrine clinic of TASH.
- To determine factors associated with treatment outcome in hyperthyroid patients at Endocrine clinic of TASH.

4. Methods

4.1.Study Area and Period

4.1.1. Study Area

The study was conducted in Tikur Anbessa Specialized Hospital, which is located in Addis Ababa, the capital city of Ethiopia. The hospital has a national endocrine referral clinic which is the only specialized clinic for comprehensive diabetic care. On average, 800 diabetic clients are seen at the national endocrine clinic as outpatient per month. The clinic had seven endocrinologists and six fellows who were working at the the time of the survey.

4.1.2. Study Period

The study was conducted from November 1/2020 to January 31/2020 for 3 consecutive months.

4.1.3. Study Design

A retrospective follow up study design was used to assess the diagnosis, follow up and treatment outcomes among patients with hyperthyroidism at Tikur Anbessa Specialized Hospital [TASH], Addis Ababa, Ethiopia.

4.2.Source Population and Study Population

4.2.1. Source and Study Population

All Hyperthyroid patients who came to the national referral endocrine clinic in the study period were included.

4.2.2. Inclusion and Exclusion Criteria

Inclusion criteria

- All hyperthyroid patients age 18 and above on ATD for more than 18 months.

Exclusion criteria

- Patients who were pregnant

4.3.Sample Size

A census was performed to those patients who were aged 18 years and above, diagnosed to have hyperthyroidism on follow up from September 2009 to August 2012 E.C, excluding pregnant women.

4.4.Variables

4.4.1. Independent Variable

- Age
- Gender
- Region
- Duration of hyperthyroidism
- Type of hyperthyroidism
- Duration of hyperthyroidism treatment

4.4.2. Dependent Variables

- Treatment outcome

4.5.Data Collection Procedure

Data was collected retrospectively from electronic medical records based on I-care and patients' card. Data regarding the research was retrieved by using a structured check list or questionnaire. The data was checked for completeness and accuracy on daily basis.

4.6.Data Analysis and Presentation

The collected data was checked for completeness, and analyzed using descriptive statistics (mean, proportion, percentage and standard Deviations) to summarize the results. Multivariate logistic regression and chi square test were done to check the association between dependent and independent variables. Statistical significance was determined at a p value of < 0.05 and CI of 95%.

4.7. Ethical Considerations

The study was conducted after securing approval of proposal by ethical review committee of Internal Medicine Department, and then approved ethical institutional review board of Addis Ababa University, College of health sciences.

4.8.Data Quality Assurance

To maintain the quality of data collected, training was given for data collectors and regular supervision was done by the principal investigator and by senior consultants. The training given was for one day focusing on how to fill the questionnaire & collect actual data. The collected data was checked for completeness and accuracy on daily basis.

4.9.Operational Definitions

Hyperthyroidism is a disease condition characterized by increased synthesis and secretion of thyroid hormone by the thyroid gland

Overt hyperthyroidism is characterized by subnormal serum TSH with elevated serum levels of T3 and/or free T4

Subclinical hyperthyroidism is characterized by subnormal serum TSH with normal serum levels of T3 and/or free T4

Graves' Disease is an autoimmune disorder in which TRAb stimulate the TSH receptor, increasing thyroid hormone production and release.

Toxic Multinodular Goiter is characterized by excess production of thyroid hormones from functionally autonomous multiple thyroid nodules.

Toxic adenomas are characterized by autonomous hormone production which is caused by somatic activating mutations of genes regulating thyroid growth and hormone synthesis

Indeterminate is when the cause of hyperthyroidism is not specified**.**

Recent TSH/FT4/FT3 the most recent laboratory values of TSH, FT4 and FT3 up on data collection.

Initial and Recent ATD indicates the ATD used at the beginning and most recent on follow-up respectively.

Remission is considered when a normal serum TSH, free T4, and total T3 for 1 year after discontinuation of ATD therapy.

Combined Therapy: includes Antithyroid drug therapy and Beta adrenergic blocker combination

Single Therapy: use of Antithyroid drug [ATD] therapy only

5. Results

5.1. Socio-demographic Characteristics of the Participants

In this study 230 patients with hyperthyroidism were involved, of which 208[90.4%] were female and 22[9.6%] were male. The female to male ratio was 9.4 to 1. The mean age of the participants was 44 years +/-13 SD. Age 40 and above accounted for 67.4%. The majority of patients with hyperthyroidism who have follow-up at endocrine clinic were from Addis Ababa 148 [64.3%] and the rest 55 [35.7%] were outside from Addis Ababa.

Table 1: Socio-demographic Characteristics of the Participants, March 2021

Characteristics	N	%
Age group (Yrs.)		
< 40 years	75	32.6
≥40 years	155	67.4
Gender		
Male	22	9.6
Female	208	90.4
Region		
Addis Ababa	148	64.3
Outside Addis Ababa	55	35.7

5.2. Clinical Information of Hyperthyroid Patients

In about 23.6% of patients the duration of diagnosis of hyperthyroidism was four years which was the highest frequency and the longest follow up duration was 32 years and median follow up period was four years. [See Fig.1]. About 95.7% of patients presented with symptoms of hyperthyroidism at diagnosis and the most common symptom was palpitation [89.6%] followed by tremor [27.8%], heat intolerance [19.1%] and weight loss [7%]. Similarly, 86.5% of patients presented with signs of hyperthyroidism at diagnosis. These include: goiter [78.2%] and exophthalmos [22.8%], tachycardia [29.6%] and HTN [12.2%]. On follow up about 86% and 61.5% of patients reported improvement of symptoms and signs, respectively. Comorbid illnesses documented include 5.7% of patients had atrial fibrillation,4.3% HF,1.7% osteoporosis and 0.4% stroke. [Fig:2].

Table 2: Clinical Information of patients with hyperthyroidism, March 2021

Symptoms	%	Signs	%
Palpitation	89.6	Goiter	78.2
Tremor	27.8	Tachycardia	29.6
Heat intolerance	19.1	Exophthalmos	22.8
Weight loss	7	HTN	12.2

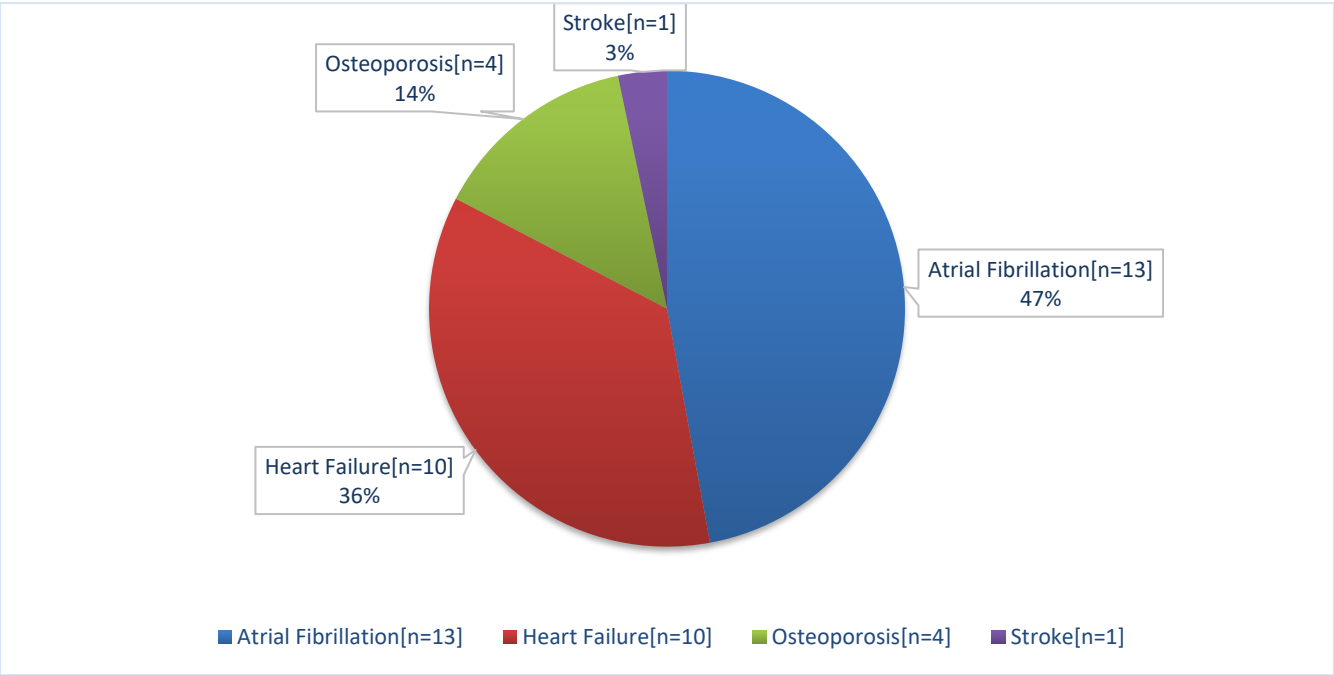

Figure 1: Complications of hyperthyroidism among study participants, March 2021

Initial thyroid function tests with missing results presented in Table 3 below showed elevated levels of FT3 and FT4 values and suppressed TSH in the majority of patients and in the recent thyroid function test normal FT3,FT4 and TSH values were seen in the majority but there were a significant number of results reported as missing.

Table 3: Baseline and Recent thyroid function test results [%]in hyperthyroid patients, March 2021

Result	FT3		FT4		TSH	
	Initial N (%)	**Recent N (%)**	**Initial N (%)**	**Recent N (%)**	**Initial N (%)**	**Recent N (%)**
Low	0%	0.9%	0%	1.3%	90.4%	43.5%
Normal	4.8%	67.4%	9.6%	66.1%	0.4%	47%
High	71.7%	14.8%	71.3%	16.5%	0%	3%
Missing	23%	**17%**	19.1%	**16.1%**	9.1%	**6.5%**

In non-parametric test (McNemar Test) done to compare the TSH status at the baseline and recent showed statistically significant (p=0.000) change from abnormal TSH to normal TSH with p value of <0.05.[Fig.2]

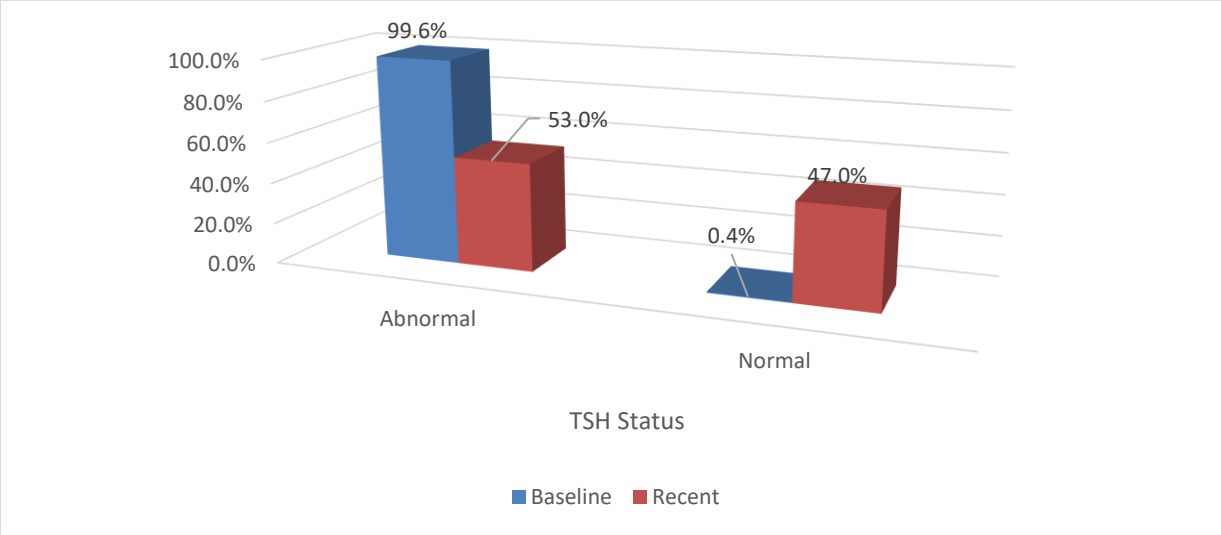

Figure 2: Baseline and recent TSH Status in Hyperthyroid patients, March 2021

In this study there was no documented TT3/TT4 ratio done as a diagnostic help for Graves' disease and Neck doppler ultrasound was done for only 18% of hyperthyroid patients. On follow up evaluation of patients electronic data recording using I- care only 5.7% of patients had recent

weight measurement and 58 % of patients had recent pulse rate measured. The most common cause of hyperthyroidism according to the study was TMNG which accounted [70.4%] followed by Graves' Disease [20.9%], TA [2.6%] and indeterminate [6.1%].

In this study, Baseline CBC was documented in 60% of patients of this 5.3% had ANC of <1000 and 94.7% had ≥1000. Half (49.1%) of the patients had baseline LFT of this 97.3% of patients had transaminases <3X ULN and 3.7% had ≥3x ULN. More than half (65.6%) of patients were using Betablockers such as propranolol (60.5%), Atenolol (31.7%) and Metoprolol (7.8%).

Of 230 patients, 93.8 % of them were on ATD. Of those who were initiated on ATDs 92.2% were on PTU, 6.0% on carbimazole and 1.8% on methimazole. Recent use of ATDs. Of those who were initiated on PTU 93.9% patients were on PTU less than 600mg per day and 6.1% on PTU ≥600mg per day. Recently 30.1% of patients were taking ≥600mg per day and 67.9% of patients taking <600mg per day [Fig 3]; Based on this more than 30% of patients with TMNG were on high dose of PTU and 19.1% of patients with GD were taking also high dose of PTU on their recent follow-up visit.

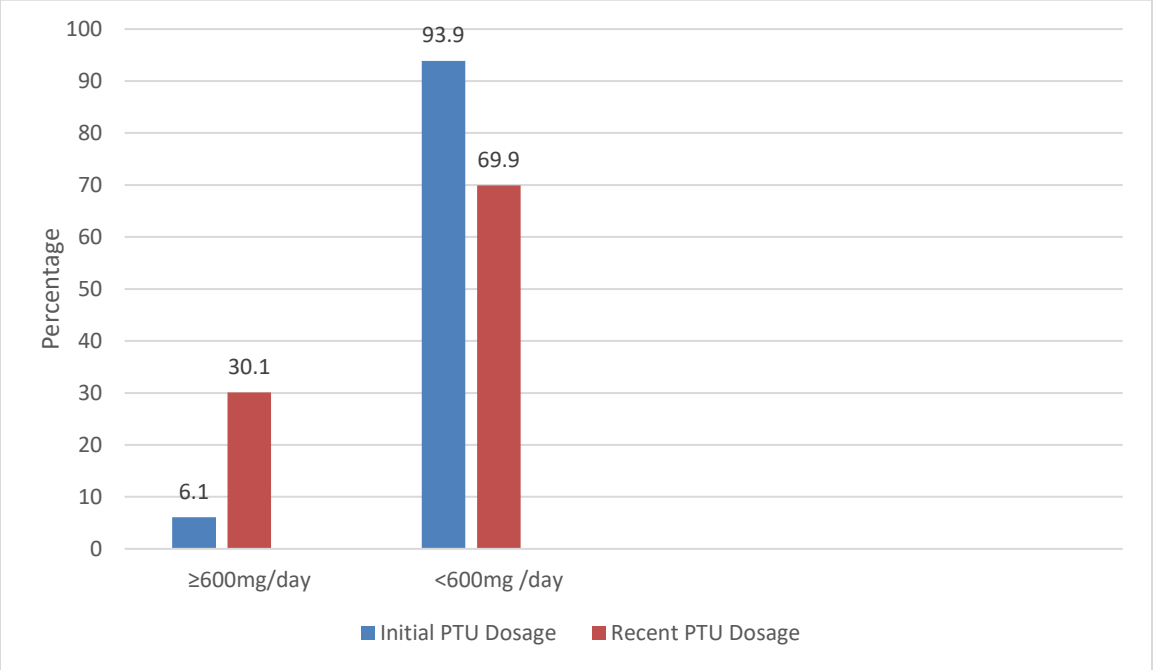

Figure 3: PTU dosages in hyperthyroid Patients, March 2021

After taking the medications, As seen on Fig.4 below 55.6% of patients were in euthyroid state,44% were hyperthyroid and 0.4% hypothyroid. Subsequently 93.8% of patients continued

ATD,5.3% discontinued,0.9% discontinued ATD and initiated on Levothyroxine. While. 4.4% of the patients developed major side effect including developed agranulocytosis (2.2%) and developed hepatotoxicity (1.3%).

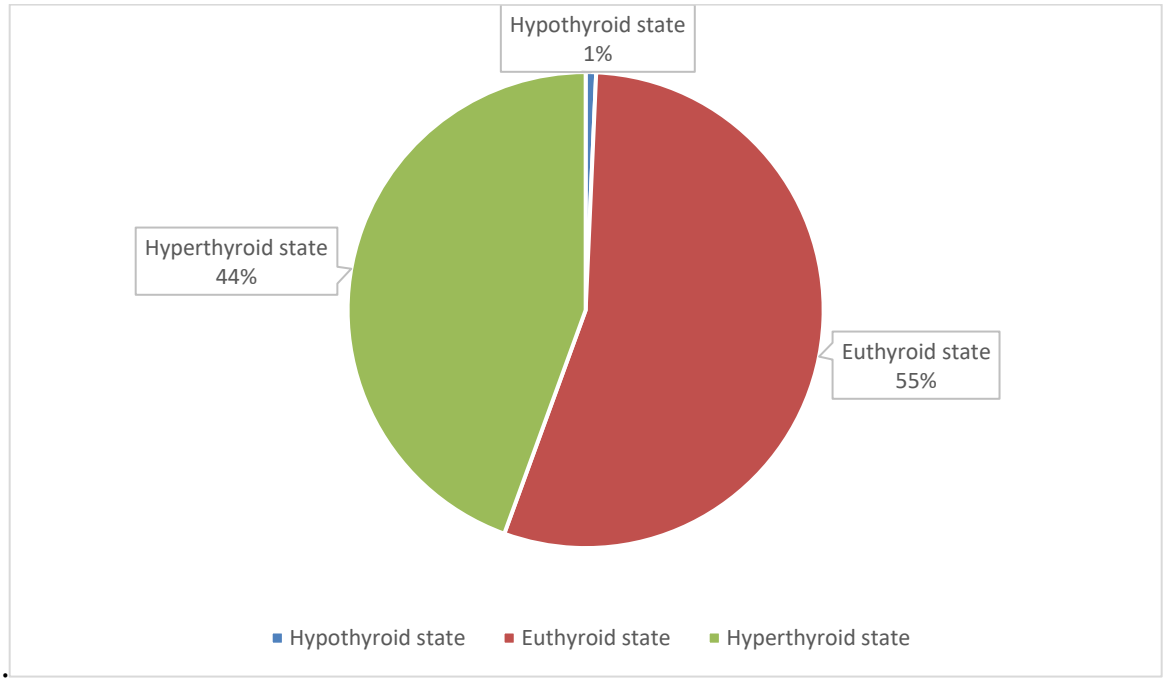

Figure 4: ATD treatment outcomes in hyperthyroid patients, March 2021

In this study thyroidectomy was planned for 19.4% of the patients but near total thyroidectomy was done for 4% of the patients only. Consequently, 36.4% became euthyroid, 36.4% hyperthyroid and 27.3% became hypothyroid.

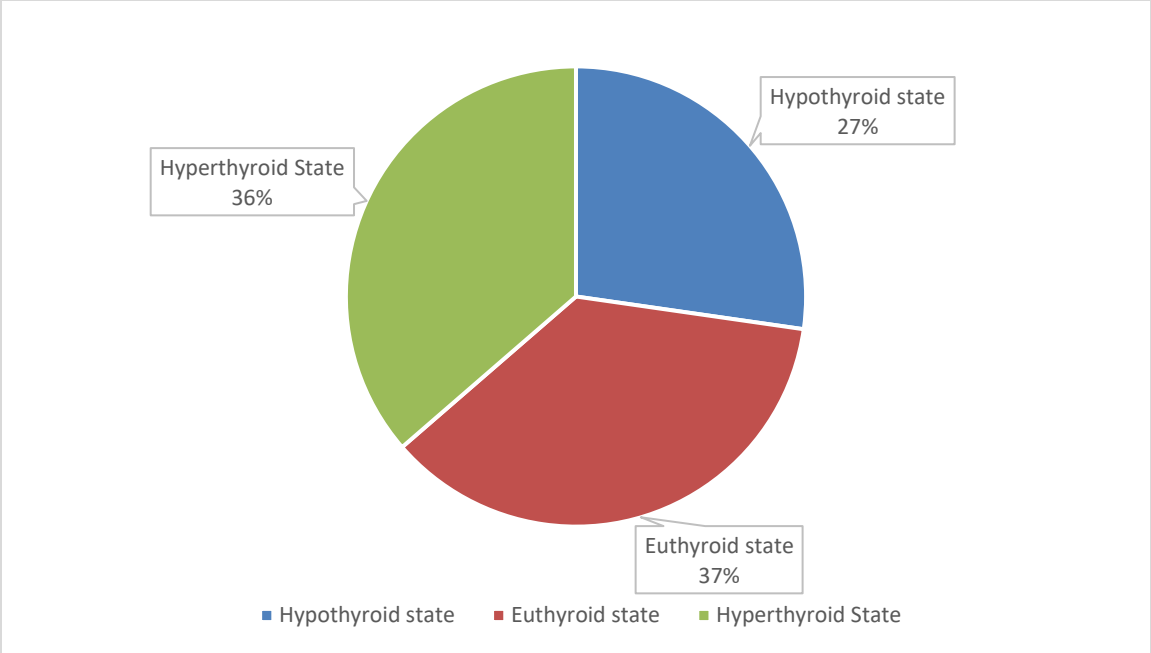

Figure 5:Post- thyroidectomy thyroid function status, March 2021

Based on previous literatures, factors such as gender, place of residence, age and duration of therapy were considered. Of these, significant association was found with therapy and duration of treatments. Those patients who had been following their treatment for four years and above, were more likely to have improved outcome compared to those who were following their treatment for less than four year (AOR=2.869, CI=1.173-7.0211, *p*=0.021).

In addition, those patients who were on combination therapy (Beta adrenergic blocker + ATD) were 2.189 times highly likely to have improved outcomes compared to those who took single therapy (ATD or Beta adrenergic blocker) (AOR=2.189, CI=1.144-4.187, *p*=0.018).

Table 4: Logistic regression analysis of factors associated with treatment outcome

Variables	Bivariate Analysis		Multivariate Analysis	
	Crude OR (95% CI)	***p* value**	**Adjusted OR (95% CI)**	***p* value**
Age (Yrs.)				
< 40	1		1	
≥ 40	1.015 (0.548, 1.881)	0.962	1.014(0.532, 1.933)	0.967
Gender				
Male	1		1	
Female	0.875 (0.304, 2.517)	0.804	0.779 (0.257, 2.356)	0.658
Region				
Out of Addis Ababa	1		1	
Addis Ababa	1.709 (0.902, 3.235)	0.100	1.615(0.831, 3.138)	0.158
Treatment				
Single	1		1	
Combination	2.309 (1.224, 4.353)	.010*	2.189 (1.144, 4.187)	0.018*
Duration of hyperthyroidism				
<4 Years	1		1	
> 4 years	2.933 (1.222, 7.043)	0.016*	5.321 (1.910, 14.822)	0.001*

**Refers presence of significant association*

6. Discussion

Among 230 hyperthyroid patients seen at National Endocrine Referral Clinic of Tikur Anbessa Specialized Hospital over a period of 3 years the commonest cause of hyperthyroidism identified was TMNG which is followed by GD and TA in respective order. This is a consistent finding with a study done under the title Pattern, clinical presentations and management of thyroid diseases in the same Hospital [3]. Unlike to this study's finding GD is the commonest cause of hyperthyroidism globally[2]. Graves' disease is an autoimmune thyroid disease mostly associated with positive TSH Receptor Antibody. Probably the low prevalence could be associated with low detection among atypical forms of GD. TRAb testing and RAIU and Scan tests are not available in our country which facilitate diagnosis of more cases of GD those who lack the typical presentation of the disease. In this study low exploitation of colour doppler ultrasound of the thyroid was observed which could also help in the diagnosis.[9].

ATDs are most widely used in the treatment of hyperthyroidism of this PTU is the main one. ATD therapy is targeted at achieving the euthyroid state as quickly and safely as possible [14]. The response to Anti thyroid drugs is not permanent and there is a high degree of recurrence after remission for those TMNG who were treated with ATDs. In this study More than ninety percent of patients with hyperthyroidism were taking PTU of these patients on recent follow up showed more than 30% are taking PTU at a dose of ≥600mg po daily because of suboptimal treatment response. This could be because PTU is less efficacious compared to methimazole or carbimazole.[29]. Though adherence and drug related conditions are difficult to describe in this retrospective study the possible reasons for poor responses could be related to more severe disease, larger thyroid glands, malabsorption. Previous studies have indicated that the bioavailability of PTU was high in hyperthyroid patients (about 75%) although considerable variation is seen among different generic preparations [12].

The first line treatment for TMNG is Radioactive Iodine Therapy or Surgery. In this study the uptake of TMNG and TA for thyroidectomy was low 4% and compared to previous study which was 16%. The difference could be attributed to the different patient population that was being investigated. According to the study the coverage of thyroidectomy was minimal and this could be because of patient and physician related factors. The unavailability of RAI therapy also creates a big gap in the management of hyperthyroidism in these patient population [15].

In this study those with longer duration of hyperthyroidism i.e. those who had been following their treatment for four years and above, were more likely to have improved outcome compared to those who were following their treatment for less than four year (AOR=2.869, CI=1.173-7.0211, p=0.021).This finding is also consistent with a study done under the title Long-term treatment of hyperthyroidism with antithyroid drugs which showed that ATD therapy is effective and safe for children and adults in the treatment of hyperthyroidism and non-inferior to radioactive iodine therapy[27]. Previous guidelines on the management of hyperthyroidism encouraged ablative therapy if patients did not achieve a remission after 12 to 18 months of ATD therapy, rendering the patient hypothyroid. Recent evidence-base medicine shows that long term ATD therapy ensures control of hyperthyroidism without replacing it with another disease, that is hypothyroidism [30].

In this retrospective study it was also found that those patients who were on combination therapy (Betadrenergic blocker and Antithyroid drug) were 2.189 times highly likely to have improved outcomes compared to those who took single therapy (Antithyroid drug alone) (AOR=2.189, CI=1.144-4.187, p=0.018).This finding is probably driven by propranolol which accounted more than 2/3 of betablockers in the study for its effect in the inhibition of peripheral conversion T4 to T3 in symptomatic hyperthyroid patients. There was a similar finding in a study under the title Short-term effects of β-adrenergic antagonists and methimazole in new-onset thyrotoxicosis caused by Graves' disease [12] although there were possible limitations like the small sample size which was too small to detect subtle differences in the improvement of quality-of-life assessments. But in our study the sample size is adequate but requires future prospective study to confirm the result.

As this is a retrospective study, incompleteness regarding patients' clinical presentations, physical examination documentation and laboratory test results were the major problems of the study.

7. Conclusion and Recommendations

From this study, the most common cause of hyperthyroidism was TMNG and Treatment outcome was strongly associated with duration of hyperthyroidism and initial usage of combination therapy.

Based on the above findings, the following recommendations are forwarded:

- Patients should be educated to adhere their medication since treatment outcomes of the majority of patients improve after prolonged follow-up.
- Clinicians should use combination of therapy [ATD and Beta-adrenergic blockers] upon initiation of therapy for better treatment outcome depending on the patient condition.
- Need to introduce computer based Follow up chart for complete clinical information of hyperthyroid patients that encompasses sociodemographic parameters, diagnosis, duration of hyperthyroidism, drug type, serial investigations, adherence to treatment and assessments of treatment outcome at each visit.
- Facilitation of training to Endocrine Fellows on neck ultrasonography which could help for bed side examination of thyroid disorders
- Availing investigations such as TRAb and first line treatment drugs such as methimazole/carbimazole
- Introduction of RAIU, scan and radioactive iodine therapy for those who have the indications
- Vital signs particularly Blood Pressure and Regular weight measurement and pulse rate should be done in the follow up of patients with hyperthyroidism as there was a gap in the documentation of these results.

Annex

Questionnaire

Annex-I; Assessment tool (checklist)

Title: Assessment of the diagnosis, follow-up and treatment outcomes in Patients with hyperthyroidism at Endocrine Clinic, TASH.

Section One: Socio-demographic Characteristics of the Patient

Serial Number_____

Question No.	Questions	Answer
101	I care	_____
102	Age (at diagnosis of hyperthyroidism)	_____ years
103	Gender	1. Male 2. Female
104	Educational Status	1.Not educated 2.Primary level 3.Secondary level 4.Tertiary level
105	Marital Status	1.Single 2.Married 3.Separated 4.Divorced
106	Occupation	1.Employed 2.Unemployed

107	Religion	1.Orthodox Christian 2.Muselim 3.Protestant 4.other [Specify]
108	Region	1.Addis Ababa 2.Oromia 3.Amhara 4.Tigray 5.Debub 6.Other Regions [Specify]

SECTION TWO: Clinical Information of the Patient

Question No.	Questions	Answer
201	Duration Since Hyperthyroidism diagnosis	____ years
202	Were Symptoms of hyperthyroidism present at diagnosis?	1. Yes 2. No
203	If yes for Q.202	1. Palpitation 2. Tremor 3. Heat intolerance 4. Weight loss 5. Others specify
204	Were signs of hyperthyroidism present at diagnosis?	1.yes 2.No

205	If yes for Q.204	1. Hypertension 2. Tachycardia 3. Exophthalmos 4. Goiter 5. Others Specify
206	Did symptoms of hyperthyroidism improve after treatment?	1.Yes 2.No
207	Did signs of hyperthyroidism improve after treatment?	1.Yes 2.No
208	Initial weight and Pulse rate	Weight _____ Kg PR _____/min
209	Recent weight and Pulse rate	Weight _____ Kg PR _____/min
210	Any use of Drugs causing hyperthyroidism?	1. Yes 2. No
211	If yes for Q.210, Name of the drug	1) Amiodarone 2) TKIs 3) Lithium 4) Others specify
212	Any Complications of hyperthyroidism present?	
213	If yes for Q.212	1) AF 2) HF 3) Osteoporosis 4) Stroke 5) Others specify
214	Baseline TFT (Encircle one) L=Low N=Normal	1. TT4 (L/N/H) 2. TT3(L/N/H) 3. FT4(L/N/H) 4. FT3(L/N/H)

	H=High	5. TSH(L/N/H)
215	Recent TFT (Encircle one) L=Low N=Normal H=High	1. TT4 (L/N/H) 2. TT3(L/N/H) 3. FT4(L/N/H) 4. FT3(L/N/H) 5. TSH(L/N/H)
216	Was TT3/TT4 Ratio done for suspected GD?	1. Yes 2. No
217	If yes for Q.216, the ratio was	1. ≥20 2. <20
218	Was TRAb done for suspected GD?	1. Yes 2. No
219	Was Color Doppler Ultrasound of Thyroid done?	1. Yes 2. No
220	If yes for Q.219, Finding suggests	1. GD 2. Thyroiditis 3. TMNG 4. TA
221	What was the Cause of hyperthyroidism?	1. GD 2. TMNG 3. TA 4. Others
222	Was Baseline CBC done?	1. Yes 2. No
223	If yes for Q.222, ANC was	1. <1000 2. ≥1000
224	Was Baseline LFT done?	1. Yes 2. No

225	If yes for Q.224, Transaminases were	1. ≥3x ULN 2. <3x ULN
226	Was Beta adrenergic blocker used?	1. Yes 2. No
227	If yes for Q.226, Which drug?	1. Propranolol 2. Atenolol 3. Metoprolol 4. Other specify
228	Was he/she on ATD?	1. Yes 2. No
229	If yes for Q.228, Name of ATD?	1. Methimazole 2. Carbimazole 3. PTU
230	If PTU used, what was the initial dosage?	1. <600mg/day 2. ≥600mg/day
231	If PTU used, what was the recent dosage?	1. <600mg/day 2. ≥600mg/day
232	Was any major Side effect of ATDs occurred?	1. Yes 2. No
233	If yes for Q.232, What was the side effect?	1. Hepatotoxicity 2. Agranulocytosis 3. Vasculitis 4. Others specify
234	What was the duration of ATD therapy?	1. ≥ 18 months 2. < 18 months
235	What was the Outcome of treatment with ATDs?	1. Euthyroid state 2. Hyperthyroid state 3. Hypothyroid state

236	What happened to ATD after outcome of Q.235?	1. continued 2. discontinued 3. discontinued and LT4 initiated
237	Was thyroidectomy planned or done?	1. Yes 2. No
238	If thyroidectomy done?	1. Total 2. Near total 3. Lobectomy
239	What was the Outcome of thyroidectomy?	1. 1.Euthyroid state 2. 2.Hyperthyroidstate 3. Hypothyroid state

Assurance of Investigators

The undersigned agree to accept responsibility for scientific ethical and technical Conduct of the research project and for the provision of required progress report.

1. _____

   Date_____ Signature _____

2. _____

   Date_____ Signature _____

3. _____

   Date_____ Signature _____

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