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Control rate of hyperthyroidism and its associated factors after prolonged use of anti-thyroid drugs in a hospital setting, Northwest Ethiopia

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Abstract

Hyperthyroidism is increased synthesis and secretion of thyroid hormones by the thyroid gland resulting in thyrotoxicosis. The modality of therapy for hyperthyroidism includes anti-thyroid drugs, radioiodine and surgery. Anti-thyroid drugs are the only available therapy for hyperthyroid patients in developing world as radioiodine is inaccessible and surgical set up does not exist as required. The aim of this study was to determine the magnitude and predictors of uncontrolled hyperthyroidism among hyperthyroid patients after prolonged anti-thyroid drug use. An institutional-based cross sectional study was conducted at the University of Gondar hospital, Northwest Ethiopia, between April 1, 2022 and October 31, 2022. A consecutive sampling method was used to recruit 317 study subjects. Data were collected through a pre-designed questionnaire. Patients were interviewed to obtain socio-demographic data and relevant medical information. Laboratory analyses were done based on the follow up protocol. Data were entered into EPI Info version 4.6.0.0 (EPI Info, Atlanta) and analyzed in STATA version 14 (Stata Corp LP, Texas, USA). Binary logistic regression model was used to identify variables associated with uncontrolled hyperthyroidism among hyperthyroid patients. *P* value < .05 was used to declare significant association. A total of 317 patients with hyperthyroidism were included in the study. The median age of the study subjects was 45 years (IQR 36–55 years). Most (95%) of the study participants were females. Toxic multi-nodular goiter was the most common cause of hyperthyroidism (92%), followed by toxic adenoma (5%) and Graves' disease (2%). On multivariate binary logistic regression, large goiter size (AOR: 3.163, 95% CI [1.333–7.506]), severe disease (AOR: 2.275, 95% CI [1.060–4.880]), infrequent iodinated salt intake (AOR: 3.668, 95% CI [1.245–10.802]), and poor adherence to anti-thyroid drug (AOR:15.724, 95% CI [5.542–44.610]) were statistically significant with uncontrolled hyperthyroidism at 12 months of anti-thyroid drug intake. A quarter of patients with hyperthyroidism didn't achieve euthyroid state after 12 months of anti-thyroid drug use. The identified predictors for non-euthyroid state were large goiter size, severe disease, infrequent iodinated salt intake, and poor adherence to anti-thyroid drug.

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, IQR = inter-quartile range, IRB = Institutional Review Board, TFT = thyroid function test, TSH = thyroid stimulating hormone, WHO = World Health Organization.

Keywords: anti-thyroid drugs, hyperthyroidism, Northwest Ethiopia, uncontrolled hyperthyroidism (non-euthyroid state)

1. Introduction

Hyperthyroidism is increased synthesis and secretion of thyroid hormones in thyroid follicular cells resulting in thyrotoxicosis. Globally, it affects about 0.2% to 1.3% of the general population, and 5- to 10-fold higher in women as compared to men. It is classified as overt or subclinical based on thyroid function tests values.[1–3] Eighty percent of hyperthyroidism is attributed to Graves' disease in iodine sufficient areas, while toxic nodular goiter account for 50% of hyperthyroidism in iodine deficient regions[3–5] Hyperthyroidism affects various systems of human body. The commonest symptoms were palpitation, heat intolerance, weight loss and tiredness, while frequently reported signs were goiter, tachycardia, nervousness and sweaty palms.[1–3,6–9] Some of the signs and symptoms

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The research protocol complied with the Declaration of Helsinki and ethical clearance was obtained from the Institutional Review Board (IRB) of the College of Medicine and Health Sciences, University of Gondar (29/7/2022, IRB No. 1794/2022). Study subjects were recruited only after written informed consent was obtained.

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could be specific for specific cause. It can be treated with anti-thyroid drugs, radioiodine, and surgery. Preferred choice of therapy may vary based on the cause of hyperthyroidism. Western practice preferred radioiodine or surgery as therapy of choice for toxic nodular disease (toxic multinodular goiter or toxic adenoma), while patients with Grave's disease were initially treated with anti-thyroid drugs.[1,2,10,11] Recent randomized control trials by Azizi F, et al documented that prolonged therapy (5–8 years) with anti-thyroid drugs was non-inferior to radioiodine in treating toxic multinodular goiter.[12,13] Anti-thyroid drugs are chosen over other options of therapy in elderly patients who are unfit for surgery and radioiodine not available, or patients residing in resource limited areas as surgical intervention and radioiodine not accessible.[2,3,10,11] Even though thiamazole is the anti-thyroid drug of choice, propylthiouracil is preferred in patients with life threatening thyrotoxicosis or thyroid storm, pregnant women in early gestation, and those allergic to thiamazole.[14–16] If left undiagnosed or untreated, hyperthyroidism will result in complications like thyroid storm, arrhythmia, heart failure, ischemic stroke, neuropsychiatric problems, and rarely cardiovascular collapse.[17–21] In developing countries including Ethiopia, undiagnosed cases are common due to poor health seeking behavior and lack of equipped laboratory tests. In addition, unavailability of possible treatment choices results in increased complications. Hyperthyroid patients in the study locality were treated medically using anti-thyroid drugs, while surgery was chosen for large sized goiter. Radioiodine was not available in the study locality, as well as in the country. Although thiamazole was the preferred choice of medical therapy for hyperthyroidism in national guideline, only propylthiouracil was available on pharmaceutical markets. Few literatures revealed that older age, toxic nodular goiter type, large goiter size, and markedly increased baseline free T4 level were the independent determinants of reduced remission rate or delayed time to normalization of thyroid function tests using anti-thyroid drugs.[8,9,22–25] This study aimed to determine the magnitude and risk factors for non-euthyroid state after 12 months of anti-thyroid drugs use. Identifying predictors of non-euthyroid state after 12 months of anti-thyroid drug use would help in considering other options of therapy.

2. Methods

2.1. Study settings

An institution based cross-sectional study was conducted at Endocrinology Clinic, University of Gondar hospital between April 1, 2022 and October 31, 2022. The hospital was located 750 km Northwest of Addis Ababa, the capital of Ethiopia. The hospital is a comprehensive and specialized tertiary hospital with a catchment population of 7 million people. The hospital had all the major and minor clinical departments. The Endocrinology Clinic provided outpatient services to patients with endocrinologic diseases, under the department of Internal Medicine.

2.2. Study population

Adult hyperthyroid patients, who were taking anti-thyroid drugs for 12 months or more, and had follow-up at Endocrinology Clinic, University Gondar hospital.

2.3. Study subjects

Eighteen years or older hyperthyroid patients, who were taking anti-thyroid drugs for 12 months, and had follow-up at Endocrinology Clinic, University of Gondar hospital, between April 1, 2022 to October 31, 2022.

2.4. Exclusion criteria

Female patients who were pregnant during the study period and patients who were not willing to be included in the study were excluded from the study.

2.5. Study variables

2.5.1. Dependent variable. Uncontrolled hyperthyroidism (non-euthyroid state) at 12-months of taking anti-thyroid drugs.

2.5.2. Independent variables. Socio-demographic characteristics – age, gender, residence (highland area vs lowland area), marital status, religion, and educational status, Clinical characteristics – type of hyperthyroid disease, World Health Organization (WHO) thyroid size, iodinated salt intake, associated complications/comorbidities, adherence to anti-thyroid medications, and baseline thyroid function tests (TFTs), and Behavioral factors – alcohol consumption, and cigarette smoking.

2.6. Sample size and sampling procedure

The sample size was calculated based on single population proportion formula at a prevalence of uncontrolled hyperthyroidism among hyperthyroid patients in Northern Ethiopia was 30%, with a confidence interval of 95% and assumed margin of error of 5%. Consecutive sampling method was used to recruit a sample size of 317 study subjects.[26]

2.7. Data collection instruments and procedures

Data were collected through a pre-designed questionnaire. Patients were interviewed to obtain socio-demographic data and relevant medical information. Focused clinical examination was done to each of the study subjects. Laboratory analyses were done based on the follow up protocol and no extra tests for the research. Thyroid function tests were determined to document euthyroid state, while complete blood counts and liver biochemical tests were measured to check for drug toxicities. Echocardiography and ECG were done to clinically suspected study subjects with heart failure and arrhythmia, respectively.

2.8. Clinical procedures

Twelve-Lead ECG (ECG 1200G, YSIP-155, Beijing, China) were performed for all patients by physician with standardization of 1 mV = 10 mm and paper speed of 25 mm/s. Abnormal findings on the ECG were interpreted by an internist.

Two-Dimensional Doppler Transthoracic Echocardiography (B/W Digital Ultrasound Scanner; ARI Group, Beijing, China) was performed for all patients by a radiologist to determine abnormalities on ventricular ejection fraction, valve morphology, ventricular wall size and motion, and atrial and ventricular chamber dimensions.

2.9. Laboratory procedures

Venous blood samples were collected from patients in plain tubes and centrifuged at 2500 rpm for 15 minutes at room temperature to obtain serum. Thyroid function tests, T3(nmol/L), free T4 (ng/dL), and thyroid stimulating hormone (TSH; mU/mL) were estimated using an automated immunoassay analyzer (MINI-VIDAS; Setema PLC, Paris, France) based on the enzyme linked fluorescent assay (ELFA) principles.

2.10. Data analysis

Data were entered into EPI Info version 4.6.0.0 (EPI Info, Atlanta) and analyzed in STATA version 14 (StataCorp LP.). Categorical

variables were reported as frequencies and percentages, and continuous variables as median and interquartile ranges (IQR). The results were summarized using frequency and tables. Predictors of uncontrolled hyperthyroidism among hyperthyroid patients, who took anti-thyroid medications for 12 months, were analyzed by applying logistic regression model. The adequacy of the model was checked by using Hosmer and Lameshow goodness-of-fit test. Those variables with a P value < .2 in the bi-variate analysis were exported to multi-variate analysis. The results were presented as odds ratio with 95% confidence interval. P value < .05 was used to declare significant association.

2.11. Ethical considerations

The research protocol complied with the Declaration of Helsinki and ethical clearance was obtained from the Institutional Review Board (IRB) of the College of Medicine and Health Sciences, University of Gondar (29/7/2022, IRB No. 1794/2022). Study subjects were recruited only after written informed consent was obtained. All data obtained were treated confidentially. Patients with hyperthyroidism were taken care of as per the recommendation of "2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis."[1]

2.12. Definition of terms

Hyperthyroidism: Suppressed TSH (TSH < 0.1 mU/L) and elevated free T4 (FT4 > 1.8 ng/dL) using immunoassay analyzer.[8,9,22]

Graves' disease: Presence of hyperthyroidism and a diffusely enlarged thyroid gland on palpation or ultrasonography, or presence of Graves' orbitopathy.

Toxic multinodular goiter: Presence of hyperthyroidism and multiple thyroid nodules on palpation or ultrasonography.

Toxic adenoma: Presence of hyperthyroidism and a solitary thyroid nodule on palpation or ultrasonography.

Euthyroid state: Normal ranges of free T4 (0.6–1.8 ng/dL) in a patient taking anti-thyroid drugs for 12 months.[8,9,22]

Non-euthyroid state: Elevated free T4 (>1.8 ng/dL) level in a patient taking anti-thyroid drugs for 12 months.[8,9,22]

Severity of hyperthyroidism (based on free T4 level).

Mild hyperthyroidism: free T4 = 1.8 to 3.9 ng/dL (≤ 2.16 × ULN).[8,9,22]

Moderate hyperthyroidism: free T4 = 3.9 to 7.7 ng/dL (2.16–4.33 × ULN).[8,9,22]

Severe hyperthyroidism: free T4 > 7.7 ng/dL (>4.33 × ULN)[8,9,22]

WHO goiter size[27]

Stage 0: The goiter is neither palpable nor visible even when the neck is extended.

Stage 1: The goiter is detected on palpation and/or visible when the neck is extended.

Stage 2: Goiter is visible when the neck in normal position.

Stage 3: Large goiter visible from a distance.

Atrial fibrillation: irregularly irregular R-R interval and indistinct P-wave on ECG tracing.

Highlands: Areas located at altitude above 1500 m above the sea level are considered highlands in Ethiopia.[28]

Lowlands: Areas located at altitude below 1500 m above the sea level are considered lowlands in Ethiopia.[28]

Good adherence to anti-thyroid drugs: if continuous, multiple interval measure of medication gaps (CMG) < 20%.[29]

Poor adherence to anti-thyroid drugs: if continuous, multiple interval measure of medication gaps (CMG) > 20%.[29]

3. Results

3.1. Socio-demographic characteristics of the study subjects

A total of 317 patients were included in the study. The median age of the study subjects was 45 years (IQR 36–55 years). Most (95%) of the study participants were females. Most (93%) of the study participants were Orthodox Christian followers. Most 297 (94%) of the study subjects lived in highland areas, which were known to be iodine deficient. All the study participants never smoked cigarettes in their life time, and never touched alcohol after anti-thyroid drug initiation (Table 1).

3.2. Clinical characteristics of the study subjects

Toxic multi-nodular goiter was the most common cause of hyperthyroidism 290 (92%), followed by toxic adenoma 17 (5%) and Graves' disease 7 (2%). Most patients had WHO stage 2 goiter 121 (38%) and WHO stage 3 goiter 108 (34%) (Table 2). The commonest presenting symptoms were anterior neck swelling 284 (90%), palpitation 267 (84%), heat intolerance 167 (53%), and excessive sweating 232 (73%). The frequently detected findings were goiter 288 (91%) and tachycardia 181 (57%) (Table 3). Hypertension 43 (14%) and diabetes mellitus 11 (4%) were often noticed comorbidities, while heart failure 27 (9%) and atrial fibrillation17 (5%) were frequently observed complications (Table 4). All study subjects were taking propylthiouracil (PTU) as anti-thyroid medication. Majority 219 (69%) were put on ß-blockers as a sympatholytic medication.

3.3. Imaging and cytological findings of study subjects

Forty-eight patients had abnormal echocardiographic findings. Dilated cardiomyopathy was the commonest abnormal echocardiographic finding 16 (33%), followed by degenerative valvular heart disease 12 (25%). Cor-pulmonale, hypertensive heart disease and ischemic heart disease were diagnosed in 6 (13%), 9 (19%), and 5 (10%) of patients, respectively. Among

Table 1

Socio-demographic and behavioral characteristics of hyperthyroid patients taking anti-thyroid drugs at University of Gondar hospital, Northwest.

Variables	Categories	Frequency	Percent
Age (yr)	18–35	78	24.6
	36–50	141	44.5
	51–65	76	24.0
	>65	22	6.9
Gender	Male	16	5.1
	Female	301	94.9
Religion	Orthodox	294	92.8
	Muslim	22	6.9
	Protestant	1	0.3
Marital status	Single	25	7.9
	Married	231	72.9
	Widowed	40	12.6
	Divorced	21	6.6
Place of residence (based on altitude)	Highland area	297	93.7
	Lowland area	20	6.3
Educational status	No formal education	203	64.0
	Primary education	51	16.1
	Secondary education	34	10.7
	College/university education	29	9.2
Cigarette smoking	Yes	0	0.0
	No	317	100
Alcohol consumption	Yes	0	0.0
	No	317	100

Table 2

Causes of hyperthyroidism and WHO goiter size of hyperthyroid patients taking anti-thyroid drugs at University of Gondar hospital, Northwest Ethiopia, April 1, 2022–October 31, 2022.

Variables	Category	Frequency	Percent
Cause of hyperthyroidism	TMNG	290	91.5
	Toxic adenoma	17	5.4
	Graves' disease	7	2.2
	Thyroiditis	1	0.3
	Others	2	0.6
WHO goiter size	Stage 0	11	3.7
	Stage 1	77	24.2
	Stage 2	121	38.1
	Stage 3	108	34.0

Others = follicular thyroid cancer, TMNG = toxic multi-nodular goiter, TSH = secreting pituitary adenoma, WHO = World Health Organization

Table 3

Clinical characteristics of hyperthyroid patients taking anti-thyroid drugs at University of Gondar hospital, Northwest Ethiopia, April 1, 2022–October 31, 2022.

Presenting symptoms	Frequency	Percent
Anterior neck swelling	284	89.6
Palpitation	267	84.2
Heat intolerance	167	52.7
Excessive sweating	232	73.2
Weight loss	31	9.8
Insomnia	25	7.9
Irritability	25	7.9
Exercise intolerance	15	4.7
Observed signs		
Goiter	288	90.9
Tachycardia	181	57.1
Nervousness	15	7.9
Proptosis	7	2.2
Lid lag or lid retraction	7	2.2

Table 4

Complications/comorbidities of hyperthyroid patients taking anti-thyroid drugs at University of Gondar hospital, Northwest Ethiopia, April 1, 2022–October 31, 2022.

Complications/comorbidities	Frequency	Percent
Heart failure	27	8.5
Atrial fibrillation	17	5.4
Hypertension	43	13.6
Diabetes	11	3.5
Others	4	1.3

NB: Others, Ischemic stroke, thyroid cancer, thyroid storm, osteoporosis.

216 patients who had neck (thyroid) ultrasonography, multiple thyroid nodule was the commonest finding 191 (88%), followed by solitary thyroid nodule 17 (8%). Seven patients had diffuse goiter, while one patient had thyroid nodule suspicion of malignancy. Among 214 patients who had thyroid fine needle aspiration cytology, 210 (98%) patients had benign nodular colloid goiter, 3 patients had adenomatous goiter, while 1 patient had papillary thyroid carcinoma.

3.4. Side effects of anti-thyroid drug use

Thirty-seven patients (11.7%) patients had white blood cell count between 3000 cells/μL to 4500/μL. Twenty-seven patients (8.5%) had absolute neutrophil count between 1500 cells/μL and 2500 cells/μL. No patient had absolute neutrophil count (ANC) < 1500 cell/μL. Elevated liver biochemical tests, ALT and AST were observed in 10 (3.2%) and 15 (4.7%) patients, respectively. No patient had ALT and AST ≥ 2-folds of upper limit of normal (ULN).

3.5. Treatment outcome of study subjects

Among 317 hyperthyroid patients, 73 (23%, 95% CI: 18.70–28.01) patients didn't achieve euthyroid state after 12 months of anti-thyroid drug use, while the remaining 244 (77%, 95% CI: 72.9–81.3) patients achieved euthyroid state.

3.6. Factors associated with uncontrolled hyperthyroidism

In bivariate binary logistic regression, age (years), WHO goiter size, iodinated salt intake, severity of hyperthyroidism, presence of comorbidities and complications, and adherence to anti-thyroid drug were statistically significant risk factors for uncontrolled hyperthyroidism at a *P* value of less than .20. When those variables in the bivariate binary logistic regression analysis were regressed into multivariate binary logistic regression, large goiter size (AOR: 3.163, 95% CI [1.333–7.506]), severe hyperthyroidism (AOR: 2.275, 95% CI [1.060–4.880]), infrequent iodinated salt intake (AOR: 3.668, 95% CI [1.245–10.802]), and poor adherence to anti-thyroid drug (AOR: 15.724, 95% CI [5.542–44.610]) were independently associated with uncontrolled hyperthyroidism at 12 months of anti-thyroid drug intake (Table 5).

4. Discussion

In this study, the magnitude of euthyroid state after 12 months of anti-thyroid drug use was 77% (95% CI: 72–81). Previous observational studies in Ethiopia revealed that 50% to 60% of patients achieved euthyroid state over 9 to 12 months of anti-thyroid drug therapy.[8,9] In European study, 96% of Graves' disease achieved euthyroid state over 12 months of drug treatment.[30] The difference in magnitude of euthyroid state among regions could be explained by the underlying cause of hyperthyroidism and the drug types used. Toxic nodular goiter, the commonest cause of hyperthyroidism in the locality, might require prolonged therapy to achieve euthyroid state.[8,9,12,13] Secondly, propylthiouracil (PTU) was the only available anti-thyroid drug locally, which was known for its suboptimal response and delayed in achieving euthyroid state as compared to the other thyrostatic drug (thiamazole).[14–16] Nearly half (45%) of the affected age group was 36 to 50 years and markedly prevalent in females, which was consistent with global reports.[1–6] The commonest symptoms, in decreasing order of frequency, were anterior neck swelling, palpitation, heat intolerance and excessive sweating. The frequently identified signs were goiter and tachycardia. This finding was comparable with world-wide reports.[1–3,7–9] Atrial fibrillation was observed in 17 (5%) hyperthyroid patients. Globally, atrial fibrillation prevalence was estimated to range from 2% to 20% in hyperthyroidism.[15] The National Registry in Europe and African meta-analysis estimated it to be 8% and 9%, respectively. While, it was 11% in previous Ethiopian report.[6,17,19] Magnitude of atrial fibrillation was within global range, and was close to European and African estimates. Atrial fibrillation in hyperthyroidism occurs due to micro-reentrant tachycardia, ectopic atrial firing, short atrial refractoriness, increased cardiomyocyte automaticity, and altered cardiomyocyte ionic channels.[17] Heart failure occurred in 27 (9%) patients as cardiac complication, which was close to African meta-analysis report (12%).[6] Heart

Table 5

Bivariate and multi-variate analysis of factors associated with achieving euthyroid state among hyperthyroid patients taking anti-thyroid drugs at University of Gondar hospital, Northwest Ethiopia, April 1, 2022–October 31, 2022.

Variables	Treatment outcome		COR (CI)	*P* value	AOR (CI)	*P* value
	Euthyroid state	Non- euthyroid state				
Age (yr)						
18–35	67	11	1			
36–50	106	35	2.011 (0.9563–4.229)	.065	1.565 (0.6823–3.591)	.290
51–65	55	21	2.325 (1.032–5.2382)	.042	1.504 (0.577–3.918)	.404
>65	16	6	2.284 (0.734–7.102)	.154	1.279 (0.324–5.042)	.725
Gender						
Male	12	4	1			
Female	232	69	0.892 (0.278–2.854)	.848		
Residence (area)						
Highland	230	67	1			
Lowland	14	6	1.471 ()0.544–3.976	.447		
BMI						
<18.5	39	11	1			
18.5–24.9	172	49	1.010 (0.481–2.118)	.979		
>25	33	13	1.396 (0.552–3.529)	.480		
WHO goiter size						
Not visible or palpable on normal position (stage 0 and I)	80	8	1		1	
Visible or palpable on normal position (stage II and III)	164	65	3.963 (1.814–8.658)	.001	3.163 (1.333–7.506)	.009
Iodinated salt intake						
Always	57	5	1		1	
Not always (infrequent)	187	68	4.145 (1.594–10.776)	.004	3.668 (1.245–10.802)	.018
ATD Adherence						
Good	238	52	1		1	
Poor	6	21	16.019 (6.160–41.653)	<.0001	15.724 (5.542–44.610)	<.001
Comorbidities/complications						
Yes	70	32	1.723 (0.988–3.003)	.055	1.259 (0.623–2.540)	.52
No	173	42	1			
Baseline FT4 level						
< 2.17 times ULN	83	14	1		1	
2.17–4.33 times ULN	42	14	1.976 (0.862–4.525)	.107	2.207 (0.877–5.552)	.093
≥4.33 times ULN	119	45	2.241 (1.156–4.346)	.017	2.275 (1.060–4.880)	.035

AOR = adjusted odds ratio, ATD = anti-thyroid drug, BMI = body mass index, CI = confidence interval, COR = crude odds ratio, FT4 = free T4 level, ULN = upper limit of normal, WHO = World Health Organization.

failure in hyperthyroidism was documented to be related to the changes in cardiac contractility, cardiac output, vascular resistance, and rhythm disturbances.[18, 19, 31] In this study, hypertension and diabetes were observed in 43 (14%) and 11 (4%) patients, respectively. Hypertension tends to occur frequently in hyperthyroidism, which is explained by increased cardiac contractility, enhanced cardiac output, and altered vascular stiffness.[31, 32] The co-occurrence of diabetes and thyroid disorder can be coined by autoimmune polyendocrine disorders.[33] In addition, enhanced insulin degradation, increased gut glucose absorption, increased hepatic glucose output, and insulin resistance in hyperthyroidism might contribute to new onset diabetes.[34] Patients with large goiter (WHO goiter stage 2 and 3) had 3 folds higher risk of uncontrolled hyperthyroidism as compared to those with small goiter (WHO goiter stage 0 and 1) (AOR: 3.163, 95% CI [1.333–7.506]). This finding was consistent with a previous hospital-based study in Ethiopia, which was found that large goiter size had delayed normalization of thyroid function tests.[9] Lower remission rate among those who had large goiter was documented in Western studies by Laurberg P. and Mohlin E.[23,35] An increase in the size of the goiter will increase the number of autonomously functioning nodules. The odds of developing uncontrolled hyperthyroidism was two folds higher in severe hyperthyroidism (FT4 > 4.33 × ULN) as compared to those with mild hyperthyroidism (<2.17 × ULN) (AOR: 2.275, 95% CI [1.060–4.880]). This was consistent with a European study in which markedly elevated baseline free T4 reduced remission rate or delayed normalization of thyroid function tests.[22,24,25] Similar findings were reported in local studies.[8,9] Patients with severe disease often need a higher initial dose and longer treatment duration with anti-thyroid drugs. Patients who were on infrequent iodinated salt intake experienced uncontrolled hyperthyroidism 4 folds higher than those, who were on always iodinated salt intake (AOR: 3.668, 95% CI [1.245–10.802]). A prospective study in China revealed that optimal iodine use during anti-thyroid drug therapy was associated with higher remission rates than iodine restriction. While a randomized study in Japan showed that restriction of dietary iodine didn't improve the effect of anti-thyroid drug therapy. These studies suggested that adequate iodine supply was needed to improve remission rate in iodine-deficient areas, while iodine restriction might not be necessary during anti-thyroid therapy in iodine-sufficient areas.[11,36,37] The odds of uncontrolled hyperthyroidism was 16 folds higher in patients with poor adherence to anti-thyroid drug as compared to those with good adherence (AOR:15.724, 95% CI [5.542–44.610]). It was documented that better adherence to anti-thyroid drug was associated with decreased events of complications such as stroke.[38]

4.1. Limitation of the study

The cross-sectional study design might have limitation on causal relationships. The study subjects were referred patients with symptomatic medical illness, who might not be a true representative of the catchment population. In addition, convenience sampling method was used, which might introduce selection bias.

5. Conclusions

A quarter of patients with hyperthyroidism didn't achieve euthyroid state after 12 months of anti-thyroid drug use. Large goiter size, severe disease, infrequent iodinated salt intake, and poor adherence to anti-thyroid drugs were predictors of non-euthyroid state. Surgical intervention might be employed in those who failed to achieve euthyroid state after prolonged anti-thyroid drug use in the study locality.

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References

[1] Ross DS, Burch HB, Cooper DS, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–421.
[2] Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, Pearce SH. European thyroid association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J. 2018;7:167–86.
[3] De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906–18.
[4] Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39–51.
[5] Ogbera AO, Kuku SF. Epidemiology of thyroid disease in Africa. Indian J Endocrinol Metab. 2011;15(Suppl 2):S82–8.
[6] Azeez TA, Adetnji TA, Adio M. Thyrotoxicosis in Africa: a systematic review and meta-analysis of the clinical manifestation. Egypt J Int Med. 2022;34:57–87.
[7] Ersumo T, Burka M, Tamrat G. Hyperthyroidism in a private medical service center, Addis Ababa: a 5-year experience. Ethiop Med J. 2020;58:1–11.
[8] Gebreyohannes EA, Ayele EM, Tesfaye SA, Seid MA. Normalization of thyroid function tests among thyrotoxicosis patients attending a University Hospital in North-West Ethiopia. Thyroid Res. 2019;12:1–8.
[9] Maldey H, Tadesse S, Alem AZ, Hagezom HM, Hagos Gufue Z. Time to euthyroidism and its determinants among thyrotoxicosis patients on anti-thyroid drug who attend to medical and ambulatory clinics of South Tigrai general hospitals. Ther Clin Risk Manag. 2021;17:1091–101.
[10] Azizi F, Malboosbaf R. Long term anti-thyroid drug treatment: a systematic review and meta-analysis. Thyroid. 2017;27:1223–31.
[11] Chung JH. Anti-thyroid drug treatment in Graves' disease. Endocrinol Metab (Seoul). 2021;36:491–9.
[12] Azizi F, takyar M, madreseh E, Amouzegar A. Treatment of toxic multinodular goiter: comparison of radioiodine and long-term methimazole treatment. Thyroid. 2019;29:625–30.
[13] Azizi F, Saadat N, Takyar MA, Abdi H, Mehran L, Amouzegar A. Efficacy and safety of long-term methimazole versus radioactive iodine in the treatment of toxic multinodular goiter. Endocrinol Metab (Seoul). 2022;37:861–9.
[14] Nakamura H, Yoshimura N, Itoh K, et al. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2007;92:2157–162.
[15] Bahn RS, Henry BS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American thyroid association and the food and drug administration. Thyroid. 2009;19:673–74.
[16] Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. J Clin Endocrinol Metab. 2009;94:1881–2.
[17] Reddy V, Taha W, Kundumadam S, Khan M. Atrial fibrillation and hyperthyroidism: a literature review. Indian Heart J. 2017;69:545–50.
[18] Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116:1725–35.
[19] Mulatu HA. Pattern and presentation of thyro-cardiac disease among patients with hyperthyroidism attending a tertiary hospital in Ethiopia: a cross-sectional study. Ethiop J Health Sci. 2019;21:887–94.
[20] Rockey PH, Griep RJ. Behavioral dysfunction in hyperthyroidism. Improvement with treatment. Arch Intern Med. 1980;140:1194–7.
[21] Akamizu T, Satoh T, Isozaki O, et al. Diagnostic criteria, clinical features and incidence of thyroid storm based on nation wide surveys. Thyroid. 2012;22:661–79.
[22] Iglesias P, Devora O, García J, Tajada P, García-Arévalot C, Díez JJ. Severe hyperthyroidism: aetiology, clinical features and treatment outcome. Clin Endocrinol (Oxf). 2010;72:551–57.
[23] Laurberg P, Hansen PEB, Iversen E, Jensen SE, Weeke J. Goitre size and outcome of medical treatment of Graves' disease. Acta Endocrinol (Copenh). 1986;111:39–43.
[24] Bringmann IM, van Leeuwen BL, Hennemann G, Beckett GJ, Toft AD. Outcome of treatment of hyperthyroidism. J Endocrinol Invest. 1999;22:250–6.
[25] Liu J, Fu J, Xu Y, Wang G. Anti-thyroid drug therapy for Graves' disease and implications for recurrence. Int J Endocrinol. 2017;2017:3813540.
[26] Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences. John Wiley & Sons; 1991:209–15.
[27] Zimmermann MB, Hess SY, Adou P, Toresanni T, Wegmüller R, Hurrell RF. Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Côte d'Ivoire. Am J Clin Nutr. 2003;77:663–7.
[28] Nigatu W. Economic Interactions of Pastoral Lowland and Highland Systems and Implications for Sustainable Livelihoods: A Case Study in Northeastern Ethiopia. Forum for Social Studies (FSS); 2011.
[29] Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40:1280–88.
[30] Martin AS, Sirbu A, Albu A, et al. The time to thyroid-stimulating hormone recovery during medical treatment in Graves' disease and autonomous hyperthyroidism. Acta Endocrinol. 2013;9:405–18.
[31] Ogbera AO, Fasanmade O, Isiba A. The scope of cardiac complications of thyrotoxicosis in Lagos, Nigeria. Pak J Med Sci. 2007;23:671–75.
[32] Rivas AN, Pena C, Kopel J, Dennis JA, Nugent K. Hypertension and hyperthyroidism: association and pathogenesis. Am J Med Sci. 2021;361:3–7.
[33] Husebye ES, Anderson MS, Kampe O. Autoimmune polyendocrine syndromes. N Engl J Med. 2018;378:1132–41.
[34] Hage M, Zantout MS, Azar ST. Thyroid disorders and diabetes mellitus. J Thyroid Res. 2011;2011:1–7.
[35] Mohlin E, Nystrom FH, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000–2010. Eur J Endocrinol. 2014;170:419–27.
[36] Huang H, Shi Y, Liang B, Cai H, Lin R. Optimal iodine supplementation during anti-thyroid drug therapy for Graves' disease is associated with lower recurrence rates than iodine restriction. Clin Endocrinol (Oxf). 2018;88:473–78.
[37] Hiraiwa T, Ito M, Imagawa A, et al. Restriction of dietary iodine does not ameliorate the early effect of anti-thyroid drug therapy for Graves' disease in an area of excessive iodine intake. J Endocrinol Invest. 2006;29:380–4.
[38] Tsai MS, Chuang PY, Huang CH, et al. Better adherence to antithyroid drug is associated with decreased risk of stroke in hyperthyroidism patients. Int J Clin Pract. 2015;69:1473–85.