JIMMA UNVERSITY

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DEPARTMENT OF INTERNAL MEDICINE

ASSESSMENT OF CHALENGES IN NORMALIZATION OF THYROID FUNCTIONTESTSAMONGTHYROTOXIC PATIENTS ONTREATMENT ATTENDING CHRONIC FOLLOWUPCLINIC AT JMC, JIMMA, SOUTHWESTERN ETHIOPIA

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JIMMA, ETHIOPIA

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ABSTRACT

Background: Thyrotoxicosis is a clinical state that results from inappropriately high thyroid hormone action in tissues. Although it is one of the common endocrine disorders, there is scarcity of data on the management of thyrotoxicosis in Africa, particularly in Ethiopia.

In Ethiopia, the prevalence of thyroid disease is reported to be 1.2%. Longer duration that takes for resolution of symptoms and normalization of TFT has been a major challenge in areas like Ethiopia where first line Antithyroiddrugs are scarce. Other factors, like high initial FT4 before initiation of treatment, longer duration of symptoms before diagnosis of thyrotoxicosis and high prevalence of Toxic Multinodular goiter also contribute for the prolonged symptom resolution and normalization of TFT.

Objective: The objective of this study was to assess factors associated with normalization of TFTs and determinants of treatment outcomes among patients with thyrotoxicosis on antithyroid drugs attending follow up clinic in JMC, Jimma Ethiopia.

Methods: A Hospital –based retrospective cohort study was conducted on medical records of 176 patients with the diagnosis of thyrotoxicosis who were attending chronic Follow up clinic of JMC between June 2016 and November 2021. The collected data was cleaned, enteredinto, and analyzed using SPSS statistical software version 26. Appropriate statistical analysis was performed and p value less than 0.05 and confidence interval of 95% was used to declare statistically significant.

Results: Data from a total of 176 were eventually analyzed. The mean age if the patients was 41.24 (± 12.003) years with female majority (92.6%).The most common etiology was TMNG (90.9%).All of the patients included in this study were taking Prophylthiouracil (PTU).Nearly 80.7% of patients had symptom resolution within a mean period of 5.31(± 2.18).Thirty-seven(21.02%) ,45(25.56%) and 43(24.43%) patients achieved normalization of TSH ,FT4 and FT3 respectively.The mean time to normalization of TSH,FT4 and FT3 was 13.81(± 7.415), 9.85 (± 7.28) and 10.51(± 7.86) respectively.

Conclusion: Though PTU is not the preferredAntithyroid agent for the treatment of thyrotoxicosis, in our study all patients used PTU for the management of hyperthyroidism.All TFTs were normalized in only one –fourth of patients .Even if majority 142(80.7%) of patients achieved resolution of symptoms , it took longer period of time than expected.

Key words: Thyrotoxicosis, normalizations of TFTs, antithyroid drugs, Jimma, Ethiopia

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LIST OF ABBREVIATONS& ACRONYMS

AF: Atrial fibrillation

AITD: Autoimmune thyroid disease

ATDs: Anti-thyroid drug

CHF: Chronic heart failure

FT4: Free thyroxin

GD: Graves' disease

JMC: JimmaMedical Center

MMI: Methimazole

PTU:Propylthiouracil

RAI: Radioactive iodine;

SPSS: Statistical Package for Social Sciences

T3: Triiodothyronine

TFT: Thyroid function test

TH: Thyroid hormone

TMNG: Toxic multinodular goiter

TSH: Thyroid stimulating hormone

WHO:World Health Organization

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CHAPTER ONE:

INTRODUCTION

1.1 Background

Thyrotoxicosis is a clinical state that results from inappropriately high thyroid hormone action in tissues [1]. It affects 1–3% of the general population and is 10 times more common in women than in men [2].

In the United States, the prevalence of thyrotoxicosis is approximately 1.2% [1]. The extent of thyroid disorders in Africa remains unknown because of under-diagnosis and underreporting but the few available studies note prevalence rate of 1.2 to 9.9% [3].

In Ethiopia, the prevalence of thyroid disease is reported to be 1.2% [3]Graves' disease (GD) is the most common cause of thyrotoxicosis. It accounts for 70–80% of cases in iodine-sufficient population and approximately 50% of cases in iodine-deficient areas [4].

Other etiologies include thyroiditis, toxic nodular goiter, toxic multinodular goiter (TMNG), toxic adenoma, and exogenous thyrotoxicosis (iatrogenic, factitious, iodine induced) [5].

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test [1]

However, when hyperthyroidism is strongly suspected, diagnostic accuracy improves when both a serum TSH and free T4 are assessed at the time of the initialevaluation.[1]

The relationship betweenfree T4 and TSH (whenthe pituitary-thyroid axis is intact) is an inverse log-linear relationship; therefore, small changes in free T4 result in large changes in serum TSH concentrations.Serum TSH levels are considerably more sensitive than direct thyroid hormone measurements for assessing thyroid hormone excess.[1]

Inovert hyperthyroidism, usually both serum free T4 and T3 estimates are elevated, and serum TSH is undetectable. The three principal treatment options for the management of thyrotoxicosis includethionamides or anti-thyroid drugs (ATDs), radioactive iodine, and surgery [1].

Untreated thyrotoxicosis can lead to serious complications such as thyroid storm, arrhythmia, hypertension, cardiac dilation, congestive heart failure (CHF), and sudden cardiac arrest ultimately improving the quality of life [6,7].

Despite methimazole (MMI) and propylthiouracil (PTU) having been used for more than half a century to treat hyperthyroidism caused by Graves' disease (GD), controversy still exists in anti-thyroid drug (ATD) therapy [18].

For example, according to a survey reported in 1991, MMI was selected as the drug for initial treatment in Japan and Europe, whereas PTU was preferred in the UnitedStates. [18].

MMI 30 mg/d normalized FT4 in more patients than PTU300 mg/d and MMI 15 mg/d for the whole group (240 patients) at 12 wk (96.5 *vs*. 78.3% and 86.2%, respectively) [10].

1.2. Statement of the problem

Thyrotoxicosis is a condition having multiple etiologies, manifestations, and potential therapies.[1] In Ethiopia, the prevalence of thyroid disease is reported to be 1.2% [3]Graves' disease (GD) is the most common cause of thyrotoxicosis. It accounts for 70–80% of cases in iodine-sufficient population and approximately 50% of cases in iodine-deficient areas .[4]

Untreated thyrotoxicosis can lead to serious complications such as thyroid storm, arrhythmia, hypertension, congestive heart failure (CHF), and sudden cardiac arrest. [6,7]

Normalization of Thyroid function test is the main outcome measure in thyrotoxicosis treatment. TSH measurement is very important for the determination of treatment outcome in hyperthyroidism because it is more specific and sensitive indicator than other TFT values [1].

The three principal treatment options for the management of thyrotoxicosis includesthionamides or anti-thyroid drugs (ATDs), radioactive iodine, and surgery [1].

The main ATD are thionamides, such as propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of the latter, methimazole (MMI) [37]. Initial choice of ATD might affect the treatment outcome [10].

MMI is recommended as preferred ATD over PTU and should be used among all patients. Except during the first trimester of pregnancy, in the treatment of thyroid storm or in patients

with minor adverse reactions to MMI [1, 10-12]. MMI is yet to be included in the national medicines formulary and standard treatment guidelineof Ethiopia. [13,14]. As a result, availability of MMI remains a challenge rendering clinician to rely mainly on the routinely available PTU [36]

According to the study done in Japan,the mean time required to normalize TH was 6.7 plus or minus 4 .6 wk by MMI 16.8 Plus or minus 13.7 wkby PTU [17]. This is much lower than Gondar, Ethiopia (13 months for normalization of TSH & 11.5month for FT4) [36].

The other determinant factor for treatment outcome of thyrotoxicosis is the initial FT4 &FT3 level [10].In those patients with initial FT4 level greater than 7 ng/dl At 4 wk after beginning treatment, 38.5% of the patients achieved normal FT4 with MMI 30 mg/d.

But only 13.0% with PTU 30mg/d and 14.3% withMMI15 mg/d, with both about 35–40% efficiency of MMI30 mg/d in normalizing FT4 [10]. Higher initial FT4 level were shown to reduce rate of TSH normalization by 0.8% [36].

Several studies have tried to correlate the impact of sex, age, goiter size, duration of symptoms before diagnosison treatment outcome of thyrotoxicosis with some conflicting results.For instance, according to a report from Sweden, age and gender did not predict treatment outcome [9].

Age slightly increased rate of TSH normalization according to the study done in Gondar, Ethiopia [36].Whereas, goiter size has been associated with failure of medical treatment by many studies [9,26,28-30],these findings contrast with some other studies from Europe and Gondar, Ethiopia [31,32,36].

Therefore, the aim of this study is to identify factors associated with normalization of TFT among patients with thyrotoxicosis who are on ATD treatment.

1.3 Significance of the study

Normalization of TFT is the main goal of ATD treatment which is very important because once patients become euthyroid they can be put on the lowest possible dose of ATD which may decrease the side effects and cost of the ATD andpatients can be given other options of management like thyroidectomy. Finally, this study can be used as a baseline for further studies.

CHAPTER TWO:

LITERATURE REVIEW

2.1 Literature Review

Thyrotoxicosis is a clinical state that results from inappropriately high thyroid hormone action in tissues[1]. TH increases tissue thermo genesis and the basal metabolic rate, and reduces serum cholesterol Levels and systemic vascular resistance.

The prevalence of hyperthyroidism is 1.2% (0.5 overt and 0.7 % subclinical) [1]. In Ethiopia, the prevalence of autoimmune thyroid disease is reported to be 1.2% [3]and reports from Libya indicate a prevalence rate of 3%[3].

The overall incidence of AITD in Tunisia is 9.9% and this was notedto have occurredin conjunction with 6.3% of other autoimmune disease [3]. The most frequent causes are Graves' disease (GD) and toxic nodular goiter.

GD is the most prevalent cause of hyperthyroidism in iodine replete geographical areas, with 20–30 annual cases per 100,000 individuals [15]. GD occurs more often in women and has a population prevalence of 1–1.5%.

Approximately 3% of women and 0.5% of men develop GD during their lifetime [16].The peak incidence of GD occurs among patients aged 30–60 years, with an increased incidence among African Americans[19].

Normalization of TFTs is the main outcome measure in thyrotoxicosis treatment.Graves' hyperthyroidism is treated by reducing TH synthesis, using ATD, or by reducing the amount of thyroid tissue with RAI treatment or total thyroidectomy [15, 33].

ATD represent the predominant therapy in Europe, Asia, and in the meantime in the USA [34, 35]. The main ATD are thionamides, such as propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of the latter, methimazole (MMI).[34]

MMI is recommended as preferredATD over PTU and should be used among all patients. Except during the first trimester of pregnancy, in the treatment of thyroid storm or in patients with minor adverse reactions to MMI [1, 10-12].

One of the treatment options of thyrotoxicosis is ATD [10].Initial choice of ATD might affect the treatment outcome[10].There have been only limited studies that compared the effectiveness of MMI and PTU to treat thyrotoxicosis caused by GD. [10]

A study which was donein Japan reported thatMMI30 mg/d normalized more rapidly TH than PTU 300 mg/d. [17].Since MMI is yet to be included in the national medicines formulary and standard treatment guideline of Ethiopia [13,14],& because of its unavailability locally PTU

remains the first line ATD in our setting, which is also the case in Gondar, Ethiopia , where all of the patients included in the study were taking PTU. [36].

The mean time required to normalize TH was 6.7 plus or minus 4 .6 wk by MMI and16.8 Plus or minus 13.7 wkby PTU [17]. This is much lower than Gondar, Ethiopia (13 months for normalization of TSH & 11.5month for FT4) (36).

The four prospective randomized controlled trials (RCTs)thatcompared to MMI and PTU also indicated the tendency that MMI is somewhat more effective. [19-22]. The other determinant factor for treatment outcome of thyrotoxicosis is the initial dose of ATD which is evidenced by a report from European Multicenter Trial Study which showed 42.2% of patients became euthyroid within 3wk on MMI 10 mg/d and 64.8% on 40 mg/d after 3 wk**,** [23]

At 6 wk, 77.5% and 92.6% of patients became euthyroid on 10 mg and 40 mg MMI, respectively [23]. Another RCT comparing the effects of lowand high dose of ATD showed similaroutcome [20]. The other determinant factor for treatment outcome of thyrotoxicosis is the initial FT4 l&FT3 level [10].

In those patients with initial FT4 level greater than7 ng/dl at 4 wk after beginning treatment,38.5% of the patients achieved normal FT4 with MMI 30 mg/d, But only 13.0% with PTU 300 mg/d and14.3% withMMI15 mg/d, with both about 35–40% efficiency of MMI30 mg/d in normalizingFT4 [10].

In those patients with initial FT4 less than7ng/d no difference was found between the treatmentsat 4 and 8 wk, but at 12 wk, MMI 30 mg/d achieved normal FT4 in every patient, While PTU 300 mg/d andMMI15 mg/d induced normal FT4 in 87.5% and 92% respectively [10].
Which is also supported by the study done in Gondar, Ethiopia, that showed higher initial FT4level were shown to reduce rate of TSH normalization by 0.8%. [36]

Analysis based on the baseline severity of hyperthyroidism is important because it is quite conceivable that a small amount of ATD may be suitable for mild GD but unsuitable for very severe hyperthyroidpatients [24].

Several studies have tried to correlate the impact of sex,age goitersize, duration of symptoms before diagnosison treatment outcome of thyrotoxicosis with some conflicting results.For instance, according to a report from Sweden, age and gender did not predict treatment outcome [9]

This is in contrast to other several studies that have reported younger patients to have higher relapse rates after medical treatment. [26,27] This is in contrast to Gondar, Ethiopia where older age has decreased the rate of FT4 normalization by 1.7%. [36]

Whereas,goiter size has been consistently associated with treatment outcome by most ofthe studies which showed larger goiters were associated with failure of medical treatment[9,26, 28-30] andthese findings contrast withsome studies from Europe [31, 32] which is also the case in Gondar, Ethiopia that did not show WHO goiter size as independent predictor of treatment outcome. [36]

Although it has been suggested previously that males suffer worse biochemical hyperthyroidism with less severe symptoms, little evidence exists to suggest any difference in treatmentoutcome [25].

Although a recent study of Italian subjects reported a small excess in the long-termrelapse rate after medical therapy in male patients, the difference between the sexes was not tested for independent association [26].

Males, however, had a markedly worse outcome after medical treatment, with a remission rate of only 19.6% compared with 40% for females[38].Thereare limited studies on TMNG as a cause of thyrotoxicosis, since the most common cause of thyrotoxicosis in the western hemisphere is GD[4], where most of the studies are done.

Those patients with GD will be euthyroid within short period of time (6weeks) than patients with TMNG (24months) [8], which is in consistent withGondar, Ethiopia[36].The other factor that was associated with decreased rate of FT4 was longer duration of symptoms before diagnosis which is in Gondar, Ethiopia (88 months) that may reflect the knowledge and attitude of the society towards hyperthyroidism [36]

Patients should be informed of side effects of antithyroid drugs and the necessity of informing the physician promptly if they should develop pruritic rash, jaundice, acolic stools or dark urine,arthralgias, abdominal pain,nausea, fatigue, fever, or pharyngitis. [1]

A study done in Japan showed the overall adverse events was higherfor PTU than MMI. PTUinduced hepatotoxicity was 26.9% whereas, it was 6.6% for MMI.The number of patients with skin eruption or urticaria were comparable for both PTU andMMI (22.1&22.3%) respectively. [10]

PTU may rarely cause agranulocytosis, whereas low doses of MMI may be less likely to do so. This was evidenced by study which found the prevalence of agranulocytosis to be 0.18 %which is lower than other studies that showed as high as 1.8%. [39,40].

A study done in Gondar, Ethiopia showed only one patient (0.47%) experienced arthralgia as an adverse effect due to PTU, and otherwise no other adverse effect was recorded. [36]

In a cohort of 591consecutive patients with hyperthyroidism due to different causes, HF was present in 6%of cases [41]. This is consistent with a study done in Gondar, Ethiopia which showed 5.2 % of patients with thyrotoxicosis who developed CHF. [36] Accordingto a study done in Denmark the prevalence atrial fibrillation orflutter in patients with hyperthyroidism was 8.3%.[42] A study from St.Paul Hospital Millennium Medical College reported a prevalence of atrialfibrillation among hyperthyroid patients to be 11%[43]. This is much higherthan the studydone in Gondar, Ethiopia which showed a prevalence of 0.96% [36].

2.2 Conceptual Framework

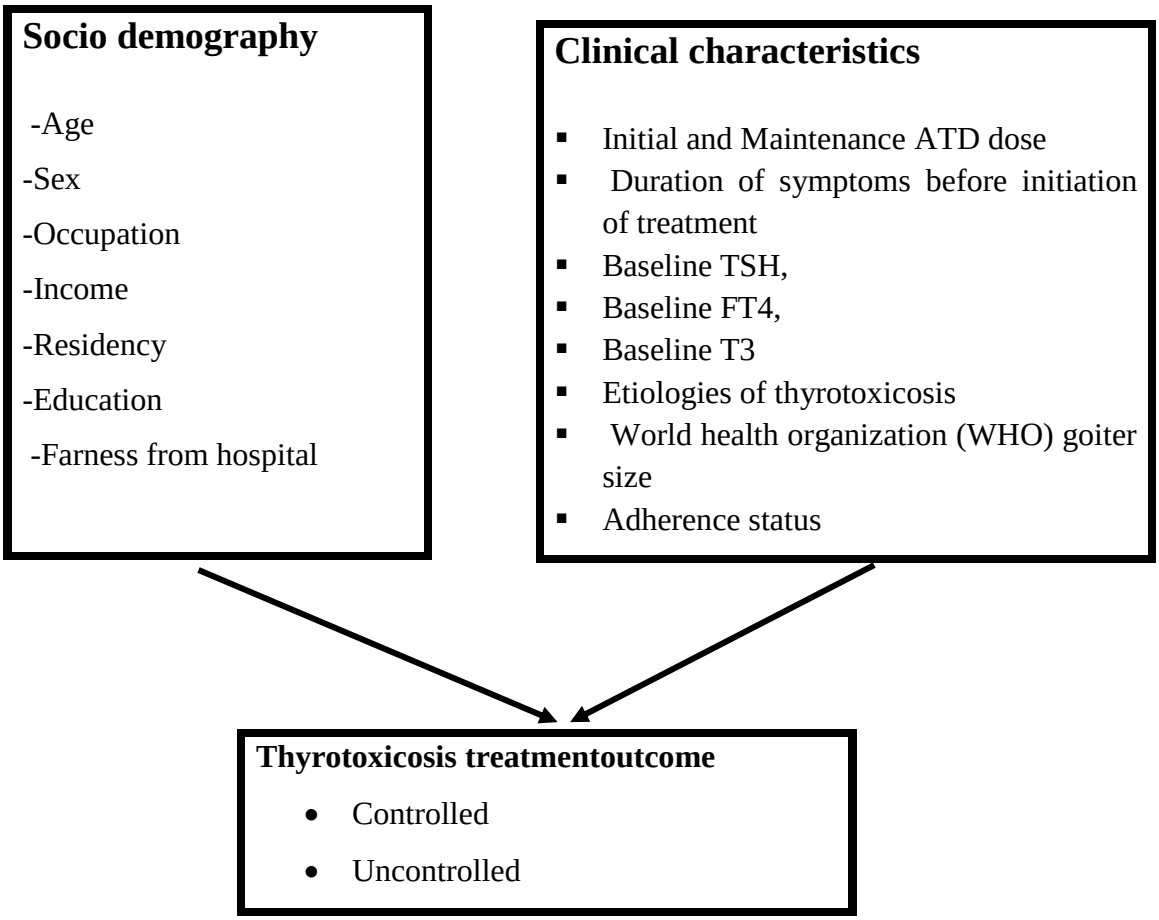

Figure 1: Shows conceptual framework of the study adopted from different literatures.

CHPTER THREE:

OBJECTIVES

3.1 General objective

- To assess factors associated with normalization of TFTs and determinants of treatment outcomes among patients with thyrotoxicosis on antithyroid drugs attending follow up clinic in JMC, Jimma, Ethiopia.

3.2 Specific objective

- To assess the clinical characteristics of patients with Thyrotoxicosis
- To assess factors associated with treatment outcome of patients with Thyrotoxicosis who are taking ATD
- To assess the side effects of ATD
- To assess the adherencestatus of patients for ATD
- To assess the prevalence of atrialfibrillation& heart failure among patients with thyrotoxicosis

CHAPTER FOUR:

METHOD AND MATERIALS

4.1 Study Area and period

The study was conducted in JMC from November 01 –December 31/2021. JMC is located in Jimma town South West of Ethiopia, 350 Kilometers from the capital, Addis Ababa. The hospital provides almost all major types of medical care. Among the different service units in JMC, chronic follow up clinic is worth mentioning, the clinic is settled in the new building on ground plus two levels under Internal Medicine Department. Patients with Thyrotoxicosis were among those having follow up every Thursday with about 15to 25 patients daily on average. The activities are accomplished by three to four residents who rotate every monthly, nurses and One Endocrinologist.

The study was conducted at chronic follow up clinic on scheduled dates of Thyrotoxicosispatients at JMC from November 01–December 312021 GC.

4.2 Study design:

Retrospective Hospital based cross-sectional study

4.3 Populations

4.3.1 Source population:

The source population for the study were all patients having follow up for Thyrotoxicosis at JMC during the study period (November 01-December 31/2021 G.C)

4.3.2 Study population:

All patients having follow up for Thyrotoxicosis at JMC during the study period (November 01-December 31/2021 G.C for whomboth exclusion and inclusion criteria fulfilled were included in the study population and patients were included until the required sample size was obtained.

4.4. Inclusion and Exclusion criteria

4.4.1 Inclusion criteria

Patients 18 years of age and older with a diagnosis of thyrotoxicosis who have received antithyroid medications for management of thyrotoxicosis were included in the study.

4.4.2 Exclusion criteria

- Patients who visited either the medical inpatient ward or chronic ambulatory clinic only once and did not have further follow-up history;
- Patients with less than 4 weeks follow-up;
- Patients with incomplete medical records of thyroid function tests (TFTS);
- Pregnant patients;
- And patients who underwent surgery for the management of thyrotoxicosis.

4.5 Sample size determination

All patientswith Thyrotoxicosis onATD who had follow up at JMC were included in the study.

4.6. Sampling technique

Consecutive sampling technique was used and every consecutive patient who fulfills inclusion criteria was included until the calculated sample size obtained.

4.7. Variables

4.7.1. Dependent Variables

Normalization of TFTs

4.7.2. Independent variables

- Age
- Sex
- Initial ATDdose,
- Maintenance ATD dose

- Duration of symptoms before diagnosis of thyrotoxicosis
- Baseline TSH
- Baseline FT4
- Baseline T3
- Etiologies of thyrotoxicosis
- World health organization (WHO) goiter size
- Adherence status
- Income
- Residency (urban or rural)
- Farness from the hospital

4.8. Data collection tooland procedure

A Checklist was used by reviewing the patient's chart and interviewing the patient. The checklist included the socio-demographic characteristics of the patients, clinical characteristics and factors associated with normalization of TFTs.

Data was collected by four interns at Follow up clinic . The data collection was done by reviewing each patients chart and patient interviewing with supervision of the whole activity by the investigator. The necessary data on associated factors were obtained by careful review of the chart and asking of the client.

4.9. Data quality control

The measures that were undertaken to ensure quality of data included Pre-testing of the data collection instrument two months ahead of data collection on patientswith thyrotoxicosis whowere havingfollow up at JMC, on five percent of the sample population (charts).Training on data collection for data collectors before data collection was started and supervision of the data collection process, data storage and management was done by principal investigator

4.10. Data processing and analysis

Collected data was, entered and analyzed using SPSS windows version 26. Descriptive analysis was carried out using frequency distributions, central tendency and dispersion measures. Presence of statistical association between dependent and independent variables was assessed using chi-square and binary logistic regression(both bivariate and multivariate analysis were checked) and Association with p- value of < 0.05 was considered to be statistically significant. Results were presented in text, tabulation and figurative presentations from which conclusions and recommendations were made. In addition, results were compared with other studies and discussed.

4.11. Operational definitions

- **Thyrotoxicosis:**refers to a clinical state that results from inappropriately high thyroid hormone action in tissues and TSH level < 0.4 mU/L.
- **TSH, FT4 and T3 normalization:** when TSH, FT4 and T3 are within the euthyroid range.
- **Euthyroid range: is considered when**
    - **TSH** is b/n 0.4–5.0 mU/L
    - **FT4** is b/n 10.4–19.6 pmol/l and
    - **T3** 0.92–2.3 nmol/l,
- **WHO goiter size:**
    - **Grade 0:** The goiter is not palpable or visible even when the neck is extended;
    - **Grade 1:** The goiter is detected on palpation and/or visible when the neck is extended;
    - **Grade 2:** Goiter is visible when neck is in the normal position;
    - **Grade 3:** Large goiter visible from distance.
- **A TMNG** is simply a late-stage goiter that's been around for a while and has had a chance to grow and become lumpy or nodules
- **Adherence status -** has been defined according to Morisky's 8 items medication adherence questionnaires.
- **GD** is an autoimmune disorder in which TRAb stimulate the TSH receptor, increasing thyroid hormone production.

- **Hyperthyroidism-** is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid and suppressed TSH levels and elevated FT3 and/or estimated FT4 levels.
- **Illiterate –** can't read and write and haven't attend formal education.
- **Income –**estimated average amount of cash money an individual earns monthly in terms of Ethiopian currency. For those without monthly salary their raw materials will be estimated in terms of Ethiopian birr.

4.12. Ethical consideration

Ethical clearance was obtained from Jimma University Faculty of MedicalSciences Ethical review committee. An official letter was be obtained from Department of Internal Medicine and was given to responsible body at chronic follow up clinic and information obtained from the records were kept confidential by not recording participants name and their phone number on questionnaires. Also, the subject matter was kept confidential if next research was needed.

CHAPTER FIVE: RESULT

5.1 Socio-demographic characteristics of the participants

A total of 176 patients were included in the study. Out of these participants163(92.6%) were females while 13 (7.4%) were males. The mean age was 41.24 (± 12.003) years.

Sixty-Five (36.9%) of the patients had no formal education whereas 42 (23.9%), 37 (21. %) and 28(15.9%) of the respondents were able to read and write, completed primary and secondary school respectively. One hundred fifty-nine (90.34%) of the respondents were married. One hundred thirty nine (79%) of the patients were house wife followed by merchant 16(9.1%).

The majority of patients 126 (71.6%) are from rural areas. The mean estimated distance from the hospital was 43.26(± 55.91) kilometers. The majority of patients 98 (55.7%) have a low middle income followed by low income 72(40.9 %).

Table 1: Socio-demographic characteristics of the patients with thyrotoxicosis who are on ATD treatment attending follow up clinic of JMC, 2021(N=176)

Variables	Category	Frequency	Percentage
Age	19-40	69	39.2%
	41-65	107	60.8%
Sex	Female	163	92.6
	Male	13	7.4
Marital status	Married	159	90.34%
	Single	17	9.66%
Educational status	No formal education	65	36.9
	Able to read and write	42	23.9
	Primary (grade1-8	37	21
	Secondary(grade 9-12)	28	15.9
	University/College	4	2.3
Occupation	Housewife	139	79%
	Merchant	16	9.1
	Farmer	13	7.4

	Government employee	6	3.4
Monthly income	<3,100	72	40.9
	3100 -12,100	98	55.7
	12,100 -37,600	6	3.4

5.2 Clinical characteristics of the patients

Out of the 176 patients 95 (54.0%) have higher WHO goiter size (grade 2and above) whereas 54(30.7%), 23 (13.1%) and 4(2.3%) of the patients have WHO goiter size grade 1, grade 3 and grade 0 respectively. Majority of patients 125 (71%) have baseline FT4 level above 7ng/dl or above 90pmol/L while 98(55.7%) and 91(51.7%) of patients have baseline TSH level of less than 0.01mu/L and baseline FT3 level of less than 5pg/ml (65pmol/L) respectively. The mean duration of symptoms before diagnosis of thyrotoxcosis was 12.14 (± 7.49) months. The most common etiology was TMNG 160 (90.9%) while GD accounting for the remaining 16 (9.1%)of patients.

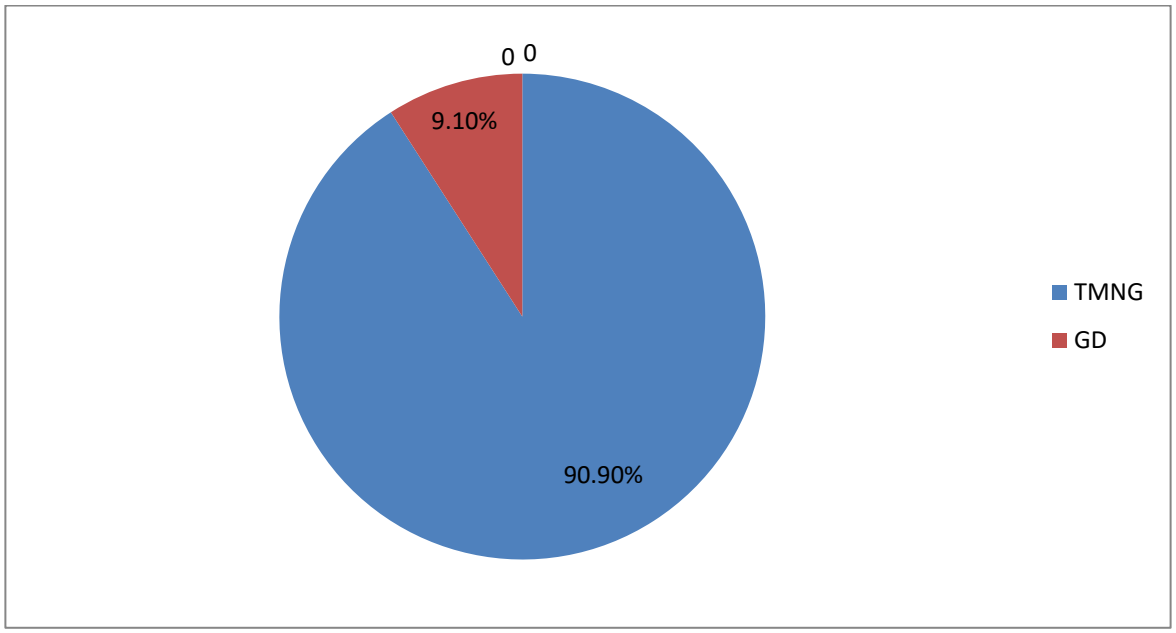

Figure 2:Etiologies of thyrotoxicosis among hyperthyroid patients attending follow up clinic of JMC.

5.2.1 Signs, symptoms, comorbidities and complications

The majority of patients experienced palpitations 154(87.5%),heat intolerance 144 (81.8%) and easy fatigability 143(81.3%). The mean pulse rate , systolic blood pressure ,diastolic blood pressure , body temperature and respiratory rate at the time of diagnosis are 108.06(± 18.77) ,128.03(± 19.96), 79.20(± 9.76), 36.23(± 0.602)and 22.16(±3.18)respectively.

Over all 12 (6.8%) of patients have co morbidities out of which DM 4(2.3%) and B.Asthma 4(2.3%) are the commonly identified comorbidities. In this study 35(19.9%) of patients developed complications of thyrotoxicosis. Congestive heart failure 32(28.2%) was the most common complication that was identified followed by atrial fibrillations16 (9.1%) ,CHF +AF 11(6.3%) and thyroid storm 3(1.7%). All of the 176 patients included in this study were taking PTU.The initial and maintenance dose of was PTU 300 mg/day in majority of patients 143(81.3%) and the remaining 33(18.7%) of patients were taking PTU 200mg/daily as initial and maintenance dose. Among drugs used for rate control propranolol was the most commonly used 141(80.1%).

Table2: Complications of thyrotoxicosis in patients attending follow up clinic of JMC

Complications	**Frequency**	**Remark**
CHF	32(28.2%)	
AF	16(9.1%)	
CHF+AF	11(6.3%)	
Thyroid storm	3(1.7%)	

Among drugs used for the treatment CHF furosemide was the most commonly used 30(17%) followed by enalapril 22(12.5%) and sprinolactone 21(11.9%).Warfarine was given for 12(6.8%) of the patients.A total of 4(2.3%) of patients experienced side effects due to PTU(2 patients developed arthralgia and the remaining 2 experienced GI intolerance). Ninety-eight (55.7%) of patients were poorly adherent to their medications while 61(34.7%) and 17(9.7%) of patients were moderately and highly adherent respectively based on the morisky adherence scale.

Table 3: Clinical characteristics of patients with thyrotoxicosis who are on ATD having follow up at JMC from November 1 2016 to December 31, 2021

Clinical characteristics		Category	Result	Remark
WHO goiter size N(%)		Grade 0	4(2.3%)	
		Grade 1	54(30.7%)	
		Grade 2	95(54%)	
		Grade 3	23(13.1%)	
Baseline FT4 levels pmol/L		>90	125(71%)	
		<90	51(29%)	
Baseline FT3 levels in pmol/L		**>65**	85(48.3)	
		<65	91(51.7%)	
Baseline TSH levels in mu/L		**<0.01**	98(55.7%)	
		0.4 – 0.01	78(44.3)	
Mean duration of symptoms before diagnosis in months (± SD)			12.14(±7.49)	
Mean systolic blood pressure at diagnosis(± SD)			128.03(±19.96)	
Mean diastolic blood pressure at diagnosis(± SD			79.20(±9.76)	
Mean Pulse rate at diagnosis (± SD)			108((± 18.77)	
Mean body temperature at diagnosis(± SD)			36.23(± 0.602)	
Mean Respiratory at diagnosis (± SD)			22.16(±3.18)	
Symptoms	**Palpitations**		154(87.5%)	
	Heat intolerance		144 (81.8%)	
	Easy fatigability		143(81.3%)	
	Weight loss		69(39.2%)	
	Increased sweating		37(21%)	
	Shortens of breath		24(13.63%)	
	Warm moist skin		17(9.65%)	

5.3 Associated factors and Treatment outcome

The majority of patients 142(80.7%) had their symptoms resolved. The mean time for symptom resolution was 5.31(± 2.183). Thirty-seven (21.02%) , 45(25.56%) and 43(24.43%) of patients achieved normalizations of TSH,FT4 and FT3 respectively. The mean time for normalization of TSH,FT4 and FT3 was 13.81(± 7.41), 9.85(± 7.82) and 10.51(± 7.86) months respectively. The study under took binary logistic regression to assess the significance of variable association with normalization of TFTs.Age, sex ,monthly income , WHO goiter size,duration of symptoms before diagnosis, etiology of thyrotoxicosis, initial and maintenance dose of PTU , adherence status baseline TSH, FT4 and FT3 levels were analyzed. Only baseline TSH (OR, 95% CI): 2.12(1.065 – 4.219 ,p=0.032), baseline FT4 (OR, 95% CI): 0.391(0.192 -0.799, p=0.01) and baseline FT3 (OR, 95% CI) :0.293(0.139 -0.617, p=0.001) were associated with normalization of TFTs but baseline FT4 failed to maintain this effect on multivariate analysis.

Table4: Predictors of normalizations of TFTs among patients with thyrotoxicosis attending follow up clinic of JMC, 2021(N=176)

Variables	Binary logistic regression		Multivariate analysis	
	COR(95% CI)	P-value	AOR(95% CI)	p-value
Age(in years)	1.336(0.664-2.690)	0.417	1.496(0.716-3.126)	0.283
Sex	4.475(0.565-35.431)	0.156	5.02(0.623-40.480)	0.130
Poor and irregular drug supply	1.759(0.888-3.485)	0.105	0.89(0.118-6.683)	0.91
Unaffordability	1.862(0.935-3.710)	0.077	2.806(0.368-21.425)	0.32
Poor drug adherence	1.156(0.585-2.284)	0.676	0.651(0.272-1.556)	0.334
Medium drug adherence	1.590(0.517-2.170	0.876	2.781(0.971-7.960)	0.057
High drug adherence	0.876(0.271-2.845)	0.828	5.2(1.023-26.435)	**0.047**
Missing to take the drugs in the past 2 weeks	1.730(0.783-3.820	0.175	3.726(1.355-10.248)	**0.011**
TMNG	0.720(0.189-2.612)	0.598	0.959(0.202-4.552)	0.957
Duration of symptoms before	6.679(0.869-51.708)	0.069	7.169(0.919-55.932)	0.06

diagnosis(in months)				
Baseline TSH	2.12(1.065-4.219)	**0.032**	0.166(0.37-0.752)	**0.02**
Baseline FT4	0.391(0.192-0.99)	**0.01**	1.851(0.466-7.68)	0.396
Baseline FT3	0.239(0.139-0.617)	**0.001**	0.73(0.016-0.324)	**0.001**

CHAPTER SIX: DISCUSSION

In this study only 21.02% of patients achieved normalizations of all TFTs (TSH, FT4 and FT3) .This is consistent with the study done in Gondar, where 55(26.32%) achieved normalization of all TFTs. [36]. Forty-five (25.56%) patients achieved normalizations of FT4 while 37(21%) and 43(24.43%) of patients achieved normalization of TSH and FT3 respectively which is lower than the report from Gondar which showed 62(29.81%) , 122(58.65%) and 79(38.16%) of patients achieving normalization of TSH, FT4 and FT3 respectively [36].

The mean time for normalization of TSH,FT4 and FT3 was 13.81**(**± 7.41**),** 9.85(± 7.82) and 10.51(± 7.86) months respectively which was longer than the previous studies that showed after 6 weeks of ATD treatment 90% of patients with GD will be euthyroid. [8]. Another prospective study also showed the cumulative recovery rates of TSH among GD patients to be: 36.7% at 3 months ,72.2% at 6 months, 86.7% at 9months and 95.6% at 12 months. [44].But the high prevalence of TMNG 160(90.9%) in the present study may be the reason for the lower rate and prolonged duration needed for normalization of TFTs. On the other hand The mean time for normalization for TFTs in the present study is in line with study from Gondar, which showed a 13(± 13.28) and 11.5(± 13.39) months for normalizations of TSH and FT4 respectively. [36].In the present study age (p=0.147) andsex (p=0.156) did not influence the time to TFTs recovery this is consistent with a study by mohlin et.al which found age and sex has no significant relation to the prognosis of the disease [9].In contrast, study from Gondar , found that age slightly increased the rate of TSH normalization [36]. Upon binary logistic regression higher baseline FT4(p=**0.01**) and FT3(p= 0.**001**) have shown statistically significant effect in normalization of TFTs.But this effect of FT4 was not maintained upon multivariate analysis (P=**0.396).** Very low baseline TSH(<0.01) was associated with treatment outcome (p=**0.032**),it was statistically significant COR(95%CI): 2.12(**1.065-4.219**). This is consistent with the study by Gebreyohannes et.al which found higher baseline FT4 level decreasing the rate of normalization of TSH by 0.8%. In this study the mean duration of symptoms before diagnosis was 12.14(±7.49) months. Bothbinary logistic regression (p=**0.069)**and multivariate analysis (p=**0.06**) did not show statistically significant effect of longer duration of symptoms in normalization of TFTs.The study from Gondar, also failed to show the effect of longer of longer duration of symptoms in normalization of TFTs upon multivariate analysis. [36]

Although previous report by mohlin et.al found palpable goiter or WHO grade 2 goiter size was associated with worse prognosis compared with no goiter (51.2 versus 68.9%) remission after 5 years , (p=0.014) [9]. The present study did not identify WHO goiter size as independent predictor of normalizations of TFTs.(p=0989). This goes with a report from Gebreyohannes et.al which failed to show the effect of WHO goiter size in TFTs recovery rate. [36]. In our study high adherence for ATD(p==**0.047)** and those patients who missed taking their ATD in the prior 2 weeks (p=**0.011)** were associated with statistically significant effect in normalization of TFTs upon multivariate analysis.

Even if majority of patients 142(80.7%) had their symptoms resolved ,it took longer time than expected by other studies (3.51(± 2.183) months in the current study). This is in contrast to a retrospective multicenter study from Tagami et.al that reported the sign and symptoms of patients with hyperthyroidism showed a significant improvement after just 4 weeks of taking beta-adrenergic blocking agents[45].If thyrotoxicosis left untreated it can result incardiovascular complications. In this study 32(28.2%),16 (9.1%) , 11(6.3%) and 3(1.7%) patients developed CHF,AF, CHF+AF and thyroid storm respectively. This is higher than the report from Gondar, where 5.245%, 0.296%, 7.68% and 1.43% patients developed CHF,AF CHF+AF and thyroid storm respectively. It is also higher than a study from a cohort of 591consecutive patients with hyperthyroidism due to different causes, HF was present in 6%of cases [41]. A study from St.Paul Hospital Millennium Medical College reported a prevalence of atria fibrillation among hyperthyroid patients to be 11%[43].There are several adverse effects that may may occur during ATD treatment. In this study a total of 4(2.3%) patients experienced side effects due to PTU(2 patients developed arthalgia and the remaining 2 experienced GI intolerance). This is higher than a report from Gebreyohannes et.al which found 1(0.47%) patients who experienced arthalgia. [36].

CHAPTER SEVEN: CONCLUSION & RECOMMENDATION

7.1 CONCLUSION

In our study PTU was the only agent used for the treatment of thyrotoxicosis, despite international guidelines' recommendation of MMI.All TFTs were normalized inonly lessthan one fourth of patients. Moreover, even in those patients who achieved normalizations of TFTs,it took longer time than expected. Though majority of patients achieved resolution of symptoms, they were not able to achieve this resolution in the recommended period of time.

7.2 RECCOMENDATION

- ✓ Patients should be advised in the importance of good drug adherence for achieving better treatment outcome.
- ✓ MMI should be included in the national medicines formulary and standard treatment guideline of Ethiopia and should be made available for our patients in order to achieve better treatment outcome
- ✓ In order to identify the reasons for poor treatment outcomes, it is also recommended to do a large-scale, multicenter prospective study.

CHAPTER 8: STRENGTHS & LIMITATIONS

8.1. Strengths

8.2.Limitations of the study

- ✓ The majorlimitations of this study were that it was a retrospective study and relied on data from the medical records.
- ✓ Large numbers of patients medical records were also missing which made to depend on a smaller sample size.
- ✓ Because of the retrospective nature the study, adherence status and adverse effects of the ATD were not assessed adequately.Therefore, interpretations of the findings of this study should take this limitations in to consideration.

9. REFERENCES:

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
2. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99(1).
3. Ogbera AO, Kuku SF. Epidemiology of thyroid diseases in Africa. Indian journal of endocrinology and metabolism. 2011;15(Suppl2):S82.
4. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018.
5. Amballi AA. Thyrotoxicosis-a review. Middle-East J Sci Res. 2007;2(3–4):98–103.
6. Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. Therapeutic advances in endocrinology and metabolism. 2010;1(3):139–45.
7. Ertek S, Cicero AF. Hyperthyroidism and cardiovascular complications: a narrative review on the basis of pathophysiology. Archives of medical science: AMS. 2013;9(5):944.
8. Katz MD, Mathias KR, Chisholm-Burns MA. Pharmacotherapy principles and practice study guide. 4th ed; 2016. p. 689–90
9. Mohlin E, Nyström HF, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000-2010. Eur J Endocrinol. 2013;23:EJE–13.
10. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Working Group of the Japan Thyroid Association for the guideline of the treatment of graves' disease. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by graves' disease. The Journal of Clinical Endocrinology & Metabolism. 2007;92(6):2157–62.
11. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. The Journal of Clinical Endocrinology & Metabolism. 2009;94(6):1881–2.
12. Cooper DS. Antithyroid drugs. N Engl J Med. 2005;352(9):905–17.
13. Food Medicine and Healthcare Administration and Control Authority of Ethiopia. Ethiopian medicinesformulary, vol. 2013. 2nd ed. Addis Ababa. p. 564–7.
14. Food Medicine and Healthcare Administration and Control Authority of Ethiopia. Ethiopia standard treatment guidelines for general hospital, vol. 2014. 3rd ed. Addis Ababa. p. 84–6.
15. Smith TJ, Hegedus L: Graves' disease. N Engl J Med 2016; 375: 1552–1565.

16. Nystrom HF, Jansson S, Berg G: Incidencerate and clinical features of hyperthyroidismin a long-term iodine sufficient area of Sweden (Gothenburg) 2003–2005. Clin Endocrinol2013; 78: 768–776.

17. Okamura K, Ikenoue H, Shiroozu A, Sato K, Yoshinari M, FujishimaM1987Reevaluation of the effects of methylmercaptoimidazole and propylthiouracilin patients with Graves' hyperthyroidism. J Clin Endocrinol Metab 65:719–72

18. Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y,Izumi M1991 Differences and similarities in the diagnosis and treatment ofGraves' disease in Europe, Japan, and the United States. Thyroid 1:129–135

19. Nicholas WC, Fischer RG, Stevenson RA, Bass JD1995 Single daily dose ofmethimazole compared to every 8 hours propylthiouracil in the treatment ofhyperthyroidism. South Med J 88:973–976

20. Kallner G, Vitols S, LjunggrenJG1996 Comparison of standardized initialdoses of two antithyroid drugs in the treatment of Graves' disease. J Intern Med239:525–529

21. Homsanit M, Sriussadaporn S, Vannasaeng S, Peerapatdit T, NitiyanantW,VichayanratA2001 Efficacy of single daily dosage of methimazole vs. propylthiouracilin the induction of euthyroidism. Clin Endocrinol (Oxf) 54:385–390

22. He CT, Hsieh AT, Pei D, Hung YJ, Wu LY, Yang TC, Lian WC, Huang WS,Kuo SW2004 Comparison of single daily dose of methimazole and propylthiouracilin the treatment of Graves' hyperthyroidism. Clin Endocrinol (Oxf)60:676–681

23. Benker G, Vitti P, Kahaly G, Raue F, Tegler L, Hirche H, Reinwein D 1995Response to methimazole in Graves' disease. The European Multicenter StudyGroup. Clin Endocrinol (Oxf) 43:257–263.

24. Page SR, Sheard CE, Herbert M, Hopton M, Jeffcoate WJ1996 A comparisonof 20 or 40 mg per day of carbimazole in the initial treatment of hyperthyroidism.Clin Endocrinol (Oxf) 45:511–516

25. Reed Larsen P, Davies TF, Hay ID**.** 1998 The thyroid gland. In: Wilson JD,Foster DW, Kronenberg HM, Reed Larsen P, eds. Williams textbook of endocrinology.Philadelphia: Saunders; 389–516.

26. Vitti P, Rago T, Chiovato L, et al.1997 Clinical features of patients withGraves' disease undergoing remission after antithyroid drug treatment. Thyroid.7:369 –375.

27. Yamada T, Aizawa T, Koizumi Y, Komiya I, Ichikawa K, Hashizume K**.** 1994 Age relatedtherapeutic response to antithyroid drug in patients with hyperthyroid Graves' disease. J Am Geriatr Soc. 42:513–516.

28. Schleusener H, Schwander J, Fischer C, et al**.** 1989 Prospective multicenter study on the prediction of relapse after antithyroid drug treatment in patientswith Graves' disease. Acta Endocrinol (Copenh). 120:689 –701.

29. Winsa B, Anders Dahlberg P, Jansson R, Agren H, Anders Karlsson F**.** 1990, Factors influencing the outcome of thyrostatic drug therapy in Graves' disease.Acta Endocrinol (Copenh). 122:622–728.

30. Laurberg P, Hansen PEB, Iversen E, Jensen SE, Weeke J.1986 Goitre size andOutcome of medical treatment of Graves' disease. Acta Endocrinol (Copenh).111:39–43.

31. Benker G, Reinwein D, Kahaly G, et al.1998 Is there a methimazole dose effecton remission rate in Graves' disease? Results from a long-term prospectivestudy. Clin Endocrinol (Oxf). 49:451– 457.

32. Schleusener H, Scwander J, Holl G, et al.1987 Do HLA Dr-typing andmeasurement of TSH-receptor antibodies help in the prediction of the clinicalcourse of Graves' thyrotoxicosis after antithyroid treatment. Acta Endocrinol(Copenh). 281:318 –324.

33. Kahaly GJ, Bartalena L, Hegedus L: The American ThyroidAssociation/AmericanAssociation of Clinical Endocrinologistsguidelines for hyperthyroidism and othercausesofthyrotoxicosis: a European perspective. Thyroid 2011; 21: 585–591

34. Emiliano AB, Governale L, Parks M, CooperDS: Shifts in propylthiouracil and methimazoleprescribing practices: antithyroid drug use in the United States from 1991 to 2008. JClin Endocrinol Metab 2010; 95: 2227–2233.

35. Brito JP, Schilz S, Singh Ospina N, Rodriguez- Gutierrez R, Maraka S, SangaralinghamLR,Montori VM: Antithyroid drugs – the mostcommon treatment for Graves' disease in theUnitedStates: a nationwide population-based study. Thyroid 2016; 26: 1144–1145

36. 36.Gebreyohannes E et al. Normalization of thyroid function tests among thyrotoxicosis patients attending a University Hospital in North-West Ethiopia. Thyroid Res,3 (2019).

37. KahalyGJ et al. Management of Graves' Hyperthyroid.Eur Thyroid J. 2018; 7:16-186.

38. Allahabadia A et al. Age and Gender predict the outcome of treatment for Graves' Hyperthyroidism. The Journal of Clinical Endocrinology & Metabolism. 2000; Vol 85: No. 3.

39. Andersohn F, Konzen C, Garbe E 2007 Systematic review:agranulocytosis induced bynonchemotherapy drugs. Ann Intern Med 146:657–665.

40. Meyer-Gessner M, Benker G, Lederbogen S, OlbrichtT,Reinwein D 1994 Antithyroid drug-induced agranulocytosis:clinical experience with ten patients treated at one institutionand review of the literature. J Endocrinol Invest 17:29–36.

41. Siu CW, Yeung CY, Lau CP, Kung AW&Tse HF. Incidence, clinicalcharacteristicsandoutcome of congestive heart failure as theinitial presentation in patients with primaryhyperthyroidism.Heart 2007 93 483–487

42. Frost L, Vestergaard P &Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Archives of Internal Medicine

43. Hailu AberaMulatu.Pattern and Presentation of Thyro-Cardiac Disease among patients with Hyperthyroidsim Attending a Tertiary Hospital in Ethiopia: A Cross Sectional Study. Ethiop J Health Sci.2018:29(1):887

44. .Martin S, Sirbu A, Albu A, Barbu CB, Florea S, Boscaiu V, Fica S. The time to thyroid-stimulating hormone recovery during medical treatment in graves'disease & autonomous hyperthyroidism. Acta Endocrinol. 2013;9(3).

45. Tagami T, Yambe Y, Tanaka T, Tanaka T, Ogo A, Yoshizumi H, Kaise K,Higashi K, Tanabe M, Shimazu S, Usui T. Short-term effects of β-adrenergicantagonists and methimazole in new-onset thyrotoxicosis caused byGraves' disease. Intern Med. 2012;51(17):2285–90.

10. ANNEX

10.1 INFORMED CONSENT FORM

Study Title: Treatment outcomes and associated factors among patients with Thyrotoxicosis who are having follow up at JMC

Principal Investigator: Adem Muktar (MD,Internal Medicine Resident)

Organization: Jimma University, Institute of Health Sciences

Sponsor: Jimma University, Institute of Health Sciences

Purpose of the Research Project: The aim of this study is to determine the treatment out comes and associated factors among patients with Thyrotoxicosis who are having follow up at JMC

Procedure: The study involves patients with Thyrotoxicosis who are on follow up at chronic illness clinic. Trained hospital staff Clinical nurses, and residents were included for this purpose.

Benefits, Risk and /or Discomfort: There is no risk from being involved in the study as there will not be any invasive procedure and patients may benefit from this project if results suggest need for further investigation or follow up.

Incentives/Payments for Participating: The participants will be provided 40 ETB for compensation of time they spend

Confidentiality: The personal information collected from the individual participants will be kept confidential and stored in a file, without their names by assigning a code number to it.

Right to Refusal or Withdraw: Participants have the full right to refuse participating and withdraw at any time from this research.

Person to contact: This research project will be reviewed and approved by the ethical review committee of Jimma University. If you have any question, you can contact the following principal investigator at any time. **Dr.Adem Muktar** (Internal medicine Resident) Tel No – 0910613495, Email address: ademmuktar444.@gmail.com

10.2. INFORMATION TO THE PARTICIPANT

Interview code no _____

Greeting self-introduction and consent, Good morning/afternoon.

My name is Dr. Adem Muktar We are conducting a scientific research to determine the treatment out comes and associated factors among patients with Thyrotoxicosis who are having follow up at chronic follow up clinic at JMC. Therefore, I am happy to inform you that you are selected as one of the participants in this study. By participating in this research project, you may feel some discomfort in wasting your time. However, your participation is definitely important in identifying patterns of treatment outcome and factors associated with it in patients with Thyrotoxicosis in our hospital. The interview may take 20-25 minutes and the information gathered will be used for writing a research paper for partial fulfilment of a specialty certificate in Internal Medicine at Jimma University

Here, I want to assure you that any information obtained from you will remain confidential and even there is no need of writing your names or any personally identifiable information. There is no risk or direct benefit in participating in this research project. Your participation is determined only by you. It is only if you are willing, I will proceed to ask you some information. Finally, you are kindly requested to give your genuine response in the interview

Certificate of Consent

Do you wish to participate in the study? A. Yes B. No If the participant agrees to participate in the study, let him/her to sign consent and proceed with interview. I have adequate information about the research and I have decided to participate in the study.

Signature ----------If the participant says "No, I don't want to participate in the study", thank him (her) and proceed to the next participant

Name of interviewer: _____Date_____/_____/____

GucaittiinEyyemamootahuugaafatan(AfaanOromoo)

Odeffannoohirmaattotaaf

Laakkofsaaddaaaf-gaaffii_____

Akkambultan/akkamooltan?

Maqaankoo Dr. Adam MukaataarinjedhamaAnisbarataadhibeekeessaa"Internal Medicine" waggaasadaffaati.NutisqorannoowaayaalaafiBu'aayaalaanboodaaNammotaucubamormaahormooniihammaaolmaddisissisuqabaniifihordooffiihospitaalameedikaalaajimmaattiqabairrattixiyyeeffata.Anisqorannooqorannookanakeessattiakkahirmaattuuffilatamuukeessangammachuuninisiniifibsa.

Afgaaffinkunhangadaqiiqaa20fudhataakkasumasodeefanoonnutiisinirraaguurrannuiccitiidhaanqabameekanturuyootahuqorannookanakeessattihirmaachuuykndhiisuunbu'aaaddattiyknmiidhaaisinirraangahuhinqabu.Qorannoookanakeessattihirmaachuunguutummaaguutuuttifedhiikeessanirrattikanhundaa'edha.Odeeffannon/Ragaannutiisinirraafudhannuwaraqaaeebbaadigiriilammafaabarumsdhibeekeessaa"Internal medicine speciality certificate" ittiinargachuufkanbarreefamudha.

Qorannookanarrattihimaachuuffedhiiqabduuree?

A.Eeyyee_____ B.Lakki_____

Yoohirmaachuuuffedhaqabaattanmallattookeessaniinnuufmirkaneessaa!

Mallattoo_____

MaqaanamaAf-gaaffiigeggeessee_____

Guyyaa _____/_____/_____

10.3. QUESTIONNAIRE

Data Collection instrument on Treatment outcomes and associated factors among patients with Thyrotoxicosis who are on treatment and having follow up at JMC.

Part one general characteristic –please circle the right answer

Card no…….

1. **Age…….**yrs

2. **Sex**

   1. Male 2. Female

3. **Ethnicity**

   1.Oromo 4.Tigre

   2.Amhara 5. Others (specify)…….

   3.Kaffa/Dawuro

4. **Religion**

   1.Orthodox 4.Wakefata

   2.Muslim 5.Others (specify)……

   3.Protestant

5. **Marital status**

   1. Single 3. Divorced

   2. Married 4. Widowed

6. **Residence**

   1. Rural 2. Urban

7. **Education**

   1. No formal education 4. Secondary(9-12)

   2. Able to write and read 5.University/College and above

   3. Primary (grade 1-8)

8. **Occupation**

   1. Student 4. Merchant (business man/woman)

   2. Farmer 5. Unemployed

   3. Government employee 6. Daily labor

7. House wife 8. Other (Specify)……

9. Monthly income in ETB(converted from 2020 World Bank category)

1. <3,1000(low) 3.12,100-37,600(high middle)
2. 3,100-12,100(low middle) 4.>37,600(high)

Part two:Clinical characteristics of the participants

10.Duration of Thyrotoxicosis diagnosis in months …….

11.Duration of symptoms before diagnosis in months …….

12.Baseline FT4

1. Less than 7 ng/dl or < 90 pmol/liter
2. Greater than 7 ng/dl or >90 pmol/liter

13.Baseline FT3

1. > 5 pg/ml 2. <5 pg/ml

14.Etiologies of thyrotoxicosis

1. GD 4. Toxic adenoma
2. TMNG 5. Other specify
3. Thyroiditis

15.World health organization (WHO) goiter size

1. Grade 0: The goiter is not palpable or visible even when the neck is extended
2. Grade 1: The goiter is detected on palpation and/or visible when the neck is extended
3. Grade 2: Goiter is visible when neck is in the normal position
4. Grade 3: Large goiter visible from distance.

16.Follow up in the clinic (in Years) ……

17.Complications of Thyrotoxicosis 1. Yes 2. No

1. If yes to question no. 17 what is it?
   1. CHF 2. AF

3. CHF+AF
4. Thyroid storm
5. Other (specify)……

18. Time since normalization of TFTs

1. < 3 month
2. 3 -6 month
3. > 1 years
4. >2 years

Part 3: Medication experience of participants

19.Time on ATDs (in Years) ……

20.Experienced drug side effect

1. GI intolerance
2. Rash
3. Arthalgia
4. Hepato toxicity
5. Agranulocytocis

21.Are you taking the drugs as exactly as your physician has ordered? 1. Yes 2. No

22.If no, to question no.21 why?

a. Forget fullness
b. Inconvenient work schedule
c. Unaffordability
d. Don't believe in the medication
e. Poor relationship between patient and physician
f. Irregular or poor drug supply
g. Drugs are too many
h. Long distance from treatment setting

Part 4. Assessment of adherence

Moinisky Medication AdhereenceScale(MMAS-8)			
No	**Question**	**Response**	
		Yes	**No**
1	Do you sometimes forget to take your pills?		
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?		
3	Have you ever cut back or stopped taking your medicine		

	without telling your doctor because you felt worse when you took it?		
4	When you travel or leave home, do you sometimes forget to bring along your medicine?		
5	Did you take all your medicine yesterday?		
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
8	How often do you have difficulty remembering to take all your medicine? Never/rarely B. Once in a while C. Sometimes D. Usually E. All the time		
Final score…….			

Thank you very much !

Name and signature of data collector

Name and signature of principal investigator

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Faculty of Public Health in effect at the time of grant is forwarded as the result of this application.

Name of the student: Adem Muktar (MD)

Date. _____ Signature _____

APPROVAL OF THE ADVISORS

Name of the first advisor: Dr. Kedir Negesso (MD, Internist)

Dr. Gobeze Tefera T(MD, Internist)

Date_____ Signature_____

Name of the second advisor: Mr. Fasil Tessema (MPH)

Date_____ Signature_____