PREVALENCE AND CLINICAL CHARACTERSTICS OF THYROID EYE DISEASE AMONG GOITER PATIENTS ATTENDED JIMMA UNIVERSITY MEDICAL CENTER SURGICAL REFERRAL CLINIC, JIMMA, ETHIOPIA

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PREVALENCE OF THYROID EYE DISEASE AMONG GOITER PATIENTS ATTENDED JUMC SURGICAL REFERRAL CLINIC

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Abstract

Background: - Graves' disease is a common autoimmune endocrine disorder characterized by thyroid hyperplasia and excessive thyroid hormone production. Thyroid eye disease results from infiltration of the orbit by auto-reactive T-lymphocytes, proliferation of orbital fibroblasts and increased orbital fat, leading to its clinical features. But the studies done on the prevalence and associated clinical features of TED are so limited.

Objective: - The main objective of the study was to assess the prevalence of TED and clinical characterstics of TED among goiter patients seen JUMC surgical referral clinic from April to July, 2018.

Methods: - Institution based cross-sectional study was carried out among 211 patients seen in JUMC surgical referral clinic from April – July 2018. Patients selected using systematic random sampling technique and structured questionnaire was used to collect data. The collected data was coded and entered into Epi data version 3.1 and analyzed using SPSS version 20. Descriptive and bivariate analyses were done and all variables having a p-value of less than 0.25 were selected for multivariable analyses. Multivariable logistic regression models were used to isolate independent predictors of Thyroid eye disease. Data was presented using tables and graphs.

Results: - Out of 211 goiter patients seen at Jimma university medical center surgical referral clinic over the 3 month study period; 27% of them were found to have thyroid eye disease. Regarding the ocular symptoms, tearing was the leading compliant of the patients followed by gritting sensation, double vision and eye pain. Among the signs of thyroid eye disease observed; lid retraction was the most frequently observed while proptosis was found only in one case and there was no exposure kerathopathy or dysthyroid optic neuropathy found.

The factors that had statistically significant association with the prevalence of thyroid eye disease were thyroid dysfunction (AOR=2.781, [95% CI 1.362, 5.678] P=0.005), smoking (AOR = 6.391, [95% CI 1.868, 21.860] P = 0.003), high blood pressure (AOR = 2.062, 95% CI 1.001 – 4.251] P = 0.050) and pulse rate (AOR=2.277[95% CI 1.003, 5.167] P=0.049).

Conclusion and recommendations: - Thyroid eye disease among goiter patients is common and there are many patients having follow up for goiter. So, we have to educate the patients and the physicians to link them to ophthalmology for detail eye examination.

Key words: - proptosis, grave's disease, thyroid eye disease

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LIST OF ABBREVIATIONS AND ACRONIUMS

CT: - Computed tomography

DON: - Dysthyroid optic neuropathy

EOM: - Extra ocular muscles

EUGOGO: - Europian group on graves ophthalmopathy

GD: - Graves' disease

GO: - graves ophthalmopathy

SPSS: - Statistical Package for the Social Sciences

TED: - Thyroid eye disease

TAO: - Thyroid associated ophthalmopathy

TFT: - Thyroid function test

TSH: - Thyroid stimulating hormone

TSHR: - Thyroid stimulating hormone receptor

VA: - visual acuity

Chapter I: - Introduction

1.1. Background

Graves' disease (GD) is characterized by thyroid hyperplasia and excessive thyroid hormone production due to autoimmune endocrine disorder (1).

It involves not only the thyroid gland but also has signs in different parts of the body. The clinical manifestations include one or more of features like, thyrotoxicosis, goiter, exophthalmos and pretibial myxedema. Eye involvement is the most common extra-thyroidal manifestation of GD. The relationship between exophthalmos and thyroid disease was first recognized by the Iranian scientist Sayyid Ismail Al-Jurjani in the 12th century (2, 3).

The aetiopathogenesis of the eye disease associated with Graves' disease is not fully known. It has varied clinical presentations; some features being more sight-threatening than others. Due to this, different names were given for the condition based on its clinical features, by its relation to Graves' disease and also just in its relation to thyroid hormone (4).

According to the Europian group on graves ophthalmopathy (EUGOGO) meeting decision, the term Graves' orbitopathy (GO) is an accurate reflection of the condition in the majority of patients. It does usually occur in the context of Graves' disease although there are exceptions. It does involve contents of the orbit so that it is reasonable to use the term orbitopathy. However, it could be in the mild form of the condition, where the symptoms and signs are predominantly related to periorbital soft tissues, the term orbitopathy may be a misnomer while thyroid eye disease is more widely explanatory (4).

Graves' disease is a disease of autoimmunity, which is characterized by the presence of antibodies directed against thyroid tissue antigens; but the final cause of autoimmunity remains unclear. The antibodies act as agonists and stimulate the thyroid gland for secretion. In active Graves' disease, T- lymphocyte suppressor cell function and also the cell number will be reduced. An abnormality in the control of autoimmune responses is suspected to be present in this disease. This in turn results in the production of high levels of autoantibodies that stimulate the thyroid causing thyroid damage and cell death (5).

Thyroid eye disease is caused by infiltration of the orbit by auto-reactive T-lymphocytes resulting in proliferation of orbital fibroblasts and increased orbital fat. Clinically recognizable GO occurs in about 25-50 smoking cases of GD in Caucasians and may be sight-threatening in 3-55% (2, 3).

The onset of TAO may not coincide with the onset of the hyperthyroid state but about 80% of cases occur in association with hyperthyroidism. TAO may present before the onset of thyroid dysfunction, when the patient is euthyroid, or during thyroid dysfunction. A study done in Europe on the temporal relationship between the onset of Graves' hyperthyroidism and the onset of Graves' ophthalmopathy in 99 patients, has showed 80% of cases of GO occurred in association with hyperthyroidism although not all coincide with the onset of hyperthyroid symptoms. Similar data have also been found by the Pisa group (6). Similar data have also been found by the Pisa group in a pooled analysis and over 40% of graves patients developed orbitopathy after the onset of hyperthyroidism while 5-10% of patients developed GO in the absence of hyperthyroidism (7).

Five to ten percent of patients called euthyroid TAO, do not develop hyperthyroidism but initially they present with manifestations of TAO and 10% of TAO patients have primary autoimmune hypothyroidism(3).

Eyelid retraction is the most frequent sign in TAO. It affects 90–98% of patients and frequently varies with attentive gaze. The other signs like, proptosis, eyelid edema and erythema results due to inflammation and secondary GAG deposition. In the muscles, this leads to dysfunction due to failure of relaxation limiting movement, causing diplopia. Orbital swelling at the apex can cause pressure on the optic nerve leading to DON (3).

Among different imaging techniques for evaluating GO, Computed tomography (CT) is the most commonly utilized. It can show muscle belly enlargement that spares the tendinous insertions, an increase in orbital fat volume and crowding of the optic nerve at the orbital apex (8).

Currently, therapeutic options include corticosteroids, external beam radiation and steroid-sparing immunosuppressive agents for reducing the inflammation during active disease, and surgery for correcting the residual abnormalities secondary to fibrosis in the inactive state of the disease. There are no effective means of preventing the disease or reliably altering its course. These interventions do not target the cause of TAO rather they are aimed at the prevention of consequences of the disease. They also do not reverse the pathological changes in the orbital tissues (4).

This study has assessed the prevalence of TED and associated factors among goiter patients seen in JUSH surgical referral clinic from April up to July 2018, to be used as a baseline data for further researchers and to forward recommendations for each concerned body based on the results.

1.2. Statement of the problem

The distribution of Graves' disease around the globe, so far as data is available, appears to be relatively equal, affecting all countries and races. The incidence of Grave's disease is reported in recent studies to be 1 to 2 cases per 1,000 populations per year in England. This rate is considerably higher than the rate of about 0.3 cases per 1,000 previous reports (4).

Grave's disease is the most common cause of hyperthyroidism, with an annual incidence of 20 to 50 cases per 100,000 persons. The incidence peaks between 30 and 50 years of age, but people can be affected at any age. The lifetime risk is 3% for women and 0.5% for men. It is more common in whites than in Asians. Severe ophthalmopathy is more likely to develop in older men than in younger persons (5). The annual incidence of Graves' ophthalmopathy is 16 cases per 100,000 women and 3 cases per 100,000 men. Clinically consequential ophthalmopathy is detected in up to 50% of patients with Graves' disease, and it threatens sight as a consequence of corneal breakdown or optic neuropathy in 3 to 5% of such patients (9).

In Europe the prevalence of GO seems to have declined in recent years, as well as that of the more severe expression of eye disease. Review of the clinical records of the first consecutive patients diagnosed at the same eye clinic in 1960 and 1990 showed a significant decrease of clinically relevant ophthalmopathy from 57% in 1960 to 37% in 1990 (4). This trend might be related to both an earlier diagnosis (facilitated by the introduction of sensitive assays of TSH in the late 1980s) and treatment by the endocrinologists as well as an enhanced attention of the ophthalmologists to the link between the initial ocular manifestations and thyroid dysfunction. Alternatively, smoking behaviour might be involved. In an international survey on the current management of GO, most respondents from Western European countries thought that the prevalence of GO has declined over the last decade, in line with the decreased prevalence of smoking. Conversely, respondents who considered that the prevalence of GO increased originated from countries such as Poland and Hungary, where the prevalence of smoking had increased since 1989 (5).

The prevalence of GO in Asians with hyperthyroidism was noted to be 35% to 60% occurring more frequently among patients aged between 30 and 49 years (6).

The incidence of TED is 16 per 100,000 females and 2.9 per 100,000 males with an approximate prevalence of 0.25% with no significant ethnic predisposition (10). The higher preponderance in females relates to the higher incidence of hyperthyroidism in females. However, for severe TED, the ratio of females to males reverses to approximately 1:4 (11).

The age-adjusted incidence was 16 cases per 100 000 population per year for females and 2.9 cases per 100 000 population per year for males. The peak incidence rates were bimodal, occurring in age groups 40–44 years and 60–64 years in females and 45–49 years and 65–69 years in males (12).

Ethnicity is likely to play an important role in the development of GO (4, 7 and 8). In a study of 155 patients with GD (116 European, 39 Indian), patients of European descent had a 6.4 times higher risk of GO compared to Indians.

Environmental factors that may incite the immune response of Graves' disease; Pregnancy, particularly the postpartum period; Iodide excess, particularly in geographic areas of iodide deficiency. Lithium therapy, perhaps by modifying immune responsiveness; Viral or bacterial infections (yersinia enterocolitica), Glucocorticoid withdrawal. Smoking is a minor risk factor for Graves' disease and a major risk factor for the development of ophthalmopathy (6, 7 and 8).

Stress may trigger an episode of Graves' disease, but there is no evidence to support this hypothesis, presumably operating through neuroendocrine effects on the immune system.

The presentation of GO also varies in different ethnic groups. Upper eyelid retraction and soft tissue involvement are reported as the commonest manifestations in Caucasians, in contrast to increased risk of exophthalmos and lower lid retraction in Asians (10, 11 & 12).

In relation to hyperthyroidism, GO may present well before the onset of thyroid dysfunction, during thyroid dysfunction or when the patient is euthyroid following therapy (15).

Thyroid eye disease is characterized by various clinical features. Inflammatory reactions to the orbital and periocular tissues cause discomfort and pain and also result in eyelid malposition and exophthalmos, distorting self-image and provoking psychological or social problems. Extraocular muscle changes lead to more serious complications, such as strabismus or visual disturbances. The activity and severity of thyroid eye disease is diverse as well (16).

General health-related quality of life is markedly impaired in patients with GO and could be even worse than in patients with other chronic conditions such as diabetes, emphysema or heart failure (17). Graves’ disease has adverse effects on quality of life, as a consequence of somatic and psychiatric symptoms and an inability to work and is associated with an increased risk of death (18).

Evaluation of the prevalence and epidemiologic characteristics of GO in goiter patients will help to have a better decision on their management and counseling patients to

increase their quality of life. Despite these facts, the information regarding the prevalence, risk factors and severity of GO in Africa and also in Ethiopia is deficient.

Regarding our study area there is no previous study done on prevalence of thyroid eye disease among goiter patients. This study will help by being base line information for further researchers and also for the physicians to take thyroid eye disease into consideration while following their patients.

1.3. Significance of the study

The findings of this research have showed that the burden of thyroid associated eye disease in JUSH is high. Early detection of the disease was not practiced proportionately as the number of goiter patients being followed, although it was important and not difficult. Inter departmental communication is needed as patients should be followed for the goiter, thyroid dysfunction and thyroid eye disease. This study has showed a way how physicians working in JUSH or in other health centers have to give concern for thyroid eye disease and follow goiter patients accordingly. Since there is shortage of data regarding epidemiology of the disease in the study area, this data can be used as a baseline data for further studies and development of action plan for the hospital and regional health bureau.

Chapter II: - Literature review

In 152 newly referred GO patients from 8 EUGOGO centers, the mean age of GO patients was 49 years (19). Graves' ophthalmopathy, like Graves' hyperthyroidism, is more common in women than in men. The female to male ratio was 9.3 in patients with mild ophthalmopathy, 3.2 in those with moderate ophthalmopathy, and 1.4 with severe ophthalmopathy. A sex-related difference in the severity of GO has also been noted, with men comprising a relatively greater proportion of cases of severe ophthalmopathy. Eye disease tends to be more severe in older patients and in men. The reason for this effect of gender is not clear but the higher prevalence of smoking among men likely plays a role.

The prevalence and risk factors for Thyroid Eye Disease was studied in dysthyroid Korean patients. All dysthyroid patients who visited endocrinology clinics in 24 general hospitals in Korea during a chosen one-week period were enrolled in this cross-sectional study. Data were collected during an interviewer-administered questionnaire and chart review. Demographic data, lifestyle risk factors, and status of thyroid disease variables were analyzed as risk factors using multivariable regression models to identify independent associations with thyroid eye disease. The relationship between demographic data, lifestyle risk factors, and status of thyroid disease and thyroid eye disease (20).

To determine the risk factors associated with activity and severity of GO among adults; a cross-sectional analytical study of 163 adults with Graves' disease (GD) from the outpatient clinics of the Philippine General Hospital was done. Demographics, clinical data, thyrotropin receptor antibody (TRAb) and urine iodine (UIE) levels were obtained. All participants were evaluated for activity and severity of GO by ophthalmologist. The population was composed mostly of females (81%) and nonsmokers (69%). Active GO was found in 8 % and 85% having mild disease. Male sex was associated with severe disease, while elevated TRAb was associated with both active and severe GO. In our setup we can't do the TRAb and the urine iodine level (21).

In China a retrospective study was conducted to identify predictive factors that can be used in screening the healthy subjects who are at high risk of developing Graves' orbitopathy. Among the factors, the incidence of Graves' orbitopathy was significantly higher in patients who were smoker than non-smoker. They have observed that the stress was significantly higher in patients with Graves' orbitopathy than those without the disease. Higher number of patients with Graves' orbitopathy had positive family history of thyroid disease when compared to patients without Graves' orbitopathy. The level of thyroxin (free form), triiodothyronine (free form), thyroid stimulating hormones receptor antibodies, and antiperoxidase antibodies were significantly higher among patients of Graves' orbitopathy when compared to the patients with Graves' diseases without orbitopathy (22).

The prevalence of Graves' ophthalmopathy among patients with Graves'disease in Indian referral center was studied. Upper eyelid retraction was the most common manifestation

54 (83%), followed by exophthalmos 49 (75%) and soft tissue involvement 26 (40%). Extra-ocular muscle involvement 3 (5%) and optic nerve dysfunction 1 (2%) were uncommon. GO was mild in 54 cases (83%), moderate-severe in 10 (15%) and sight-threatening (due to optic nerve dysfunction) in only 1 patient (2%). Most patients 63 (97%) had clinically inactive GO, of whom 32 (49%) had a CAS of 1-2. Only two patients (3%) had active GO with CAS 4 and 5 and required immunosuppressive therapy with systemic steroids (24).

In Southern Australia, there was a study done to assess the risk factors for developing eye disease in patients with Graves' hyperthyroidism. The patients' age, gender, duration of Graves' hyperthyroidism as well as eye disease, family history of Graves' disease, ethnicity and smoking status were studied for their correlation with development of graves' eye disease. Among the study patients, 604 (58%) had Graves' eye disease, while 438 patients did not have eye disease. The proportion of women to men was similar in both patients with Graves' eye disease and without Graves' eye disease. A higher proportion of cases were smokers (59%) and Caucasians (80%). The risk of having Graves' eye disease was two times higher in smokers, as compared with non-smokers. The presence of a family history of Graves' disease and of serum TSH receptor antibodies did not differ between patients with Graves' eye disease and without Graves' eye disease. The risk of Graves' eye disease was 7 times lower in patients treated with anti-thyroid medications than those not receiving anti thyroid treatment. Among the patients with Graves' eye disease, 51 (8%) had dysthyroid optic neuropathy (24).

According to a study done in Mashhad, about 50% of patients with Grave's disease developed GO and severe forms affect 3% to 5% of patients. GO was found to affect females 6 times more frequently than males (86% versus 14% of cases, respectively), but the female: male ratio was reduced to 4:1 in severe forms of eye disease (25).

There was a Pilot study done in Southwestern Nigeria on the ocular signs accompanying thyroid dysfunction in a black African population. Out of 75 patients studied, Two-thirds of them reported ocular symptoms consisting mainly of painless eye swelling (66.7%) and ocular irritation (58%). Conjunctival injection, lid lag and lid retraction were the commonest ocular signs. Chemosis, severe proptosis and ocular motility disorder were very rare. Optic neuropathy was found in 4 patients but was related to pre-existing glaucoma. Majority of patients required only ocular emollients and tear supplements (26).

In Ethiopia there was a prospective study done and evaluated the clinical manifestations, severity, complication and management of Graves' thyroid ophthalmopathy (GTO) in 37 patients. Twenty-seven were females and 10 were males (F:M = 2.7:1). The mean age was 35 years (range 19-70 years). GTO was found in 30 (81.1%) hyperthyroid, 1 (2.7%) hypothyroid and 5 (13.5%) euthyroid patients. Upper lid retraction was the most common clinical finding, being detected in 31 (83.8%) of the patients. One (2.7%) patient had marked extraocular

muscle involvement, involving the inferior rectus muscle of one eye. None of the patients had sight loss from the complications of GTO. As the study included only 37 patients; larger prospective studies are suggested to evaluate both the prevalence and possible racial difference in its clinical presentation (27).

Conceptual framework

The conceptual framework for this study was based on literature that explains the impact of multiple of risk factors for thyroid eye disease as shown on the figure below.

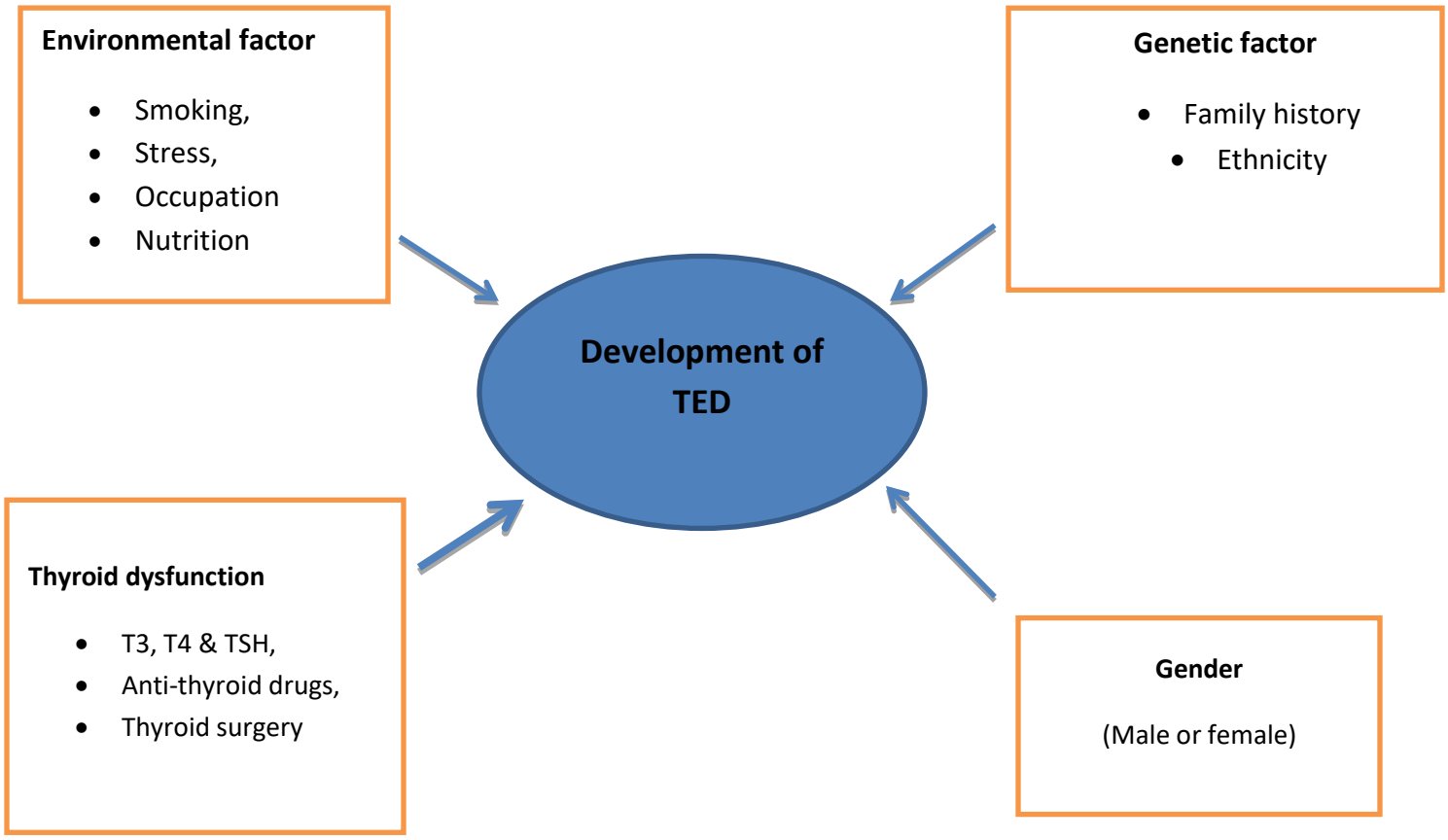

Figure 1: - factors associated with TED

Source: Developed after reviewing literatures

Chapter III: - Objectives of the study

3.1. General objective

To assess the prevalence of TED and clinical characterstics of TED among goiter patients seen JUSH surgical referral clinic from April to July, 2018.

3.2. Specific objectives

- To assess the prevalence of TED among goiter patients seen at surgical referral clinic
- To assess the clinical picture of TED among goiter patients seen at surgical referral clinic
- To identify factors associated with development of TED in goiter patients

Chapter IV: - Methods and material

4.1. Study area and period

4.1.1. Study area

Jimma is located in the southwest of Ethiopia & Western Oromia region, 352 km far from the capital city, Addis Ababa (AA). Jimma town is the administrative center of Jimma Zone and it is one of the commercial centers for south western Ethiopia.

According to Jimma Town Health office, the estimated population of Jimma town for 2009 E.C is 174,778 (Male 87,879 and Female 86,999).
JU was established as a public higher education institution in December 1997in Jimma Institute of Health Sciences by splitting the health section in to two faculties- namely Faculty of Public Health, Faculty of Medical Sciences; and adding two new faculties- namely, Faculty of Business and Economics, and Faculty of Technology, which are the founding organs of the present Jimma University.

Jimma university medical center is the only referral hospital in the southwest Ethiopia providing service for approximately 15000 inpatients and160000 out patients in a year coming from catchment population of about 15 million people. It has a total of 1448 staffs from which 816 are technical and the remaining 587 are supportive staffs.

4.1.2. Study period

The study was conducted from April to July, 2018.

4.2. Study design

Institutional based cross-sectional study was employed on patients attended at surgical referral clinic for goiter.

4.3. Populations

4.3.1. Source population

Patients attended at surgical referral clinic for goiter in JUMC.

4.3.2. Study population

Sample patients selected by systematic random sampling

4.3.3. Study unit

Selected individual Patient

4.4. Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- All goiter patients who attended the surgical referral clinic

4.4.2 Exclusion criteria

- Patients with another known eye disease that had similar presentation with TED like pseudo orbital tumor, optic nerve tumor
- Patients with similar presentation as goiter but had other diagnosis, like cyst, thyroid gland malignancy

4.5. Sample size and sampling technique

Sample size was determined using single population proportion formula as stated below.

$$n = \frac{(Z_{1-\alpha/2})^2 p(1-p)}{d^2}$$

n = minimum sample size,

$Z_{1-\alpha/2}$ = significance level at α =0.05(1.96)

d= margin of error (5%)

P= prevalence thyroid eye disease = 50%

n= 384

Since source population was less than 10,000, using correction formula

$n = \frac{n_o}{1+\frac{n_o}{N}}$, Where: - N= Population size (352)

n = 192 and taking 10% non-response rate n = 211

4.6. Sampling procedure

Systematic random sampling technique was used to get the study population from all goiter patients seen from April up to July, 2018. Non response rate of 10% was used. The previous year record was evaluated and the number of patients seen at surgical referral clinic over 3 consecutive period of time was 352. Sample size was calculated using this number as N and every two patients were selected until the sample size is attained.

$K = N/n = 1.67 = 2$

4.7. Variables of the study

Dependent variable

- Thyroid eye disease

Independent variables

- Socio-demographic factors
  - Age
  - Sex
  - Place of residence
  - Occupation
- Environmental factors
  - Smoking
  - Pregnancy
- Thyroid related factors
  - Thyroid hormone level(T_3, T_4, TSH)
  - Medication use
  - Thyroid surgery

- Genetic factors
  - Family history

4.8. Data collection procedure

Pretested, structured questionnaire was used to collect data. Patients were informed about the research and the socio demographic data were collected by ophthalmic nurse. Factors that contribute to the development or severity of TED like smoking, pregnancy, any use of medication, history of thyroid surgery and thyroid hormone level were assessed.

Systemic manifestations of hyperthyroidism like, hot intolerance, palpitation, tachycardia and pretibial myxedema were checked. Patients were asked if they had experienced double vision, pain in the eye, redness, tearing and foreign body sensation.

Visual acuity was measured in well-lighted class rooms using the Snellen E chart by ophthalmic nurse. Other detail eye examinations like evaluation for lid retraction, lid lag, eyelid and conjunctival edema, proptosis measurement by using Hertel's exophthalmometry, motility examination and corneal evaluation were done by final year ophthalmic resident. Those patients with V/A< 6/9 without TED manifestations were referred to JUDO OPD for further evaluation and management.

4.9. Data analysis:

The data collected was exported to SPSS after entered into Epi data version 3.1. They were cleaned and coded using SPSS version 20.0 for analysis. Descriptive statistics (frequencies and percentages) were computed to show the picture of the data. Statistical tests at 95% CI were made & used for determining the independent predictor variables. Chi-Square tests and binomial multiple regression analysis technique was used to evaluate the differences in the distribution of categorical variables for study groups. The crude and adjusted odds ratios together with their corresponding 95% confidence intervals were computed at a P-value < 0.05.

4.10. Data quality control

Data was double entered into EPI data version 3.1, trained Ophthalmic Nurses and general nurses were involved in the collection of socio-demographic, etc from the patents. Two-day training was given for data collectors regarding study objective, interview techniques, measurements and ethical issues during data collection. Pretest was done among 5% of the total sample size before three days of the actual data collection in order to assess its clarity, length, completeness and consistency, language barriers and contextual gaps on the structured questionnaires. The questionnaires were translated in to Amharic /Afan Oromo to facilitate understanding of the respondents and also they were checked daily for accuracy, consistency, and completeness. The instruments were standardized and checked about their functionality.

4.11. Ethical consideration:

Before starting the research ethical review committee of Jimma University College of Health Sciences has approved this research project. A support letter was obtained from the ethical board of Jimma University College of health sciences and given to the head of Jimma university medical center. Each study participant was informed about the research and reassured that confidentiality of information will be maintained during data collection, analysis, interpretation and publication of results. Patients found to have TAO were referred to JUDO for further management and follow up.

4.12. Operational definitions

Exophthalmos – proptosis secondary to endocrinological dysfunction (15)

Euthyroidism: -TSH = 0.25 - 5 µIU/ml; T3 = 0.9 – 2.33 nmol/L and T4= 60 - 120 nmol/L

Hyperthyroidism: - TSH <0.25 µIU/ml; T3 > 2.33nmol/L and T4 >120nmol/L

Hypothyroidism: - TSH > 0.5 µIU/ml; T3 < 0.9 nmol/L and T4 < 60 nmol/L

Normal B/P: - Less than 120/80 mm Hg (41)

Elevated B/P: - Systolic between 120-129 and diastolic less than 80 (41)

Stage 1 hypertension: - Systolic between 130-139 or diastolic between 80-89 (41)

Stage 2 hypertension: - Systolic at least 140 or diastolic at least 90 mm Hg (41)

Lid lag: - when excursion of the upper eyelid often lags behind eyeball movement on vertical downward pursuit (42)

Lid retraction: - when upper lid margin is covering <2mm of the upper cornea when measured from the upper limbus (42).

Mild retraction: - when the upper lid margin is between -2 – 0 mm (on limbus). The minus sign shows that it is 2mm below the upper limbus (42).

Moderate retraction: - when the upper lid margin is between upper limbus and 2mm above it (0 - +2mm) (42).

Severe retraction: - when the upper lid margin lies above 2mm from the upper limbus (42).

Proptosis: – Anterior displacement of globe (15)

No proptosis: - If the measured distance between lateral orbital margin to corneal apex is between 12–21 mm (15)

Mild proptosis: - when the measured distance between lateral orbital margin to corneal apex is between 21 - 23mm (15)

Moderate proptosis: - when the measured distance between lateral orbital margin to corneal apex is between 24 - 27mm (15).

Severe proptosis: - when the measured distance between lateral orbital margin to corneal apex is ≥ 28 (15)

Smoking: Current or past daily, weekly or occasional consumption of cigarettes (35).

4.13. Dissemination of Findings

The findings of the research will be distributed to Jimma University postgraduate and research study office and other concerned bodies. It will be dispersed by presenting on national ophthalmic association meetings and through a publication in international journals.

Chapter V:- RESULTS

Out of the total 211 participants of the study 196 (92.9%) were females and 15 (7.1%) were males. Most of the study participants were in the age range between 15-30 100(47.4%) followed by age category of 31-45 years - 77(36.5%) **(Table 1)**.

Regarding their place of residence 111(52.6%) of the participants were from urban and the rest were from rural area. Majority of the patients were farmers 102(48.3%) followed by merchants 44(20.9%) and government workers 35(16.6%) **(Table 1)**.

Table 1:- Socio-demographic characteristics of goiter patients seen from April to July 2018

	No. (%)
Sex	
Female	196 (92.9)
Male	15 (7.1)
Age	
15-30	100 (47.4)
31-45	77 (36.5)
>=46	34 (16.1)
Place of residence	
Urban	111 (52.6)
Rural	100 (47.4)
Occupation	
Famer	102 (48.3)
Government employee	35 (16.6)
Merchant	44 (20.9)
Daily Labourer	10 (4.7)
Private business owner	2 (0.9)
Do not have work	18 (8.5)

Out of the 211 patients 134 (63.5%) were using drugs while the rest 77 (36.5%) were not using. Majority of the drug used was PTU (58.3%) followed by thyroxin (3.3%), propranolol (1.4%) and calcium (0.5%) **(Figure 1).**

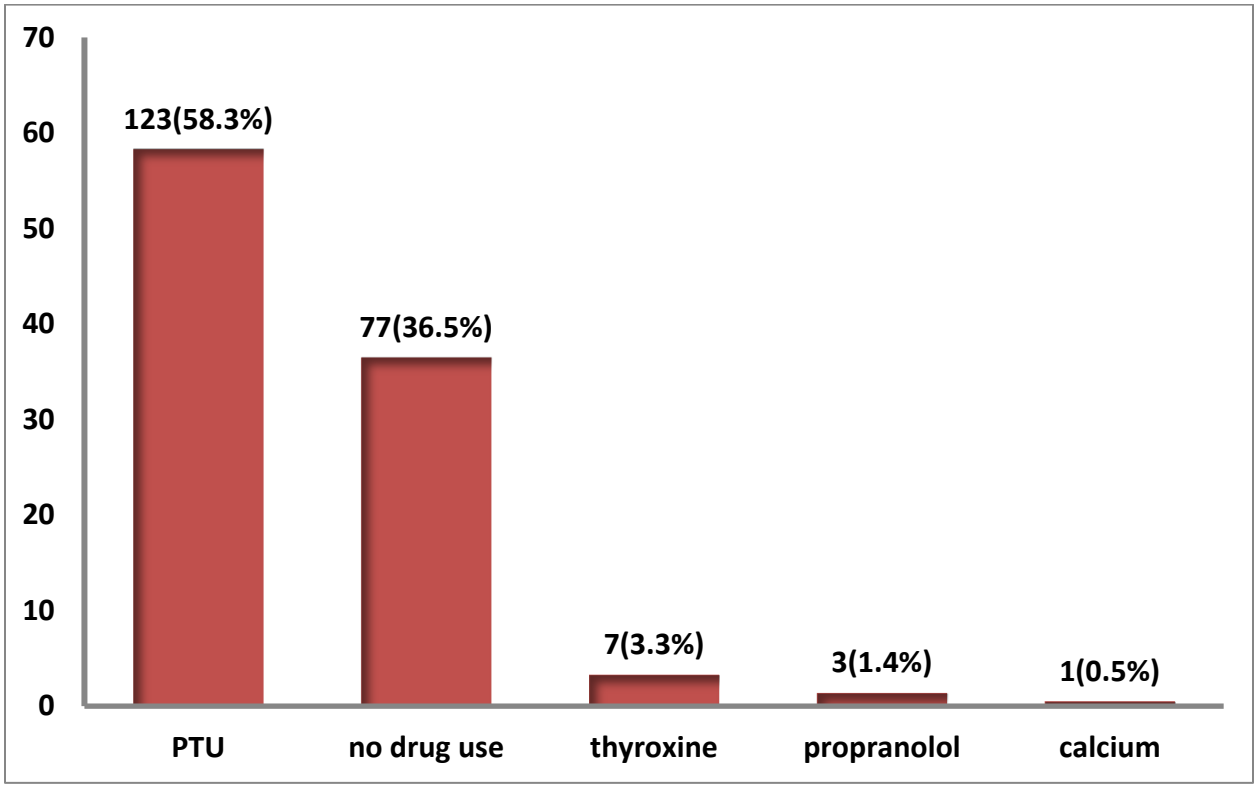

Figure 2: - pattern of drug use among goiter patients seen from April to July 2018

Among a total of 211 goiter patients, 15 (7.1%) had neck surgery for goiter **(figure 2)**.

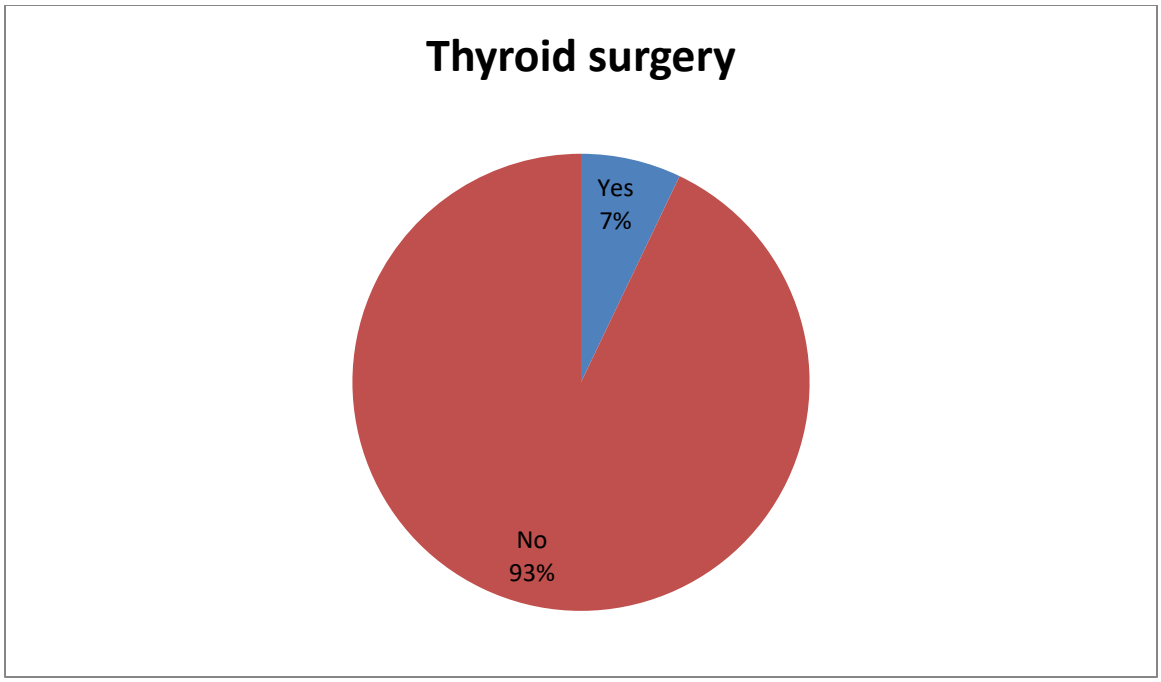

Figure 3: - History of neck surgery of goiter patients seen from April to July 2018

Concerning systemic complaints of goiter patients, shortness of breath was present in 182 (86.3%) patients; palpitation in 177 (83.9%) patients and hot intolerance in 157 (74.4%) patients **(Table 2).**

Regarding the clinical signs, blood pressure level ≥140/90 in 6 (2.8%) of patients and pulse rate above 100 beats/minute in 37(17.5%) patients. Hand trimmer was observed in 30 (14.2%) patients and pretibial edema was present in only 2 patients **(Table 2).**

Table 2: - Systemic symptoms and signs seen among goiter patients from Aprill to Jully 2018

Symptoms	**No (%)**
Shortness of breath	182(86.3%)
Palpitation	177(83.9%)
Hot intolerance	157(74.4%)
Blood pressure	
<= 120/80	132(62.6%)
121-129/80	60(28.4%)
130-139/80-89	13(6.2%)
≥140/90	6(2.8%)
Pulse rate	
60 – 100	174(82.5%)
>100	37(17.5%)
Hand trimmer	30(14.2%)
Pretibial edema	2(.9%)
Total	211

Regarding the presence of anterior neck swelling 193(91.5%) patients had visible anterior neck swelling that moves with swallowing. The rest 18(8.5%) patients had no visible neck swelling and 15(83%) of these patients had previous thyroid surgery **(Table 3)**.

Table 3: - Presence of anterior neck swelling in goiter patients seen from April to July 2018

Anterior neck swelling		
Yes		No
Nodular	Multi nodular	
56 (26.5%)	137 (64.9%)	18(8.5%)

Results of thyroid function test shows; TSH < 0.25 micro IU/ml in 113(53.6%) patients; 0.25 - 5 micro IU/ml in 81(38.4%) patients; >5 micro IU/ml in 12(5.7%) patients.TSH was not recorded in 5(2.4%) patients. T3 was < 0.92 nmol/L in 15(7.1%) patients; 0.92 - 2.33 nmol/L in 82(38.9%) patients; > 2.33 nmol/L in 56(26.5%) and it was not recorded in 58(27.5%) patients. T4 was < 60 nmol/L in 15(7.1%) patients; 60 - 120 nmol/L in 94(44.5%) patients; > 120 nmol/L in 42(19.9%) patients and it was not recorded in 60(28.4%) patients **(Table 4).**

Table 4: - TFT results of goiter patients seen from April to July 2018

TFT results	No (%)
TSH (micro IU/ml)	
< 0.25	113(53.6%)
0.25 - 5	81(38.4%)
>5	12(5.7%)
Not recorded	5(2.4%)
T3 (nmol/L)	
< 0.92	15(7.1%)
0.92 - 2.33	82(38.9%)
> 2.33	56(26.5%)
Not recorded	58(27.5%)
T4 (nmol/L)	
< 60	15(7.1%)
60 - 120	94(44.5%)
> 120	42(19.9%)
Not recorded	60(28.4%)

Based on the above findings on the TFT, majority of the patients were euthyroid 104(49.3%), followed by hyperthyroidism 60(28.4%) and hypothyroidism 17(7.6%) **(Figure 3).**

Among the euthyroid patients 73 (54.5%) were on antithyroid medications while 61(45.5%) were not on drugs.

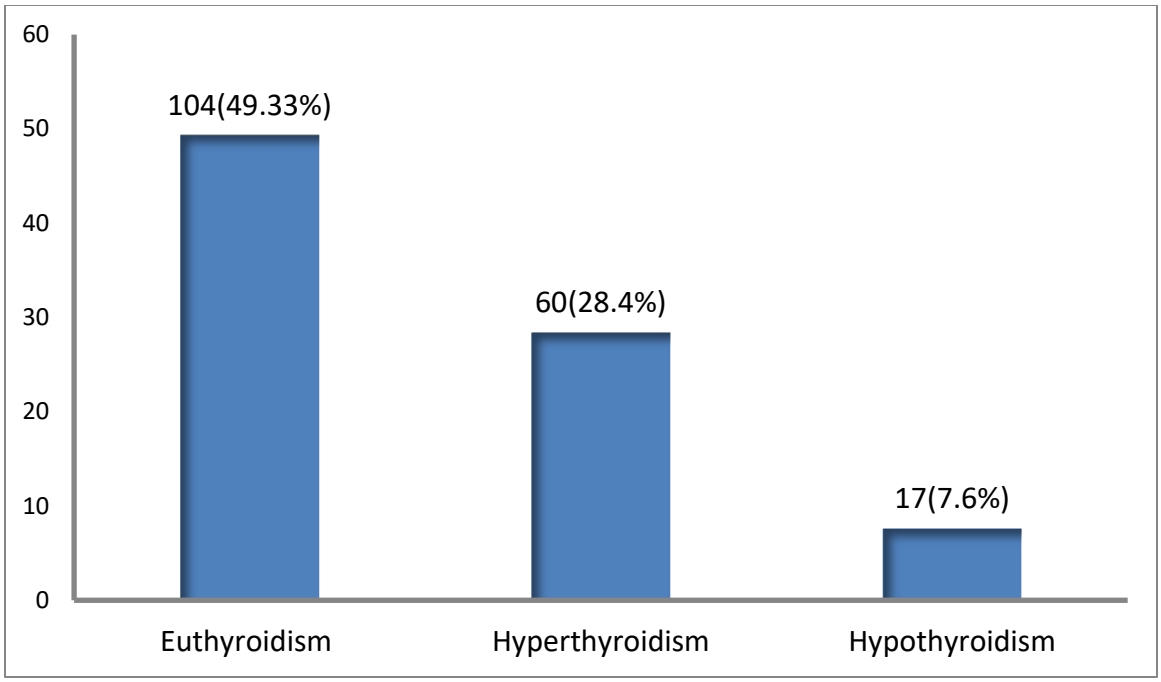

Figure 4: - thyroid function test result of TED patients seen from April to July 2018

The ocular symptoms found in the study subjects were, tearing 21(10%); gritting sensation 12(5.7%) double vision 9(4.3%) and eye pain 7(3.3%) (**Table 5).**

Table 5: - ocular symptoms and signs identified in goiter patients seen from April to July 2018

Ocular symptoms	**No (%)**
Tearing	21(10%)
Gritting sensation	12(5.7%)
Double vision	9(4.3%)
Eye pain	7(3.3%)

Among the 211 goiter patients studied thyroid eye disease was present in 57(27%) goiter patients **(Figure 4).**

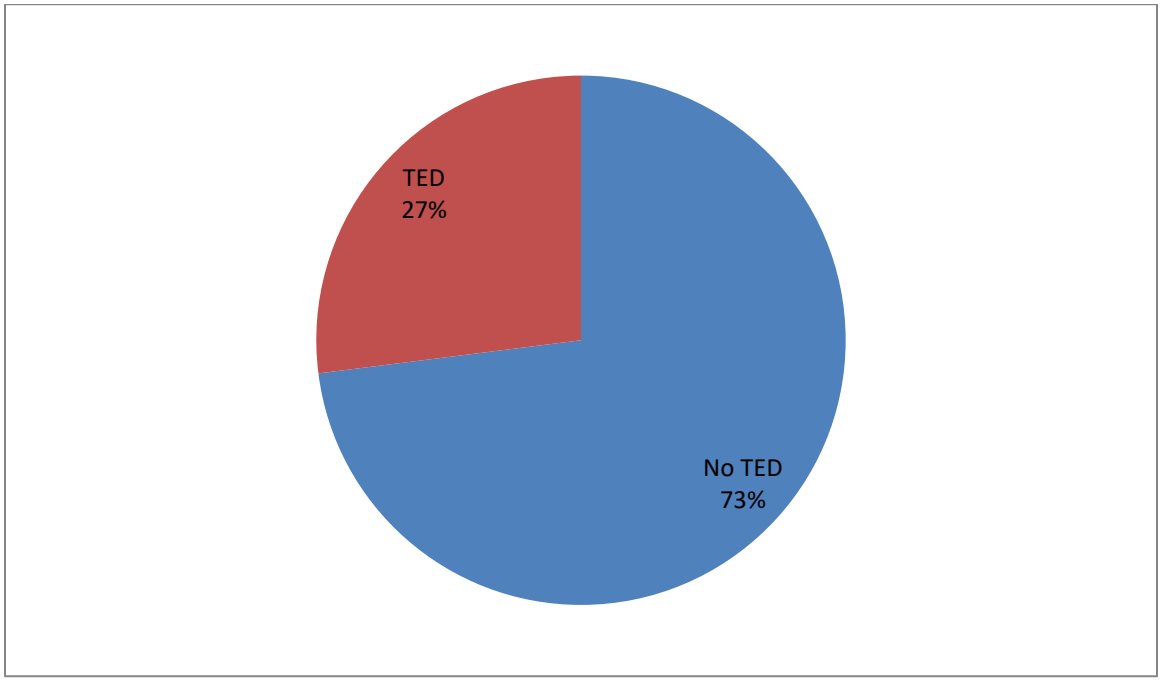

Figure 5: - TED detected among goiter patients seen from April to July 2018

The clinical signs of thyroid eye disease found in the study subjects were; lid retraction in 40 (19%) patients; conjunctival redness in 24 (11.4%) patients; eyelid swelling in 13(6.2 %) patients, lid lag in 5 patients (2.4%) and eyelid erythema in 3(1.4%) patients. There was 1 patient with unilateral proptosis and there was no dysthroid optic nerve dysfunction seen **(Figure 5).**

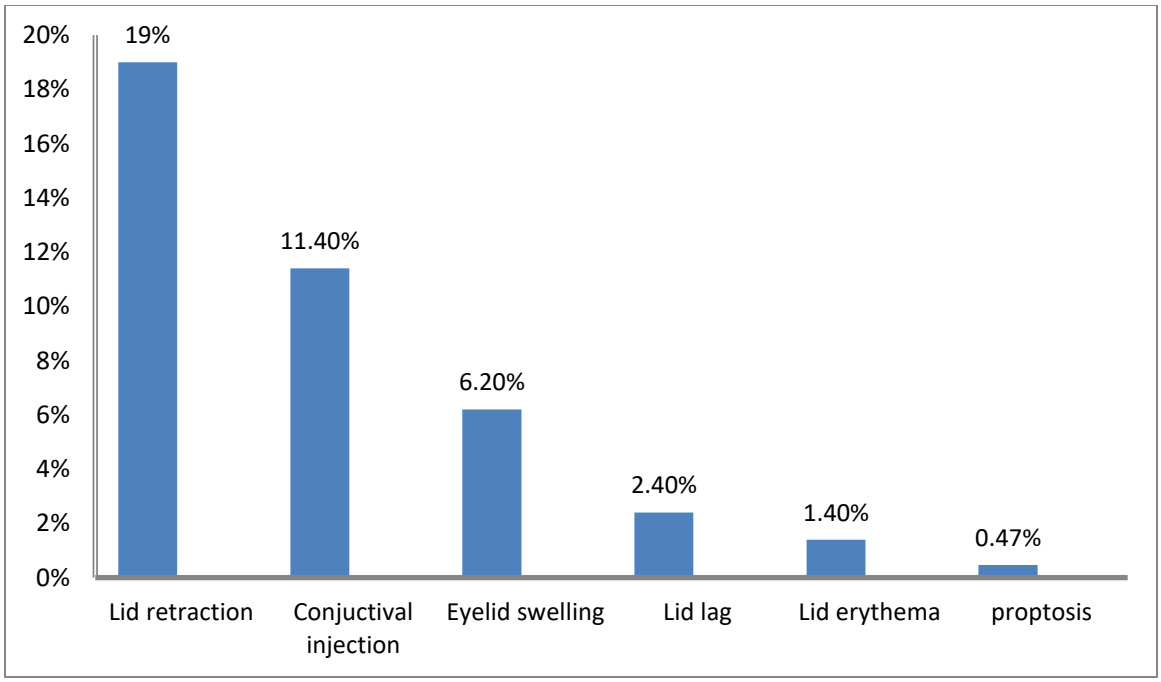

Figure 6: - pattern of clinical features seen in patients diagnosed with TED among goiter patients seen from April to July 2018

Out of the patients with TED, 28(49.1%) were hyperthyroids while 24(42.1%) were euthyroid and 5(8.8%) were hypothyroid.

Among TED patient, 53(93%) were females and 4(7%) were males. While 37(65%) of them had history of use of medication while the rest 20(35%) patients were not using any drug. Among the drugs they took PTU was the major type followed by propranolol, thyroxin and calcium.

Regarding the occupation of TED patients, 25(43.9%) of them were farmers, while 16(28%) of them were merchants and 9(15.8%) of them were government employee. Out of TED patients, 33(57.9%) of them were living in urban While 26(45.6%) were from rural.

On history of cigarrate smoking 13 participants had a history of cigarette smoking. Two were males and the rest 11 were females who were passive smokers. Only one of the men was a past smoker. He has smoked for 10 years and stopped 8 years back. Out of the smokers, 63% of them had signs of TED.

As shown in the table below, the bivariate analysis has showed that cigarrate smoking, thyroid dysfunction and blood pressure were significantly associated (P value <0.05) with the prevalence of TED **(Table 6)**.

Table 6: - Bivariate analysis for factors associated with TED among goiter patients seen from April to July 2018

VARIABLES	TED		COR	95% Confidence Interval		P
	YES	NO		Lower	Upper	
Thyroid surgery						
Yes	1(6.7%)	14(93.3%)	5.600	0.719	43.600	0.100*
No	56(28.6%)	140(71.4%)	.	.	.	.
Sex						
Female	53(27.0%)	143(73.0%)	1.019	0.311	3.340	0.975
Male	4(26.7%)	11(73.3%)	.	.	.	.
Thyroid dysfunction						
Yes	21(43.8%)	27(56.2%)	2.744	1.390	5.415	0.004*
No	36(22.1%)	127(77.9%)	.	.	.	.
BP						
<=120/80	42(31.8%)	90(68.2%)	1.991	1.018	3.895	0.044*
>120/80	15(19.0%)	64(81.0%)	.	.	.	.
Occupation						
Farmer	25(24.5%)	77(75.5%)	0.533	0.187	1.515	0.238*
Government employee	9(25.7%)	26(74.3%)	0.568	0.265	1.218	0.146*
Merchant	16(36.4%)	28(63.6%)	0.606	0.228	1.607	0.314
Others *	7(23.3%)	23(76.7%)	.	.	.	.
Pulse						
60 – 100	43(24.7%)	131(75.3%)	1.854	0.877	3.919	0.106*
>=100	14(37.8%)	23(62.2%)	.	.	.	.
Drugs used						
PTU	35(28.5%)	88(71.5%)	1.212	0.646	2.275	0 .549
Propranolol	1(33.3%)	2(66.7%)	1.524	0.131	17.668	0.736
Others**	21(24.7%)	64(75.3%)	.	.	.	.
Age						
17 – 50years	37(24.2%)	116(75.8%)	0.606	0.315	1.168	0.134*
>= 50years	20(34.5%)	38(65.5%)	.	.	.	.
Place of residence						
Urban	33(29.7%)	78(70.3%)	1.340	0.725	2.474	0.350
Rural	24(24.0%)	76(76.0%)	.	.	.	.
Anterior neck swelling						
Yes	56(29.2%)	136(70.8%)	7.412	0.966	56.863	0.054*
No	1(5.3%)	18(94.7%)				
Cigar rate smoking						
Yes	8(61.5%)	5(38.5%)	4.865	1.521	15.567	0.008*
No	49(24.7%)	49(75.3%)				

***** Candidate variables for multivariable

On multivariate analysis; participants of the study with thyroid hormone dysfunction were three times more likely to develop TED than euthyroid patients, with a P value of 0.005 (AOR= 2.78; 95% CI 1.362, 5.678). Patients with history of cigarrate smoking had 6 times higher risk of developing TED than non-smokers with P value of 0.003 (AOR= 6.391; 95% CI 1.868, 21.860). Participant of the study with high blood pressure had two times higher chance to have TED with P value of 0.050 (AOR = 2.062, 95% CI 1.001 – 4.251]). Patients with high pulse rate were two times more likely to have TED with P value of 0.049 (AOR=2.277[95% CI 1.003, 5.167]) **(Table 7)**.

Table 7: - Multivariable logistic regression model predicting the likelihood of thyroid eye diseases among patients with Goiter, Jimma University Medical Center, 2018

PREDICTORS	THYROID EYE DISEASE		COR	AOR	95% CI		P
	YES	NO			LOWER	UPPER	
Cigarrate smoking							
Yes	8(61.5%)	5(38.5%)	4.865	6.391	1.868	21.860	0.003
No	49(24.7%)	149(75.3%)	1				
Thyroid dysfunction							
Yes	21(43.8%)	27(56.2%)	2.744	2.781	1.362	5.678	0.005
No	36(22.1%)	127(77.9%)	1				
Pulse rate							
60 – 100	43(24.7%)	131(75.3%)	1				
>=100	14(37.8%)	23(62.2%)	1.854	2.277	1.003	5.167	0.049
Blood pressure							
<=120/80	42(31.8%)	90(68.2%)	1				
>120/80	15(19.0%)	64(81.0%)	1.991	2.062	1.001	4.251	0.050

1 = reference Hosmer and Lemeshow goodness-of-fit test = 0.596

Chapter VI: - Discussion

This study has found the prevalence of TED among goiter patients seen at JUSH surgical referral clinic over three month period to be 27%. According to study done in Ghana prevalence of TED among patients with thyroid disorder was higher than our finding (60.30%) (44).The prevalence of TED in our study was lower compared to the prevalence in Malaysia (14) which was 34.7% and in Europe (37.5%) (19). On the other hand, the result was almost similar with the prevalence of thyroid eye disease in India which was 28% (24) and in Korea (21.3%) (20). But, there was a difference in clinical activity and severity of cases. It is possible that the difference in epidemiology and clinical pictures of TED could be related to the low prevalence of smoking in our population or difference in environment or genetic factors. There are genes involved in regulating T cell, which is necessary in autoimmune thyroid disease. These include, the genes for the α-chain of the interleukin-2 receptor (CD25) as well as thyroid specific genes including thyroglobulin (Tg) and the TSHR (43). The similarity of prevalence could be due to similarity in selection of the study population or use of the same criteria to define TED.

As this study tried to show, there was a significant association between the development of TED and thyroid dysfunction. This was a similar result to a study done in Addis Ababa that has showed TED to be diagnosed in 83.8 % of dysthyroid patients and 13.5 % euthyroid patients (27). Also a study done in Nijeria has found that, 78% of patients with TED to be hyperthyroid, 11.8% euthyroid and only 9.8% of patients hypothyroid (19). Although the result has similarity to our study finding, the number of patients having hyperthyroidism was much higher. This could be due to difference in patient selection in which our study participated all goiter patients while the other study involved patients with grave's disease only.

Our study showed that, among patients with TED, 49% of them were hyperthyroids, 42% euthyroids and 8.8% of them were hypothyroids based on TSH, T3 and T4 results. Except few patients (36.5%) the majority of patients (63.5%) were using of antithyroid hormone drug (propylthiouracil). This could increase number of euthyroid and hypothyroid patients making prevaleneof TED among these groups higher than clinically expected. The participant's age at the time of diagnosis, their social habit and their medication use will be the reason for the difference in the thyroid function test results. Also the interpretation for the tests of T3, T4 and TSH vary greatly according to the laboratory's reference range in different countries and regions.

In our study, patients with smoking history had 6 times higher risk for the development of TED compared to those with no smoking history. Similarly, a study conducted in China have shown, 38% of patients with smoking history had prevalence of TED (22). According to a study done in India, the risk of having Graves' eye disease was two times higher in smokers, as compared with non-smokers (24). Europian patients who smoke were found to have a 5 times higher risk of developing TED than those who do not (42). Pryor WA and Stone K proposed that the formation of superoxide radicals and tissue hypoxia may be the underlying pathogenesis. Superoxide radicals can induce orbital fibroblasts from patients with TAO to proliferate and cigarette smoke

either contains or can generate a variety of oxidants and free radicals. In vitro and in vivo studies showed that anti thyroid drugs and antioxidants influence parameters of oxidative stress both in retro orbital tissue and in the whole organism (22).

Concerning the sex as risk factor, our present study showed that prevalence of TED varies by sex with higher proportion of female compared to male with a ratio of 13:1 although statistically it was not significant. The clinical severity didn't show difference among them. In a study that was conducted in Korea the prevalence of TED was high in female with female-to-male ratio of 3.9: 1. Also a study done in Nigeria showed, the prevalence of TED in female to male ratio was 5:1; while in Ghana the male: female ratio was 1:4.45(24 -26). The number of males in our study was minimal and history of smoking was not as high as studies in other areas. This may account for the difference in clinical severity and the criteria for classifying TED into different severity grades could be different.

According to our study, there was statistically significant association with development of TED and high blood pressure. The Kotsis et al study that was published by the Journal of Hypertension in 2007 showed that hyperthyroidism had association high systolic blood pressure and high pulse pressure over a twenty-four-hour period compared with euthyroids (30).

High pulse rate (≥100 beat/min) had statistically significant relation with development of TED with the P value of 0.049. The majority of patients having TED were hyperthyroid. With high amounts of T3 and T4 excreting into the body, this can spike the metabolism rate. In this process, a patient may notice the heart rate increasing rapidly, blood pressure that is elevated, and tremors in the hands and feet (29).

Strength of the study and Limitation of the study

The strength of this study was being the first for such kind of study in this study area. The orther was the use of appropriate instruments for clinical assessment, like, exophthalmometer, snellen chart, torch and rulers in a relatively comfortable room for patient examination.

On the other hand, the limitations that we faced while doing the study includes, inadequacy of laboratory investigation results and lack of orbital imaging to determine extra-ocular muscle involvement.

Chapter VII: - Conclusion and Recommendation

7.1. Conclusion

The prevalence of thyroid eye disease among goiter patients seen in JUMC surgical referral clinic was 27%.

The ocular symptoms identified in goiter patients were; tearing, gritting sensation, double vision and eye pain. The ocular signs of thyroid eye disease observed were; lid retraction, conjunctival injection, eyelid swelling and lid lag.

The factors that had statistically significant association with the prevalence of thyroid eye disease were thyroid dysfunction, smoking, high blood pressure and pulse rate. Other factors clinically taken as risk for development of TED like, sex, drug use and family history were not statistically significant.

7.2. Recommendation

As the results of this research indicated, thyroid eye disease is common in patients who have a follow up for goiter at surgical referral clinic of JUSH. Based on this, my recommendations are;

1. Creating referral linkage with ophthalmology unit

2. Awareness creation of the surgeons, internists who are following to treat or identify and refer the patient

3. Giving health education to patients to

    a. Avoid risk factors like smoking and use their anti-thyroid drugs appropriately
    b. Watch for eye complaints and to be checked by physician early.

4. Conducting further research to assess the severity of TED in the study area

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JIMMA UNIVERSITY

INISTITUTE OF HEALTH, FACULTY OF MEDICAL SCIENCE

DEPARTMENT OF OPHTHALMOLOGY

SPECALITY IN OPHTHALMOLOGY

Information sheet for study participants

I am _____, a physician working in JUDO. Prevalence of TED among goiter patients seen in JUSH. If you are willing we want you to participate in the study. So we are going to ask you some questions concerning your health status and health related conditions, as well as we will do some physical examinations.

The study will not affect your medical care you need to get; there is no obligation in participating in the study. The information obtained from you will be kept confidential and will be used for the research purpose only. You don`t need to state your name. If you agree to participate in the study please answer these questions. You can also leave the research any time you want to leave.

If you have any questions concerning the study you can contact the principal investigators by the address found below.

Name of the principal investigator _____

Address_____

Signature _____

Data collection format

Study of prevalence of TED among goiter patients seen in JUSH

Identification no _____

1. Age
2. Sex male☐ Female ☐
3. Occupation
4. Place of residence
    a. Region
    b. Woreda
    c. Kebele
    d. Urban or rural?
5. Do you smoke cigarate? YES ☐ NO ☐
    a. If yes how many packs per day?
    b. For how long did you smoke?
6. Have you used any medication?
    a. If yes what?
7. Have you undergone neck surgery? YES ☐ NO ☐
8. Do you have family history of the same illness?
9. Are you pregnant? YES ☐ NO ☐
    a. If yes, what is the gestational age?
10. Thyroid function test result T3_____, T4_____ and TSH_____
11. Do you have shortness of breath? YES ☐ NO ☐
12. Do you have palpitation? YES ☐ NO ☐
13. Do you have hot intolerance? YES ☐ NO ☐
14. Do you have double vision? YES ☐ NO ☐
15. Do you have eye pain? YES ☐ NO ☐
    a. If yes, at rest ☐ on eye movement ☐
16. Do you have gritting sensation? YES ☐ NO ☐
17. Do you have fear of light? YES ☐ NO ☐
18. Do you have tearing? YES ☐ NO ☐
19. Have you gone to eye clinic for your complaints? YES ☐ NO ☐

Physical examination

Is there anterior neck swelling that moves with swallowing? YES ☐ NO ☐

If yes characterize the mass

Multinodular ☐

Nodular ☐

Pulse rate (PR) = _____pulse/min

Blood pressure (BP) = _____mmHg

Hand trimmer YES ☐ NO ☐

Pretibial edema YES ☐ NO ☐

Ophthalmic manifestations

Lid retraction OD_____ OS_____

Lid lag OD_____ OS_____

Eyelid Erythema OD_____ OS_____

None

Close to the margin

Diffused

Proptosis OD_____ OS_____

Conjunctival Redness OD_____ OS_____

None

Excluding the caruncle

Diffused

If there is proptosis

	OD	OS
Measurement		
Ocular motility		
Differential IOP		
Conjunctiva		
Tear breakup time		
Cornea		
RAPD		
Fundus examination		
U/S of the orbit and globe		

DECLARATION

DECLARATION

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: Dagmawit Kifle (MD)

Date._____ Signature _____

APPROVAL OF THE FIRST ADVISOR

Name of the first advisor: Aemero Abateneh(MD, Asspciate Professor of Ophthalmology)

Date._____ Signature _____

APPROVAL OF THE SECOND ADVISOR

Name of the second advisor: SisayBekela (MD, Assistant Professor of Ophthalmology)

Date._____ Signature _____

APPROVAL OF THE THIRD ADVISOR

Name of the third advisor: Tsedeka Asaminew (MD, Assistant Professor of Ophthalmology)

Date._____ Signature _____