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ORIGINAL ARTICLE

Probing the underlying causes of thyrotoxicosis and its applied significance: a comprehensive evaluation

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ABSTRACT

OBJECTIVES: To determine the significance of etiological basis of thyrotoxicosis in guiding optimal treatment selection and its correlation with age and the presence of goiter.

METHODS: This cross-sectional study was conducted at MTI-Hayatabad Medical Complex in Peshawar, Pakistan, from December 2022 to May 2023. Utilizing nonprobability-consecutive sampling, we enrolled 119 participants, focusing on individuals presenting with thyrotoxicosis confirmed by thyroid function tests (TFTs). Those already undergoing treatment for hyperthyroidism were also included. Essential diagnostic assessments, such as radioiodine scans, erythrocyte sedimentation rate (ESR) and thyroid receptor stimulating antibody tests, were performed as needed. Patients with chronic renal disease, chronic liver disease, and pregnant and lactating women were excluded.

RESULTS: The mean age of participants was 40.39±13.65 years, with 84.03% having TSH <0.1 mIU/L. Elevated ESR (74.17±33.62 mm/1st hour) was noted in thyroiditis. Females constituted 72.3%. Overt hyperthyroidism (51.3%) and Graves' disease (50.4%) were prevalent. Inappropriately treated cases were 19.3%. Graves' disease patients with thyroid receptor stimulating antibodies showed 88% positivity. Treatment modalities included anti-thyroid drugs (43.7%), radioactive iodine therapy (28.6%), conservative (12.6%) and surgery (10.1%). Thyroid dysfunction was most prevalent in the age range of 31-40 years (32.7%). Goiter was absent in 44.5% of participants. Notably, 17.6% had apathetic hyperthyroidism.

CONCLUSION: This research emphasizes the vital understanding of thyroid dysfunctions in Pakistan, revealing Graves' disease as the primary cause of overt hyperthyroidism. Females, particularly aged 31-40, exhibit higher susceptibility. Emphasizing the importance of accurate diagnosis, this study highlights the prevalence of inappropriate prior treatments in thyrotoxicosis cases.

KEYWORDS: Thyroid Gland (MeSH); Thyroid Hormones (MeSH); Etiological factor (Non-MeSH); Hyperthyroidism (MeSH); Thyrotoxicosis (MeSH); Graves Disease (MeSH); Thyroxine (MeSH); Overt hyperthyroidism (Non-MeSH); Receptors, Thyrotropin (MeSH).

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INTRODUCTION

Thyroid hormones play critical roles in growth, brain development, reproductive health, and the management of energy metabolism. Thyroid dysfunction, encompassing conditions such as hypothyroidism and hyperthyroidism, is widespread and can result in significant health complications worldwide.[1,2] Globally, the incidence of thyroid disease is on the rise, with approximately 200 million individuals diagnosed worldwide.[3] Thyroid disorders are also prevalent in developing countries as well. A study in Nepal revealed that 33.66% of the population experienced thyroid disorders. Among these cases, overt hyperthyroidism was predominant at 14.9%, followed by subclinical hyperthyroidism at 9.9%.[4] Thyrotoxicosis is common across the globe with prevalence ranging from 0.1% to 3.4%.[5]

The prevalence and recognition of hyperthyroidism necessitate treatment strategies tailored to the cause and severity of the disease. Graves' disease is identified as the leading cause of hyperthyroidism, succeeded by toxic adenoma, toxic multinodular goiter, thyroiditis, and side effects from specific medications like amiodarone.[6-9] Diagnostic procedures, particularly when TSH levels are abnormal, include a variety of tests. Notably, the radioactive thyroid scan differentiates between pathological states, and despite its limitations, the measurement of serum TSH-receptor antibody (TRAb) levels is considered the definitive diagnostic tool for Graves' disease.[10,11] Other potential causes, such as Struma ovarii and both therapeutic and clandestine consumption of thyroid hormones, are also considered. Comprehensive diagnostic approaches, incorporating thyroid function tests, scans, antibody assessments, and erythrocyte sedimentation rate (ESR) evaluations, facilitate informed clinical decisions.[12]

The misdiagnosis of hyperthyroidism can severely impact patient health.[7,13] The thyroid scan has become an invaluable diagnostic instrument, preventing the incorrect treatment of conditions like thyroiditis.[11] Treatment options, which vary according to the underlying cause, include anti-thyroid drugs, radioactive iodine ablation, and surgical interventions.[14-16]

Understanding the etiological factors of thyroid dysfunction is crucial to avoid inappropriate treatments. There is a paucity of research on the mismanagement of thyrotoxicosis

within the Pakistani demographic. Empirical treatment protocols for thyroid dysfunction can lead to unnecessary expenditure, wasted resources, and detrimental health outcomes. This study was planned to underscore the significance of identifying the etiological factors behind thyrotoxicosis in patients and to investigate the predisposition of etiologies across different age groups.

METHODS

This cross-sectional study was carried out at the Department of Endocrinology, Medical Teaching Institution, Hayatabad Medical Complex, Peshawar, Pakistan, spanning from December 2022 to May 2023. Ethical clearance was secured from the Institutional Research and Ethical Board (HMC-QAD-F-00-Approval No. 1158, dated: February 3, 2023). A total of 119 participants were enrolled using non-probability consecutive sampling. Informed consent was obtained from the participants. Inclusion criteria comprised individuals displaying symptoms indicative of thyrotoxicosis or those with known hyperthyroidism under treatment. Exclusions encompassed patients with chronic liver disease, chronic kidney disease, and pregnant or lactating women.

All patients underwent thyroid function tests (TFTs), which included assessments for thyroid Stimulating Hormone (TSH), free Thyroxine (T4), and free Triiodothyronine (T3). Patients with persistent subclinical hyperthyroidism (lasting for more than 3 months) and patients with overt hyperthyroidism determined by TFTs were advised to have a Thyroid scan. A positive diagnosis of Graves' disease, thyroiditis, toxic multinodular goiter (MNG), or toxic adenoma was made. For participants with a thyroid scan consistent with Graves' disease, TRAbs were obtained where possible due to cost limitations. In the case of thyroiditis, an ESR was acquired. Patients with multinodular goiter having both hot and cold nodules were advised a neck ultrasound with Thyroid imaging reporting and data system (TIRADS) scores to evaluate the need for fine needle aspiration cytology. Following the diagnosis, patients were provided with the most suitable treatment options, including anti-thyroid drugs, surgery, radioiodine therapy, steroidal and non-steroidal medications, or, in some cases, mere observation.

The minimum sample size calculated through the WHO formula was 68, and the number of patients included in the study was 119. The CI was 95%, with 5% absolute precision, and the estimated prevalence was 4.6%.[9] The data was analyzed using SPSS version 26 after being checked, sorted, categorized, and coded accordingly. Descriptive statistics were used to summarize the data. The categorical variables were reported in frequencies and percentages. Mean and standard deviations were estimated for numerical variables. The chi-square test was used to find the association between age categories and the presence of goiter with diagnosis. P-Value < 0.05 was considered significant.

RESULTS

Out of 119 study participants, majority were females (n=86; 72.3%). The mean age of study participants was 40.39±13.65 years. Mean (±SD) T4, T3 & TSH were 16.59±7.53 mcg/dl, 2.55±2.91 ng/ml and 0.29±1.68 m IU/L respectively. TSH was less than 0.1 in 84.03% (n=100/119), between 0.1 to less than 0.5 in 11.76% (n=14/119) and 0.5 or above in 4.2% (n=5/119) due to overtreatment of some patient at the time of presentation. ESR was raised in all patients with thyroiditis, with a mean value of 74.17±33.62 mm/1st hour.

TFTs revealed that 51.3% (n=61/119) of participants had overt hyperthyroidism, with subclinical hyperthyroidism observed in 38.7% (n=46/119) of participants (Table I). The most prevalent underlying conditions were Graves' disease (n=60, 50.4%), followed by Thyroiditis (n=21, 17.6%), and Toxic Adenoma (n=19, 16%).

Among all participants, 19.3% (n=23/119) had experienced inappropriate treatment in the past (Table II). Goiter was absent in 44.5% (n=53/119) of patients, and 17.6% (n=21/119) did not manifest any symptoms, indicative of an apathetic presentation. Thyroid scan reports revealed that 51.3% (61/119) exhibited diffuse increased uptake.

In Graves' disease patients who underwent TRAbs testing, 88% (22/25)

Table I: Gender, biochemical interpretation, diagnosis and duration in months

Variables		Frequency (n=119)	Percentage
Gender	Male	33	27.7
	Female	86	72.3
Biochemical interpretation	Overt Hyperthyroidism	61	51.3
	Subclinical Hyperthyroidism	46	38.7
	T3 Thyrotoxicosis	12	10
Diagnosis	Graves' disease	60	50.4
	Thyroiditis	21	17.6
	Toxic Adenoma	19	16
	Toxic MNG	17	14.3
	Drug-induced	1	0.8
	TSHoma	1	0.8
Duration in months	>6 months	60	50.4
	<6 months	59	49.6

Toxic MNG: Toxic multinodular goiter, TSHoma: TSH producing pituitary adenoma/Thyrotropinoma.

Table II: Characteristics of treatment approaches, goiter, symptom, and thyroid scan findings in study participants (n=119)

Variables		Frequency	Percentage
Inappropriate treatment	Yes	23	19.3
	No	96	80.7
Goiter	Yes	66	55.5
	No	53	44.5
Sign and symptoms	Yes	98	82.4
	No	21	17.6
Thyroid scan report	Diffuse increase uptake (graves)	61	51.3
	Depressed/low/absent uptake	22	18.5
	Solitary increased uptake/ toxic adenoma	19	16
	Multifocal increased uptake	17	14.3

revealed positive results, confirming the diagnosis (Table III). Treatment recommendations were tailored to each disorder, with anti-thyroid drugs prescribed for 43.7% (n=52/119) of patients, followed by radioactive iodine therapy for 28.6% (n=34/119), while surgery was offered in 10.1% (n=12/119) of cases.Thyroid dysfunction was most prevalent in the age range of 31-40 years, accounting for 32.7% (n=39/119), followed by the age range of 41-50 years at 28.5% (34/119). Among specific disorders, Graves' disease was most prevalent, constituting 20.1% (24/119) in the age range of 31 to 40 years, while toxic adenoma and toxic multinodular goiter each represented 5.8% (7/119) in the age range of 41 to 50 years (Table IV).

The association between goiter presence and various types of thyrotoxicosis varies. Graves' disease was present in 54.7% of patients without goiter and 46.9% with goiter. Thyroiditis (26.4%) and toxic adenoma (16.9%) were more common in those without goiter compared to those with goiter (Table V).

DISCUSSION

In our study of 119 participants, predominantly female (72.3%), findings revealed widespread thyroid dysfunction, with Graves' disease being the most common condition (50.4%). The majority of patients (51.3%) exhibited overt hyperthyroidism and a significant portion had been previously subjected to inappropriate treatments (19.3%). Diagnostic tests, including TRAbs, confirmed Graves' disease in 88% of tested individuals. Treatment strategies varied, with anti-thyroid drugs being the most prescribed option (43.7%). The presence of goiter showed variable associations with different thyroid conditions, indicating diverse clinical presentations across the spectrum of thyroid diseases.

In our study, the mean age of participants was 40.39±13.65 years, closely aligning with Ullah F, et al., 2022 study,[10] which reported a mean age of 40.82±13.77 years. The gender distribution showed a significant female predominance (72.3%), consistent with Ahn HY, et al., findings that hyperthyroidism is approximately 2.5 times more common in women than in men.[17]

Overt hyperthyroidism was the predominant biochemical finding in our study, constituting 51.3% (n=61/119), followed by subclinical hyperthyroidism at 38.7% (n=46/119). Comparatively, a study by Yadav NK, et al., (2013)[4] reported higher prevalence of overt hyperthyroidism (14.9%) than subclinical hyperthyroidism (9.9%).

Graves' disease emerged as the leading cause of hyperthyroidism in our study at 50.4% (n=60/119), with thyroiditis, toxic adenoma, and toxic multinodular goiter following at 17.6% (21/119), 16% (19/119), and 14.3% (17/119) respectively. Contrary to a study by Pooria A, et al., (2021),[13] which reported Graves' disease as the most common cause in 62.04%, our study observed a higher prevalence of thyroiditis, possibly attributed to increased tertiary care referrals due to pain and acute onset in addition to demographic variability. Akhtar S, et al., (2001) [18] reported a hyperthyroidism prevalence of 5.1%, subclinical hyperthyroidism rate of 5.8%, and a 5.26% hyperthyroidism prevalence in females compared to 3.12% in males, emphasizing the higher prevalence in our study due to inclusion of clinically and biochemically proven hyperthyroidism patients.

A significant observation from our study was that 19.3% (n=23/119) of patients received inappropriate treatment at presentation. This was primarily attributed to empiric treatment based on initial thyroid function tests, influenced by factors such as patient inappropriate preference due to lack of disease insight secondary to lack of proper counselling non-guideline-based practices, anti-thyroid drug use in thyroiditis, and financial constraints. The long-term inappropriate adherence to oral anti-thyroid drugs and atypical clinical and biochemical presentations also contributed to this phenomenon. A study by Subbiah K, et al., (2021)[7] underscored the diagnostic challenges, exemplified by mistreatment of a patient with thyroiditis as Graves' disease. Goiter was absent in 44.5% of patients, indicating its inconsistency as a feature in thyrotoxicosis. Our study identified apathetic hyperthyroidism in 17.6% (n=21/119) of patients, aligning with findings studied by Weihua W, et al., (2010)[19], who investigated factors contributing to apathetic hyperthyroidism.

Patients with Graves' disease exhibited TRAbs in 88% (n=22/25) of cases where tested, and one case was associated with a TSH-producing pituitary adenoma. Treatment recommendations varied, with 43.7%

Table III: Diagnostic and management outcomes in patients with thyroid disorders (n=119)

Variables		Frequency	Percentage
TRAbs (done for 25 patients)	Positive	22/25	88*
	Negative	3/25	12*
	Not done	36	59.01
TSHoma	Yes	1	0.8
	No	118	99.2
SHBG	Raised	1	0.8
	Not done in	118	99.2
Management offered	ATD	52	43.7
	RAI	34	28.6
	Conservative	15	12.6
	Surgery	12	10.1
	Steroid therapy	6	5

TRAbs: TSH receptor stimulating antibodies, SHBG: sex hormone binding globulin, ATD: anti-thyroid drugs; RAI: radioactive iodine therapy, *Percentage calculated for 25 patients undergoing TRAbs RAbs

(n=52/119) prescribed anti-thyroid drugs, 28.6% (n=34/119) receiving radioactive iodine therapy, and 10.1% (n=12/119) undergoing surgery. Ahn HY, et al.,(2023)[17] reported a dissimilar approach, with 93.7% of patients offered anti-thyroid drugs, possibly attributed to the long duration of enrolling all new cases in their study (2003 to 2018) and unique population factors in Korea, including high iodine intake and genetic influences. Contrary to our findings, Ullah F, et al., (2022)[10] reported TRAbs positivity in 6.06% of all hyperthyroid patients. This discrepancy can be attributed to differences in testing approaches; while they conducted TRAbs testing in all hyperthyroid patients, our study limited testing to those with thyroid scan-proven Graves' disease, primarily due to cost constraints.

In our study, thyroid dysfunction was most prevalent in the age range of 31-40 years (32.6%), followed by the age range of 41-50 years (28.3%). The age distribution of hyperthyroidism diagnoses shifted over time, with the majority of diagnoses occurring in individuals in their 50s in 2003-2004, and in their 60s in 2017-2018.[17] This change suggests a potential evolution in the demographics and prevalence of underlying thyroid disorders. Graves' disease was most common in the age range of 31-40 years (20.1%), followed by the age range of ≤ 30 years (15.1%). Toxic adenoma and toxic MNG were prevalent disorders in the age range of 41-50 years (5.8% each). A study by Alam Z, et al., (2019)[11] in the district of Mardan, Pakistan, showed a higher prevalence of both subclinical and overt hyperthyroidisms among patients aged 16-30 years (2.04%) and 31-45 years (1.46%), contrasting with our results. The disparity could be attributed to differences in lifestyles, dietary intake, broader inclusion criteria, and the inclusion of all tested populations as well as patients with hypothyroidism. Conversely, Iqbal MA et al. (2016)[20] found that people above 25 years had thyroid dysfunction in 69.49% (n=328/472), potentially influenced by a wide age range of 25 to 100 years and the inclusion of hypothyroid patients.

In our research,44.5% of thyrotoxicosis patients did not exhibit goiter, underscoring that goiter's presence is not a consistent indicator of hyperthyroidism, akin to findings by Iqbal MA, et al., in 2016,[20] where goiter was present in 44.4% of hyperthyroid cases. Misuse of anti-thyroid medications like propylthiouracil and excessive iodine intake were noted as potential causes for goiter development. Financial constraints limited the assessment of TRAbs levels in all patients with Graves' disease, highlighting a need for further studies equipped with adequate resources to evaluate TRAbs levels comprehensively.

Table IV: Distribution of thyroid disorders across age groups (N=119)

Diagnosis	≤ 30 years	31 to 40 years	41 to 50 years	>50
Graves' disease	18 (15.1%)	24 (20.1%)	13 (10.9%)	5 (4.20%)
Toxic adenoma	4 (3.3%)	5 (4.2%)	7 (5.8%)	3 (2.5%)
Toxic MNG	3 (2.5%)	2 (1.6%)	7 (5.8%)	5 (4.2%)
Thyroiditis	0	8 (6.7%)	6 (5%)	7 (5.8%)
Drug-induced	0	0	0	1 (0.8)
TSHoma	0	0	1 (0.8%)	0
Total	25 (21%)	39 (32.8%)	34 (28.6%)	21 (17.6%)

MNG: Toxic multinodular goiter; TSHoma: TSH producing pituitary adenoma

Table V: Association of goiter presence with diagnosed thyroid disorders (n=119)

Diagnosis	Presence of goiter	
	No (n=53)	Yes (n=66)
Graves' disease	29/53 (54.7%)	31/66 (46.9%)
Thyroiditis	14/53 (26.4%)	7/66 (10.6%)
Toxic Adenoma	9/53 (16.9%)	10/66 (15.1%)
Toxic MNG	1/53 (1.8%)	16/66 (24.2%)
Drug-induced	0	1/66 (1.51%)
TSHoma	0	1/66 (1.51%)

Toxic MNG: Toxic multinodular goiter, TSHoma: TSH producing adenoma/Thyrotropinoma

CONCLUSION

This study provides significant insight into thyroid dysfunctions in the Pakistani population. Graves' disease emerges as the primary contributor to overt hyperthyroidism, followed closely by thyroiditis, toxic adenoma, and toxic multinodular goiter. Females exhibit a higher susceptibility, particularly in the age group of 31 to 40 years, offering essential diagnostic indicators for healthcare practitioners.

A significant deviation from the norm, our findings challenge the necessity of goiter presence for diagnosing thyrotoxicosis. This paradigm-shift calls for a reevaluation of diagnostic criteria, emphasizing a comprehensive assessment that extends beyond visible symptoms. Additionally, recognizing instances of inappropriate treatment emphasizes a worrisome aspect of current healthcare practices, emphasizing the need for enhanced clinical awareness and focused educational efforts to ensure precise diagnosis and proper management.

Beyond clinical implications, the research advocates for a broader public health discourse on thyroid health. Early detection and intervention can significantly alleviate the burden of thyroid diseases, highlighting the importance of proactive healthcare strategies.

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AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

FI: Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

TG: Concept and study design, acquisition of data, drafting the manuscript, approval of the final version to be published

MAS & RA: Analysis and interpretation of data, critical review, approval of the final version to be published

Author agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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