Original Article

Frequency of Graves Disease in Hyperthyroid Patients and its Associated Comorbidities

Graves Disease in Hyperthyroidism

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ABSTRACT

Objective: To find out frequency of Grave's disease in hyperthyroid patients and to measure the associated comorbidities in hyperthyroid patients.

Study Design: Descriptive Cross-Sectional study

Place and Duration of Study: This study was conducted at the Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK) from Jan to June 2022.

Materials and Methods: Diagnosed Hyperthyroid Patients were selected and age ranging from 20 to 60 years for study purpose. Non probability convenience sampling was used and sample size was 100. Data was analyzed by using SPSS version 24.

Results: According to this study data mean age of the participants was 36.92 ± 7.47. Out of 100 participants who were diagnosed hyperthyroid patients, 43% were further diagnosed having Graves' disease. Graves' disease is 3 to 4 times high in females (74%) compared to males. Cardiovascular diseases (42%) are commonest comorbidities associated with hyperthyroidism.

Conclusion: This study concluded that Graves' disease is the more common cause of hyperthyroidism females are affected four times higher than male with Grave's disease in their 3rd to 5th decades of life in our public health care system. Comorbidities are very common in hyperthyroidism because of involvement of multiple organs and worsen the prognosis of the disease hence increase mortality.

Key Words: Graves, Disease, Hyperthyroid Patients, Associated Comorbidities

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INTRODUCTION

Hyperthyroidism also called hyper-active thyroid is a state in which the thyroid gland secretes enough amounts of free thyroid hormones. Thyroid gland produces two important hormones, Thyroxin (T4) and Tri-iodothyronine (T3) is a small, butterfly-shaped gland situated at lower anterior part of the neck.[1]

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These hormones T4 and T3 are regulated by Thyroid stimulating hormone (TSH), released from anterior pituitary gland in response to thyrotrophin releasing hormone (TRH) from hypothalamus[2]. Hormones secreted from the thyroid gland, have widespread actions over the body, they are major regulator of the body energy, metabolism and body development. Their actions includes regulating neurological, cardiovascular, musculoskeletal and reproductive functions[3,4].

Thyrotoxicosis a clinical state during which T4 and T3 levels are raised in blood, in which the thyroid hormone is toxic to tissues and produces specific clinical features[5]. Causes of high levels of thyroid hormones in blood are:

- Graves' disease
- Toxic multi-nodular goiter
- Thyroiditis
- External supplement of thyroid hormone
- Drugs (Amiodarone)
- Postpartum thyroiditis (PPT)
- Strumaovarii (Monodermal teratoma)
- Excess iodine consumption
- Pituitary adenoma[6,7].

Clinical presentation of hyperthyroidism: Main clinical signs are anxiety, weight loss, heat intolerance, hair loss (especially of the outer third of the eyebrows), muscle weakness, fatigue, hyperactivity, irritability, hyperglycemia, polyuria, delirium, polydipsia, tremor, pretibial myxedema (in Graves' disease), and perspiration[8]. Panic attacks, inability to concentrate, and memory problems may also occur. Psychosis and paranoia, common during thyroid storm, are rare with milder hyperthyroidism[9]. Addition to above symptoms, other symptoms may also present like palpitations, arrhythmias, dyspnea, loss of libido, amenorrhea, nausea, vomiting, diarrhea and feminization[10].

Graves' Disease: Among the causes of thyrotoxicosis, Graves' disease has significantly high prevalence. The data from western world suggest 60-80% prevalence of Graves' disease prevail among hyperthyroid patients worldwide. Female to male ratio of 7-10:1. Most cases reports from India described only 2-3 fold excess of female disease[11]. Graves' disease, autoimmune disorder of thyroid gland can either cause glandular destruction and hormone deficiencies called hypothyroidism or over production of thyroid hormone[12].

In Graves' disease forms the similar antibodies like TSH, which in turn causing the thyroid gland to secrete more thyroid hormone beyond the body requirements. This over production of TSH may result is overactive thyroid. An overactive thyroid can lead to speed up of all function of the body, like increase heartbeat, increase blood pressure and increase metabolism in turn produce energy. There are three types of auto antibodies identified for TSH receptor stimulation are:

1. TSI (Thyroid Stimulating Immunoglobulin):
2. Thyroid Growth Immunoglobulin (TGI):
3. Thyrotrophin Binding-Inhibiting Immunoglobulin (TBII):

Clinical presentation and lab tests to differentiate graves' disease from other causes of hyperthyroidism: Graves' disease can be diagnosed with a careful history and physical examination. Suggestive features of Graves' disease include a positive family history, the presence of orbitopathy, diffusely enlarged thyroid with or without bruit and pretibial myxedema[13]. Clinical manifestations of Graves' disease are:

- Exophthalmos (protrusion of eye)
- Pretibial myxedema
- Increase cardiac rate
- Weight loss, muscular fatigue, increased appetite etc,

Thyroid Function Test: Initially the primary test for the confirmation of hyperthyroidism is to measurement the level of TSH, secreted by the pituitary gland. A low level of TSH reveals that there is raised level of T_4 and/or T_3 in the blood.

Thyroid function test results in different causes of Hyperthyroidism

Sr. No.	Condition	TSH	T3/T4	TSI
1	Graves' disease	↓	↑	+
2	Thyroiditis (with hyperthyroidism)	↓	↑	−
3	Thyroid nodules (hot, or toxic)	↓	↑	−

Thyroid specific Antibody tests: Determine the level of anti-TSH-receptor antibodies in Graves' disease, or anti-thyroid-peroxidase in Hashimoto's thyroiditis, may also contribute in the diagnosis.

Thyroid scan: It is a peculiar test for the diagnosis of hyperthyroidism, and it differentiate it from thyroiditis.

Comorbidities associated with hyperthyroidism: Comorbidities, especially cardiovascular diseases, have most important influence on mortality. However, available studies are unpredictable when controlling for comorbidity. Some studies have highlighted the importance for control of cardiovascular diseases, some for diabetes, and some control for cancer.

A study concluded that hyperthyroidism is associated with a 21% increased risk in mortality due to all causes. The most common diseases explained in groups are myocardial infarction, heart failure, vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, gastric ulcer, liver disease, diabetes mellitus with or without complications, hemiplegia, kidney disease, cancer, cancer with metastases, lymphoma, leukemia, liver failure, and AIDS[14].

Epidemiology: Graves' disease is the most common cause of Hyperthyroidism and affects nearly 0.5 percent of the population and is the under lying cause of 50-80 percent of all cases of hyperthyroidism.[15, 16]

In the United States, there is an estimate of 30 cases per 100,000 persons every year diagnosed to have Graves' disease. It is said to be the most prevalent autoimmune disease in the whole of America, having been diagnosed in 60-80% of patients with hyperthyroidism[17.]

Graves's disease is more common in women than it is with men and children. It has an annual incidence of 0.5 per 1000 of women, mostly affecting those in the 40 to 60 years old age bracket. Its prevalence rates are similar in Caucasians and Asians, but are lower in Africans[18].

In Pakistan the exact burden of this disease is not yet established. However limited studies were available as reported by Khan A et al in 2002, which showed that prevalence of hyperthyroidism and sub-clinical hyperthyroidism was 5.1% and 5.8% respectively[19] and was higher in females than males. Peak presentation occurs in the 3rd and 4th decades of life while the disease is rare in first decades and in the elderly[20].

MATERIALS AND METHODS

Study Setting: This descriptive Cross-Sectional study was conducted at Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK).

Sample Size was calculated using Open-Epi software, with 95% confidence interval and 5% margin of error. The calculated sample size was 100. Non-probability convenience sampling was used.

Inclusion criteria

1. Adults of both gender
2. Age between 20 to 60 years.
3. Diagnosed patients of Hyperthyroidism and all types of Goiter
4. Presence of either exophthalmos and / or pretibial myxedema.

Exclusion criteria

1. Age under 20 or over 60 years
2. History of Thyroid ablation or Thyroidectomy
3. Use of Centroids.
4. Excessive use of iodinated salts, drugs and sea foods.

Data Collection Procedure: After approval from Institutional Review Board, the diagnosed cases of Hyperthyroidism visited Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK), fulfilling the criteria were included in this study. After taking written consent the information were gathered on the pre-designed questionnaire for record. Demographic (age and sex) and clinical sign and symptom data were collected through structured questionnaire. Thyroid function test (TSH/ FT4/FT3), were done to confirm diagnosis.

Data Analysis Procedure: The data was analyzed in version 24 of the Statistical Package for Social Sciences (SPSS). For categorical variables, frequency and percentage were calculated. The data was formulated through Graphs and Charts.

RESULTS

Total hundred hyperthyroid patients were selected from Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK).

The table 1 shows that mean age of the participants was (36.92 ± 7.47). 48% percent participants were between 41 to 50 years of age, 25% were between 51 to 60 years, 21% were between 31 to 40 years only 06% participants were below 30 years of age. There was no or limited role of education in this disease majority of the subject were graduate (47%). 72% participants were from urban setting only 28% participants were from rural areas. Socioeconomic status was observed and majority of the participants were belonging to middle class (table 1).

Table No.1: Socio-demographic characteristics of Participants (n= 100)

Sr. No.	Characteristics	Category	Frequency	Percentage
1	Age of Participant (in years)	21-30	06	6%
		31-40	21	21%
		41-50	48	48%
		51-60	25	25%
2	Educational status	Primary	23	23%
		Secondary	30	30%
		Graduate	47	47%
3	Residence of Participants	Urban	72	(72%)
		Rural	28	(28%)
4	Socioeconomic Status of Participants	Lower Class	36	(36%)
		Middle Class	49	(49%)
		Upper Class	15	(15%)

Table No.2: 1. Gender distribution in hyperthyroid patients (n=100). 2. Gender distribution in Graves' disease (n=43)

Sr. No.	Characteristics	Category	Frequency	Percentage
1	Gender distribution of participants of hyperthyroid patients (n=100).	Male	31	(31%)
		Female	69	(69.0%)
2	Gender distribution of participants with Graves' Disease (n=43)	Male	11	(26%)
		Female	32	(74%)

Sr. No.01 of table 2 shows gender distribution in hyperthyroidism and is clearly evident in this study that is common female (69%) as compared to male (31%).
Se. No.02 shows gender distribution in Graves' disease, 31 (74%) out of total 43 were female and remaining 11 (26%) were male (table 2).

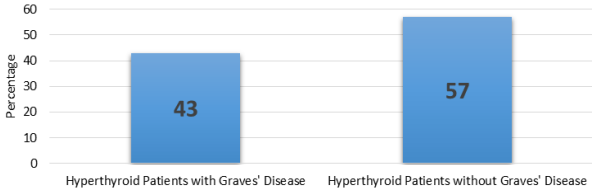

Figure No. 1: Percentage of Graves 'disease in Diagnosed hyperthyroid Patients (n=100)

The above graph shows the percentage of hyperthyroid patients who were diagnosed as Graves' disease. 43% participants were positive with Graves' disease and remaining 57 % were hyperthyroid but shown no signs of Graves' disease at the time of study.

Table No.3: Cardinal Clinical Signs and Symptoms of Graves' disease noticed in hyperthyroid patients (n=100)

Sr. No.	Clinical presentation	Frequency	Proportion
1	Exophthalmos / Opthalmoplagia (protrusion of eye)	34	34%
2	Pretibial myxedema	11	11%
3	Diffuse Goiter	47	47%
4	Palpitation (Increase cardiac rate)	74	74%
5	Weight loss, muscular fatigue, increased appetite etc.	82	82%

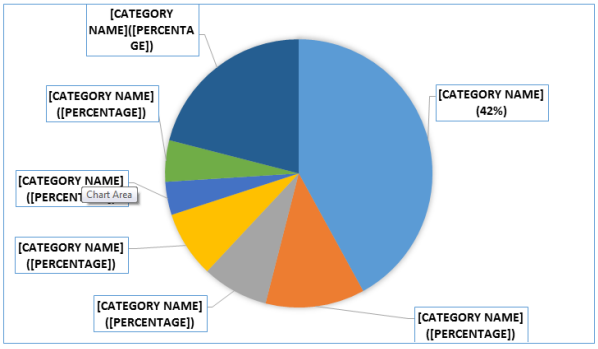

Figure No.2: Development of comorbidity in already diagnosed patients of hyperthyroidism (n=100)

The above chart shows pattern of comorbidities in hyperthyroid patients. It was seen in this study that cardiovascular diseases are (42%) and very common, diabetes was second common disease (12%) was noted. Other diseases like Chronic Lung disease were (8%), Hematological disorders were (8%) Chronic Renal failure were (4%) and others were (5%). 21% patients presented with no associated disease at the time of data collection.

DISCUSSION

In this study frequency of Graves' disease was observed in diagnosed hyperthyroid patients visiting in different tertiary care hospital of Karachi and it was concluded that 43% cases had findings of Graves' disease and it was the most common cause of hyperthyroidism. This is in accordance with the study conducted by Vanderpump et al which also show the same prevalence and frequency[11].
In this study Graves' disease was found four times higher in female than male. Female to male ratio was 4:1. Previous study also supported that Graves' disease is more common among female than male. Peak incidence of Graves' disease in current study was seen in middle age between third to fifth decades of life. Similar results were reported by a study conducted by Zimmerman MB et al in 2009[20].
Graves' disease can be diagnosed on the basis of cardinal clinical signs and elevated serum T4 and T3 levels present in hyperthyroid patients. Goiter with either exophthalmos and/ or pretibial myxedema are classical presentation of Graves' disease. In this study diffuse goiter was reported in (47%) patients with exophthalmos (34%) and pretibial myxedema (11%) cases. Palpitation was noted in (74%) and weight loss was very common and seen in (82%) cases. All 43 cases diagnosed as Graves' disease had common clinical presentation of palpitation, exophthalmos and weight loss. DeGroot LJ in his study pointed out similar signs and symptoms for the diagnosis of Graves' disease[21].
Comorbidities are very common in hyperthyroid patients because of involvement of almost all tissues and organs of the body. These comorbidities are associated with (21%) increased risk of mortality. The most common comorbidities recorded in our study were cardiovascular diseases (myocardial infarction, heart failure, vascular disease, cerebrovascular disease) 42%, second common disease was Diabetes (12%). Other diseases like chronic lung disease (8%), hematological disorders (8%) Chronic renal failure (4%) were noteworthy. A study conducted by Brandt F. et al also gave similar results in his study and ranked cardiovascular disease at top[14]. This study is in accordance with that study as well.

CONCLUSION

This study concluded that Graves' disease is the more common cause of hyperthyroidism females are affected four times higher than male with Grave's disease in their 3rd to 5th decades of life in our public health care

system. Comorbidities are very common in hyperthyroidism because of involvement of multiple organs and worsen the prognosis of the disease and increase mortality. Further studies are need to be conducted this study on larger scale with full diagnostic criteria.

Author's Contribution:

Concept & Design of Study:	Syed Masood Hussain, Mubashir Shaikh
Drafting:	Muhammad Siddique Rajput, Muhammad Akbar
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Revisiting Critically:	Syed Masood Hussain, Mubashir Shaikh
Final Approval of version:	Syed Masood Hussain, Mubashir Shaikh

Conflict of Interest: The study has no conflict of interest to declare by any author.

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