



## CARDIAC MANIFESTATIONS IN THYROTOXICOSIS: A CROSS-SECTIONAL STUDY.

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### ABSTRACT

**Objective:** To determine the frequency of cardiovascular (CVS) symptoms in patients presenting with thyrotoxicosis.

**Design:** cross sectional study

**Place & duration of study:** Medical and Cardiology department of Peoples University of Medical & Health Sciences for Women (PUMHSW) Hospital Nawabshah from June 2022 to May 2023.

**Methodology:** Adult male and female patient with age of 18 years and above presented to the outpatient/inpatient of medical/cardiology department with specific signs and symptoms with elevated serum T3 level, serum T4 level or low serum TSH level were enrolled. All data including signs and symptoms of hyperthyroidism, and results of biochemical, electrocardiographic, and echocardiographic findings of all patients were collected through questionnaire.

**Results:** total 150 patients were enrolled. Among them, 80.2% of subjects were female, while 19.8% were male with mean age  $41.19 \pm 11.078\%$ . The palpitations were the most common manifestation (69.00%). During cardiac examination, tachycardia was noted in 82.6% of the subjects, hypertension in 42.2%, and elevated pulse pressure in 32.8%. The mean pulse rate was  $121.3103 \pm 105.98568$  beats per minute and mean pulse pressure was  $53.3 \pm 8103$  mm Hg. On cardiac auscultation the loud S1 was found in in 76.7% of patients and a systolic ejection murmur at pulmonary area in 25.9% of subjects (Table 2).

**Conclusion.** In patients with thyrotoxicosis palpitation, chest pain, breathlessness were the dominant cardiac manifestations. So, all patients with thyrotoxicosis presenting with these manifestations should be screened for cardiovascular problems.

**Keywords:** Thyrotoxicosis Cardiac Manifestations

### **Introduction**

Clinically the thyroid disorders are the one of most common endocrinological disorder seen after the diabetes mellitus. <sup>1</sup>The prevalence of hyperthyroidism is lower than the prevalence of hypothyroidism that is about 2%. <sup>2</sup>

Hyperthyroidism results due to excess production of thyroid hormone caused by extra synthesis and liberation of thyroid hormones by thyroid tissues, whereas thyrotoxicosis refers to the clinical symptoms occurs due to excess of thyroid hormones in the body, whatever the source. <sup>3</sup>

The most common causes of thyrotoxicosis are “Graves’s disease, toxic multinodular goiter, and toxic adenoma”. Few cases may be caused by sub-acute thyroiditis. <sup>4</sup>The hyperthyroidism or Thyrotoxicosis may be diagnosed by estimation of thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine T3 (fT3) levels. <sup>5</sup>

By several mechanism the cardiovascular system (CVS) affected by thyroid hormones. The direct effects of excess T3 and T4 over the myocardium and pulmonary vessels are increasing cardiac rate and contractility, rising in systolic and mean pulmonary artery pressures and enhancing of cardiac output, diastolic relaxation, and oxygen consumption. Additionally, thyroid hormones decrease the systemic vascular resistance and diastolic pressure. <sup>6</sup>

The clinical presentation of cardiac manifestations of excess thyroid hormones depends on the duration, severity of the thyroid disease and on blood levels of thyroid hormone. <sup>7</sup> The most common clinical manifestations of hyperthyroidism are; palpitations, dyspnea, exercise intolerance, angina-like chest pain, peripheral edema, and congestive heart failure. The most common cardiovascular signs are sinus tachycardia, atrial fibrillation (AF), nonspecific ST -T changes, ventricular hypertrophy, and dilated cardiomyopathy. Sinus tachycardia is characteristic of this disease and AF is also most likely to be identified with thyrotoxicosis. <sup>8</sup>the patients having AF can lead to brain strokes, a most lethal complication of AF. <sup>9</sup>

Cardiac involvement in thyrotoxicosis causes significant morbidity and mortality. Mortality is increased by 20%, in patients with hyperthyroidism due death occurred by cardiac problems. <sup>10</sup>Early diagnosis and appropriate therapy can reverse the condition.

In Pakistan limited data is available on the cardiac manifestations of hyperthyroidism. The study by Khurana *et al* Studies from other African countries showed that cardiovascular abnormalities are common clinical presentations of patients with hyperthyroidism with prevalence ranging between 8-22%, leading to increased morbidity and mortality in this group of patients. <sup>5,6</sup>

The clinical presentation and laboratory features of thyrotoxicosis have been poorly studied, especially in our settings. The aim of our study was to determine the frequency of cardiovascular (CVS) symptoms in patients presenting with thyrotoxicosis. The early detection and diagnosis of cardiac manifestation of thyrotoxicosis may help in decreasing the mortality.

### **Materials And Methods**

This study was conducted in the medical department and Cardiology department of Peoples University of Medical & Health Sciences for Women (PUMHSW) hospital, a tertiary care hospital in Sindh, Pakistan. This descriptive cross-sectional study was conducted from June 2022 to May 2023 after approval from the ethics committee of PUMHSW Nawabshah. To achieve the required sample size for this study sample size was calculated using WHO sample size calculator and consecutive non-probability sampling method was used to collect the data. Patients presenting with co-morbidity like, hypertension (HTN), diabetes mellitus (DM), congestive heart failure, and coronary artery disease (CAD) were excluded from study. Patients over 18 years of age and of either sex who presented to the outpatient medical department or admitted in medical or in cardiology ward with signs and symptoms of thyrotoxicosis during the study period were enrolled in the study. After informing the details and purpose of study the written informed consent was taken from the patients

or next of kin. Detailed history and examination were performed by researchers and total of 150 patients were enrolled in the study during the defined study period. After all aseptic measures, 10 ml of blood was drawn and sent to the Research and Diagnostic Laboratory of PUMHSW, for complete blood count, renal function test, liver function test, serum electrolytes, lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], serum triglycerides), and thyroid profile (TSH, T3, T4). The diagnosis of thyrotoxicosis was done by patients presenting with specific signs and symptoms with elevated serum T3 level ( $>200$  ng/dl), serum T4 level ( $>12$  mcg/dl), or low serum TSH level ( $<0.3$  mU/ml). BP Chest radiography (PA), electrocardiography (ECG), and 2D examination (ECHO) were performed in all patients. by using a structured questionnaire, all data including signs and symptoms of hyperthyroidism, and results of biochemical, ECG and echocardiographic findings of all patients were collected.

The data was analysed by using SPSS software (IBM version 27). For continuous variables such as age, the thyroid profile was calculated as mean, percentage, and standard deviation by using descriptive statistics, whereas categorical variables like sex, cardiac manifestations were presented as numbers and percentages (%). Pearson chi-square test was used as test of significance for comparison of categorical variable and its association was considered significant when p-value was less than 0.05.

## Results

The mean age of the subjects in our study was  $41.19 \pm 11.078\%$ . The most common age group was 41–60 years with 51.7%, followed by the 20–40 years group with 37.9%. Regarding gender, 80.2% of subjects were female, while 19.8% were male. Graves' disease was the most common etiology of thyrotoxicosis, accounting for 58.00%, with multinodular goiter in second place, accounting for 22.4%. The most common noncardiac symptoms were heat intolerance (80%), fatigue (65.0%), and weight loss (80.3%), and in many patients (83.4%) these symptoms had been present for less than a year (Table 1).

The mean TSH level was  $0.0898 \pm 0.271$  uIU/ml. The mean T4 level was  $15.0998 \pm 2.56$  ug/dl. The mean T3 level was  $5.0975 \pm 0.0858$  nmol/L.

Regarding cardiac symptoms, palpitations were the most common manifestation and were noted in 69.00% of the subjects. In addition, almost 18.1% of the subjects had no cardiac symptoms. During cardiac examination, tachycardia was noted in 82.6% of the subjects, hypertension in 42.2%, and elevated pulse pressure in 32.8%. The mean pulse rate was  $121.3103 \pm 105.98568$  beats per minute and mean pulse pressure was  $53.3 \pm 8103$  mm Hg. On cardiac auscultation the loud S1 was found in in 76.7% of patients and a systolic ejection murmur at pulmonary area in 25.9% of subjects (Table 2).

Lymphocytic infiltrates (56.9%) were common finding on FNAC, followed by colloid nodules (19.0%) and benign nodular goiter (14.7%) respectfully. (Table 3).

**TABLE 1: Baseline characteristics of study subjects (N = 116).**

| Variable             | Number | Percentage |
|----------------------|--------|------------|
| Age Scale (in years) |        |            |
| <20                  | 10     | 8.6        |
| 20-40                | 44     | 37.9       |
| 41-60                | 60     | 51.7       |
| >60                  | 2      | 1.7        |
| Gender               |        |            |
| Male                 | 34     | 29.3       |
| Female               | 82     | 70.7       |

|  |     |      |
|--|-----|------|
| <b>Causes of Thyrotoxicosis (Ultrasound)</b>                               |     |      |
| Grave's disease  | 58  | 50.0 |
| Multinodular goiter  | 26  | 22.4 |
| Solitary nodule  | 10  | 8.6  |
| <b>Clinical Presentation</b>   |     |      |
| <i>Non-Cardiac</i>   |     |      |
| Heat Intolerance   | 90  | 77.6 |
| Weight Loss  | 87  | 75.0 |
| Increased Appetite   | 19  | 16.4 |
| Diarrhea   | 24  | 20.7 |
| Tremor   | 7   | 6.0  |
| Mix symptoms(Heat intolerance ,<br>Weight loss, Increased appetite, Tremor | 27  | 23.3 |
| <b>Duration of Symptoms</b>  |     |      |
| <12 months   | 103 | 88.8 |
| 1-2 years  | 8   | 6.9  |
| >2 years   | 5   | 4.3  |

**TABLE 2: thyroid Laboratory Parameters (116)**

| Parameters   | Minimum | Maximum | Mean   | Std. deviation |
|--------------|---------|---------|--------|----------------|
| TSH (uIU/ml) | 0.001   | 1.03    | 0.0898 | 0.271          |
| T3 (nmol/L)  | 3.99    | 7.01    | 5.0975 | 0.858          |
| T4 (ug/dl)   | 12.01   | 20.00   | 15.09  | 2.56           |

**TABLE 3: Diagnosis by FNAC among study subjects (N = 116).**

| Parameters            | Number | %    |
|-----------------------|--------|------|
| Follicular adenoma    | 6      | 5.2  |
| Benign nodular goiter | 17     | 14.7 |

**TABLE 4: Signs and symptoms of cardiovascular systemamong study subjects (N = 116).**

| VARIABLES                                  | Number (n) | Percentage (%) |
|--|------------|----------------|
| <i>Cardiac Symptoms</i>                    |            |                |
| Palpitations                               | 80         | 69.0           |
| Edema                                      | 11         | 9.5            |
| No cardiac symptoms                        | 25         | 21.6           |
| <i>Cardiovascular signs</i>                |            |                |
| Tacchycardia                               | 88         | 75.9           |
| Atrial Fibrillation                        | 24         | 20.7           |
| Hypertension                               | 11         | 9.5            |
| Wide pulse pressure                        | 37         | 31.9           |
| Loud S1                                    | 89         | 76.7           |
| Ejection Systolic Murmer at pulmonary Area | 30         | 25.9           |
| Pansystolic murmur at mitral area          | 17         | 14.7           |
| Early Diastolic Murmur at Aortic area      | 10         | 8.6            |
| Cardiac Failure                            | 16         | 13.8           |
| MIX SIGNS (Tychaycardia, Loud S1, Murmer)  | 33         | 28.4           |
| No cardiac signs                           | 12         | 10.3           |

**TABLE 5: X-ray, ECG and Echocardiography findings. (N = 116).**

| Variables                    | Number | %    |
|------------------------------|--------|------|
| Chest X-ray findings         |        |      |
| Normal                       | 64     | 55.2 |
| Cardiomegaly                 | 40     | 34.5 |
| Pulmonary hypertension       | 12     | 10.3 |
| Normal                       | 12     | 10.3 |
| ECG abnormal findings        |        |      |
| Sinus tachycardia            | 67     | 57.8 |
| Atrial fibrillation          | 30     | 25.9 |
| Left ventricular hypertrophy | 7      | 6.0  |
| Normal                       | 12     | 10.3 |
| Echocardiographic findings   |        |      |
| Systolic dysfunction         | 23     | 19.8 |
| Diastolic dysfunction        | 8      | 6.9  |
| Mitral regurgitation         | 23     | 19.8 |
| Left ventricular hypertrophy | 19     | 16.4 |
| Pulmonary hypertension       | 2      | 1.7  |
| Aortic regurgitation         | 3      | 2.6  |
| Tricuspid regurgitation      | 3      | 2.6  |
| No abnormality               | 35     | 30.2 |

## Discussion

Cardiac manifestations in thyrotoxicosis usually caused by enhanced sympathoadrenal activity or it could be due direct effect of thyroid hormones on heart.<sup>11</sup>

Thyroid hormones affects the cardiovascular system especially the heart directly and indirectly, especially through genomic and nongenomic mechanisms. These hormones especially T3 binds to nuclear receptor and affects the transcription of various genes, and these genes have important roles in cardiovascular function.<sup>12,13</sup> The cell membrane transport of calcium and other ions is mostly function of nongenomic effects. In addition, T3 also has heart indirectly via effects on the peripheral circulation. All these effects the hearts hemodynamics, cardiac filling, and myocardial contractility.<sup>14</sup>

The study by Ojamaa K *et al*<sup>15</sup> concluded that the thyroid hormones also alter cardiac muscle by downregulating the beta ( $\beta$ )- chain and upregulating the alpha ( $\alpha$ )-chain. In addition, by increasing calcium uptake during diastole it also effect on the sarco/endoplasmic reticulum.<sup>16</sup> Through acting on other ion channels such as Na/K-ATPase, Na/Ca<sup>++</sup> exchanger, and some voltage-gated K channels the thyroid hormone affects myocardial and vascular properties of body. The thyroid hormone also effects on cardiovascular system through change of hemodynamic balance in the body through stimulating to use oxygen more quickly, increasing metabolic product output, and relaxes the smooth muscle of arterial wall, all these ultimately leads peripheral vasodilation.<sup>17</sup>

The age group commonly affected in this is 20-60 which accounts for more 80% of the cases, almost same findings observed in other studies conducted in Pakistan.<sup>18</sup> Thyrotoxicosis is common in females as compared to males, same findings observed in our study where females were 72.4%. This also seen in other national and international studies.<sup>18,19</sup>

The most prevalent presenting symptoms in this study were heat intolerance (77.6%), weight loss (475.0%). These results consistence with other studies conducted in Pakistan<sup>20</sup> and in India.<sup>21,22</sup> The graves' disease is common etiological factor of thyrotoxicosis in our study, and it was responsible for thyrotoxicosis in 50.0% of the study subjects, almost same as observed by Khurana NK<sup>19</sup> and Nijithet *al*.<sup>21</sup>

In our study showed that the palpitation (69%76.4%) was the most common cardiac symptom as observed by other studies conducted in India. A study by Khurana *et al*<sup>19</sup> observed 72% and by Kandan *Vet al*<sup>22</sup>, it was 78%. The breathlessness (25%) and chest pain (4.3%) other less common symptoms observed in our study. Almost same frequency by other studies.<sup>19,21-22</sup>

Regarding the clinical signs the tachycardia (pulse rate >100 beats per minute) is commonly seen and it was observed in 88% of the subjects in this study, which was also observed by Kandan V *et al*.<sup>22</sup> and by Zargar AH *et al*.<sup>23</sup>

In our study 30 (25.9%) of subjects were present with atrial fibrillation. The prevalence of atrial fibrillation in thyrotoxicosis varies in different studies it was observed between 6 to 28%. Kandan V *et al*,<sup>22</sup> Barsela S *et al*<sup>24</sup> observed AF in 21% of patients, Nijith L *et al*<sup>22</sup> observed in 17.1%, and in same country, India, the Khurana *et al*<sup>19</sup> observed atrial fibrillation in 22%. Study in Saudi Arabia by Zargar *et al*<sup>23</sup> observed only 8.9%.

The lesser levels of TSH level in the blood is the major risk factor for the development of AF and it results higher mortality and morbidity due to embolic events.<sup>24</sup>

The 23 (19.8%) patients present with systolic dysfunction in our study, same results were seen in study conducted by Mercé J *et al*.<sup>25</sup> and 18% of subjects had systolic dysfunction. Almost same observations were seen in studies done by Nijith L *et al*<sup>21</sup> 17.8%, but studies done by Khurana NK *et al*<sup>19</sup> Kandan V *et al*<sup>22</sup> in same country they found a significantly lower prevalence of systolic dysfunction (3%).

The diastolic dysfunction in our study was 6.9%. Kundan *et al*<sup>22</sup> observed the 12% of patients with diastolic dysfunction in thyrotoxicosis. Nijith L *et al*<sup>21</sup> observed 10.8%, varies Khurana NK *et al*<sup>19</sup> observed only in 01% may be technical error.

In our study the pulmonary hypertension was present in 10.3% of patients, almost same as observed by Kundan *et al* in India<sup>22</sup>. Sui *et al*,<sup>26</sup> found higher cases and it were up to 47% patients with pulmonary hypertension with normal LV systolic function. May be the Inadequate sample size or technical issues may be the reason for the difference.

Over all the cardiovascular manifestations in thyrotoxicosis observed in our study are almost same as current studies. This manifestation may lead to serious mortality and morbidity so the early identification and treatment of these are important to save the lives.

### **Limitations**

This is the first research in our tertiary hospital to identify the cardiovascular manifestations in patients with thyrotoxicosis. because all participants were from a single institution so the sample size was limited and less heterogeneous. Second, the long-term effects of cardiovascular symptoms could not be assessed because the study was cross-sectional.

### **Conclusions**

The findings of our study showed that thyrotoxicosis was common in the third and fourth decades of life. Females were dominant as compared to males. Palpitation, chest pain, breathlessness were the dominant cardiac manifestations in thyrotoxicosis. So, it is recommended that all patients with thyrotoxicosis should be screened for cardiovascular problems. And patients with unexplained cardiovascular disease should be evaluated for thyroid diseases.

### **ETHICAL APPROVAL:**

Ethical approval was obtained from The PUMHSW's Ethical Review Committee (reference number).

### **PATIENTS' CONSENT:**

All participants provided written consent.

### **CONFLICTING OF INTEREST:**

The authors declared no competing interest.

**AUTHORS' CONTRIBUTION:**

Kumar J: Conceived the study and were involved in process mapping.

Khuhro BA: Involved in the data collection, interpretation, and drafting.

Jamali AA: Gave substantial contribution to interpretation of data and write-up of the manuscript.

Lohano AK, Arbab IA: Reviewed and revised the manuscript for important intellectual content.

Khuhro BA, Soomro MK: Critically reviewed and edited the final manuscript.

All the authors have approved the final version of the manuscript to be published.

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