



ORIGINAL ARTICLE

## Frequency of hypothyroidism among patients of pulmonary hypertension.

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**Article Citation:** Sami H, Butt NI, Tareen MQK, Khan S, Mahmood K, Ashfaq F. Frequency of hypothyroidism among patients of pulmonary hypertension. Professional Med J 2023; 30(01):10-13. <https://doi.org/10.29309/TPMJ/2023.30.01.7096>

**ABSTRACT... Objective:** To determine the frequency of hypothyroidism in patients with pulmonary hypertension. **Study Design:** Observational Cross-sectional study. **Setting:** Department of Medicine, Sandeman Provincial Hospital, Bolan University of Medical & Health Sciences Quetta Pakistan. **Period:** March 2020 to March 2021. **Material & Methods:** Pulmonary Hypertension was defined as mPASP of  $\geq 25$  mm Hg at rest on transthoracic echocardiogram and hypothyroidism was labeled when TSH was high with low Free T4 and/or Free T3. Patients with congestive cardiac failure, pulmonary malignancy or pulmonary metastasis assessed by history and examination were excluded from the study. Using non-probability consecutive sampling, 186 patients of both genders, aged 20-65 years with pulmonary hypertension were included. Demographic information along with clinical variables noted, echocardiography was done and thyroid profile was sent for each patient. **Results:** Mean age was  $41.2 \pm 11.2$  years with 56 (30.1%) males and 130 (69.9%) females. The mean height, weight and BMI were  $1.6 \pm 0.2$  meters,  $56.5 \pm 14.4$  kilograms and  $21.8 \pm 3.6$  kg/m<sup>2</sup> respectively. The mean mPASP was  $40.2 \pm 7.1$  mmHg. The mean serum TSH, free T3 and free T4 levels were  $6.6 \pm 4.8$  IU/L,  $2.5 \pm 1.0$  pmol/L and  $1.1 \pm 0.4$  pmol/L respectively. In our study, hypothyroidism was seen in 46 (24.7%) and was not significantly associated with age, gender, BMI or mPASP. **Conclusion:** Hypothyroidism was noted in about a quarter of the patients with pulmonary hypertension in this study.

**Key words:** Hypothyroidism, Pulmonary Hypertension, Pulmonary Artery Systolic Pressure.

## INTRODUCTION

Clinical features of hypothyroidism are non-specific and diverse including menstrual abnormalities in women, depression, constipation, coarse dry hair and dry skin, hair loss, lethargy, cold intolerance, bradycardia, weight gain and occasionally goiter.<sup>1</sup> Thyroid disorders may be accountable for various alterations in cardiovascular system pathophysiology and this may help in explaining the possible link of thyroid disorders with cardiovascular diseases.<sup>2,3</sup> Hypothyroidism is also called underactive thyroid disease and women are more likely to develop hypothyroidism than men.<sup>4</sup> Thyroid disorders are seen more frequently in patients with pulmonary hypertension (24%) as compared to other pulmonary disorders (15%) while in the general population hypothyroidism was seen in 8% women and 3% men.<sup>5,6</sup> The association of hypothyroidism with pulmonary

hypertension has been documented in some studies however prospective studies are uncommon with prevalence of hypothyroidism varying from 10% to 24%.<sup>2,4,6</sup> The study by Curnock et al.<sup>7</sup> with 27.5% men and 72.5% women with mean age  $43.5 \pm 15.9$  years and mean pulmonary artery systolic pressure  $58.7 \pm 14.8$  mmHg reported hypothyroidism in 22.5% patients with pulmonary hypertension. We do not know whether ethnic differences play a role in pathogenesis and outcome of hypothyroidism and pulmonary hypertension.

The rationale of our study was to determine the frequency of hypothyroidism in patients of pulmonary hypertension in Pakistani population and to document association of hypothyroidism with demographic variables.

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**Article received on:** 21/04/2022  
**Accepted for publication:** 19/09/2022

## MATERIAL & METHODS

The present observational cross-sectional study was undertaken at Department of Medicine, Sandeman Provincial Hospital, Bolan University of Medical & Health Sciences Quetta Pakistan from March 2020 to March 2021 to find out frequency of hypothyroidism among patients of pulmonary hypertension. Pulmonary Hypertension was labeled as mean pulmonary artery systolic pressure (mPASP) of  $\geq 25$  mm Hg while at rest measured on transthoracic echocardiogram. Moderate pulmonary hypertension was defined as mPASP 25-44 mmHg while severe pulmonary hypertension as mPASP  $\geq 45$  mmHg at rest. Normal ranges of serum TSH, free T3 and free T4 levels were 0.39-6.16 IU/ml, 1.4-4.2 pg/ml and 0.8-2.0 ng/ml respectively and hypothyroidism was labeled when TSH was high with low free T4 and/or free T3.

The calculated sample size was 186 patients<sup>7</sup> with 6% margin of error and 95% confidence level. Patients with congestive cardiac failure (ejection fraction  $\leq 30\%$  on echocardiography), pulmonary malignancy or pulmonary metastasis assessed by history and examination were excluded from the study. Using non-probability consecutive sampling, 186 patients of both genders, aged 20-65 years with pulmonary hypertension were included. Data was collected after Institutional ERB approval (973) and taking informed consent from the patients. Demographic information along with clinical variables of each patient was noted. Echocardiography was done to note mPASP and thyroid profile was sent for each patient. Data was compiled and analyzed through SPSS Version 20.0. Frequency and percentage was computed for qualitative variables while mean $\pm$ SD was calculated for quantitative variables. Stratification was done using Chi-square test keeping p-value  $\leq 0.05$  significant.

## RESULTS

A total of 186 patients with pulmonary hypertension were enrolled in our study having mean age of  $41.2 \pm 11.2$  years with 56 (30.1%) males and 130 (69.9%) females. Eighty-two (44.2%) were  $\leq 42$  years of age while 104 (55.8%) were aged  $\geq 43$  years. The mean height, weight and BMI

were  $1.6 \pm 0.2$  meters,  $56.5 \pm 14.4$  kilograms and  $21.8 \pm 3.6$  kg/m<sup>2</sup> respectively. Normal BMI was seen in 152 (81.7%). The mean of mean pulmonary artery systolic pressure (mPASP) was  $40.2 \pm 7.1$  mmHg. Moderate Pulmonary Hypertension was seen in 130 (69.9%) while 56 (30.1%) had severe pulmonary hypertension. The mean serum TSH, free T3 and free T4 levels were  $6.6 \pm 4.8$  IU/L,  $2.5 \pm 1.0$  pmol/L and  $1.1 \pm 0.4$  pmol/L respectively. In our study, hypothyroidism was seen in 46 (24.7%) patients. On stratification, hypothyroidism was not significantly associated with age, gender, BMI or mPASP as shown in Table-I.

| Clinical Variables             | Hypothyroidism |             | P-Value |
|--------------------------------|----------------|-------------|---------|
|                                | Present        | Absent      |         |
| <b>Age (years):</b>            |                |             |         |
| 20-42                          | 21 (25.6%)     | 61 (74.4%)  | 0.769   |
| 43-65                          | 25 (24.1%)     | 79 (75.9%)  |         |
| <b>Sex:</b>                    |                |             |         |
| Male                           | 13 (23.2%)     | 43 (76.8%)  | 0.753   |
| Female                         | 33 (25.4%)     | 97 (74.6%)  |         |
| <b>BMI (kg/m<sup>2</sup>):</b> |                |             |         |
| 17-24                          | 39 (25.6%)     | 113 (74.4%) | 0.103   |
| 25-30                          | 07 (20.5%)     | 27 (79.5%)  |         |
| <b>mPASP (mmHg):</b>           |                |             |         |
| 28-44                          | 30 (23.1%)     | 100 (76.9%) | 0.360   |
| 45-60                          | 16 (28.6%)     | 40 (71.4%)  |         |

**Table-I. Stratification of outcome (hypothyroidism) with regards to clinical variables**

## DISCUSSION

The hallmark of pulmonary hypertension is raised mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance caused by progressive pulmonary vascular remodeling which can result in right ventricular dysfunction if left untreated and subsequently right heart failure.<sup>6</sup> PHTN is defined as mPASP  $\geq 25$  mm Hg at rest or mPASP  $\geq 35$  mm Hg on exercise, with left ventricular end-diastolic pressure  $< 15$  mm Hg. The Dana Point Classification of pulmonary hypertension broadly classifies it into primary, secondary to left heart diseases, lung pathology, chronic thromboembolism, or metabolic causes.<sup>8</sup> Thyroid dysfunction, which belongs to the last category, may be a cause of pulmonary hypertension. The association of

hypothyroidism with pulmonary hypertension has been documented in some studies however prospective studies are uncommon with prevalence of hypothyroidism varying from 10% to 24%.<sup>2,4,6</sup>

In our study, female predominance was seen at 130 (69.9%) and hypothyroidism was reported in 46 (24.7%) patients with pulmonary hypertension. This is comparable to the study by Curnock et al.<sup>7</sup> with 27.5% men and 72.5% women with mean age  $43.5 \pm 15.9$  years and mean pulmonary artery systolic pressure  $58.7 \pm 14.8$  mmHg reporting hypothyroidism in 22.5% patients with pulmonary hypertension. In our study the mean mPASP was  $40.2 \pm 7.1$  mmHg with moderate pulmonary hypertension in 130 (69.9%) while 56 (30.1%) had severe pulmonary hypertension. Of the 130 with moderate pulmonary hypertension 30 (23.1%) were hypothyroid as compared to 16 (28.6%) of the 56 with severe pulmonary hypertension, but there was no significant association seen (p-value 0.360). The mean serum TSH, free T3 and free T4 levels were  $6.6 \pm 4.8$  IU/L,  $2.5 \pm 1.0$  pmol/L and  $1.1 \pm 0.4$  pmol/L respectively in our study, however hypothyroidism was not significantly associated with age (p-value: 0.769), gender (p-value: 0.753) and BMI (p-value: 0.103). In the study by Li et al.<sup>9</sup> with 356 patients of pulmonary hypertension and 698 controls without pulmonary hypertension were assessed to show thyroid disease in 85 (24%) with pulmonary hypertension as compared to 107 (15%) in controls. Ghamra et al.<sup>10</sup> demonstrated 20.1% prevalence of hypothyroidism in pulmonary hypertension patients.

Whether autoimmunity is a shared factor in etiology of both disorders and whether hypothyroidism plays a role in vasomotor instability of pulmonary hypertension is yet to be determined. Reports showing improvement in Raynaud's phenomena in hypothyroid patients after thyroid hormone replacement may suggest a possible vasomotor role of thyroxine.<sup>11</sup> Furthermore pulmonary hypertension is frequently seen in autoimmune connective tissue diseases and autoimmune antibodies such as antithyroglobulin antibodies are often seen in primary pulmonary hypertension patients without any overt thyroid disorder.<sup>12,13</sup> In

conclusion, we recommend routine assessment of thyroid status in patients of pulmonary hypertension especially those with right ventricular failure and low functional capacity. Further trials should be conducted to document whether or not thyroxine replacement therapy will improve morbidity and mortality caused by pulmonary hypertension. Our study was a single center study with a relatively small sample size and we recommend further studies with larger sample size to be conducted.

## CONCLUSION

In our study, hypothyroidism was noted in about a quarter of the patients with pulmonary hypertension. Therefore, we recommend routine checking of thyroid status of pulmonary hypertension patients so that this treatable cause may be rectified to reduce disease burden and morbidity.







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### AUTHORSHIP AND CONTRIBUTION DECLARATION

| No. | Author(s) Full Name  | Contribution to the paper  | Author(s) Signature   |
|-----|----------------------|--|---|
| 1   | Hiba Sami            | Collection and assembly of data, drafting of the manuscript.                               |  |
| 2   | Nauman Ismat Butt    | Analysis and interpretation of the data, Literature review and drafting of the manuscript. |  |
| 3   | M. Qasim Khan Tareen | Conception and design, drafting of the manuscript.   |  |
| 4   | Saima Khan           | Conception and design, Collection and assembly of data, Critical revision and review.      |  |
| 5   | Khalid Mahmood       | Conception and design, Collection and assembly of data, Critical revision and review.      |  |
| 6   | Fahmina Ashfaq       | Analysis and Interpretation of the data, Critical revision and review.                     |  |