ANALYSIS OF PATIENTS FOR PULMONARY HYPERTENSION USING 2D ECHO IN THYROID DISORDER: A TEACHING HOSPITAL BASED OBSERVATIONAL STUDY.

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Abstract:

Background: It can be primary or secondary. In contrast to primary Pulmonary Arterial Hypertension (PAH) which is a diagnosis of exclusion, secondary PAH is caused by various conditions most common being cardiac diseases, respiratory diseases or both co-existing.Thyroid dysfunction is known to cause Pulmonary Hypertension (PH) which is also known to be reversible by restoration of euthyroid state. Hence, timely diagnosis and institution of medications can prevent as well as treat the secondary PAH in these patients.

Aims and Objectives: To Analyze the patients for presence of Pulmonary Hypertension using 2D ECHO in thyroid disorder.

Materials and Methods: It was an observational prospective study which included 52 newly diagnosed patients with thyroid dysfunction. All were subjected to 2D echocardiography with detailed history and physical examination. Repeat echocardiographic assessment was done after 6 months of treatment for few patients to look for resolution of Pulmonary Hypertension (PH). The statistical analysis was carried out to determine the association of Pulmonary Hypertension with thyroid dysfunction using student's t-test and chi-square test of association.

Results and Observations: The study included 38 (74%) females and 14 (26%) males. PH was present in 11 (22%) patients. Repeat echocardiography after 10 months of treatment (Eltroxin 1.6 microgram/kg for hypothyroid patients and Carbimazole (5/10 mg BD/TDS for hyperthyroid) was performed (those who were diagnosed with Pulmonary Hypertension at the time of diagnosis of thyroid dysfunction) and reduction in Pulmonary Artery Systolic Pressure (PASP) was observed.

Conclusion:Significant percentage of patients with hypothyroidism developed various cardiovascular morbidities like DCM and pericardial effusion, moreover the level of T4 below a lower threshold level in hypothyroidism does not influence the severity of DCM or pericardial effusion or chamber size. High prevalence of Pulmonary Hypertension was observed in patients with thyroid dysfunctions at the time of diagnosis in the treatment naïve patients in the current study and it also reversed with treatment on repeat 2D-echo. It is, therefore, suggested that every patient of thyroid dysfunction should be screened for Pulmonary Hypertension, even though further studies are needed to substantiate this, due to an inherent small sample size of the study.

Keywords: Pulmonary Artery Systolic Pressure (PASP), Thyroid Disorder**,** Hypothyroidism, Hyperthyroidism, Pulmonary Hypertension(PH), Pulmonary Artery Hypertension (PAH).

Introduction:

Pulmonary Artery Hypertension (PAH) is a hemodynamic and pathophysiological condition defined as an increase in mean Pulmonary Artery Pressure (mPAP) > 25 mm Hg at rest and > 30 mm Hg during exercise, as assessed by right heart catheterization.[1] CAD risk in Hypothyroidism As a result of increases in risk factors including hypercholesterolemia, hypertension, and elevated levels of homocysteine, patients with hypothyroidism may have increased risk for atherosclerosis and coronary and systemic vascular disease. [2,3] Recent studies have shown increases in abdominal aortic atherosclerosis in elderly women patients with even mild hypothyroidism.[4] .It can be primary or secondary. In contrast to primary PAH which is a diagnosis of exclusion, secondary Pulmonary Hypertension (PH) is caused by various conditions most common being cardiac diseases, respiratory diseases or both co-existing. Among the less common causes are connective tissue diseases, haemoglobinopathies like sickle cell anemia, infections like HIV, metabolic disorders like glycogen storage diseases, drugs, toxins, thyroid dysfunction etc.[5] A study suggested that, there was an increased incidence of PH in patients with thyroid dysfunctions (hypothyroidism and hyperthyroidism) and has been kept under WHO Group V of Dana Point, 2008 Classification of PAH[6] .PH secondary to thyroid dysfunction is found to be reversible by restoration of euthyroid state i.e., they have a good prognosis if diagnosed and treated timely . There are a lot of patients of thyroid dysfunction who have unexplained dyspnea and the underlying cause maybe Pulmonary Hypertension. Hence, the purpose of our study was to observe the prevalence of Pulmonary Hypertension in newly diagnosed, treatment naïve patients of thyroid dysfunction (both hypo and hyperthyroidism) using 2D-echocardiographic assessment and to assess the reversibility of PH with treatment, documented by 2D-echocardiography.

Materials And Methods:

This was Observational study carried out in Dr Patnam Mahender Reddy Institute Of Medical Sciences, Chevella, Telangana, Bharat. Duration of Study - April 2022 to March 2023

Sample Size: 52 cases

Sampling Method: Simple random sampling All cases taken for the study are evaluated as follows, Cases coming to our Hospital either on OPD / IPD basis were screened for clinical evidence of hypothyroidism or hyperthyroidism as per the prestructured proforma. Thyroid function tests were done in all cases using Enzyme immunoassay to confirm the presence of hypo or hyperthyroidism. Electrocardiography was recorded in all the patients. Chest X-rays were done and examined for roentgenographic signs of pulmonary hypertension, i.e. right descending pulmonary artery diameter of >1.8 cm. 2D-Echocardiography was done in all cases and screened for the presence and severity of pulmonary hypertension.

Right ventricular systolic pressure (RVSP) was determined by the Tricuspid Regurgitation Jet using Bernouli equation by using 2D-Echocardiography.CVP was not elevated on clinical examination and therefore assumed to be 5 mmHg. Mean right atrial pressure (RAP) is equivalent to CVP. Pulmonary Artery Systolic Pressure (PASP) was calculated by adding up RAP and RVSP. Patients with PASP of >30 mmHg were treated for the underlying hypothyroidism (thyroxine) and hyperthyroidism (Carbimazole) and reassessed after a period of 10 months with 2D-Echocardiography for the reduction in PASP.

INCLUSION CRITERIA-

1. Patients with hypo/hyperthyroidism.
2. Patients more than 18 years of age, both male and female
3. Patients willing to participate in the study

EXCLUSION CRITERIA- Patients with/who are
1. Clinical features of chronic pulmonary diseases like COAD, interstitial lung disease
2. Known cases of connective tissue diseases.
3. Underlying cardiac diseases like VSD, cardiomyopathies, myocarditis etc.
4. Chronic liver disease or cirrhosis.
5. Chronic hypoxemia.
6. Patients on treatment for thyroid disorders for more than 6 months.

Results and Observations:

In our study out of the 52 cases, 38 (74%) cases were of Hypothyroidism and 14 (26%) cases were of Hyperthyroidism.

Table 1: Distribution of mean PASP using 2D-ECHO.

		Mean± Sd	P value
Variables	Hypothyroidism	Hyperthyroidism	
2D-ECHO PASP(RVSP+RA)	26.97±5.16	30.62±9.57	0.09

Unpaired t test is applied. P value is significant if < 0.05 PASP value in patients with hyperthyroidism was 30.62mm Hg while that in the patients with hypothyroidism was 26.97mm Hg. Difference between them was comparable.

Table 2: Comparison of PASP in Hypothyroidism and Hyperthyroidism

PASP Group			Thyroid Status		Grand total
	Hypothyroidism		Hyperthyroidism		
	N	%	N	%	
Normal (PASP≤ 30 mm Hg)	31	81.08	10	69.23	41
Mild (PASP 31 to 45 mm Hg)	7	18.92	2	15.38	9
Moderate (PASP 46 to 60 mm Hg)	0	0	2	15.38	2
Severe (PASP>60 mm Hg	0	0	0	0	0
Grand total	38	74	14	26	52

81.08% patients with hypothyroidism and 69.23% patients with hyperthyroidism had normal PASP level. While 15.38% patients with hyperthyroidism had mild and moderate PASP each, only 18.92% with hypothyroidism had mild PASP.

Table 3: Comparison of PASP in the follow up group: pre treatment and post treatment.

		Mean± Sd	P value
Variables	Before	After follow up	
2D-ECHO PASP(RVSP+RA)	38.82±5.51	30±5.14	0.001

Paired t test is applied. P value is significant if < 0.05. The mean PASP by Doppler Echocardiography was 38.82 mm of Hg in the pre-treatment group. And the mean PASP during the follow up (after 10 months) was 30 mm of Hg**.**

Table 4: Comparison of TSH, T3, T4 and PASP among patients of Hypothyroidism in the follow up group, pre and post.

Variables	Hypothyroidism (Mean± Sd)		P value
	Before	After follow up	
TSH (uIU/ml)	16.62±10.36	3.52±1.57	0.01

T3 (ng/ml)	0.67±0.19	1.14±0.42	0.05
T4 (ug/dl	5.14±2.83	8.66±1.55	0.004
2D-ECHO PASP mm Hg	36.14±3.29	29.71±5.5	0.006

Paired 't' test applied. 'P' value is significant if < 0.05 Among the patients in the Hypothyroidism group with Pulmonary Hypertension, the pre-treatment values of TSH and PASP were high and reduced in the follow-up (after 10 months of treatment).

Table 5: Comparison of TSH, T3, T4 and PASP among patients of Hyperthyroidism in the follow up group, pre and post treatment.

Variables	Hyperthyroidism (Mean± Sd)		P value
	Before	After follow up	
TSH (uIU/ml)	0.1±0.04	2.54±1.84	0.07
T3 (ng/ml)	2.9±0.72	1.16±0.20	0.018
T4 (ug/dl	16.83±2.88	9.53±1.34	0.013
2D-ECHO PASP mm Hg	43.5±5.80	30.5±5.2	0.023

Paired 't' test applied. 'P' value is significant if < 0.05 Among the patients in the Hyperthyroidism group with Pulmonary Hypertension, the mean pre-treatment value of TSH was 0.1 and increased to 2.54 in the follow up. Mean PASP value was 43.5 and reduced in the follow-up (after 10 months of treatment) to 30.5.

Discussion:

Cardiovascular manifestations are frequently seen in both hypothyroidism and hyperthyroidism. The spectrum of CVS manifestations in thyroid dysfunctions includes pulmonary artery hypertension, pericardial effusion, DCMP, arrhythmias, systolic as well as diastolic dysfunction and pulmonary regurgitation [7]. Several studies have shown associations between thyroid disease and pulmonary hypertension. In Pulmonary Artery Hypertension (PAH) there is a sustained increase in pulmonary artery pressure and a progressive increase in pulmonary vascular resistance, which leads to right ventricular insufficiency and often premature death. Mean pulmonary artery pressure (MPAP), under physiological conditions and at sea level, is < 20 mmHg, and pulmonary artery systolic pressure (PASP) is < 30 mmHg. In a study by Marvisi M et al., prevalence of Pulmonary Hypertension in recently diagnosed hyperthyroids was found to be 35% [8] while in his other study, involving 114 patients with hyperthyroidism (47 with Graves' disease and 67 with multinodular goiter), the prevalence of Pulmonary Hypertension was 43% [9] . Here PASP, as estimated by echocardiography, was > 30 mmHg. In a study by Mercé J et al. of 39 patients recently diagnosed with hyperthyroidism, the prevalence of Pulmonary Hypertension (PASP> 35mm Hg) was found to be 41% [10] . In a retrospective study by Curnock AL et al., the prevalence of hypothyroidism in 41 patients with PH was found to be 22.5% which was higher than the incidence that we found in our study. In a study by Li JH et al., 356 patients having PAH and 698 controls not having PAH were retrospectively evaluated. Of the patients with PAH, thyroid disease was present in 85 patients(24%), and 107 (15%) in controls.[11] In our study PASP in hyperthyroidism was 30.62 while hypothyroidism was 26.97. Difference between them was comparable. 30.76% patients with hyperthyroidism had mild PASP and whereas 18.92% with hypothyroidism had mild to moderate PASP. Our finding on PASP is on the line with published studies. Reversibility of pulmonary hypertension after treatment of hypothyroidism and hyperthyroidism Mean PASP values among patients in the follow up group (11 patients: 7 hypothyroids and 4 hyperthyroids) were 38.82 and 30, pre-treatment and post-treatment respectively. This shows a decrease in the overall PASP values following treatment. Mean TSH, T3, T4 and PASP (pre-treatment) values among the follow up patients were 16.62, 0.67, 5.14, and 36.14 respectively in the hypothyroidism group. Posttreatment

values of Mean TSH, T3, T4 and PASP were 3.52, 1.14, 8.66, and 29.71. Mean TSH value was decreased after 10 months of follow up while values of T3 and T4 had increased after 10 months of follow up. Mean PASP value also decreased in the follow up after 10 months following treatment. Mean TSH, T3, T4 and PASP (pre-treatment) values among the follow up patients were 0.1, 2.9, 16.83, and 43.5 respectively in the hyperthyroidism group. Posttreatment values of Mean TSH, T3, T4 and PASP were 2.54, 1.16, 9.53, and 30.5. Mean TSH value was increased after 10 months of follow up while values of T3 and T4 had decreased after 10 months of follow up. Mean PASP values also decreased in the follow up after 10 months following treatment. The change in PASP after the treatment was comparable with the findings of other studies. In a study by Thurnheer R et al. in 1997 [12], in 4 hyperthyroid cases mean pre-treatment PASP was 40 ± 11 mmHg. which decreased to 25 ± 6 mmHg after treatment with radioactive iodine or ethionamides. In an observational study by Marvisi M et al.,6 in 34 hyperthyroid patients (17 without treatment; 17 treated with methimazole; control group 17), mild pulmonary hypertension was present in 35% of the patients in the untreated hyperthyroid group (mean PASP of 28.88 ± 6.41 mmHg) and in none of the patients of the other groups. In other study by Marvisi M et al. , the role of methimazole in the regulation of pulmonary vascular resistance in hyperthyroid patients with PAH was studied. After treatment for a period of 15 days, PASP values in the methimazole group decreased from a value of 34.3 ± 3.2 mmHg to 29.2 ± 3.3 mmHg , compared to the partial thyroidectomy group, where decrease was from 34.3 ± 3.0 mmHg to 34.1 ± 2.9 mmHg($p < 0.001$). Methimazole's role in regulating production of N(G)-nitro-L-arginine methyl ester (L-NAME), an arginine analogue, producing acute NO synthesis inhibition has been shown in some studies. In literature, the etiology of strong relationship between thyroid disease and pulmonary hypertension remains unclear. One possible explanation is that increased total blood volume contributes to increased pulmonary blood flow and pulmonary vascular resistance. Another possibility is the direct effect of thyroid hormones on the pulmonary vasculature. This theory is supported by, the reversible change of pulmonary hypertension seen after successful treatment of hyperthyroidism. The mechanisms include an increase in metabolism of intrinsic pulmonary vasodilating substances and a decrease in vasoconstrictor metabolism. Besides the effect of an excess of thyroid hormones, systemic auto antibodies may also play a role in pulmonary vascular endothelium injury and lead to pulmonary hypertension. The development of PH in a patient of thyroid dysfunction was not affected by its type (p-value 0.113) or the serum TSH levels in the study. Autoimmunity seems to have a role in the development of PH in thyroid dysfunctions, as observed in the study by raised anti TPO levels [13,14].

Conclusion:

Significant percentage of patients with hypothyroidism developed various cardiovascular morbidities like DCM and pericardial effusion; moreover the level of T4 below a lower threshold level in hypothyroidism does not influence the severity of DCM or pericardial effusion or chamber size. High prevalence of Pulmonary Hypertension was observed in patients with thyroid dysfunctions at the time of diagnosis in the treatment naïve patients in the current study and it also reversed with treatment on repeat 2D-echo. It is, therefore, suggested that every patient of thyroid dysfunction should be screened for Pulmonary Hypertension, even though further studies are needed to substantiate this, due to an inherent small sample size of the study. My study was a prospective observational study and patients of hypothyroidism/hyperthyroidism with Pulmonary Hypertension were treated for hypo/hyperthyroidism and were reassessed after 10 months.

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