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A prospective study of two-dimensional echocardiographic assessment of pulmonary artery hypertension in thyroid dysfunction

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Abstract
Introduction: The association between hyperthyroidism and Pulmonary hypertension has been described previously. Though some studies evaluated the prevalence of Pulmonary hypertension in patients with hypothyroidism and hyperthyroidism and treatment modalities for reduction of PAH,very few studies have evaluated the effects of treatment of thyroid disease in treatment of *PAH*.
Aim: To study the occurrence of Pulmonary hypertension in patients with hypothyroidism and hyperthyroidism and the reversibility of Pulmonary hypertension on treating the underlying hypothyroidism and hyperthyroidism thereby reducing the mortality and morbidity associated with Pulmonary hypertension.
Material and Methods: Total of 75 patients attending outdoor department or admitted in various wards of Guru Nanak Dev Hospital, Amritsar were taken. The patients were divided into 2 groups namely: Group I including 50 Patients of hypothyroidism and hyperthyroidism and Group II with 25 Patients as control. Every subject was subjected to transthoracic two-dimensional echocardiography and pulmonary artery systolic pressure was obtained. All the patients were treated for underlying thyroid dysfunction and those having higher PASP were subjected to repeat two-dimensional echocardiography after a period of 12 weeks of treatment and repeat pulmonary artery systolic pressures were obtained.
Results: Hypothyroidism is more common form of thyroid disorder with female predominance. Pulmonary artery hypertension was detected in 24% patients with thyroid dysfunction. None of the patient from the control group had elevated PASP. Pulmonary artery hypertension was more common in hyperthyroid patients. Mean average of PASP in group 1 was 26.89±7.29 whereas in group 2 it was 23.60±1.70.Inhyperthyroid patients mean PASP was 31.10±9.80 whereas in hypothyroid patients it was 25.09±5.09. Mean PASP in the pre-treatment group was 36.71±5.96 mmHg whereas in post- treatment group it decreased to 30.27±4.77mmHg.
Conclusion: Pulmonary artery hypertension can be reversed after correction of underlying thyroid disorder. Results of our study showed importance of early echocardiography in patients with thyroid dysfunctions for early diagnosis of pulmonary artery hypertension and to timely prevent it.

Keywords: Pulmonary hypertension, hypothyroidism, hyperthyroidism, pulmonary artery hypertension(PAH), pulmonary artery systolic pressure(PASP)

Introduction

Thyroid disease is quite common. Current estimates suggest that it affects as many as 9% to 15% of the adult female population and a smaller percentage of adult males[1]. The cardiovascular signs and symptoms of thyroid disease are some of the most profound and clinically relevant findings that accompany both hyperthyroidism and hypothyroidism[2].

Thyroid hormone causes decreased resistance in peripheral arterioles through a direct effect on VSM and decreased mean arterial pressure, which, when sensed in the kidneys, activates the renin-angiotensin-aldosterone system and increases renal sodium absorption. T3 also increases erythropoietin synthesis, which leads to an increase in red cell mass. These changes combine to promote an increase in blood volume and preload. In hyperthyroidism, these combined effects increase cardiac output 50% to 300% higher than in normal individuals. In hypothyroidism, the cardiovascular effects are diametrically opposite and cardiac output may decrease by 30% to 50%[3].Whereas the effects of T3 on the heart are well recognized. The ability of thyroid hormone to alter VSM and endothelial cell function are also important.

The association between hyperthyroidism and Pulmonary hypertension has been described since the early 1980s. Nakchandi *et al.* [4] suggested that Pulmonary hypertension in a patient with hyperthyroidism was probably caused by a high cardiac output, endothelial damage/ dysfunction, or increased metabolism of intrinsic pulmonary vasodilating substance, also acetylcholine which induces pulmonary vasodilator response, plays a role. In the presence of hyperthyroidism, it is possible that the cholinergic output is decreased and the vasodilator

response is diminished thus increasing pulmonary vascular resistance. Some studies have shown the prevalence of Pulmonary arterial hypertension (PAH) in patients with hyperthyroidism[5,6].

The treatment of PAH has possible effects on the thyroid. Prostacyclin (epoprostenol) as well as prostacyclin analog (iloprost) are used in the treatment of PAH plays an important role in the modulation of thyroid function[7,8].L-arginine, an NO synthase substrate, increase the production of NO and has been used in the treatment of PAH. In addition, it is known that the production of NO is decreased in patients with hyperthyroidism.

Though some studies evaluated the prevalence of Pulmonary hypertension in patients with hypothyroidism and hyperthyroidism and treatment modalities for reduction of PAH. Very few studies have evaluated the effects of treatment of thyroid disease in treatment of PAH.

Hence this study has been undertaken to study the occurrence of Pulmonary hypertension in patients with hypothyroidism and hyperthyroidism and the reversibility of Pulmonary hypertension on treating the underlying hypothyroidism and hyperthyroidism thereby reducing the mortality and morbidity associated with Pulmonary hypertension.

Material and Methods

The present open label, prospective single centre study was conducted on 75 patients attending outdoor department or admitted in various wards of Guru Nanak Dev Hospital, Amritsar. Diabetic patients (Both type 1 and type 2 Diabetics.) Patients having thyroiditis, with other endocrine disorders, pregnant patients, anemic patients having hemoglobin less than 10 mg%, drug induced thyroid disorders, with any other hyperdynamic state, with chronic renal failure and patients with significant coronary artery disease or cardiomyopathy or valvular heart diseases were excluded from the study.

Patients fulfilling the above-mentioned criteria were apprised of the type of study being carried out and their informed and written consent was obtained. The patients were divided into 2 groups namely: Group I including 50 Patients of hypothyroidism and hyperthyroidism and Group II with 25 Patients as control. After detailed history and clinical examinaton, all patients underwent fasting thyroid function test which included T3, T4 and TSH. Routine investigations like Hb, TLC, DLC, LFTs, RFTs, X-Ray Chest for heart size. Transthoracic two-dimensional echocardiography was done in every case at base line and after euthyroid state.

T3, T4 and TSH Estimation: The quantitative determination of T3 (triiodothyronine), T4 (thyroxine) and TSH (thyroid stimulating hormone) were done by enzyme immunoassay using commercially available kits.

Echocardiography: A trans thoracic echocardiography (TTE) examination was performed in all subjects using available Color Doppler Echocardiography (CDE) machine with an adult transducer of 2.5m Hz (Philips IE33). Parasternal long and short-axis, apical 4 chamber and two chamber views were obtained. 2D Echocardiography was done in all cases and screened for the presence and severity of Pulmonary hypertension. Normal PASP values taken were < 30mmHg. Mild pulmonary arterial hypertension (PAH) – pulmonary artery systolic pressure (PASP between 31-45mmHg; moderate PAH – PASP between 46-60mmHg and severe PAH – PASP >60mmHg. Patients with PASP of >30 mmHg were treated for the underlying hypothyroidism (thyroxine) and hyperthyroidism (Carbimazole) and reassessed after a period of 3 months (12 weeks) with 2D Echocardiography for the reduction in PASP.

Statistical Analysis

Results of demographic characteristics and echocardiographic parameters were expressed as mean±standard deviation. All parameters of the two groups were compared using appropriate statistical methods.P value <0.05 was considered as statistically significant.

Results

The results of the our study show that in group I out of 50 cases 35 (70%) patients were of hypothyroidism and 15 (30%) patients were of hyperthyroidism. Majority of patients in group 1 and 2 were in the age group 21- 60 years. The mean age in hypothyroidism patients was 43.37±11.56 and in hyperthyroidism was 38.53±10.93.

In group I total no. of patients were 50, out of which 39 (78%) were female and 11 (22%) were male. In group II, total no. of patients were 25, out of which 19 (76%) were female and 6 (24%) male.

Among the patients with hypothyroidism weight gain (71.43%) was the most common symptom followed by lethargy (68.57%). In patients with hyperthyroidism, palpitation (80%) and weight loss (80%) were the most common symptoms followed by breathlessness (73.33%). In hyperthyroidism patients had goiter (26.67%), lethargy (6.67%), hyperactivity/irritability (60%), heat intolerance (33.33%), weight loss (80%), tachycardia (66.67%). Mean pulse rate was found to be 101.93+-13.67.

Mean PASP in group I was 26.89±7.29 and in group II was 23.60±1.70. p value was 0.029 which is statistically significant (p<0.05).Mean value of TSH, T3 and T4 in patients with hypothyroidism and hyperthyroidism as observed are tabulated in table1. Differences between all above mentioned parameters were found to be statistically highly significant.

Table 1: Mean Value of PASP, TSH, T3 and T4 in Patients with Hypothyroidism And Hyperthyroidism

	Hypothyroidism	Hyperthyroidism	Total
2D Echo PASP (mm of Hg)	25.09±5.09	31.10±9.80	26.89±7.29
TSH (uIU/ml)	17.06±13.14	0.64±1.76	12.13±13.36
T3 (ng/ml)	0.89±0.67	2.89±1.90	1.49±1.48
T4 (ug/dl)	6.18±2.85	14.98±5.67	8.82±5.61

On comparison of PASP values in both groups it was observed that 10% of patients in group I had PASP values between 10 to 20 mmHg while none of the patients in group II had values <20mmHg. 66% of patients in group I and 100% patients of group II had PASP values between 20-30 mmHg. 18% of patients of group I had PASP values between 31-45 mmHg while none of the patients from group II had PASP >30mmHg. 6% of patients of group I had PASP values between 46-60 mmHg while none of the patients from group II had values >46mmHg. None of the patients from group I or group II had PASP values >60mmHg.(Figure 1)

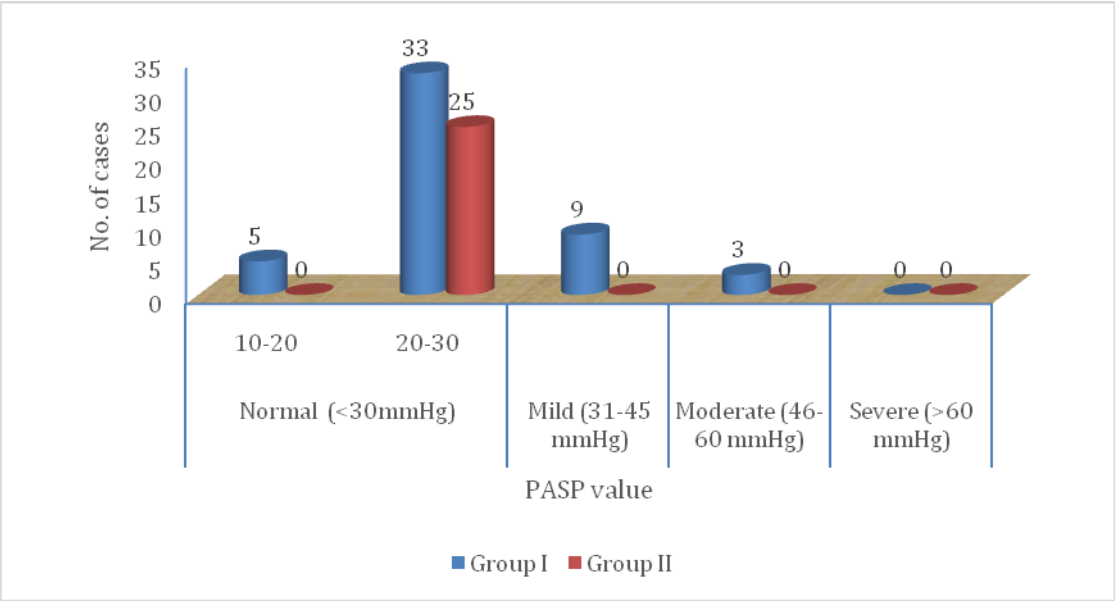

Fig 1: Comparison of PASP in Patients in Group I and Group II

Further, on comparison of PASP values between hypo and hyperthyroidism patients, 82.86% of patients with hypothyroidism and 60% of patients with hyperthyroidism had normal PASP values (<30 mmHg). 17.14% of patients with hypothyroidism and 20% of patients with hyperthyroidism had mild pulmonary artery hypertension (PASP 31-45 mmHg). 20% of patients with hyperthyroidism and no patients with hypothyroidism had moderate pulmonary artery hypertension (PASP 46-60 mmHg). None of the patients both with hypothyroidism or hyperthyroidism had severe pulmonary artery hypertension (PASP >60 mmHg). (figure 2)

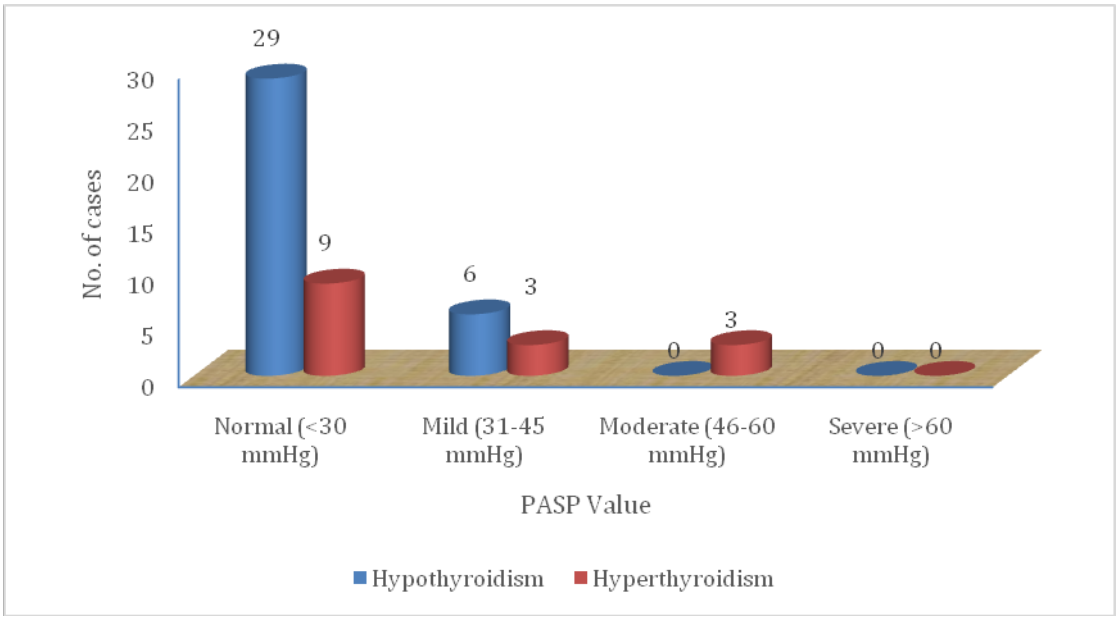

Fig 2: Comparison of PASP Values Within Hypothyroidism and Hyperthyroidism Patients

Pretreatment and post treatment comparisons

The mean PASP value by Doppler echocardiography was 36.72±5.96 mmHg in the pre-treatment group. And the mean PASP in post-treatment patients was 30.27 ± in 4.77 mmHg. Difference between both the values was statistically significant (p=0.001).

Among the patients with hypothyroidism with PAH, the pre-treatment values of TSH (16.62±10.36 uIU/ml) and that of PASP (33.83±2.40 mmHg) were high. The values of TSH (5.75±4.33 uIU/ml) and PASP (27.16±1.72 mmHg) reduced after the treatment for 12 weeks. The difference was statistically significant. (Table 2)

Table 2: Comparison of PASP, TSH, T3, T4 and Mean PASP Among Patients with Hypothyroidism Pre-Treatment and Post-Treatment

Variable (Mean±SD)	Hypothyroidism		P value
	Pre-treatment	Post-treatment	
TSH (uIU/ml)	17.24±11.25	5.75±4.33	0.041
T3 (ng/ml)	0.96±0.43	1.57±0.41	0.031
T4 (ug/dl)	5.91±1.60	9.36±1.78	0.006
PASP (mmHg)	33.83±2.40	27.16±1.72	0.001

Further Among the patients with hyperthyroidism with PAH, the mean pre-treatment values of TSH (0.166±0.12 uIU/ml) increased to 2.54±1.90 and that of PASP (40.02±7.35 mmHg) decreased to 31.40±5.41mmHg, after the treatment for 12 weeks. The difference was statistically significant. (Table 3)

Table 3: Comparison of TSH, T3, T4 and mean PASP among patients with hyperthyroidism pre-treatment and post-treatment

Variable (Mean±SD)	Hyperthyroidism		P value
	Pre-treatment	Post-treatment	
TSH (uIU/ml)	0.166±0.12	2.54±1.90	0.023
T3 (ng/ml)	2.24±0.26	1.32±0.26	0.001
T4 (ug/dl)	14.01±053	9.55±0.89	0.002
PASP (mmHg)	40.02±7.35	31.40±5.41	0.047

Discussion

The cardiac complications of long-standing hypothyroidism and hyperthyroidism are serious if are not diagnosed properly earlier. Several studies have shown associations between thyroid disease and Pulmonary hypertension. As a non- invasive method, 2D-echocardiography can play an important role in recognizing the pulmonary artery hypertension. In the present study we carried out an investigation of pulmonary artery systolic pressures in both hypothyroid and hyperthyroid patients to study the occurrence of pulmonary artery hypertension and the reversibility of Pulmonary hypertension on treating the underlying thyroid dysfunction.

Hypothyroidism is more common form of thyroid disorder. In the present study, we also observed that our study sample comprised of 70% hypothyroid and 30% cases of hyperthyroidism. Our study showed that female preponderance was seen in both hypothyroidism and hyperthyroidism. In similarity to ours Vanderpump MPJ *et al*.[9,10]. MulkiShilpa *et al*. [11] and Vishwanath *et al*. [12] also reported such predominance in their studies.

In our study Pulmonary artery hypertension was detected in 24% patients with thyroid dysfunction. None of the patient from the control group had elevated PASP. It was more common in hyperthyroid patients. High PASP was seen in 40% cases of hyperthyroidism as compared to 17.14% cases in hypothyroidism.

In a study Marvisi M *et al*,evaluated patients recently diagnosed with hyperthyroidism, the prevalence of PAH was found to be 35%[13]. In another study by Marvisi M *et al*, involving 114 patients with hyperthyroidism (47 with Graves' disease and 67 with multinodular goiter), the prevalence of PAH was found to be 43%[14]. In those two studies, a diagnosis of PAH was made when PASP, as estimated by echocardiography, was >30mmHg.In other study by Merce J *et al*. [15] of 39 consecutive patients recently diagnosed with hyperthyroidism, the prevalence of PAH was found to be 41%, a diagnosis of PAH was made when PASP, as estimated by echocardiography, was > 35 mmHg.

In a retrospective study by Curnock *et al*,[16] the prevalence of hypothyroidism in 41 patients with PAH (MPAP > 25 mmHg at rest, as estimated by right heart catheterization) was found to be 22.5% which was definitely higher than the incidence(17.14%) that we found in our study.

Our study showed an overall decrease in the PASP values following treatment of underlying thyroid dysfunction. Mean PASP values among patients in the follow up group {12 patients; hypothyroidism (6) and hyperthyroidism (6)} was compared to the pre-treatment values. In hypothyroidism patients; the pre-treatment Mean TSH, T3, T4 and PASP values were 17.24±11.25ulU/ml, 0.96±0.43ng/ml, 5.91±1.60ug/ml and 33.83±2.40mmHg respectively. Post-treatment values of Mean TSH, T3, T4 and PASP were 5.75±4.33, 1.57±0.41, 9.36±1.78and 1.72 respectively. It was seen that the mean TSH values decreased after 12 weeks of treatment while values of T3 and T4 increased after treatment. Mean PASP values also decreased in the follow up group.

In the patients with hyperthyroidism, pre-treatment Mean TSH, T3, T4 and PASP values were 0.166±0.12uIU/ml, 2.24±0.26ng/ml, 14.01±0.53ug/dl and 40.02±7.365 mmHg respectively. Post treatment Mean TSH, T3, T4 and PASP values were 2.54±1.90uIU/ml, 1.32±0.26ng/ml, 9.55±0.89ug/dl and 31.40±5.41mmHg respectively. It was seen that the mean TSH values increased after 12 weeks of treatment while values of T3 and T4 decreased after treatment. Mean PASP values also decreased in the follow up group. The change in the PASP values after treatment was statistically significant.

In a study conducted by Thurnheer R *et al*,[17] in 1997, 4 cases of hyperthyroidism and concomitant PAH were described. The mean pre-treatment PASP was 40±11mmHg. The patients were treated with radioactive iodine or ethionamides. After the treatment PASP decreased to a mean of 25+-6 mmHg in all patients.

Marvisi M *et al*,[13] studied the role of methimazole in the regulation of pulmonary vascular resistance in patients with hyperthyroidism and PAH were evaluated in patients treated with methimazole. Author found that the previous studies have demonstrated that methimazole can regulate the production of N (G)-nitro-L-arginine methy1 ester (L-NAME), an arginine analogue, producing acute NO synthesis inhibition, as well as presenting vasoactive properties related to the pulmonary and systemic vasculature.

It is seen that even small differences in thyroid function are associated with measurable differences in energy expenditure. A prolonged decrease in energy expenditure might well lead to increase in body weight. In our study, we found that BMI of the patients with hypothyroidism (26.86kg/m^2) was significantly higher as compared to patients with hyperthyroidism

($20.9kg/m^2$). In a study of elderly subjects conducted by Lindeman RD *et al*. [18] in 2003, a possible association between mild hyperthyroidism and BMI was found among women.

Patients with hyperthyroidism mostly presented with hyperactivity/irritability, heat intolerance, weight loss, palpitations, breathlessness and tachycardia. While patients with hypothyroidism frequently encountered clinical features included weight gain/ edema, lethargy, constipation and delayed ankle jerk.

Khurram I *et al* in their study of 394 patients with hypothyroidism reported weakness as one of the commonest symptoms (98%) followed by lethargy (67.9%) Constipation (60.0%), Depression (53.7%), cold intolerance (50.9%), weight gain (44.9%) Parenthesia (46.2%), Menorrhagia (38.6%), hoarse voice (36.7%), Edema of face (63.3%), Peripheral edema (60.6%), Skin changes (14.7%), Dyspnea (30.2%), Slow relaxation of deep tendon reflexes (21%)[19].

Singhal *et al* had given usual symptoms as irritability, heat intolerance and excessive sweating, palpitations weight loss with increased appetite, increased bowel frequency, and oligomenorrhoea. Author concluded that the people with hyperthyroidism also often have tachycardia, fine tremors, warm and moist skin, muscle weakness and eyelid retraction or lid lag[20].

Conclusion

Results of our study showed importance of early echocardiography in patients with thyroid dysfunctions for early diagnosis of pulmonary artery hypertension and to timely prevent it. Also, our results suggest that Pulmonary artery hypertension can be reversed after correction of underlying thyroid disorder. Hence, Thyroid dysfunction being a significant cause of pulmonary artery hypertension must be excluded in patients with unexplained Pulmonary hypertension.

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