PULMONARY HYPERTENSION IN HYPOTHYROIDISM- A PROSPECTIVE, INTERVENTIONAL STUDY

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ABSTRACT

BACKGROUND

Hypothyroidism, a frequent endocrine disorder affects ~11% of the Indians. Though there are studies reporting the co-occurrence of hypothyroidism and Pulmonary Arterial Hypertension (PAH), evidence-based literature is very limited.

The aim of the study is to evaluate the occurrence and severity of PAH in patients diagnosed with hypothyroidism and to examine the reversibility of the disease on treating the underlying hypothyroidism.

MATERIALS AND METHODS

The prospective, interventional study was conducted at a tertiary care center in south India for a period of one year. Subjects with clinical and biochemical evidence of hypothyroidism were included in the study. Doppler echocardiography was used for diagnosing PAH in recruited subjects. Subjects with PAH were treated for the underlying hypothyroidism and a follow-up was conducted after 10 months. The subjects with and without PAH were compared for various clinical and demographic variables and their significance was studied. All the statistical analyses were performed using MedCalc software. P value <0.05 was considered as statistically significant.

RESULTS

The study enrolled a total of 75 subjects with a mean age of 46.33 ± 13.98 years. Abnormal mean pulmonary artery pressure (mild and moderate) was noted only in 7 subjects. Variables like age, gender, goitre, T3 and T4 levels did not show significant variation between hypothyroid subjects with and without PAH. The follow-up conducted after 10 months of treatment for hypothyroidism demonstrated improvement in mean pulmonary artery pressure and Thyroid Stimulating Hormone (TSH) levels in a remarkable number of hypothyroid subjects with PAH.

CONCLUSION

Further studies are needed to corroborate the association between PAH and hypothyroidism. Clinical variables like goitre, T3 and T4 may not be associated with the possible development of PAH in hypothyroidism.

KEYWORDS

Hypothyroidism, Pulmonary Arterial Hypertension, Mean Pulmonary Artery Pressure, TSH, Goitre.

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BACKGROUND

Hypothyroidism is one among the most prevalent endocrine disorders worldwide.[1] A higher burden of hypothyroidism has been reported in India affecting ~11% of the population compared to other countries like UK (2%) and USA (4-6%).[2] Pulmonary arterial hypertension is a lethal disease characterised by elevated pulmonary vascular resistance and pulmonary arterial pressure subsequently resulting in right ventricular failure.[3] The diagnosis of PAH is often challenging due to the occurrence of nonspecific symptoms and other common diseases.[4] Several studies have delineated the association of PAH with diseases like haemoglobinopathies, portal hypertension, connective tissue diseases, congenital heart diseases, collagen diseases and HIV infection.[4,5] Moreover, thyroid dysfunction has been reported in a significant proportion (around 35-65%) of patients with PAH.[4] The association between PAH and hypothyroidism has been profoundly discussed in literature.

Various studies have reported an increased prevalence of hypothyroidism in patients with idiopathic/primary PAH.[6] Increased preponderance of idiopathic PAH has been reported in women and middle-aged adults.[4] The prevalence of hypothyroidism reported by Curnock et al in patients with primary PAH was 22.5%.[6] Similarly, a higher prevalence (49%) of PAH has also been reported in hypothyroidism.[7] The probable explanation for the co-occurrence could be the role played by autoimmunity.[7] This is supported by the evidence of serological markers of autoimmunity or connective tissue disease noted in patients with both primary PAH and hypothyroidism.[8] The coexistence of PAH and hypothyroidism could be attributed to the changes induced in cardiac contractility, cardiac output, blood pressure, myocardial oxygen consumption and pulmonary

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vascular resistance by the thyroid disease.[9] Therefore, it has been proposed that the cardiovascular changes could be reversible with the appropriate recognition and treatment of the underlying thyroid disease.[9] Furthermore, the association of hypothyroidism with respiratory disorders like hypoxia and hypoventilation can aggravate the concomitant PAH.[10] The present study was intended to evaluate the occurrence and severity of PAH in patients diagnosed with hypothyroidism and to examine the reversibility of the disease on treating the underlying hypothyroidism.

MATERIALS AND METHODS

The prospective, interventional study was conducted at a tertiary care center in South India for a period of one year from January 2015 to December 2015. The study was approved by the institutional ethics committee and informed consent was obtained from all the participants. The study included both inpatients and outpatients with clinical and biochemical evidence of hypothyroidism. The study excluded subjects with chronic hypoxaemia, chronic liver disease or cirrhosis, clinical features of pulmonary diseases and connective tissue disorders, underlying cardiac diseases (ventricular septal defect, cardiomyopathies, myocarditis etc.), smokers, HIV patients and those on anorectic, contraceptive, chemotherapeutic or vasoactive drugs.

A prestructured pro forma was used to screen the subjects for clinical evidence of hypothyroidism. The presence of hypothyroidism was confirmed in all the subjects based on the thyroid function test using enzyme immunoassay. The occurrence and severity of PAH was assessed in the subjects by estimating the Mean Pulmonary Artery Pressure (MPAP), using Doppler echocardiography. Hypothyroid patients with PAH were treated for the underlying hypothyroidism (thyroxine) and were reassessed after a period of 10 months with Doppler echocardiography to analyse the variation in Pulmonary Artery Systolic Pressure (PASP). Right Ventricular Systolic Pressure (RVSP) was calculated based on the pressure gradient between the right ventricle and atrium measured by continuous wave Doppler echocardiography according to the standard technique. Central Venous Pressure (CVP) was not elevated on clinical examination and was therefore assumed to be 5 mmHg. PASP was calculated by adding Right Arterial Pressure (RAP) and RVSP.

Statistics- The variables with normal distribution were compared by independent t-test, those without normal distribution by Mann-Whitney U test and categorical variables by Chi-square test. The baseline and follow-up MPAP, TSH, T3 and T4 were assessed by delta method. As per this method, the results were quantified as improved, stable or worsened. The obtained counts data were documented. P value <0.05 was considered as statistically significant. All the statistical analyses were performed using MedCalc software version 14.8.1.

RESULTS

The study enrolled a total of 75 subjects with a mean age of 46.33 ± 13.98. The male-to-female ratio noted was 0.27:1. The descriptive data of the various demographic and clinical variables of the subjects are provided in Table 1. Goitre was present in only 19 subjects. The mean TSH level of the subjects was 12.57 ranging from 5.04 to 145 µIU/mL.

Factors	Values
Age	46.33 ± 13.98*
Gender (M/F)	16/59
Goitre (Y/N)	19/56
TSH	12.57 (5.04-145.0)#
T3	0.79 (0.10-1.35)#
T4	6.59 ± 2.97*

Table 1. Descriptive Data of Demographic and Clinical Variables in 3 Hypothyroidism Patients with Pulmonary Hypertension

*mean ± SD, #median (range).

The mean pulmonary artery pressure was found to be normal in 68 subjects and abnormal in 7 subjects (6 had mild and 1 had moderate MPAP). The comparison of variables like age, gender, goitre, T3 and T4 levels, among subjects with normal and abnormal MPAP values did not reveal a significant variation in these factors among the two groups (Table 2). The mean age was higher in subjects with abnormal MPAP value (49.71 ± 11.04) compared to those with normal MPAP value (45.99 ± 14.27), however, the difference observed was not statistically significant (P 0.5052). Similarly, T3 and T4 levels were normal in majority of the subjects with both abnormal and normal MPAP.

Factors	MPAP Normal (n=68)	MPAP Abnormal (n=7)	P value
Age	45.99 ± 14.27*	49.71 ± 11.04*	0.5052
Gender (M/F)	14/54	2/5	0.9948
Goitre (Y/N)	17/51	2/5	0.803
T3 (normal/abnormal)	55/13	5/2	0.9210
T4 (normal/abnormal)	50/18	3/4	0.2072

Table 2. Comparison of Demographic and Clinical Variables in Hypothyroidism Patients with Pulmonary Hypertension

*mean ± SD.

Among the seven follow-up subjects, improved MPAP and TSH levels were noted in a significant number of subjects (n=6) and remained unchanged in one subject in each group (Table 3). None of the subjects reported abnormal MPAP value, T4 or TSH levels. However, worsening of T3 level was noted in one patient. Additionally, a higher number of subjects had improved T4 level (n=4), whereas improved T3 level was noted only in two subjects.

Factors	Improved	Stable	Worsened
MPAP	6	1	0
TSH	6	1	0
T3	2	4	1
T4	4	3	0

Table 3. Delta Analysis of Baseline and Follow-up Variables in Hypothyroidism Patients with Pulmonary Hypertension (N=7)

DISCUSSION

Studies have shown increased preponderance of thyroid diseases in women than men. A cross-sectional, multi-center, epidemiological study conducted in 8 cities of India by Unnikrishnan and colleagues have found hypothyroidism in 15.86% of women compared to only 5.02% in men. The study has reported a significant association of hypothyroidism with female gender and old age.[11] In concurrence with these findings, the present study has also noted an increased prevalence of thyroid diseases in women than men (78.6%). Unnikrishnan et al have noted a significant predominance of hypothyroidism among older adults belonging to the age group of 36-45 years compared to the young adults (18-35 years).[11] In addition, highest frequency of hypothyroidism (13.11%) was noted in subjects belonging to the age group of 46-54 years. The mean age of hypothyroidism noted in the present study was 46 years.

Studies dating back a decade have reported the occurrence of PAH in hypothyroidism as high as 49%.[7] Similarly, hypothyroidism has also been reported in subjects with Primary Pulmonary Hypertension (PPH). Curnock et al have reported a higher prevalence of hypothyroidism (22.5%) in PPH.[6] Additionally, Senthilvelan et al have discussed the occurrence of concomitant thyroid dysfunction in around 30-60% of the patients with PAH.[12] However, mean PAH was found to be normal in majority of the present study subjects with hypothyroidism (90.66%; 68 out of 75 subjects). In addition, PAH (mild and moderate) was noted only in a significantly lesser number of subjects with hypothyroidism (9.33%; 7 out of 75 subjects). The study underscores the need of further evidence to substantiate the association between thyroid disease and unexplained PH.

The current study revealed that clinical factors like goitre, T3 and T4 levels are not correlated with PAH in hypothyroid subjects as no significant variation was noted for these variables among hypothyroid subjects with and without PAH. Literature evidence on the association of goitre and thyroid disease markers like T3 and T4 with PAH in hypothyroid patients is very limited. However, the presence of toxic multinodular goitre in hyperthyroid subjects with concomitant PAH has been extensively evaluated.[9] Corroborating the current study finding, Vakilian et al have reported that there is no meaningful correlation between MPAP and thyroid parameters (T3, T4). In line with the present study, Vakilian et al showed that factors like age, gender and TSH level were not significantly correlated with MPAP.[13]

The co-existence of PAH and hypothyroidism could be attributed to the known autoimmune basis of both the diseases.[8] The presence of positive serological markers of autoimmunity and clinical evidence of connective tissue diseases have been reported in both hypothyroidism and PPH.[8] Moreover, autoimmune antibodies were found to be associated with PPH even in the absence of clinical autoimmune disease.[8] An early study by Yanai-Landau et al conducted on 40 subjects with PPH has reported circulating autoantibodies and multi-antibody responses among 62.4% and 47.5% of the subjects, respectively. The study attributing the disease to immune dysregulation revealed the presence of autoantibodies such as antinuclear, anti-ssDNA and antithyroglobulin, most frequently among patients with PPH.[14] A correspondence published by Kashyap et al have highlighted the significance of exploring the possibility of having inflammation as the common link between thyroid dysfunction and PPH.[8] The researchers have also recommended screening of patients with PPH for the possibility of coexisting hypothyroidism.

Hypothyroidism has been found to have a significant influence on the tissue levels of endothelin-1 in animal models. Endothelin-1 (ET-1), a potent vasoconstrictor peptide facilitates the pathogenesis of the PPH.[6] The peptide mediates vascular remodelling by stimulating vasoconstriction, protein synthesis, smooth muscle proliferation and synthesis of various growth factors and cytokines. In PAH patients, the elevated levels of ET-1 contributes to increase in pulmonary arterial pressure, pulmonary vascular resistance and decreased cardiac output.[12] ET-1 also plays an important role in the regulation of thyroid homeostasis. The binding of endothelin to their specific receptors on the thyroid gland alters the functional capacity of the gland.[12] Similarly, a review by Marvisi et al (2013) has discussed the possible mechanisms involved in the direct influence of thyroid hormone on pulmonary vasculature. These include enhanced catecholamine sensitivity, increased metabolism of intrinsic pulmonary vasodilating substances (prostacyclin and nitric oxide) and decreased metabolism of vasoconstrictors (endothelin-1, serotonin and thromboxane).[9]

In the present study, a marked improvement was noted in mean PAH and TSH in the patients undergoing treatment for hypothyroidism after a 10-month follow-up period. However, the T3 and T4 levels did not show a notable improvement. This observation suggests that PAH can be reversed with the correction of the underlying hypothyroidism. Silva et al (2009) have noted only a slight increase in the pulmonary artery pressure of patients with thyroid disease, which subsequently reversed with the treatment for thyroid disease.[4] These findings substantiate the present study reporting only a mild and moderate increase of MPAP (in around 9% of the study population) in hypothyroid patients.

Evidence-based literature evaluating the association between PAH in hypothyroidism is very limited.[4] The present study holds immense significance as it could be considered as one of its kind evaluating the occurrence and severity of PAH in patients diagnosed with hypothyroidism. However, the study holds limitations like single center study, small

sample size and the use of only Doppler echocardiography to assess PAH. This entails the need for prospective studies involving larger sample size with an adequate followup to substantiate the current study findings.

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