

# Pulmonary Function in Hypothyroidism Before and After Restoration of Euthyroid Status

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## Abstract

**Objective.** Pulmonary manifestations are rarely a major problem in hypothyroid patients; though subtle restrictive pattern on spirometry has been reported. The effect of thyroxine replacement on spirometric indices has not been adequately studied.

**Methods.** Patients with primary hypothyroidism (thyroid stimulating hormone [TSH] >15 mIU/L) not having any known pulmonary or cardiac pathological (N=42) were screened for inclusion in the study. All patients underwent spirometry and following parameters were recorded: forced expiratory volume in the first second (FEV<sub>1</sub>), forced vital capacity (FVC), FEV<sub>1</sub>/FVC ratio, mid-expiratory flow rate (FEF<sub>25%-75%</sub>), peak expiratory flow rate (PEFR), both as absolute values and as a percentage of the predicted value. Subsequently, patients were started on levothyroxine replacement treatment and the dosage was titrated to achieve euthyroid state. Spirometry was repeated two months or more after the restoration of the euthyroid state.

**Results.** Their mean age was 37.1±12.6 years. No significant correlation was observed between thyroxine (T4) and thyroid stimulating hormone (TSH) and any of the baseline spirometric parameters. Comparison of spirometric parameters (as percentage of predicted values) before and after treatment showed a clinically significant improvement in FVC, FEV<sub>1</sub> and FEF<sub>25%-75%</sub> (P< 0.05).

**Conclusions.** Hypothyroidism was characterised by an asymptomatic; yet predominant restrictive pattern of pulmonary function abnormality. After thyroxine replacement, there was a significant improvement in the restrictive pattern. [Indian J Chest Dis Allied Sci 2020;62:51-56]

**Key words:** Hypothyroidism, Pulmonary functions

## Introduction

Pulmonary manifestations are rarely a major problem in hypothyroid patients; though several abnormalities in respiratory reserve have been observed. Pulmonary manifestations may range from mild dyspnoea to life threatening respiratory failure.<sup>1</sup> There is also a high incidence of obstructive sleep apnoea in untreated hypothyroidism.<sup>2</sup> Impaired ventilatory response to hypoxia and hypercapnia are noted in primary hypothyroidism.<sup>3</sup> Mild to severe diaphragmatic dysfunction has also been reported in patients with hypothyroidism.<sup>4</sup>

There are also defects in spirometric indices in hypothyroidism in comparison with normal

individuals.<sup>5-8</sup> These are suggestive of a restrictive pathology rather than an obstructive pathology and possibly may result from interstitial oedema as a manifestation of myxoedema itself, as well as from respiratory muscle weakness. However, there is a paucity of longitudinal studies documenting the recovery from these subtle defects in spirometry after a period of adequate thyroid replacement. The present study was planned to address the changes in pulmonary function tests after thyroxine replacement therapy in hypothyroid patients.

## Material and Methods

This prospective longitudinal before and after interventional study included adult patients, aged more

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than 18 years, attending Endocrine Services at The Sri Venkateswara Institute of Medical Sciences, Tirupati with newly diagnosed (*i.e.*, previously untreated) or inadequately treated primary hypothyroidism with a thyroid stimulating hormone (TSH) >15mIU/L. Current smokers, obese individuals with body mass index (BMI) >30kg/m<sup>2</sup> and those with known pulmonary disease (such as, chronic obstructive pulmonary disease, bronchial asthma, interstitial lung disease, pneumoconiosis or any other underlying pulmonary parenchymal or airway pathology that might affect the pulmonary function as evaluated by spirometry) were excluded. Patients with left ventricular dysfunction, left-sided cardiac valvular heart disease or any other cardiac pathology that might cause passive venous congestion of the lungs or pulmonary oedema, and thereby, affect the spirometry were also excluded. Likewise, patients with chronic kidney disease (glomerular filtration rate <60mL/min/1.730m<sup>2</sup> body surface area) and those with chest wall deformities or neuromuscular disease that might be expected to affect results of spirometry were excluded.

After taking informed consent, a detailed clinical assessment of each patient, *i.e.*, history and physical examination including examination of thyroid gland was performed. Plasma sample for thyroxine (T4) and TSH was collected to confirm the diagnosis of hypothyroidism. Height on a stadiometer and weight on a beam balance were recorded. Patients were subjected to spirometry at Pulmonology laboratory in the Department of Medicine using spirometer (Easy One Pro™ Lab, Medical Technologies Andover, MA, USA) as per the standard protocol described earlier.<sup>9,10</sup> Following parameters were recorded: forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), FEV<sub>1</sub>/FVC ratio, mid expiratory flow rate (FEV<sub>25%-75%</sub>), peak expiratory flow rate (PEFR), both as absolute values and as a percentage of the predicted value for age, height and sex as applicable.

The patients were then started on thyroxine replacement in doses titrated to achieve a normal TSH of 0.5-5mIU/L. Monitoring of TSH was done at 4-6 weekly intervals till it reached the normal value. Two months or more after achieving euthyroid status, each patient was subjected to repeat spirometry to determine the same pulmonary function tests (*i.e.*, FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, FEV<sub>25%-75%</sub> and PEFR).

Restriction was defined as an FVC <80% of predicted with a normal or increased FEV<sub>1</sub>/FVC ratio.<sup>11</sup> The severity of restriction was classified based on reduction in FVC (percentage of predicted)<sup>11</sup> as shown in table 1. Obstruction was defined as decreased FEV<sub>1</sub>/FVC ratio (<0.7) and FEV<sub>1</sub> <80% of predicted.<sup>12</sup> Severity of

obstruction was classified based on reduction in FEV<sub>1</sub> (percentage of predicted)<sup>12</sup> as shown in table 1. Mixed restriction and obstruction was defined as low FVC (<80% predicted), FEV<sub>1</sub> (<80% predicted) along with reduced FEV<sub>1</sub>/FVC (<0.7).<sup>12</sup>

### Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation; those which were not normally distributed were expressed as median or interquartile range (IQR). Comparison between baseline and post-treatment values for each variable was performed by the Wilcoxon signed rank test. Comparison of proportions of ordinal variables between baseline and post treatment time periods were done by the McNemar's Chi-square test or the Kendall tau test for paired data. A P-value of <0.05 was considered as statistically significant for all the above tests.

**Table 1 Classification of severity of restriction**

Severity of Restriction	FVC (% Predicted)	FEV <sub>1</sub> (% Predicted)
Mild	< LLN but ≥70	<100 and ≥70
Moderate	<70 and ≥60	<70 and ≥60
Moderately severe	<60 and ≥50	<60 and ≥50
Severe	<50 and ≥34	<50 and ≥34
Very severe	<34	<34

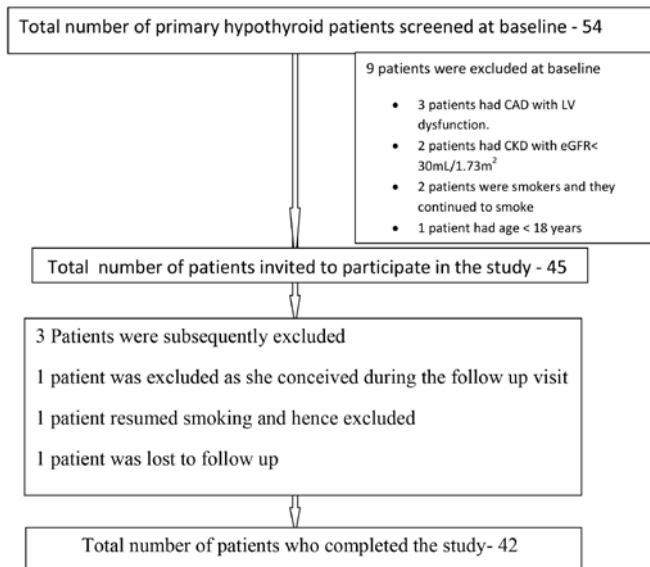
*Definition of abbreviations:* FVC=Forced vital capacity, FEV<sub>1</sub>=Forced expiratory volume in first second, LLN= Lower limit of normal

*Based on reference 11*

### Results

Forty-five patients with TSH >15 mIU/L, fulfilling all inclusion and exclusion criteria were included in the study. Subsequent to their initial recruitment and sample collection, three patients were excluded. One patient following the initial sampling had conceived and was excluded from the study as pregnancy was expected to alter the pulmonary function tests. Another patient was excluded as he resumed smoking during the study. A third patient was lost to follow-up. The flow chart depicting the pattern of recruitment is shown in figure 1. Forty-two patients completed the study; of which 33 were females and 9 were males. On examination, goiter was noted in 64% of the patients.

The mean age of the patients at entry into the study was 37.1±12.6 years. Mean BMI (body mass index) of the patients at the time of study entry was 25.2±3.9 kg/m<sup>2</sup> while that at two months or more after becoming euthyroid was 24.2±3.8 kg/m<sup>2</sup> (P<0.001). All the patients who completed the study were euthyroid on a stable



**Figure 1. Consort diagram showing the recruitment of patients**

dose of levothyroxine for at least two months before final testing. The median interquartile range (IQR) of T4 was 27.5 (10–50.7) ng/mL and 106 (93.5–126.7) ng/mL; P<0.001 at recruitment and at the end of the study, respectively. TSH was 124 (73–220) mIU/L and 1.3 (0.2–3.6) mIU/L (P<0.001) at the beginning and at the end of the study, respectively.

**Spirometry in patients with hypothyroidism**

No significant correlation was noted between T4 and TSH and any of the baseline spirometric parameters (FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FEV<sub>25%-75%</sub>, PEFR) (Table 2).

Comparison of spirometric parameters as a percentage of predicted values before and after treatment showed a clinically significant increase in FVC, FEV<sub>1</sub>, FEV<sub>25%-75%</sub> (Table 3). No significant change was noted

**Table 2. Coefficients of correlation for different pulmonary function parameters (expressed as a percentage of the predicted for age sex and height) with the circulating T4 (ng/mL) and TSH (mIU/L)**

Pulmonary Function Parameter	T4 (ng/mL)		TSH mIU/L	
	r-value	P-value	r-value	P-value
FVC	0.058	0.784	-0.046	0.771
FEV <sub>1</sub>	0.028	0.862	-0.019	0.906
FEV <sub>1</sub> /FVC	-0.088	0.580	0.051	0.749
FEV <sub>25%-75%</sub>	-0.043	0.788	0.110	0.489
PEFR	0.082	0.606	-0.007	0.963

*Definition of abbreviations:* FVC=Forced vital capacity, FEV<sub>1</sub>=Forced expiratory volume in first second, FEV<sub>25%-75%</sub>=Mid expiratory flow rate, PEFR= Peak expiratory flow rate

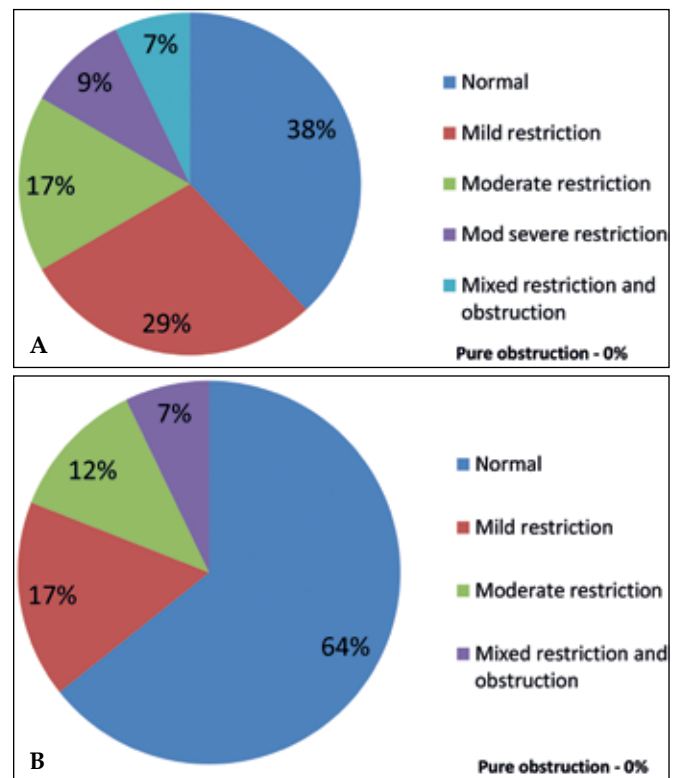
in FEV<sub>1</sub>/FVC ratio and the PEFR. At study entry 23 of 42 patients (55%) had a pure restrictive physiology (Figure 2A). Three patients had mixed restriction and obstructive pattern. None of the patients had a purely obstructive pattern. After restoration of euthyroidism; only 12 of 42 patients (29%) (Figure 2B) continued to have a pure restrictive pattern of pulmonary function tests (P<0.01).

At baseline among 23 patients with pure restrictive pattern; 12 had mild restriction, seven had moderate restriction, four had moderate-to-severe restriction and none had severe restriction.

**Table 3. Comparison of spirometric parameters (as a percentage of predicted values) before and after treatment**

Pulmonary Function Parameters	Before Treatment	After Treatment	P-value
FVC	74.81±13.33	83.98±3.06	< 0.001
FEV <sub>1</sub>	72.19±14.58	82.31±13.24	< 0.001
FEV <sub>1</sub> /FVC	96.19±9.41	98.24±7.05	0.176
FEV <sub>25%-75%</sub>	64.33±22.76	75.64±24.68	0.007
PEFR	64.90±24.59	70.19±20.15	0.200

*Definition of abbreviations:* FVC=Forced vital capacity, FEV<sub>1</sub>=Forced expiratory volume in first second, FEV<sub>25%-75%</sub>= Mid-expiratory flow rate, PEFR=Peak expiratory flow rate



**Figure 2. Classification of pulmonary function tests (A) before treatment (n=42) and (B) after restoration of euthyroidism (n=42)**

Post-treatment among 12 patients with pure restrictive physiology, seven had mild restriction, five had moderate restriction. The distribution of severity of restriction was significantly different ( $P < 0.001$ ) before and after replacement thyroxine therapy (Table 4). Three patients at baseline had mixed restrictive and obstructive pattern. After restoration of euthyroidism there was an improvement noted in both the restrictive and obstructive components in them (Table 5).

**Table 4. Comparison of distribution of patients (N=39) into different categories based on severity of restriction before and after restoration of euthyroidism.**

Grade of Restriction	Before Treatment	After Treatment	P-value
Normal	16	27	< 0.001
Mild	12	7	
Moderate; and moderately severe	11	5	

$P < 0.05$  is considered as clinically significant.

**Table 5. Comparison of patients with mixed spirometric pattern before and after restoration of euthyroidism.**

	Before Treatment	After Treatment
Patient 1	Severe restriction and severe obstruction	Moderately severe restriction and obstruction
Patient 2	Moderate restriction and severe obstruction	Mild restriction and moderate obstruction
Patient 3	Severe restriction and obstruction	Mild restriction and mild obstruction

## Discussion

Evidence is available<sup>13,14</sup> demonstrating effects of hypothyroidism on various systems, like nervous system and cardiovascular system. However, there is paucity of data with respect to its effect on respiratory system. In this prospective study, we have demonstrated the effects of thyroid hormone on the respiratory system by spirometry before and after restoration of euthyroidism. In our study, patients with overt hypothyroidism were assessed for pulmonary function by spirometry at baseline and two months or more after restoration of euthyroidism. We observed a predominant restrictive pattern of pulmonary function which improved significantly following restoration of euthyroidism.

A large study on spirometric patterns in hypothyroidism<sup>5</sup> compared the spirometric parameters in patients with clinical and subclinical hypothyroidism to that of healthy controls. The authors observed a significantly reduced FVC, FEV<sub>1</sub>, FEF<sub>25%-75%</sub> in overt hypothyroid and subclinical hypothyroid patients

compared to healthy subjects which was consistent with our study. But FEV<sub>1</sub>/FVC was similar across all the three groups suggestive of a restrictive pattern of spirometry in patients with clinical and subclinical hypothyroidism. However, this was a cross-sectional case control study. Similar results have also been reported in other studies.<sup>6,8,15,16</sup>

Bassi *et al*<sup>17</sup> compared spirometry in untreated hypothyroid patients with hypothyroidism on thyroxine replacement for the past 6-8 months. They also showed a significantly higher FVC, FEV<sub>1</sub> and FEF<sub>25%-75%</sub> in the latter group, without a difference in FEV<sub>1</sub>/FVC. Another longitudinal before and after intervention study involving hypothyroid patients showed a prevalence of 86% restrictive pathology at baseline, which reduced to 60% after treatment.<sup>16</sup> In our study, restrictive spirometry pattern was noted in 61% patients at baseline, which decreased to 36% post treatment. We also noticed a significant increase in FVC, FEV<sub>1</sub>, FEF<sub>25%-75%</sub> following restoration of euthyroidism which was similar to observations reported in another study.<sup>18</sup> Increase in flow rates after treatment may well occur as a consequence of increase in FVC; however, the FEV<sub>1</sub>/FVC ratio (which is a better indicator of obstruction than the flow rates alone) did not change after treatment ( $P = 0.176$ ). It is not clear whether a longer period of thyroxine therapy would have restored the remaining 28% patients also to a normal pulmonary physiology.

These results could be due to effects of thyroid hormone on respiratory function at various levels. Overt hypothyroidism is associated with depression and global cognitive dysfunction resulting in reduced drive and motivation.<sup>19-21</sup> As spirometry is a subjective test which requires patient's understanding and motivation, it may be affected by the lack of drive that characterises hypothyroidism.

Restrictive pattern of spirometry observed in our study can also be explained by respiratory muscle weakness seen in patients with hypothyroidism.<sup>15,16</sup> Both inspiratory and expiratory muscle weakness are noted in hypothyroidism. In a study<sup>15</sup> a lower maximal inspiratory mouth pressure (P<sub>I</sub>max) and maximal expiratory mouth pressure (P<sub>E</sub>max) in patients with hypothyroidism as compared to healthy controls, suggestive of a reduction in respiratory muscle force in hypothyroidism was reported. Siafakas *et al*<sup>16</sup> studied respiratory muscle function in hypothyroidism before and after treatment and the changes in the spirometric parameters were similar to our study. In addition, they also studied that there was a significant increase in P<sub>I</sub>max and P<sub>E</sub>max following thyroxine replacement in hypothyroid patients suggestive of an improvement in the muscle strength.



Finally, as in all restrictive lung diseases, loss of volume could also be due to thickening of the alveolar exchange interface, in particular the interalveolar septae. In hypothyroidism, this may involve the deposition of glycosaminoglycans. Untreated or partially treated cases of hypothyroidism have been characterised by the deposition of glycosaminoglycans in several tissues as demonstrated in an autopsy study.<sup>22</sup> Deposition of glycosaminoglycans in the skin and subcutaneous tissue also explains the appearance of non-pitting oedema all over the body characteristically described as “myxoedema”. A similar deposit in the lung parenchyma in the interalveolar septae could lead to a restrictive physiology on spirometry, as seen in our study. The reduction in diffusion capacity of carbon monoxide (DLCO) observed in a study would support this hypothesis.<sup>15</sup> Reduced compliance of lungs due to surfactant deficiency has also been demonstrated in animal studies.<sup>23</sup> Studies have also shown that thyroxine is essential for formation of type 2 pneumatocytes involved in surfactant production.<sup>24</sup>

However, due to the inherent difficulty in obtaining parenchymal lung tissue for histology, there are no histopathological descriptions of interalveolar septal morphology in hypothyroidism in humans. Such a picture would be eminently reversible by treatment with thyroxine (in the same manner that “myxoedema” is reversed) and may explain the improvement in FVC following treatment in our study. Further follow up is required to study if the residual PFT abnormalities in the form of persistent asymptomatic restrictive pathology in approximately a third of the patients in our study could be due to a permanent form of restrictive lung pathology, or would likely clear up after a few more months of thyroxine treatment.

A major strength of our study was its before-after interventional design. All the patients in our study had long-standing primary hypothyroidism as compared to previous studies which included both spontaneous and short term iatrogenic hypothyroidism.<sup>15</sup> All the patients in our study were assessed two months or more after the attainment of euthyroidism allowing sufficient time for stabilisation of dynamic changes in spirometry.

## Conclusions

Hypothyroidism is characterised by an asymptomatic yet predominant restrictive pattern of pulmonary physiology. Following thyroxine replacement, there is a significant improvement noted in spirometric indices indicative of restriction.

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