Section: Miscellaneous

Original Research Article

PREVALENCE OF EUTHYROID SICK SYNDROME IN NEWLY DETECTED PULMONARY TUBERCULOSIS PATIENTS AND THE CORRELATION OF THE SAME WITH FAILURE AT THE END OF INTENSIVE PHASE

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ABSTRACT

Background: Pulmonary tuberculosis is associated with significant systemic illness, which may affect thyroid hormone metabolism. Euthyroid sick syndrome (ESS) has been reported in tuberculosis patients, but its relationship with disease burden and sputum conversion during treatment is not well established. **Aim and Objectives:** To determine the prevalence of ESS in newly diagnosed sputum-positive pulmonary tuberculosis patients and to correlate its presence with bacillary burden and failure of sputum conversion at the end of the intensive phase of treatment. **Materials and Methods:** This prospective observational study was conducted at RNTCP centres in Chennai (March–October 2017), including 120 newly diagnosed sputum-positive pulmonary tuberculosis patients. Thyroid function tests were performed at baseline, and sputum conversion was assessed at the end of the intensive phase. **Results:** ESS was present in 109 patients (90.83%), while 11 patients (9.17%) had normal thyroid function (NTF). Patients with ESS had higher sputum bacillary grades (2+ and 3+), whereas all patients with NTF had only 1+ positivity ($p < 0.001$). Mean FT3 levels were significantly lower in the ESS group (1.79 ± 0.36 vs 2.97 ± 0.32; $p < 0.001$). ESS patients had significantly lower serum albumin (2.97 ± 0.87 vs 3.57 ± 0.89 g/dL; $p = 0.031$) and higher serum creatinine levels (0.90 ± 0.19 vs 0.75 ± 0.11 mg/dL; $p = 0.015$). Sputum non-conversion occurred in 18/109 (16.5%) ESS patients and 0/11 patients with NTF. **Conclusion:** ESS and low FT3 levels were associated with higher disease burden and poor early treatment response. Thyroid function abnormalities may represent potential indicators of disease severity in pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) remains a major public health challenge worldwide, particularly in low- and middle-income countries, even with the effective anti-tuberculosis drugs and sustained global control efforts.[1] India carries the highest global burden of tuberculosis, contributing a substantial proportion of newly detected pulmonary TB cases each year, resulting in significant morbidity, mortality, and socioeconomic impact.[2] Pulmonary tuberculosis (TB) represents the most common clinical form of TB and is the principal contributor to disease transmission and long-term morbidity.[1] Clearance of Mycobacterium tuberculosis is the primary goal of treatment. Treatment outcomes are recognised to be influenced by host-related metabolic and endocrine factors.[3]

Euthyroid sick syndrome (ESS), also known as non-thyroidal illness syndrome, describes alterations in thyroid hormone levels during systemic illness in the absence of intrinsic thyroid disease. The typical biochemical pattern in ESS is a reduction in serum triiodothyronine (T3) levels, with normal or near-normal thyroxine (T4) and thyroid-stimulating hormone (TSH) concentrations.[4] These hormonal changes are considered an adaptive response to severe systemic illness and inflammation rather than primary thyroid dysfunction.

Several studies have shown that the degree of thyroid hormone alteration correlates with illness severity and clinical outcomes in both acute and chronic disease states.[5] Pulmonary TB is associated with prolonged systemic inflammation, increased metabolic demand, weight loss, and nutritional deficiencies, which may predispose patients to the development of ESS.[6] Studies evaluating thyroid function in pulmonary TB patients have reported that ESS is observed at the time of diagnosis. Changed

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thyroid hormone levels, particularly reduced T3, may show disease severity and systemic inflammatory burden in tuberculosis patients.[7] ESS may serve as a marker of underlying disease burden in pulmonary TB. Sputum smear grading is a widely used indicator of bacillary load and disease severity in pulmonary TB.[3]

The initial phase of anti-tuberculosis treatment, typically the first two months of therapy, aims to reduce the bacillary load and to convert the sputum test from positive to negative.[8] Pulmonary TB patients with a high bacillary infection have a high chance of experiencing delayed treatment response, treatment failure, and development of drug-resistant tuberculosis.[6] Failure of sputum conversion at the end of the intensive phase is associated with persistent infection and an increased risk of multidrug-resistant tuberculosis.[8]

Early identification of patients at risk for sputum non-conversion remains a significant clinical challenge. Its presence at baseline may be associated with higher bacillary burden and delayed sputum clearance in pulmonary TB patients.[7] Prospective data evaluating the prevalence of ESS in newly detected sputum-positive pulmonary TB patients and its association with bacillary load and sputum conversion failure at the end of the intensive phase remain limited.[8]

Aim and Objectives

This study aims to evaluate ESS in patients presenting with newly diagnosed sputum-positive pulmonary tuberculosis, to correlate the presence of ESS with bacillary burden in these patients, and to determine the failure of sputum conversion at the end of the intensive phase of treatment.

MATERIALS AND METHODS

This prospective observational study was conducted at the Revised National Tuberculosis Control Programme (RNTCP) Centres of Government Kilpauk Medical College Hospital and Otteri Tuberculosis Hospital, Chennai, from March 2017 to October 2017. Ethical clearance was obtained from the Institutional Ethics Committee prior to the study, and written informed consent was obtained from all patients.

Inclusion Criteria

Newly diagnosed sputum smear-positive pulmonary TB patients were included.

Exclusion Criteria

Patients with pulmonary TB associated with systemic illnesses such as diabetes mellitus, HIV infection, coronary artery disease, chronic kidney disease (medical history), and chronic liver disease, patients with known thyroid disorders, patients receiving medications known to interfere with thyroid function, and critically ill pulmonary TB patients were excluded from the study.

Methods

120 patients who met the inclusion criteria and did not fall under any of the exclusion criteria were included in the study after initial evaluation. Patients were enrolled consecutively after confirmation of pulmonary TB by sputum smear microscopy for acid-fast bacilli (AFB). Patients with known thyroid disorders, those receiving thyroid medications, steroids, or other drugs known to affect thyroid function were excluded. Diabetes mellitus was excluded because of its known independent effects on thyroid hormone metabolism, and chronic kidney disease was excluded to avoid confounding of thyroid function parameters and renal biochemical measurements. During the first visit, and prior to initiation of anti-tuberculosis therapy (ATT), each patient underwent a detailed clinical assessment, and demographic details, including age, sex, and type of patient (outpatient/inpatient), were recorded using a structured proforma. Baseline sputum smear grading (1+, 2+, 3+, 4+) was documented as per standard guidelines to assess bacillary load.

At baseline, venous blood samples were collected under aseptic precautions for thyroid function testing and biochemical analysis. Thyroid function tests—including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)—were measured using a standardised chemiluminescent immunoassay method in the central laboratory. The laboratory reference ranges were: FT3: 2.30–4.20 pg/mL, FT4: 0.89–1.76 ng/dL, and TSH: 0.55–4.78 µIU/mL. Patients with isolated low FT3 levels along with normal FT4 and TSH were classified as having ESS, while those with all parameters within the reference range were categorised as having Normal Thyroid Function (NTF). Among patients diagnosed with ESS, serum FT3 levels were further categorised into three grades based on the degree of reduction: Grade I (2.0–2.3 pg/mL), Grade II (1.5–2.0 pg/mL), and Grade III (0.5–1.5 pg/mL). This grading was used to assess the severity of thyroid hormone derangement and its association with sputum bacillary load.

Baseline serum creatinine levels were measured in all participants prior to initiation of ATT. Serum albumin and creatinine were analysed as biochemical indicators of nutritional and renal status, respectively, to explore possible systemic correlates of ESS. Additional biochemical investigations included serum bilirubin, SGOT, SGPT, and urea, measured using automated biochemistry analysers. These biochemical parameters were not used to define eligibility but were evaluated as secondary laboratory associations. All patients were initiated on standard first-line anti-tubercular therapy as per national guidelines and were followed up during the course of treatment. Sputum smear examination was repeated at the end of the intensive phase (2 months) to assess sputum conversion. Patients were categorised at two months as sputum negative, sputum positive, not taken treatment, dropped out, or dead/defaulter based on clinical records and TB treatment registers.

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Patients who showed delayed or failed sputum conversion were identified to facilitate early detection of possible drug-resistant tuberculosis. All collected data were entered into a pre-designed data collection sheet and subsequently transferred to a digital database for analysis. Data accuracy was ensured through cross-verification with laboratory registers and TB clinic records.

Statistical analysis: Descriptive statistics were used to summarise. Continuous variables were expressed as mean and standard deviation and were analysed using the unpaired t-test. Categorical variables were expressed as proportions and were analysed using the chi-square test or Fisher's exact test, as appropriate. A p-value of < 0.05 was considered statistically significant. Data analysis was performed using SPSS software version 26. Only univariate analyses were performed.

RESULTS

Among 120 newly detected sputum-positive pulmonary TB patients, 109 (90.83%) had ESS and 11 (9.17%) had NTF. The ESS group had a higher mean age (47.18 ± 13.81 years) than the NTF group (39.09 ± 14.52 years), though this difference was not significant ($p = 0.068$). Males predominated in both groups (84.4% vs. 90.91%), and most patients were managed as outpatients, with no significant association between age, sex, or patient type and thyroid status. ESS was significantly associated with higher sputum bacillary grades (2+ and 3+), whereas all patients with NTF had only 1+ positivity ($p < 0.001$) [Table 1].

Table 1: Baseline demographic, clinical characteristics and AFB sputum grading of groups

Variable	Category	ESS Group (n=109)	NTF Group (n=11)	P value
Thyroid Status	—	109 (90.83%)	11 (9.17%)	—
Age (years)	Mean ± SD	47.18 ± 13.81	39.09 ± 14.52	0.068
Sex	Male	92 (84.4%)	10 (90.91%)	>0.9999
	Female	17 (15.6%)	1 (9.09%)	
Type of Patient	Outpatient	71 (65.14%)	10 (90.91%)	0.101
	Inpatient	38 (34.86%)	1 (9.09%)	
AFB Grading	1+	8 (7.34%)	11 (100%)	<0.001
	2+	56 (51.38%)	0	
	3+	39 (35.78%)	0	
	4+	6 (5.5%)	0	

Mean FT3 levels were significantly lower in the ESS group than in the NTF group (1.79 ± 0.36 vs. 2.97 ± 0.32; $p < 0.001$), while FT4 and TSH levels were comparable between groups. ESS patients also had significantly lower serum albumin (2.97 ± 0.87 vs. 3.57 ± 0.89; $p = 0.031$) and higher serum creatinine levels (0.90 ± 0.19 vs. 0.75 ± 0.11; $p = 0.016$). Urea, SGOT, and SGPT levels did not differ significantly between the groups [Table 2].

Table 2: Thyroid, liver, nutritional and renal profile according to thyroid status

Parameter	ESS	NTF	P value
FT3	1.79 ± 0.36	2.97 ± 0.32	<0.001
FT4	1.19 ± 0.42	1.24 ± 0.13	0.668
TSH	3.18 ± 0.82	3.49 ± 0.66	0.236
Serum Bilirubin (mg/dL)	0.87 ± 0.41	0.74 ± 0.15	0.282
SGOT (IU/L)	28.13 ± 8.18	26.82 ± 7.57	0.612
SGPT (IU/L)	33.13 ± 41.74	23.55 ± 8.59	0.451
Albumin (g/dL)	2.97 ± 0.87	3.57 ± 0.89	0.031
Urea (mg/dL)	31.39 ± 11.79	26.91 ± 18.68	0.261
Creatinine (mg/dL)	0.90 ± 0.19	0.75 ± 0.11	0.016

At two months in the ESS group (n=109), sputum negativity was observed in 75 patients (1+:7, 2+:49, 3+:18, 4+:1), while 18 patients remained sputum positive (2+:1, 3+:13, 4+:4). One patient did not take treatment, 9 patients dropped out, and 6 were dead/defaulters. The association was significant ($p < 0.001$) [Table 3].

Table 3: Treatment Outcomes Based on Sputum Grading at 2 Months – ESS Group (n = 109)

AFB Grade	Negative	Positive	Not Taken Tablets	Dropped Out	Dead/Defaulter	P value
1+	7	0	0	0	1	<0.001
2+	49	1	1	4	1	
3+	18	13	0	5	3	
4+	1	4	0	0	1	
Total	75	18	1	9	6	

All 11 NTF patients belonged to the 1+ sputum grading category. Among them, 9 patients (100%) became sputum negative, 1 patient did not take treatment, and 1 patient dropped out. There were no

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sputum-positive cases and no deaths/defaulters. No statistically significant association was observed between sputum grading and treatment outcome in the NTF group (p > 0.9999) [Table 4].

Table 4: Treatment outcomes based on Sputum Grading –NTF Group

AFB Grade	Negative	Positive	Not Taken Tablets	Dropped Out	Dead/Defaulter	P value
1+	9	0	1	1	0	>0.9999
2+	0	0	0	0	0	
3+	0	0	0	0	0	
4+	0	0	0	0	0	
Total	9	0	1	1	0	

Among AFB-positive ESS patients (n=109), FT3 Grade I, II and III were observed in 36, 53 and 20 patients. Higher sputum grades showed greater FT3 derangement, with Grade III FT3 predominating in 3+ cases (14). A significant association was noted between FT3 levels and sputum grading (p = 0.009) [Table 5].

Table 5: FT3 Levels Vs Sputum Grading Among AFB-Positive ESS Patients (n = 109)

AFB Grade	FT3 Grade I	FT3 Grade II	FT3 Grade III	P value
1+	5	3	0	0.009
2+	21	30	5	
3+	7	18	14	
4+	3	2	1	
Total	36	53	20	

DISCUSSION

Pulmonary TB is a systemic disease that can significantly alter thyroid function, particularly through the development of ESS. This study aimed to assess the prevalence of ESS in newly diagnosed sputum-positive pulmonary TB patients and to examine its association with bacillary burden and delayed sputum conversion following the intensive phase of treatment. Understanding this relationship may help identify patients at risk of delayed treatment response and adverse outcomes.

ESS was prevalent among newly detected sputum-positive pulmonary TB patients, while only a small proportion had NTF. Pankaj Kumar et al. found that ESS was the most common thyroid abnormality in newly detected smear-positive pulmonary TB patients, which supports the high prevalence of ESS observed in our study.[9] Similarly, Dash et al. found ESS in approximately 35.82% of newly diagnosed pulmonary TB patients. This supports that ESS is common in active TB; the higher prevalence observed in our cohort may reflect differences in disease severity or patient characteristics.[7] Similarly, Gopala V et al. reported ESS was the most common thyroid abnormality at the time of pulmonary TB diagnosis, with 42% of patients showing ESS at baseline, while only 30% were euthyroid. Our study demonstrated a higher prevalence, due to greater disease severity or population differences.[10]

The ESS group had a higher mean age, but this difference was not significant and more males in both groups. Most patients were treated as outpatients, and no significant association was observed between demographic factors and thyroid status. In a study by Chow et al., ESS was seen in a majority of newly diagnosed pulmonary TB patients at the time of presentation, and patients with very low free T3 levels had worse outcomes, which aligns with our observation that ESS is present in pulmonary TB and may be linked with disease severity.[11] Similarly, Dash et al. reported that ESS was observed in patients belonging to older age groups, and male patients formed the majority of the study population, which is similar to our findings.[7] As in our study, no statistically significant association between age or sex and thyroid dysfunction status was emphasised.

ESS was associated with higher sputum bacillary grades, whereas NTF was associated with lower grades. FT3 levels were significantly lower in ESS, while FT4 and TSH levels were comparable between groups. Chow et al. reported that pulmonary TB patients who presented with very low free T3 levels tended to have more severe illness and poorer survival compared to those without ESS.[11] Yang et al. involving 495 patients with severe pulmonary TB, about 77.4% of patients had low serum FT3 levels at presentation, and those with low FT3 had significantly higher 28-day and 90-day mortalities compared with patients with normal FT3 levels.[12] This supports the association between low FT3 and greater disease severity.

ESS was associated with lower serum albumin and higher creatinine levels. Urea and liver enzyme levels did not differ significantly between groups. Hoque et al. found that smear-positive pulmonary TB patients were found to have lower serum albumin levels, with mean values around 3 g/dL, compared to healthy matched controls whose albumin levels were above 4 g/dL. Previous studies have reported reduced creatinine clearance, suggesting impaired renal function.[13] Similarly, Nakarani et al. found that pulmonary TB patients had significantly lower serum albumin and higher creatinine levels compared with healthy controls, while urea did not differ significantly. This supports our observation that ESS is associated with hypoalbuminemia and elevated

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creatinine in TB patients, even though other parameters were comparable between groups.[14] These findings indicate that ESS is common and is associated with higher bacillary burden and delayed sputum conversion.

Patients with ESS and higher baseline sputum grades were more to have poor treatment outcomes, including delayed sputum conversion. These outcomes were not observed in patients with NTF. Lower FT3 levels were found to be associated with higher sputum bacillary load. This suggests that reduced FT3 was associated with greater disease severity. Chow et al. ESS was present in 63% of patients at baseline, and low or undetectable FT3 levels were associated with greater disease severity and poorer outcomes. Mortality was significantly higher in patients with ESS (12/25) compared to those with NTF (1/15; $p < 0.02$), with undetectable FT3 linked to a 75% mortality rate. In survivors, thyroid function normalised during treatment, with FT4 levels improving within one month.[11] Although the study focused on mortality rather than sputum conversion, it demonstrated that baseline ESS and low FT3 were markers of poor treatment response and adverse outcomes in pulmonary tuberculosis.

Similarly, Yang et al. observed that pulmonary TB patients with low serum FT3 levels had more severe disease and poorer outcomes. This supports the association of low FT3 with higher bacillary burden and delayed sputum conversion.[12] Khan et al. found that many patients take a longer time for sputum culture conversion, and delayed conversion was seen in those with malnutrition and more advanced disease. There was a higher initial bacterial load, and the delayed culture conversion was associated with poorer treatment outcomes.[15] This supports our finding that patients with higher sputum grades, those with ESS and low FT3 levels, delayed sputum conversion and worse clinical outcomes.

Limitations

This was a single-centre, hospital-based study, which may limit generalisability, particularly to patients with milder disease. The small number of patients with NTF limited group comparisons. Nutritional status was not assessed, with serum albumin used only as an indirect marker. Drug resistance testing was not performed, thyroid function was assessed only at baseline, and multivariate analysis was not conducted; residual confounding cannot be excluded.

CONCLUSION

ESS is common in newly diagnosed sputum-positive pulmonary TB patients, presenting with low FT3 and normal FT4 and TSH. Patients with ESS had higher sputum bacillary grades, indicating more severe disease. Failure of sputum conversion at the end of the intensive phase occurred only in ESS patients with high baseline grades, while patients with NTF showed complete conversion and better outcomes. Lower FT3 levels were also associated with poor nutritional status. ESS and low FT3 levels were associated with greater bacillary infection and delayed sputum conversion during the intensive phase of treatment. However, further prospective studies with multivariate analysis are required to establish their independent predictive utility.

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