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Thyroid Function in Newly Diagnosed Pulmonary Tuberculosis Patients Pre- and -Post Intensive Phase: A Study in a Tertiary Medical College in Eastern Uttar Pradesh

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Abstract: ***The link between Tuberculosis and Thyroid Dysfunction is not well defined. In this prospective observational study conducted at SRNH Prayagraj from February 2023 to May 2024, the thyroid function status of 61 newly diagnosed patients of Pulmonary Tuberculosis was assessed.75.4% were found to have low free T3 levels. The free T4 and TSH levels were found to fall within the normal range for 77% and 65.6% of patients respectively. At the initiation of Anti – Tubercular Therapy, 23% of patients possessed low s. TSH levels, and 11.5% possessed high s. TSH levels. The mean TSH at baseline was 2.37±4.71 µIU/ml, which rose to 3.13 ± 4.44 µIU/ml at the end of the 2 – month Intensive Period. The rise in TSH at the end of two months suggests a transition from nonthyroidal illness syndrome hormone pattern to subclinical hypothyroidism.***

Keywords: tuberculosis, thyroid disorders, nonthyroidal illness syndrome, subclinical hypothyroidism, hypothyroidism, hyperthyroidism, anti - tubercular therapy, pulmonary tuberculosis

1. Introduction

Tuberculosis has been a scourge of humanity since antiquity[1]. Caused by *Mycobacterium tuberculosis*[2], the common mode of transmission is via droplet nuclei containing said bacteria inhaled by susceptible persons[2]. The most common site for infection, therefore, are the lungs[2]; although the pulmonary infection may be accompanied by extrapulmonary involvement in up to one - third of cases[2]. The prevalence of Tuberculosis Infection in India was estimated to be 36%[3] among the general population; once infected, lifetime risk of development of disease is 10 - 15% [4]. India with a population of 1.4 billion has almost 500 million people at risk of developing overt Tuberculosis.

The thyroid hormones, namely triiodothyronine (T3) and thyroxine (T4), are hormones produced and released by the thyroid gland, and are primarily responsible for regulation of metabolism[5]. The prevalence of thyroid dysfunction in India has been estimated to fall between 5.2% to 11%[6].

However, many illnesses can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease due to the release of cytokines; such as IL - 6[2]. It is also postulated that certain drugs used in the ATT regimens such as ethionamide[7] and rifampicin[8] may cause hypothyroidism.

Yet, the link between Tuberculosis itself, and thyroid dysfunction, is not well defined. With half a billion people[3] at risk of developing overt tuberculosis, every effort must be made to ascertain the association between these two diseases; and reduce the relevant disease burden.

Pulmonary Tuberculosis: Diagnosis and Case Definition
Pulmonary Tuberculosis may be either Presumptive or Microbiologically Confirmed.
Presumptive Pulmonary Tuberculosis is defined as any of[9]:

- Cough for ≥ 2 weeks
- Fever for ≥ 2 weeks
- Haemoptysis
- Significant weight loss (>4.5 kg or >5% of one's body weight lost in a period of 6– 12 months[2])
- Any CXR abnormality

Microbiologically Confirmed Tuberculosis:
presence of M. tuberculosis demonstrated via[9]:

- Sputum Smear Microscopy: ZN Stain, Florescent Staining
- Culture: LJ Media, BACTEC MGIT 960, BactiAlert
- Rapid Molecular Tests: Line Probe Assay, NAAT

Tuberculosis may also be classified on the Basis of Past ATT consumption[9]:
New Case: Never taken ATT OR taken for < 1 month
Previously Treated: > 1 month

- Recurrent TB: previously cured / completed treatment; and now microbiologically confirmed TB
- Treatment After Failure
- Treatment After Loss to Follow – Up: lost after ≥ 1 month of ATT
- Other

Tuberculosis may be Drug – Sensitive, or Drug – Resistant. Presumptive DR - TB may be elucidated as[9]:

- Patients who have failed treatment with first – line drugs
- contacts of DR – TB
- previously treated TB patients
- PLHWA with TB
- Patients who are positive on follow – up sputum examination

Pulmonary Tuberculosis: Treatment

Once the decision to initiate ATT is made in a case of Presumptive Drug Sensitive Pulmonary Tuberculosis, whether it be clinical or microbiologically confirmed, four or five anti - tubercular drugs[10] are started based on the weight category of the patient.

Recommended Doses of Anti – Tubercular Drugs[10]

	dose mg/kg	range mg/kg
Isoniazid: H	5	4 – 6
Rifampicin: R	10	8 – 12
Pyrazinamide: Z	15	12 – 18
Ethambutol: E	25	20 – 30
Streptomycin: S	15	15 – 20

Regimen for New DS - TB[10]

Intensive Phase	Continuation Phase
2HRZE	4HRE

Regimen for Previously Treated DS - TB[10]

Intensive Phase		Continuation Phase
2HRZES	1HRZE	5HRE

Classification of Thyroid Dysfunction

Most thyroid dysfunction can be diagnosed via the biochemical quantification of TSH, T4, and T3 in an early morning fasting peripheral blood sample[11].

Labaratory Classification of Thyroid Dysfunction[12, 13]

	TSH (µIU/ml)	T4 (ng/ml)	T3 (pg/ml)
Clinical Hypothyroidism	>7.0		
Subclinical Hypothyroidism	4.94 – 7.0		
Euthyroidism	0.5 – 4.94	0.7 – 1.48	1.71 – 3.71
Subclinical Hyperthyroidism	0.5 – 0.01		
Thyrotoxicosis	< 0.01		

2. Past Literature

There have been not many direct studies attempting to link Tuberculosis and Thyroid Dysfunction; however the "Effect of anti - tuberculosis treatment on thyroid profile in newly detected smear positive pulmonary tuberculosis cases" study by Varghese et al study sought to determine how antituberculosis medication affected the thyroid profile in newly diagnosed sputum smear - positive pulmonary tuberculosis cases. At the beginning of the six - month period, every patient was euthyroid; just 5% of them were still so by the conclusion of six months. It was discovered that the trend of sick euthyroid syndrome was declining and the trend of hypothyroidism was rising. The authors speculate that rifampicin, a cytochrome P450 inducer, is likely responsible for this result. It increases hepatic metabolism of thyroid hormone and biliary excretion of iodothyronine conjugates, hence boosting thyroid clearance and perhaps causing hypothyroidism[14].

Another study was the "Thyroid profile in pulmonary tuberculosis patients: a prospective study in a tertiary medical college of southern Odisha" study by Dash et al which was conducted to determine the thyroid profile status in new sputum smear positive pulmonary tuberculosis patients. The study revealed that 48 patients out of 134, that is 35.82%, had thyroid dysfunction in the form of sick euthyroid syndrome[15].

3. Materials and Methods

A prospective observational study was carried out at Swaroop Rani Nehru Hospital, Prayagraj from February 2023 to May 2024. New Cases of Pulmonary Tuberculosis from the Department of Medicine or Department of Pulmonary Medicine were enrolled in the study.

***Inclusion Criteria*: all of**

- Newly (<2 weeks) Diagnosed
- Presumptive or Microbiologically Conformed Pulmonary Tuberculosis
- ≥ 18 years

***Exclusion Criteria:* any of**

- Previously consumed ATT for ≥ 1 month
- History of previously diagnosed or currently active extrapulmonary tuberculosis
- History of or current thyroid dysfunction
- Current pregnancy or lactation
- Currently on amiodarone or lithium
- Known immunocompromised state

The free s. TSH, free s. T3, free s. T4 of these patients were measured at the initiation of standard Anti – Tubercular Therapy along with other anthropological and hematological parameters. After two months, their s. TSH was measured at the completion of the Intensive Phase.

4. Results

A total of sixty- one patients enrolled in the study. Of these, 54.1% were male and 45.9% were female.

Sex	N	%
Male	33	54.1%
Female	28	45.9%
Total	61	100.0%

41% of the study population was aged 18 – 35; 23% 36 – 50 while 29.5% was aged 51 – 65 years. Patients aged above 65 years comprised 6.5% of the study.

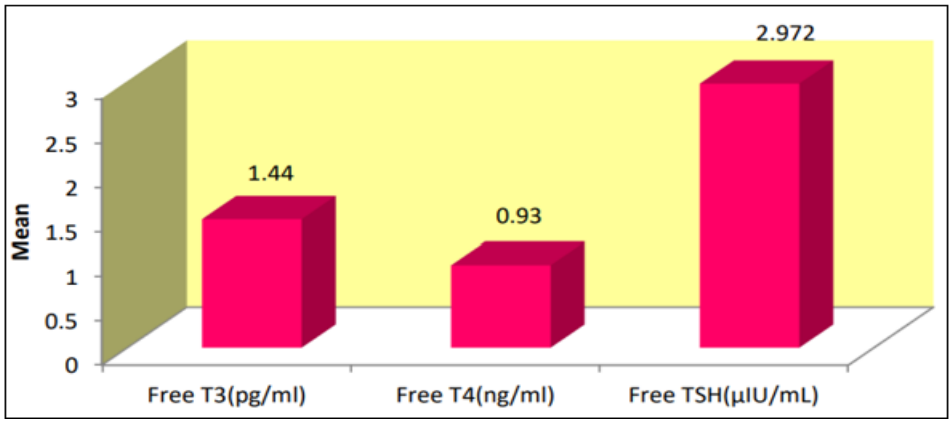
Age intervals	Frequency	Percent
18 to 35 years	25	41.0
36 - 50 years	14	23.0
51 - 65 years	18	29.5
Above 65 years	4	6.5
Total	61	100.0

Of these 61, four were found to have s. TSH > 10 µIU/mL and were initiated on standard levothyroxine therapy in

accordance with the guidelines[11] issued by the Indian Thyroid Society. They were excluded from the re - assessment of s. TSH done two months later. No patients with TSH < 0.01 µIU/mL were elicited.

After analyzing the Data of 61 participants, it was found that the mean s. T3 was 1.44 (Normal: 1.71 – 3.71 pg/mL); s. T4 0.93 (Normal: 0.7 – 1.48 ng/mL); and the mean s. TSH at baseline was 2.972 (Normal: 0.5 – 4.94 µIU/ml).

Baseline Thyroid Status

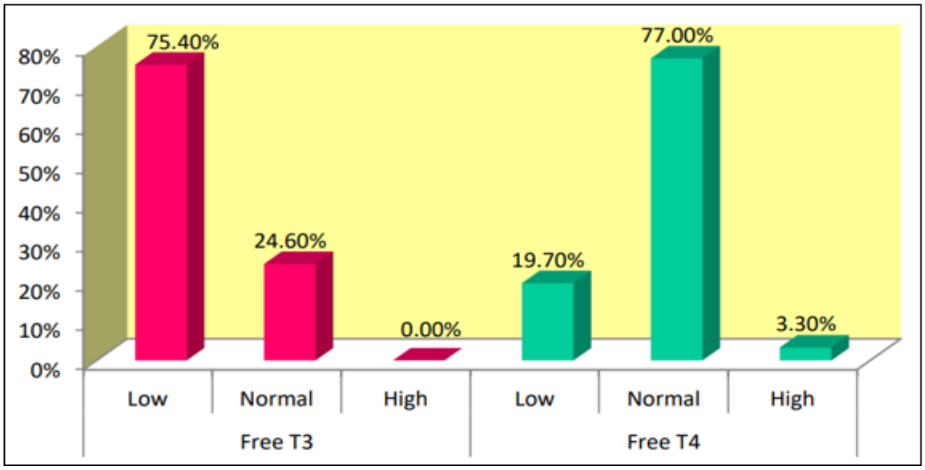


75.4% of the patients were found to have **low s. T3** at baseline; contrasted with 19.7% of patients who had low s. T4. Merely 23% of the patients had low s. TSH at presentation; 65.6% had s. TSH within normal limits; and 11.5% of patients had high s. TSH at baseline.

Distribution of Free T3 and Free T4 levels of study population

		N	%
free s. T3	**Low**	**46**	**75.4**
	Normal	15	24.6
	High	0	0
	Total	61	100
Free s. T4	Low	12	19.7
	Normal	47	77
	High	2	3.3
	Total	61	100

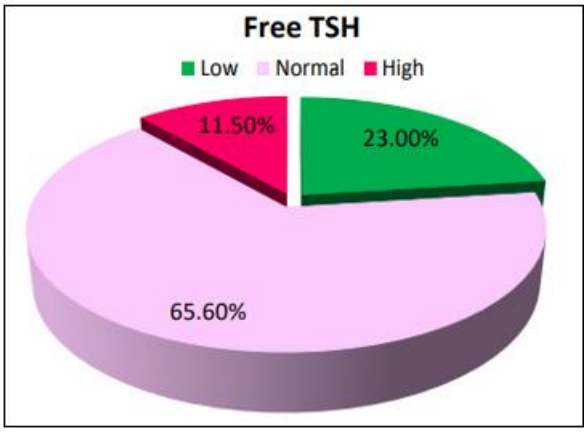
s.T3 and s.T4 distribution



Free TSH status at baseline of study population

Free s. TSH (µIU/mL)	N	%
Low (<0.05)	14	23
Normal (4.94 – 0.05)	40	65.6
High (>4.94)	7	11.5
Total	61	100

s. TSH status at baseline



71.4% of the patients with low s. TSH were 18 – 35 year old; whereas 57.1% of the patients with high s. TSH were aged 51 – 65 (p value 0.001)

Age intervals	Free TSH						p – value
	Low (n=14)		Normal (n=40)		High (n=7)		
	N	%	N	%	N	%	
18 to 35 years	10	71.4%	15	37.5%	0	.0%	0.001
36 - 50 years	1	7.1%	11	27.5%	2	28.6%	
51 - 65 years	2	14.3%	12	30.0%	4	57.1%	
Above 65 years	1	7.1%	2	5.0%	1	14.3%	
Mean ± SD	33.86±16.98		41.78±15.84		57.14±9.04		<0.001

85.7% of the patients with high s. TSH were male (p value 0.028)

Gender	Free TSH					
	Low (n=14)		Normal (n=40)		High (n=7)	
	N	%	N	%	N	%
Male	6	42.9%	21	52.5%	6	85.7%
Female	8	57.1%	19	47.5%	1	14.3%

Excluding four patients with clinical hypothyroidism which were supplemented with thyroxine, the mean s. TSH was 2.37 µIU/mL at baseline, which increased to 3.13 µIU/mL after two months of intensive phase. This represented a 24.28% mean change (p value <0.001).

Paired Samples Statistics						
Free TSH (µIU/mL)	N	Mean	SD	Mean difference	% mean change	p - value
At baseline	57	2.37	4.71	0.76	24.28%	<0.001
After 2 months of ATT	57	3.13	4.44			

5. Discussion

61 Newly Diagnosed Pulmonary Tuberculosis patients were enrolled in a prospective observational study in which the male population comprised 54.1% and the female population, 45.9%. Majority of the patients (41.0%) were between the ages of 18 and 35, followed by 36 to 50 - year - olds (23%), and 51 to 65 - year - olds (29.5%). People over the age of 65 made up the smallest category, accounting for 6.6%.

In the current study, before the initiation of ATT, free T3, free T4, and free TSH were assessed in all 61 patients, and they were found to have free T3 (pg/ml) = 1.44±0.52, free T4 (ng/ml) = 0.93±0.32, and free TSH (IU/mL) = 2.972±6.279. The study indicated that 75.4% had low free T3, whereas 24.6% had normal levels. Regarding Free T4 levels, 19.7% of the people had low levels, 77.0% had normal levels, and 3.3% had high levels.

In terms of TSH, 14 (23.0%) of participants had low Free TSH levels at initiation of ATT, 40 (65.6%) had normal values, and 7 (11.5%) had high levels of s. TSH. The majority (71.4%) of individuals with low Free TSH levels were between the ages of 18 - 35, and the majority (57.1%) of the subjects with elevated Free TSH levels were 51 to 65 years of age (p = 0.001). The findings also revealed that 85.7% of those with elevated levels were males (p = 0.028).

On following up with the study subjects after 2 months, the TSH was found to show rising trends. The mean TSH at baseline evaluation before initiation of ATT was 2.37 µIU/mL±4.71. The mean TSH value rose to 3.13 µIU/mL ± 4.44 at the completion of the 2 - month study period. The statistical analysis indicates that this mean change of 24.28% was statistically significant (p < 0.001), suggesting a significant alteration in free TSH levels resulting from two months of ATT.

In nonthyroidal illness syndrome[16], the most common hormone pattern is a decrease in total and unbound T3 levels – low T3 syndrome[17] – with normal s. T4 and s. TSH. It is generally assumed that this low T3 state is adaptive. Very sick patients may exhibit a low T4 syndrome[17] – a fall in total T4 as well as T3 levels. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in patients concurrently suffering from a non – thyroidal illness. The exact mechanisms underlying the phenomena remain unclear but may be mediated by cytokines including IL - 12 and IL - 18[16].

The diagnosis of NTI is frequently presumptive; and most authorities recommend monitoring the patient's thyroid function tests[17].

With 75.4% of the study population possessing low T3 levels; and 19.7% with low T4 levels, it may be assumed that the prevalence of low T3 syndrome state, and low T4 state, requires further investigation for proper assessment in patients suffering from Tuberculosis.

6. Conclusion

The most common hormone pattern in sick euthyroid syndrome is a decrease in total and unbound T3 levels (low T3 syndrome) with normal s. T4 and s. TSH. Our study posits that low T3 syndrome may be prevalent in patients of Pulmonary Tuberculosis. The rise in TSH at the end of two months suggests a transition from sick euthyroid syndrome hormone pattern to subclinical hypothyroidism. The rising TSH after ATT initiation may be in part due to rifampicin, which is a potent cytochrome P450 inducer. Perhaps in the future, thyroid function tests may be used as an adjunctive tool to diagnose Tuberculosis.

The authors declare no conflict of interest and nil financial interest.

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