

Effect of anti-tuberculosis treatment on thyroid profile in newly detected smear positive pulmonary tuberculosis cases

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Abstract

Background: Even though thyroid function is mandatory test before the initiation of MDR TB drugs, no such protocols exist in new smear positive pulmonary tuberculosis patients. Therefore, we conducted a study to know effect of anti - tubercular treatment on thyroid profile in new smear positive pulmonary tuberculosis cases.

Methods: Hospital based prospective observational study conducted at department of Respiratory medicine, S. P. Medical College and P.B.M Hospital, Bikaner. A total of 100 laboratory diagnosed pulmonary tuberculosis patients, who have consented to participate in the study during treatment was selected. Cases diagnosed as a “new case” of tuberculosis; Possessing at least two positive sputum smear test positive for Acid Fast Bacilli and only those newly micro bio logically diagnosed pulmonary tuberculosis cases, who were willing to participate during treatment were included.

Results: On observing the values of free T3 over the study period it was noted that free T3 showed a declining

trend. The mean free T3 at the start of study was 2.81 with a standard deviation of 0.52 and It had dropped to 1.76 with a standard deviation of 0.61 at the end of 3 months and finally to 1.64 with a standard deviation of 0.48 at the end of 6 months. The p value during study was found to be <0.001 and was found to be statistically significant. Free T4 values in study participants over the 6-month period, T4 also showed a declining trend. The mean free T4 at the start of study before initiation of ATT was 1.34 with a standard deviation of 0.28. At the end of 3 months it dropped to 1.12 with a standard deviation of 0.19 and to 0.99 with a standard deviation of 0.21 at the end of 6 months. The p value during the study period was found to be <0.001 and was found to be statistically significant. On following up the study subjects over the 6-month study period, TSH was found to show rising trends. The mean TSH at baseline evaluation before initiation of ATT was 1.64. The mean TSH value rose to 3.22 at the end of 3 months and 4.31 at the end of 6 months study period. The p value was found to be <0.001 and was statistically significant. Primary hypo

thyroidism was increasing from 10% (at the end of 3 months) to 63% (at the end of 6 months) and sub-clinical hypothyroidism was increasing from 6% (at the end of 3 months) to 29% (at the end of 6 months). Euthyroid patients were decreasing from 10% (at the end of 3 months) to 5% (at the end of 6 months).

Conclusion: New smear positive pulmonary tuberculosis can cause thyroid dysfunction at various stages of treatment.

Among the thyroid dysfunction, sick euthyroid syndrome and hypothyroidism was the major thyroid dysfunction observed in present study. Sick euthyroid syndrome was found to be a temporary reversible condition with highest incidence at the end of three months and was significantly reducing towards the end of treatment and absent after 6 weeks after stoppage of treatment.

Keywords: T3, T4, TSH, TB

Introduction

Tuberculosis is a bacterial disease spread from one person to another principally by airborne transmission. The causal agent is *Mycobacterium tuberculosis* (the tubercle bacillus). Tuberculosis can affect any organ in the body. Pulmonary tuberculosis is the most frequent site of involvement; extrapulmonary tuberculosis is less frequent. Only pulmonary tuberculosis is infectious.¹

TB is associated with diffuse functional impairment of most endocrine organs. The spectrum of TB associated endocrinopathies is extensive. The prevalence of TB involvement of thyroid gland ranges from 2 to 7%. The commonest manifestation of pulmonary tuberculosis involving thyroid gland was found to be sick euthyroid syndrome.⁸ The exact mechanism responsible for the alteration is still unknown, though the following mechanisms were suggested; like decreased T4 to T3 conversion, decreased TSH production.² A minority of patients with TB presents with clinically overt symptoms;

hence, the need among clinicians to possess a high index of suspicion for early diagnosis and initiation of appropriate treatment. There were many studies done in MDR TB cases to know the incidence of drug induced hypothyroidism.³⁻⁴

Even though thyroid function is mandatory test before the initiation of MDR TB drugs, no such protocols exist in new smear positive pulmonary tuberculosis patients. Therefore, we conducted a study to know effect of anti-tubercular treatment on thyroid profile in new smear positive pulmonary tuberculosis cases.

Materials and methods

Study design: Hospital based Prospective observational study.

Study duration: 6 Months.

Study place: Department of Pulmonary medicine, S.P. Medical College and P.B.M Hospital, Bikaner

Sample size

Sample size was calculated at 95% confidence interval to verify an expected 25% proportion of thyroid disorders in newly diagnosed sputum smear positive pulmonary tuberculosis patients (based on study) at 10% precision / absolute allowable error. Sample size was calculated using the formula for sample size for estimation of proportion –

$$N = \frac{Z_{1-\alpha/2}^2 P (1 - P)}{E^2}$$

Were,

$Z_{1-\alpha/2}^2$ = Standard normal deviate for 95% confidence interval (taken as 1.96)

P = expected proportion of thyroid disorders in newly diagnosed sputum smear positive pulmonary tuberculosis patients taken as 25% as per reference article varghese V et al (2018).

E = Precision / allowable error (taken as 10%)

Sample size was calculated to be to be minimum 75 subjects which was enhanced and rounded off to 100 subjects.

Inclusion Criteria

- Patients with newly detected smear positive pulmonary tuberculosis
- Age more than 18 years.
- Patients who will give written informed consent
- Patients with normal thyroid function test

Exclusion Criteria

- Patients who are suspects and diagnosed to have multidrug resistant pulmonary tuberculosis.
- Patients with known and newly diagnosed thyroid disorders (Medical and Surgical)
- Patients who are acutely ill with possibility of sick euthyroid syndrome
- Patients with HIV seropositive status
- Patients not willing to give informed consent

Data Collection

All patients attending Pulmonary medicine outpatient department with symptoms of pulmonary tuberculosis was advised to perform two early morning samples of sputum smear microscopy in our designated microscopy centre (DMC) to assess for acid fast bacilli. If sputum is found to be positive for acid fast bacilli, patients was included in the study. The following patients was assessed for thyroid function test which includes Thyroid stimulating hormone (TSH), Free T3 and T4 by electrochemiluminescence (ECL) method using COBAS e411 machine. Physicians’ opinion was taken if the thyroid function test is found to be abnormal on all subsequent visits and orders was carried out. Patients was started on antituberculosis treatment as per current RNTCP guidelines. Thyroid function testing is repeated at the end of third month and at the end of treatment. Based on

thyroid dysfunction, patients was classified as euthyroid (Normal TSH, free T3 and free T4), Primary hypothyroidism (High TSH with low free T4 and free T3), Subclinical hypothyroidism (High TSH and normal free T4 and free T3) and sick euthyroid (low free T3 with normal TSH and free T4 or low free T4 and free T3 with normal TSH).

Table 1:

Thyroid Dysfunction	No of cases	Percentage
Euthyroid (T3, T4, TSH Normal)	10	10.00
Sick Thyroid (T3 Low, T4 & TSH Normal or T3 & T4 Low, TSH Normal)	74	74.00
Subclinical hypothyroidism (T3 & T4 Normal, TSH High)	6	6.00
Primary Hypothyroidism (T3 & T4 Low, TSH High)	10	10.00
Total	100	100.00

Statistical Analysis

Statistical package for IBM SPSS for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp., was used to perform statistical analyse. Microsoft 2019 excel book was used for tables and graphs

Results

Table 1: General characteristics

Mean age in yrs	48.36±8.35 yrs
Male: Female	76:24
BMI in kg/MT in kg/mt2	22.06±1.02

Table 2: Thyroid Status wise Distribution of study subjects at 3 months after initiation of ATT

On evaluating thyroid status, 10 patients (10%) were euthyroid, 74 patients (74%) had sick euthyroid status and 16 patients (16%) were found to have hypo thyr

dis. Out of the 16 patients (16%) with hypothyroidism, 10 patients (10%) had primary hypo thyroidism and 6 patients (6%) had subclinical hypothyroidism.

Table 3: Thyroid Dysfunction wise Distribution of study subjects at 6 months after initiation of ATT

Thyroid Dysfunction	No of cases	Percentage
Euthyroid (T3, T4, TSH normal)	5	5.00
Sick Thyroid (T3 Low, T4 & TSH normal or T3 & T4 low, TSH normal)	32	32.00
Subclinical hypothyroidism (T3 & T4 normal, TSH high)	29	29.00
Primary Hypothyroidism (T3 & T4 low, TSH high)	34	34.00
Total	100	100.00

On evaluating thyroid status, 5 patients (5%) were euthyroid, 32 patients (32%) had sick euthyroid status, 34 patients (34%) had primary hypothyroidism and 29 patients (29%) had subclinical hypothyroidism.

Table 4: Distribution of free T3 over the study period

	Free T3		p-value
	Mean	SD	
Before initiation of after initiation of ATT	2.81	0.52	0.001
3 months after initiation of ATT	1.76	0.61	
6 months after initiation of ATT	1.64	0.48	

On observing the values of free T3 over the study period it was noted that free T3 showed a declining trend. The mean free T3 at the start of study was 2.81 with a standard deviation of 0.52 and It had dropped to 1.76 with a standard deviation of 0.61 at the end of 3 months and finally to 1.64 with a standard deviation of 0.48 at

the end of 6 months. The p value during study was found to be <0.001 and was found to be statistically significant.

Table 5: Distribution of free T4 over the study period

	Free T4		p-value
	Mean	SD	
Before initiation of after initiation of ATT	1.34	0.28	0.001
3 months after initiation of ATT	1.12	0.19	
6 months after initiation of ATT	0.99	0.21	

Free T4 values in study participants over the 6month period, T4 also showed a declining trend. The mean free T4 at the start of study before initiation of ATT was 1.34 with a standard deviation of 0.28.. At the end of 3 months it dropped to 1.12 with a standard deviation of 0.19 and to 0.99 with a standard deviation of 0.21 at the end of 6 months. The p value during the study period was found to be <0.001 and was found to be statistically significant

Table 6: Distribution of free TSH over the study period

	Free TSH		p-value
	Mean	SD	
Before initiation of after initiation of ATT	1.64	0.95	0.001
3 months after initiation of ATT	3.22	0.84	
6 months after initiation of ATT	4.31	0.65	

On following up the study subjects over the 6-monthstudy period, TSH was found to show rising trends. The mean TSH at baseline evaluation before initiation of ATT was 1.64. The mean TSH value rose to 3.22 at the end of 3 months and 4.31 at the end of 6 months study period. The p value was found to be <0.001 and was statistically significant.

Discussion

Thyroid profile in the form of TSH, free T3 and free T4 was measured for all new smear positive pulmonary tuberculosis patients.

Before the initiation of ATT, free T3, free T4 and TSH were assessed in all 100 patients and all patients were found to have normal thyroid parameters, i.e. all patients were found to be euthyroid. At 3 months follow up after initiation of ATT, Thyroid function tests were re-evaluated in all study subjects. Free T3 was found to be low in 84 patients (84.00%), free T4 was low in 14 patients (14.00%) and TSH was found to be in normal in 84 patients (84.00%) and high TSH values were noted in the remaining 16 patients (16.00%). At 6 months follow up after initiation of ATT, Thyroid function tests were re-evaluated in all study subjects. Free T3 was found to be low in 86 patients (86.00%), free T4 was low in 34 patients (34.00%) and TSH was found to be normal in 37 patients (37.00%) and high TSH values were noted in the remaining 63 patients (63.00%).

In our study observing the values of free T3 over the study period it was noted that free T3 showed a declining trend. The mean free T3 at the start of study was 2.81 with a standard deviation of 0.52 and It had dropped to 1.76 with a standard deviation of 0.61 at the end of 3 months and finally to 1.64 with a standard deviation of 0.48 at the end of 6 months. The p value during study was found to be <0.001 and was found to be statistically significant. Free T4 values in study participants over the 6-month period, T4 also showed a declining trend. The mean free T4 at the start of study before initiation of ATT was 1.34 with a standard deviation of 0.28. At the end of 3 months it dropped to 1.12 with a standard deviation of 0.19 and to 0.99 with a standard deviation of 0.21 at the end of 6 months. The p value during the study period was found to be <0.001 and was found to be

statistically significant. On following up the study subjects over the 6-month study period, TSH was found to show rising trends. The mean TSH at baseline evaluation before initiation of ATT was 1.64. The mean TSH value rose to 3.22 at the end of 3 months and 4.31 at the end of 6 months study period. The p value was found to be <0.001 and was statistically significant.

Chow CC et al ⁵ performed thyroid function test on 40 patients with pulmonary tuberculosis before starting ATT and at 1,2 and 4 months respectively. Out of 40 patients, 63% had sick euthyroid syndrome at presentation and mean free T3 among them was 1.6 and 4.4 in patients with normal thyroid function, was probably because of tuberculosis which caused altered thyroid hormone metabolism leading to the development of hypothyroidism and sick Euthyroidism..

Kim D et al ⁶ also conducted a similar study on 3 patients with pulmonary tuberculosis in euthyroid patients with underlying Hashimoto's thyroiditis and found that free T4 was reduced on all the three patients during the course of treatment with ATT and was normalized after the treatment was over.

In present study we presume that effective anti-tuberculous treatment caused normalization of free T4 at the end of 6 months. The mean TSH values (Normal: 0.27-4.2 micro-IU/ml) were found to be 1.67(Before initiation of ATT), 3.20 (3months after ATT) and 4.38 (6 months after ATT) respectively. TSH values were found to be increasing in majority of patients during the course of treatment. At the end of treatment, 38 patients (63%) had increased TSH values.

The increasing trend was probably due to increasing trend of primary hypothyroidism at the end of 6 months

During the course of anti-tuberculous treatment, Primary hypothyroidism was increasing from 10% (at the end of 3

months) to 63% (at the end of 6 months) and sub-clinical hypothyroidism was increasing from 6% (at the end of 3 months) to 29% (at the end of 6 months). Euthyroid patients were decreasing from 10% (at the end of 3 months) to 5% (at the end of 6 months). All the patients had normal thyroid function before initiating ATT; hence there were no sick euthyroid patients at the beginning of present study. At the end of three months, prevalence of sick euthyroid syndrome was found to be 74%, which decreased to 32% at the end of six months. Among the sick euthyroid patients, low T3 variant was majority in present study during the follow-up visits (at the end of 6 months, 29 patients were low T3 variant and 3 patients were low T3, T4 variant).

Limitation of present study was that hypothyroidism patients found at the end of treatment could not be followed up to know whether thyroid functions reverted to normal after stopping ATT.

Conclusion

In present study, new smear positive pulmonary tuberculosis can cause thyroid dysfunction at various stages of treatment. Among the thyroid dysfunction, sick euthyroid syndrome and hypothyroidism was the major thyroid dysfunction observed in present study.

Sick euthyroid syndrome was found to be a temporary reversible condition with highest incidence at the end of three months and was significantly reducing towards the end of treatment and absent after 6 weeks after stoppage of treatment, however none of these patients were acutely sick during the study and all these patients were euthyroid at the beginning of present study. Hence, we recommend that these patients should be kept under follow up after the diagnosis instead of treating with thyroid supplements. Hypothyroidism was the other major thyroid dysfunction observed during the course of treatment, with highest prevalence at the end of

six months. Among the anti-tubercular drugs used, rifampicin which was given for entire six months in all our patients, was probably the cause for thyroid dysfunction noticed during the course of treatment. Hence, authors recommend that these patients should be started on thyroid supplements after the diagnosis of significant hypothyroidism.

Rifampicin, which may have caused thyroid dysfunction in present study, should be continued due to its importance in the treatment of tuberculosis rather than stopping it and starting an alternate drug.

Authors recommend thyroid function test to be done in all cases of smear positive pulmonary tuberculosis before initiating treatment, during the course of treatment and if found to be abnormal follow up TFT is advised 6-8 weeks after the stoppage of treatment for better assessment of thyroid function.

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