

Original Research Article

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

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ABSTRACT

Background: Tuberculosis being a systemic disease and has a capacity for wide spread dissemination. Present study aims to identify the effects of antituberculous treatment on thyroid profile in new smear positive pulmonary tuberculosis cases.

Methods: This study was conducted among 60 new smear positive pulmonary tuberculosis cases attending pulmonary medicine OPD from May 2015 to April 2017. Thyroid function test in the form of free T3, free T4 and TSH was measured before initiating Anti tuberculosis treatment (ATT), at 3 months and at the end of 6 months.

Results: Out of 60 patients enrolled in present study, majority were males. Diabetes mellitus was the major co morbidity. Sick euthyroid was found to have decreasing trend during the course of treatment, and hypothyroidism was found to be increasing trend end of 6 months.

Conclusions: The common Thyroid Dysfunction seen during the study period was Hypothyroidism and Sick euthyroid. Anti-tuberculous medication preferably Rifampicin probably would explain the cause for these thyroid dysfunctions noticed during the study time. And those patients with significant hypothyroid need to started on thyroid supplements. Among the drugs used for treatment, rifampicin 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.

Keywords: Anti-tuberculosis treatment, Hypothyroidism, Thyroid stimulating hormone

INTRODUCTION

Tuberculosis is an infectious disease caused by mycobacterium tuberculosis. It is known by various other names through out the history like Consumption, phthisis, scrofula, Pott's disease and white Plague. In 1890 Robert Koch developed tuberculin, a purified protein derivative, which was proved to be an ineffective means of immunization. In 1908, Charles Mantoux found that it was an effective intradermal test for diagnosing tuberculosis.¹ Developing country like India account for one fourth of the global TB burden and it is estimated that TB kills more adults in India more than any other

infectious disease. According to the latest survey it is estimated that it kills 2 persons in every 5 minutes.²

The prevalence of TB involvement of thyroid gland ranges from 2-7%. The most common manifestation of pulmonary tuberculosis involving thyroid gland was found to be sick euthyroid syndrome.³ Many studies were done in MDR TB patients to know the incidence of drug induced hypothyroidism.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.

METHODS

This study was an institutional prospective cohort study done in the department of Pulmonary Medicine in Mahatma Gandhi Medical College and research institute, Pondicherry from May 2015-April 2017 and Institutional Human Ethical Committee(IHEC) approved this study.

Inclusion criteria

- Patients with newly detected smear positive pulmonary tuberculosis
- Age more than 18 years.

Exclusion criteria

- Patients who are suspects and diagnosed to have multidrug resistant pulmonary tuberculosis.
- Patient 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

Methodology

All patients attending Pulmonary medicine outpatient department with symptoms of pulmonary tuberculosis are 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 are 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 are 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 were 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).⁵

RESULTS

In a series of 60 cases of pulmonary tuberculosis, the youngest was 20 year old and the eldest was 70 year old. Maximum number of patients belonged to the age group between 40-50 years with a mean age of 49±16 years (Table 1).

Table 1: Age distribution.

	Total number of participants	Mean	Standard deviation
Age in years	60	49.3	16.3

Out of the 60 patients 46(76.7%) were males and 14 (23.3%) were females. Male to female ratio was 3.28:1 (Table 2).

Table 2: Gender distribution.

Gender	Number	Frequency
Male	46	76.7
Female	14	23.3
Total	60	100

Among the 60 study subjects 34 (56.7%) had comorbidities. Out of this 56.7%, the most common was diabetes mellitus and it was found in 30 patients (50%). Diabetes was followed by coronary artery disease in 5 patients (8.3%).

Table 3: Distribution of co-morbidities.

Co-morbidities	Number*	Frequency*
Absent	26	43.3
Present	34	56.7
Diabetes mellitus	30	50.0
Coronary artery disease	5	8.3
Chronic kidney disease	1	1.7
SLE	1	1.7
Acute kidney injury	1	1.7
Hypertension	1	1.7
Vocal cord palsy	1	1.7
Interstitial lung disease	1	1.7

Before the initiation of ATT, free T3, free T4 and TSH were assessed in all 60 patients and all patients were found to have normal thyroid parameters, i. e. all patients were found to be euthyroid (Table 4).

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 51 patients (85%), free T4 was low in 9 patients (15%) and TSH was found to be in normal in 50 patients (83.3%) and high TSH values were noted in the remaining 10 patients (16.7%).

Table 4: Thyroid parameters before initiation of ATT.

Thyroid status	Free T3		Free T4		TSH	
	Number	Frequency	Number	Frequency	Number	Frequency
Low values	0	0.0	0	0.0	0	0.0
Normal	60	100.0	60	100.0	60	100.0
High values	0	0.0	0	0.0	0	0.0
Total	60	100	60	100	60	100

Table 5: Thyroid parameters at 3 months after initiation of ATT.

Thyroid status	Free T3		Free T4		TSH	
	Number	Frequency	Number	Frequency	Number	Frequency
Low values	51	85	9	15.0	0	0.0
Normal	9	15	51	85.0	50	83.3
High values	0	0.0	0	0.0	10	16.7
Total	60	100	60	100	60	100

On evaluating the thyroid status, 5 patients (8.3%) were euthyroid, 45 patients (75%) had sick euthyroid status and 16.7% were found to have hypothyroidism. Out of

the 10 patients (16.7%) with hypothyroidism, 6 patients (10%) had primary hypothyroidism and 4 patients (6.7%) had subclinical hypothyroidism (Table 5).

Table 6: Thyroid parameters at 6 months after initiation of ATT.

Thyroid status	Free T3		Free T4		TSH	
	Number	Frequency	Number	Frequency	Number	Frequency
Low values	52	86.7	20	33.3	0	0.0
Normal	8	13.3	40	66.7	22	36.7
High values	0	0.0	0	0.0	38	63.3
Total	60	100	60	100	60	100

df- degree of freedom, *Repeated measures of ANOVA

At the end of 6 months, free T3 was found to be low in 52 patients (86.7%), free T4 was normal in 40 patients (66.7%). High TSH levels were found in the 38 patients

(63.3%). On evaluating the thyroid status, we found that only 3 patients (5%) were euthyroid, 19 patients (31.7%) had sick euthyroid status and 38 patients (63.3%) had hypothyroidism (Table 6).

Table 7: Distribution of free T3 over the study period.

	Total number of participants	Mean free T3	Standard deviation	F value, df	P value*
Before initiation of ATT	60	2.80	0.54	82.75, 2	<0.001
3 months after initiation of ATT	60	1.74	0.62		
6 months after initiation of ATT	60	1.61	0.53		

df- degree of freedom, *Repeated measures of ANOVA

Table 8: Distribution of free T4 over the study period.

	Total number of participants	Mean of free T4	Standard deviation	F value, df	P value*
Before initiation of ATT	60	1.32	0.19	47.32, 2	<0.001
3 months after initiation of ATT	60	1.10	0.23		
6 months after initiation of ATT	60	0.99	0.25		

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 2.80 with a standard deviation of 0.54 and it had dropped to 1.74 with a standard deviation of 0.62 at the end of 3 months and finally to 1.61 with a standard deviation of 0.53 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 7).

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 1.32 with a standard deviation of 0.19. At the end of 3 months it dropped to 1.10 with a standard deviation of 0.23 and to 0.99 with a standard deviation of 0.25 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 8).

Table 9: Distribution of TSH over the study period.

	Total number of participants	Median of TSH	Inter quartile range	Chi square value, df	P value*
Before initiation of ATT	60	1.67	1.04-2.64	96.63, 2	<0.001
3 months after initiation of ATT	60	3.20	2.10-3.99		
6 months after initiation of ATT	60	4.38	3.62-4.99		

On following up the study subjects over the 6-month study period, TSH was found to show rising trends. The median TSH at baseline evaluation before initiation of ATT was 1.67. The median TSH value rose to 3.20 at the end of 3 months and to 4.38 at the end of 6 months study period. The chi square value during the study period was 96.63 and p value was found to be <0.001 and was statistically significant (Table 9).

DISCUSSION

Thyroid profile in the form of TSH, free T3 and free T4 was measured for all new smear positive pulmonary tuberculosis patients. Once the thyroid results are known, these patients are classified into following categories: Euthyroidism, Primary hypothyroidism, subclinical hypothyroidism and sick euthyroidism. This study was done over a period of 18 months.

During present study free T3 was measured three times. The mean free T3 during present study (Normal: 2-4.4pg/ml) were 2.80 (Before initiation of ATT), 1.74 (3months after ATT) and 1.61 (6 months after ATT) and it was found to be statistically significant (P value <0.001). During the study mean free T3 was found to be decreasing during the course of treatment and at the end of 6 months, 52 patients (86%) had low free T3. Chow CC et al performed thyroid function test on 40 patients with pulmonary tuberculosis before starting ATT and at 1, 2 and 4 months respectively.⁷ 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. Similar to other studies we also found that mean free T3 was decreasing during the course of treatment and was probably because of tuberculosis which caused altered thyroid hormone metabolism leading to the development of hypothyroidism and sick euthyroidism.⁸ Free T4 (Normal :0.93-1.7 ng/dl) was also repeated three times as similar to free T3. The mean free

T4 values were found to be 1.32 (Before initiation of ATT), 1.10(3 months after ATT) and 0.99 (6 months after ATT) respectively. Free T4 was normal in majority of patients (66%) at the end of 6 months. Kim D et al 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.⁹ In present study we presume that effective antituberculous treatment caused normalization of free T4 at the end of 6 months.¹⁰

The mean TSH values (Normal:0.27-4.2 micro IU/ml) were found to be 1.67 (Before initiation of ATT), 3.20 (3 months 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.¹¹

All the hypothyroid patients were divided into two categories: Primary hypothyroidism (High TSH with low free T4 and free T3) and Subclinical hypothyroidism (High TSH and normal free T4 and free T3). During the course of anti-tuberculous treatment, hypothyroidism was increasing from 10%(at the end of 3 months) to 63% (at the end of 6 months). High prevalence of hypothyroidism may be explained by rifampicin, being a cytochrome P450 inducer, it can cause marked reductions in thyroid hormone levels in the serum as it increases T4 clearance because of enhanced hepatic T4 metabolism and biliary excretion of iodothyronine conjugates, hence it was concluded that rifampicin has a direct downward effect on free T4 and free T3 levels leading to increasing incidence of hypothyroidism at the end of 6 months.¹²

Sick euthyroid syndrome was diagnosed in present study by low free T3 with normal TSH and free T4 or low free T4 and free T3 with normal TSH (46). 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 75%, which decreased to 31% at the end of six months. None of the patients in present study was acutely sick requiring ICU care. All the 19 patients (31%) at the end of six months were followed up and repeat thyroid function test was done which was within normal limits. Among the sick euthyroid patients, low T3 variant was majority in present study during the follow up visits (63% at the end of 3 months and 21% at the end of 6 months). Pulmonary tuberculosis is found to inhibit 5'-monodeiodinase which converted T4 to T3, leading to low T3 level in majority of the patients. Other reason was postulated was cytokines like IL -1 released by this inflammatory condition can inhibit release of TSH leading to normal TSH in all our patients.¹³

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 (75%) 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, authors 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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