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Original article

Evaluation of Effect of Antitubercular Drugs on Thyroid Profile in Euthyroid Individuals

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ABSTRACT

Background: India is the highest TB burden country in the world and Tuberculosis being a systemic disease, it has capacity for wide spread dissemination. Some studies done in the past provided variable evidences suggesting Thyroid dysfunction can occur following antitubercular therapy, hence we have taken up this study. **Methods:** 50 freshly detected pulmonary and extra pulmonary tuberculosis cases were included in this study. Plasma levels of T3, T4 and TSH was measured before initiating Anti tuberculosis treatment (ATT) and repeated at the end of 6 months. **Results:** Post treatment 2(4%) subjects had change in T3 level above the normal reference range, no changes observed in T4 levels after the treatment. Post treatment 1(2%) subject had TSH of <0.3 Miu/ml indicating transition in to the hyperthyroid range, majority i.e. 32(64%) subjects had TSH level within normal reference range, whereas 17(34%) subjects had TSH level above the normal reference range falling into Subclinical Hypothyroid range. **Conclusion:** The common Thyroid Dysfunction seen during the study period was Hypothyroidism. Anti-tubercular medication preferably Rifampicin probably would explain the cause for these thyroid dysfunctions noticed during the study time.

KEYWORDS:Anti-tuberculosis treatment, Hypothyroidism, rifampicin, TSH.

INTRODUCTION

Tuberculosis (TB) continues to remain one of the most pressing health problems in India. Being highest TB burden country in the world, India accounts for one fifth of the global incidence - an estimated 1.96million cases annually out of 8.8 million new cases worldwide. Approximately 2.9million people die from tuberculosis each year worldwide; about one fifth of them in India alone. An average smear positive tuberculosis incidence in India is 69.2% higher in urban compared to rural areas [1].

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 [2]. Many studies were done in MDR TB patients to know the incidence of drug induced hypothyroidism. [3] 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.

Few of the studies observed that there is fall in T4, FT4 and rT3 by about 40% and a decrease in T3 by 25% occurred. It is hypothesized that an increased clearance of T4 and rT3 but not of T3 seems likely following rifampicin, which could be due to enhanced hepatic metabolism by induction of Cytochrome P450 complex (CYP3A) and biliary excretion. Therefore, increase in the dose requirement in hypothyroid patients who are on thyroid replacement therapy [4].

Therefore, we conducted a study to evaluate the effect of anti-tubercular treatment on thyroid function in euthyroid individuals.

MATERIALS AND METHODS

This study was an institutional prospective observational study done in the department of Medicine at Dr. B.R. Ambedkar Medical College and Hospital. Bangalore from 2010-2012 and Institutional Human Ethical Committee (IHEC) approved this study.

Evaluation and investigations

50 Tuberculosis patients were randomly selected and recruited to our study with prior consent. Study details were explained to them in local language. Thyroid function was assessed by measuring T3, T4 and TSH value before and after initiating antitubercular therapy (ATT).

Inclusion criteria

1. Patients with newly detected smear positive pulmonary and extra pulmonary tuberculosis
2. Age: 18 years- 65 years

Exclusion criteria:

1. Suspected and diagnosed cases of multidrug resistant pulmonary tuberculosis.
2. Patient with known and newly diagnosed thyroid disorders (Medical and Surgical)
3. HIV patients.
4. Patients who are on antiepileptic drugs.

RESULTS

In a series of 50 cases of tuberculosis, majority of study subjects were in the age group of 21 – 30 years. i,e 14(28%) and mean age was 37.88±13.87 (Table 1). In our study of 50 subjects 37 (74%) were males and 13 (26%) were females. Male to female ratio was 2.84:1(Table 2)

Table 1: Age distribution of subjects studied.

Age in years	Number of patients	%
18-20	4	8.0
21-30	14	28.0
31-40	10	20.0
41-50	12	24.0
51-60	8	16.0
>60	2	4.0
Total	50	100.0

Mean ± SD: 37.88±13.87

Table 2: Gender distribution of subjects studied.

Gender	Number of patients	%
Male	37	74.0
Female	13	26.0
Total	50	100.0

Fever was the most frequent symptom amounting to 43 (86%) of patients and next most common being cough in 21 (42%) of patients (Table 3). The least common symptoms were weight loss, haemoptysis and head ache amounting to 1 each (2 %).

Table 3: Distribution of Complaints of subjects studied.

Complaints	Number of patients (n=50)	%
1.Fever	43	86.0
2.Cough	21	42.0
3.Breathlessness	6	12.0
4.Abdominal distention	4	8.0
5.Pain abdomen	2	4.0

6.Weight loss	1	2.0
7.Head ache, vomiting	1	2.0
8.Haemoptysis	1	2.0

In our study most of the patients i.e. 16 (32%) were Sputum positive bilateral Pulmonary TB, next most common form of Tuberculosis was TB.Peritonitis (16%), Tubercular lymphadenitis (14%), Tubercular pleural effusion (8%), Sputum negative pulmonary TB (8%), Sputum positive Right sided Pulmonary TB (6%), Sputum positive Left sided Pulmonary TB (6%).TB meningitis, Phlyctenular conjunctivitis and Ileocaecal TB amounted to 2% each. (Table 4)

Table 4:Distribution of Diagnosis of subjects studied.

Diagnosis	Number of patients (n=50)	%
1. B/L Sputum +vePulm. TB	16	32.0
2.Rt. Sided Sputum + vePulm.TB	3	6.0
3.Lt. Sided Sputu +vePulm.TB	3	6.0
4.Tubercular Pleural effusion	4	8.0
5.TB. Lymphadenitis	7	14.0
6.Sputum –vePulm.TB	4	8.0
7. TB. Peritonitis	8	16.0
8.TB Patients with DM2	8	16.0
9.TB Meningitis	1	2.0
10.Phlyctenular conjunctivitis	1	2.0
11.Ileocaecal TB	1	2.0

In the subjects studied 48 (96%) had elevated Erythrocyte Sedimentation Rate whereas 2 (4%) had normal Erythrocyte Sedimentation Rate. Among the subjects having elevated Erythrocyte Sedimentation Rate majority 19 (38%) had ESR range between 50 – 100 mm/1hr. 10 (20%) of the subjects had ESR of >100 mm/1hr. The mean ESR recorded was 67.25 mm/1hr (Table 5).

Table 5: Distribution of ESR of subjects studied.

ESR	Number of patients	%
<20	2	4.0
20 – 50	13	26.0
50 – 100	19	38.0
>100	10	20.0
Not recorded	4	8.0
Total	50	100.0

Mean ± SD: 67.25±32.26

In our study none of the subjects had any thyroid abnormality at the time of diagnosis of Tuberculosis. Post treatment 2(4%) subjects had change in T3 level above the normal reference range, whereas majority 48(96%) of the subjects had T3 levels within the normal reference range. There were no changes observed in T4 levels after the treatment. Post treatment 1(2%) subject had TSH of <0.3 Miu/ml indicating transition in to the Hyperthyroid range, majority i.e. 32(64%) subjects had TSH level within normal reference range, whereas 17(34%) subjects had TSH level above the normal reference range falling them in to Subclinical Hypothyroid range (Table 6).

Table 6: Distribution of thyroid parameters of Subjects studied.

Thyroid parameters	Pre treatment (n=50)	Post treatment (n=50)	% change
T3 (ng /ml)			
• <0.5	0	0	0.0
• 0.5-2.0	50(100.0%)	48(96.0%)	-4.0%
• >2.0	0	2(4.0%)	+4.0%
T4 (µg/ml)			
• <4.8	0	0	0.0
• 4.8-14	50(100.0%)	50(100.0%)	0.0
• >14	0	0	0.0
TSH (Miu/ml)			
• <0.3	0	1(2.0%)	+2.0%
• 0.3-6.0	50(100%)	32(64.0%)	-36.0%
• >6.0	0(0%)	17(34.0%)	+34.0%

In our study changes in T3,T4,TSH were compared pre and post anti tubercular therapy using **Student t-test by** from the table it is evident that there was statistically highly significant change in TSH value post anti tubercular therapy with P value <0.001. Whereas Changes in T3 & T4 post therapy was statistically not significant.(Table 7)

Table 7:Comparison of thyroid parameters of subjects studied.

Thyroid parameters	Pre treatment	Post treatment	P value
T3 (ng/ml)	1.18±0.35	1.04±0.55	0.169
T4(µg/ml)	8.14±2.03	7.77±2.18	0.220
TSH (Miu/ml)	3.08±1.60	4.91±2.67	<0.001**

DISCUSSION

In our study none of the subjects had any thyroid abnormality at the time of diagnosis of Tuberculosis. Post treatment 2(4%) subjects had change in T3 level above the normal reference range, whereas majority 48(96%) of the subjects had T3 levels within the normal reference range. There were no changes observed in T4 levels after the treatment. Post treatment 1(2%) subject had TSH of <0.3 Miu/ml indicating transition in to the Hyperthyroid range, Majority i.e. 32(64%) subjects had TSH level within normal reference range, whereas 17(34%) subjects had TSH level above the normal reference range falling them in to Subclinical Hypothyroid range.

Also in our study changes in T3, T4 and TSH were compared before and after antitubercular therapy using Student t-test, there was statistically highly significant change in TSH values post antitubercular therapy with P value <0.001.There was no statistically significant change in T3 and T4 values were observed post antitubercular therapy.

Reports have shown that HIV and TB infections cause alteration in thyroid function[5],[6].Hence, we have excluded HIV patients and only euthyroid patients at the time of initiating ATT were included in study group.

Reports have shown that there is alteration in thyroid hormone levels in patients with non-thyroid illnesses such as TB. This alteration has been attributed to anti-TB drugs especially, the second line anti-TB drugs which cause more adverse effects than the first-line anti-TB drugs used for the treatment of drug-sensitive TB[7].In our study subclinical hypothyroidism was evident with 1st line ATT at the end of 6 months.

Takasu N et al[8] studied 67 subjects of tuberculosis who were treated with rifampicin. Of the 67 patients, 42 had negative tests for anti-thyroid antibodies (ATA) and 25 had positive tests for ATA. The diagnosis of Hashimoto's thyroiditis was made on the basis of positive tests for ATA. After the administration of rifampicin, TSH levels were not

significantly altered in all of the 42 ATA-negative patients and, but TSH levels increased in the three of the ATA-positives patients. Three euthyroid Hashimoto's patients developed hypothyroidism after the administration of rifampicin. This rifampicin induced hypothyroidism resolved in each, once rifampicin was discontinued. These 3 Patients who developed hypothyroidism received T4 supplementation. When rifampicin was discontinued, the hypothyroidism resolved. After the course of rifampicin-therapy had been completed, T4 was discontinued. At-risk patients who receive rifampicin may become hypothyroid.

Ohnhaus EE et al [9] while studying effect of various drugs on Thyroid hormone observed that the indices of thyroid function did not change following phenobarbital and antipyrine, but after 14 days of rifampicin T4, FT4 and rT3 decreased by about 14%, and T3 increased by 25%.

In addition, the impact of rifampicin on the clearance of injected I^{125}-T4 was investigated in six additional volunteers by blocking thyroid iodine uptake. The I^{125}-T4 half-life decreased from 155 to 106 h and its clearance increased from 25 to 50 ml/h, while a fall in T4, FT4 and rT3 by about 40% and no rise but a decrease in T3 by 25% occurred. Therefore, an increased clearance of T4 and rT3 but not of T3 seems likely following rifampicin, which might be due to enhanced hepatic metabolism and biliary excretion.

Study by A.R. Hill et al[10] observed that with therapy of TB (with isoniazid [INH], rifampicin [RIF], ethambutol and/or pyrazinamide), TBG increased above control values and T3RU decreased ($P < 0.001$). These changes were weakly correlated with liver enzyme activities but did not predict clinical hepatitis, which developed in only 1 patient. T3 was initially subnormal in 61% of 38 TB patients, while T4, thyrotropin (TSH) and TBG were normal. T3, TTR and albumin, all negative acute phase reactants, increased towards normal by day 10 ($P < 0.001$). Thyroid function remained unaltered in 14 control patients taking INH, whereas T3RU decreased (binding increased) and T3 increased in 15 taking INH and RIF ($P < 0.001$).

All the hypothyroid patients could be 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). According to a study done by Varghese et al 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.[11]

TB patients manifest the expected low T3 of non-thyroid illness, but, unlike most sick patients, usually have normal or increased serum binding of thyroid hormones. Chemotherapy further increases binding by increasing TBG, an effect probably due to RIF.

The above all studies state that there can be fall in T3 and values can occur probably due to cytP450 enzyme induced hepatic metabolism and increased biliary excretion leading to elevation of TSH levels, which was also observed in our study i.e. there was marginal and statistically insignificant fall in T3 levels and statistically significant elevation of TSH levels above the normal reference range.

CONCLUSION

The subjects during the course of antitubercular therapy should be monitored for signs and symptoms of hypothyroidism aseuthyroid individual may become Subclinical hypothyroidism with therapy. If a tuberculosis patient is known to have hypothyroidism, while receiving antitubercular therapy the dose of thyroid supplement needs to be escalated with regular monitoring of thyroid function test.

Competing interest: The authors declare that they have no competing interests.

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