

Assessment of Baseline Biochemical Thyroid Function in Patients with Multi-Drug Resistant Tuberculosis in Maiduguri

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ABSTRACT

Background: Most publications on disturbance of thyroid function among patients with drug resistant tuberculosis (DR-TB) have focused mainly on the effects of treatment with second line drugs. Some patients with newly diagnosed DR-TB are likely to have disturbed thyroid function at baseline. These groups of patients need to be actively looked out for in order to institute appropriate therapy to prevent further deterioration.

Methods: This is a prospective review of thyroid function on patients newly diagnosed with Rifampicin-Resistant TB/Multidrug resistant TB (RR-TB/MDR-TB) who underwent baseline thyroid function test (TSH, T3 and T4) at the University of Maiduguri Teaching Hospital (UMTH) between January 2016 and December 2018.

Results: Sixty-two patients were diagnosed with RR-TB, 58% of them were females, with ages ranging between 16 and 70 years. Forty-seven (75.8%) were aged between 20 and 49 years. The baseline results showed that 77.4% were euthyroid, while 16.1% had one form of thyroid disorder or another; Non-thyroidal illnesses (NTIs) were reported in 6.5% of the study population. Of the 16.1% of results that indicated presence of thyroid disorders, 60% were hyperthyroid, 10% had subclinical hyperthyroidism, 20% subclinical hypothyroidism and only 10% were hypothyroid.

Conclusion: Determination of baseline thyroid function in newly diagnosed patients with DR-TB is vital to identify patients with baseline thyroid dysfunction. This will guide proper intervention before commencing second line anti-TB medications that are known to affect thyroid function. Follow-up thyroid function tests, especially among those with hyperthyroidism will show the effect of thionamide therapy and whether they progress to develop any alterations in the reported parameters.

Keywords: Baseline, Thyroid function, rifampicin-resistance, Multi-drug resistance, tuberculosis, Nigeria

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Introduction

Emergence of rifampicin-resistant TB (RR-TB), a surrogate of multidrug-resistant tuberculosis (MDR-TB) is now a growing health problem in most of the developing as well as developed countries.¹ MDR-TB is defined as resistance to Isoniazid and Rifampicin with or without resistance to other first line anti-TB drugs.^{2,3} The prevalence of MDR-TB is 1-3% among new cases and around 12-17% in retreatment or failure cases.⁴ Multidrug-resistant tuberculosis (MDR TB) has also emerged as a major infectious disease problem throughout the world with higher mortality among HIV co-infected, compared to HIV uninfected,

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patients (adjusted excess hazard ratio, 5.6 [95% CI, 3.2–9.7]).⁵ In 2015, the world health organization (WHO) estimated that 580,000 cases of TB resistant to at least rifampicin (RR-TB), of whom, 480,000 (83%) also had resistance to Isoniazid (MDR-TB) were reported globally,⁴ has emerged. For the purpose of this study MDR-TB will be used to represent RR-TB.

Nigeria is among the high tuberculosis (TB) burden countries in the world with 570,000 new TB cases each year as well as one of the top 10 countries with high MDR-TB cases globally.^{4,6,7} Thyroid dysfunction, a well-known disorder in TB patients, is often overlooked; hence the magnitude of the problem remains unclear. Few studies from countries in different parts of the world have reported varying prevalence of hypothyroidism ranging between 2.3% and 69%.⁸⁻¹³ A recent study in Ibadan, Nigeria¹⁴ reported prevalence of 4.35%, 7.83% and 1.74% for sick euthyroid syndrome, subclinical hypothyroidism and subclinical hyperthyroidism, respectively.

The exact mechanism responsible for the alteration in thyroid function among TB patients is still unknown. Reports have shown that TB infection causes sick euthyroid syndrome possibly by decreasing the conversion of T4 to T3, increasing T4 to rT3 conversion, and decreasing thyroid stimulating hormone (TSH) synthesis.¹⁵⁻¹⁷ Anti-TB drugs, thionamides [prothionamide (PTH) and ethionamide (ETH)] and para-aminosalicylic acid (PAS), used for the treatment of MDR-TB have been known to cause hypothyroidism by inhibiting thyroid hormone synthesis through inhibition of uptake of iodine into thyroid cells, and hence blocking organification.^{4, 18-20} A previous study from the northeast region has reported that thyroid disorders, including endemic

goitre, are common.²¹ Information on baseline thyroid hormone status of MDR-TB patients will identify those with thyroid dysfunction prior to commencement of therapy. Furthermore, commencement of second-line therapy for MDR-TB might further worsen an existing thyroid dysfunction requiring thyroid hormone replacement. We hereby report, for the first time, the baseline thyroid function parameters of patients with MDR-TB prior to the commencement of therapy from northeastern Nigeria.

Patients and methods

This is a prospective assessment of consecutive patients who were newly diagnosed to have MDR-TB using Xpert MTB/RIF assay from the University of Maiduguri Teaching Hospital (UMTH) between January 2016 and December 2018. The patients were drawn from the general outpatient department, medical outpatient clinics and medical wards and recruited into the study after giving an informed verbal consent for participation. Ethical approval was obtained from the Institutional Review Board of the UMTH. From the 62 patients enrolled in the study 5mL of venous blood was aseptically drawn via the antecubital fossa for the estimation of TSH, T3 and T4. The blood sample was left to clot after which serum was separated from cells by centrifugation at 5,000rpm for 5 minutes. The serum was frozen until analysis. Thyroid stimulating hormone (TSH) and thyroid hormones (T4 and T3) were analyzed using *e114 autoanalyzer (ISN Products Nigeria LTD) Roche Diagnostics Deutschland GmbH in Nigeria*. Apart from the quality control reagent supplied by the company used in every batch analysis, repeat analysis of previous samples is usually included as part of quality control check.



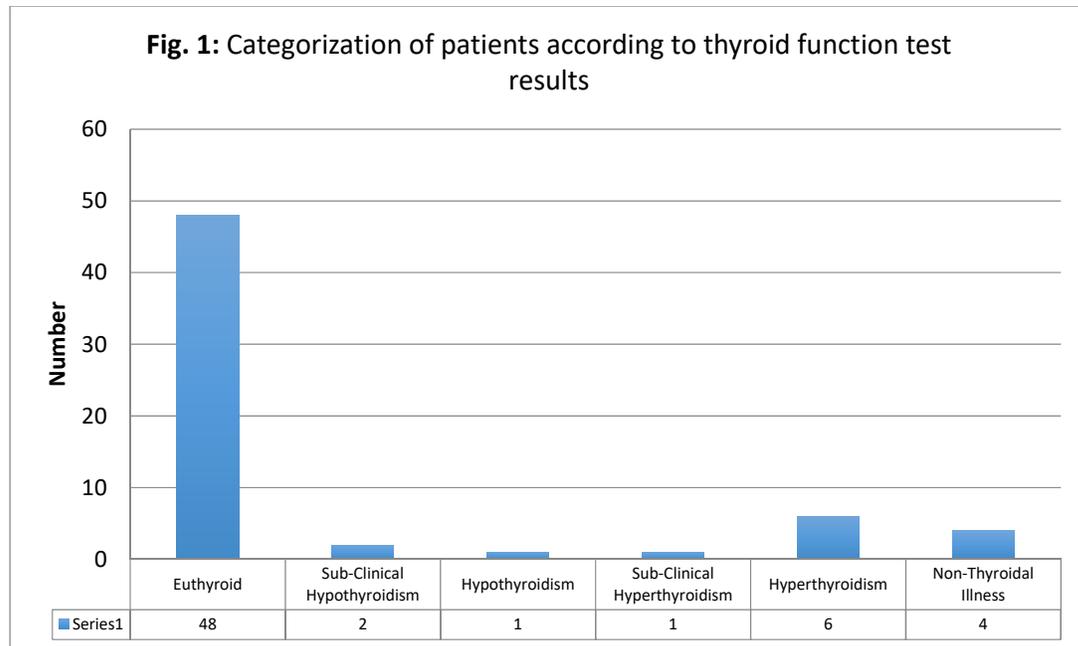
TSH values were considered abnormal if they were outside the reference range (0.4-7.0mIU/ml). For T3 and T4, values outside the reference range 0.6-2.0ng/ml and 5.0-14.0 µg/dl respectively were considered abnormal. According to the results, thyroid function tests were categorized into euthyroid, subclinical hypothyroidism, frank hypothyroidism, subclinical hyperthyroidism, frank hyperthyroidism, or Non-thyroidal illnesses (NTI).

Results:

During the study period, 62 patients were diagnosed with MDR-TB, 57% of them males (M:F=1.4:1). The ages of the studied patients ranged between 16 years and 70 years and majority (75.8%) of them were aged 20 years to 49 years. However, the ages of 6 (9.7%) were not clearly indicated (Table 2).

Table 1: Age and gender distribution of patients enrolled in the study

Age Range	Male	Female	Total
≤19	0	1	1(1.6)
20-29	8	12	20(32.3)
30-39	10	5	15(24.2)
40-49	8	4	12(19.4)
50-59	4	0	4(6.5)
60-69	2	1	3(4.8)
≥70	1	0	1(1.6)
No age indicated	3	3	6(9.7)



Overall, 16.1% of the study population had thyroid disorder, while 6.5% were classified as having non-thyroidal illnesses (NTIs). Of those with thyroid disorders, 60% were hyperthyroid, 10% had subclinical hyperthyroidism, 20% subclinical

hypothyroidism, and 10% were hypothyroid. Looking closely at the data, there were 8 (57%) males with thyroid abnormalities compared with 6 (43%) females, with non-thyroidal illness being more common amongst females. The gender



distribution among the study population is presented in table 2, below.

Table 2: Gender Distribution of thyroid abnormalities

Gender	Sub-clinical hypothyroidism	Hypothyroidism	Sub-clinical hyperthyroidism	Hyperthyroidism	Non-thyroidal illness
Male	2	0	1	4	1
Female	0	1	0	2	3

Discussion

During the study period more males (1.4 times) than females were diagnosed with RR-TB than females, thus showing more preponderance towards males. This is in contrast to a previous report by Ige *et al*, in Ibadan.¹⁴ The vulnerable age group affected by MDR-TB in this study is 20-49yrs, considered the most productive in an average society. A similar finding with other reports from the South-west^{14,22} and South-east⁸ of Nigeria signifying that the impact of tuberculosis in the societal economy is not only in the cost of treatment alone but by decreasing productivity as well. MDR-TB is therefore gradually eliminating the productive age group particularly in the developing world plagued by the HIV pandemic, like Nigeria.

Alterations in thyroid function due either to non-thyroidal illnesses or as adverse effect of drugs used in treatment of tuberculosis have been reported not only amongst adults but in the paediatric population as well.¹⁸ There are very few studies to the best of our knowledge that reported on thyroid function test before commencement of second-line antituberculosis drugs making comparison of our findings difficult. Alterations in thyroid function among critically ill patients have

been highly associated with adverse patient outcomes and increased mortality.¹⁵ Active Pulmonary tuberculosis is one of the causes of sick euthyroid syndrome, otherwise known as non-thyroidal illness (NTI).^{15,19} In this study 6.5% of our subjects were found to have NTI, which is similar to findings from the Southern part of Nigeria.^{7,14} However, higher prevalences were found in two studies conducted in South Africa,^{19,23} though their study patients were on admission and might have other illnesses that may explain the higher prevalence. The studies also did not state whether patients were on first or second-line anti-TB medications. Protracted critical illness is often associated with a disruption of the hypothalamic-pituitary-thyroid axis, resulting in reduced stimulation of the thyrotropes and impairment of thyroid hormone release. Thyroid dysfunction among adult patients with TB has been described in the African context.^{20,24,25}

Initially, NTI is a consequence of the acute phase response to systemic illness and macronutrient restriction, which might be beneficial. Pathogenesis of NTI in long-term critical illness is more complex and includes suppression of hypothalamic thyrotropin-releasing hormone, accounting for



persistently reduced secretion of thyroid-stimulating hormone despite low plasma thyroid hormone levels.

Subclinical hypothyroidism was recorded in 3.20% of our study population, less than that reported in Ibadan (7.83%).¹⁴ However, subclinical hyperthyroidism in this study (1.60%) is similar to the finding in Ibadan (1.74%).¹⁴ The prevalence of hypothyroidism (1.6%), a common finding in most published studies, was low; compared with the least reported from South Korea (2.3%).²⁶

One of the unique findings in this study is the high prevalence of hyperthyroidism (9.70%). Hyperthyroidism, among patients with TB has not been a common finding in the literature. This, however, is not entirely surprising going by a recent report by Mshelia *et al* from the same environment where 81.1% of subjects screened for thyroid disorders had hyperthyroidism.^{21,21} Iodine deficiency is still common^{27,28} despite iodine fortification of foods/salt. Iodine deficiency is a major public health problem throughout Africa and is the commonest cause of thyroid disorders.²⁹ Some of the manifestations of iodine deficiency disorders (IDD) in adults include spontaneous hyperthyroidism in the elderly, and iodine-induced hyperthyroidism.³⁰ This could be the explanation of this finding in the present study.

Thyroid hormones are essential for the regulation of energy metabolism, and for the physiological function of virtually all tissues. Consequently, disordered thyroid function can alter the metabolism of some medications, including those used for tuberculosis treatment. Depending on the pharmacokinetic properties of the individual drug, changes in the rate of metabolism can range from profound to moderate or negligible. Since renal function is also

influenced by thyroid disease, changes in renal elimination of drugs, which are excreted in the urine mainly unchanged, have to be considered as another reason for altered drug disposition in thyroid disease. Screening and treatment of thyroid dysfunction among patients with MDR-TB will, therefore, aid in determining and improving the prognosis of such patients.

Conclusion: Thyroid disorders are common in our environment. Patients with TB that require either first or second-line ant-TB drugs should be screened for thyroid disorders, and if present, the disorder should be corrected before commencement of TB treatment, especially with thionamides. With the high rate of hyperthyroidism among the studied population, it would be expected that the use of thionamides would be beneficial. Follow up assessment of these patients will highlight the impact of thionamide therapy on patients with baseline hyperthyroidism.

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