Thyroid function in multidrug-resistant tuberculosis patients with or without human immunodeficiency virus (HIV) infection before commencement of MDR-TB drug regimen.

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Abstract

Background: Mycobacterium tuberculosis and human immunodeficiency virus (HIV) are known to cause abnormal thyroid function. There is little information on whether HIV infection aggravates alteration of thyroid function in patients with MDR-TB.

Objectives: This study was carried out to determine if HIV co-infection alters serum levels of thyroid hormones (T3, T4) and thyroid stimulating hormone (TSH) in patients with MDR-TB patients and to find out the frequency of subclinical thyroid dysfunction before the commencement of MDR-TB therapy.

Methods: This observational and cross-sectional study involved all the newly admitted patients in MDR-TB Referral Centre, University College Hospital, Ibadan, Nigeria between July 2010 and December 2014. Serum levels of thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were determined using ELISA.

Results: Enrolled were 115 patients with MDR-TB, out of which 22 (19.13%) had MDR-TB/HIV co-infection. Sick euthyroid syndrome (SES), subclinical hypothyroidism and subclinical hyperthyroidism were observed in 5 (4.35%), 9 (7.83%) and 2 (1.74%) patients respectively. The median level of TSH was insignificantly higher while the median levels of T3 and T4 were insignificantly lower in patients with MDR-TB/HIV co-infection compared with patients with MDRT-TB only.

Conclusion: It could be concluded from this study that patients with MDR-TB/HIV co-infection have a similar thyroid function as patients having MDR-TB without HIV infection before commencement of MDR-TB drug regimen. Also, there is a possibility of subclinical thyroid dysfunction in patients with MDR-TB/HIV co-infection even, before the commencement of MDR-TB therapy.

Keywords: HIV, multidrug-resistant TB, subclinical thyroid dysfunction, thyroid hormones.

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Introduction

Multidrug-resistant tuberculosis (MDR-TB) continues to be a public health problem because of its increasing trend[1,2]. Due to the ineffectiveness of two most effective anti-TB drugs (isoniazid and rifampicin), treatment of MDR-TB becomes challenging as it involves combination of a minimum of 5 drugs for at least 20 months[3,4]. Management of MDR-TB is daunting especially, when it co-exists with HIV infection. It has been shown that management of MDR-TB or MDR-TB with HIV co-infection is associated with some adverse events such as alteration in thyroid hormone levels[4,5,6]. Thus, the need to determine the status of thyroid hormones before the commencement of therapy cannot be over emphasized.

The thyroid gland plays an important role in the maintenance of body metabolism. Principally, it secretes thyroxine (T4) and triiodothyronine (T3)under the influence of thyroid stimulating hormones[7,8]. 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[9]. The exact mechanism responsible

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for the alteration is still unknown[8,10], though the following mechanisms were suggested; viz: decreased T4 to T3 conversion, decreased TSH production and action of drugs such as ethionamide and prothionamide used for the treatment of MDR-TB on the thyroid causing hypothyroidism by inhibiting thyroid hormone synthesis through inhibition of iodine organification[11-13]. Similarly, antiretroviral therapies such as stavudine, amprenavir and lopinavir have been associated with hypothyroidism[14,15]. It is therefore important to assess thyroid function test before commencement of MDR drug regimen.

Although WHO guidelines recommended that TSH level should be monitored in patients with MDR-TB at least every 6 months[12], there is lack of information on whether HIV infection has an additional effect on the alteration of thyroid hormones in patients with MDR-TB. Information on thyroid hormone status of MDR-TB patients will identify MDR-TB patients with subclinical thyroid dysfunction who might benefit from appropriate clinical intervention before the commencement of MDR-TB drug regimen which could get worse with the commencement of the therapy. To provide information on thyroid function in Nigerian MDR-TB patients with HIV co-infection, we determined the serum levels of thyroid hormones in patients with MDR-TB and MDR-TB/HIV co-infection.

Methods

Subjects

This observational and cross-sectional study involved all the MDR-TB patients admitted at the MDR-TB Referral Centre, University College Hospital, Ibadan, Nigeria between July 2010 and December 2014. Enrolled were 115 patients with MDR-TB, out of which 22 (19.13%) had MDR-TB/HIV co-infection.

Data collection

Height (m), body weight (kg) and body mass index (kg/m^2) were taken using standard methods. Serum levels of TSH, free T4 (fT4) and free T3 (fT3) were determined using ELISA (Biotek, USA). Assessment of thyroid function is part of the pre-treatment medical assessment usually carried out on patients referred to the MDR-TB Unit of the hospital and 0.4 – 4.0 IU/ml, 59 – 153 nmol/L and 0.56 – 1.88 ng/ml were considered as the reference ranges for TSH, T4 and T3 respectively.

*Stati*stical analysis

The distribution of all the variables was assessed using histogram with normal curve. All the variables except TSH, fT4 and fT3 had Gaussian distribution. Depending on the Gaussian distribution, differences of variables between groups were assessed using the Student's t, Mann Whitney U and Fisher's exact test. Results are presented as mean ± standard deviation or median (interquartile range). P values less than 0.05 were considered as statistically significant.

Results

Majority of the patients had normal thyroid profile. Five (4.35%), 9 (7.83%) and 2 (1.74%) patients had sick euthyroid syndrome (normal TSH level with low T3 and/or T4 level), subclinical hypothyroidism (high TSH with normal T3 and T4) and subclinical hyperthyroidism (low TSH with normal T3 and T4) respectively.

As shown in Table 1, the median level of TSH was slightly higher while the median levels of T3 and T4 were slightly lower in patients with MDR-TB/HIV co-infection compared with MDR-TB patients only. However, the differences in the medians were not statistically significant. Similarly, the mean body weight and BMI were similar between the 2 groups.

Table 1: Demographic characteristics, thyroid stimulating hormone and thyroid hormones levels in MDR-TB patients with or without HIV infection

	MDR-TB (n = 93)	MDR-TB/HIV (n = 22)	*P*-values
Age (years)	35.44 ± 11.07	33.18 ± 9.18	0.377
Height (m)	1.63 ± 0.26	1.66 ± 0.11	0.617
Body weight (kg)	48.40 ± 13.26	50.27 ± 8.75	0.530
BMI (kg/m^2)	16.95 ± 4.91	18.13 ± 2.58	0.276
TSH (IU/ml)	1.85 (1.13 – 3.48)	1.90(1.38 – 2.48)	0.822
fT_4 (nmol/L)	91.00 (70.00 – 107.00)	88.00 (62.75 – 103.70)	0.516
fT_3 (ng/ml)	1.15 (0.75 – 1.60)	1.12 (0.69 – 1.65)	0.797

BMI= body mass index, TSH=thyroid stimulating hormone, fT_4 =free thyroxine, fT3 = free triiodothyronine, values are presented in mean ± standard deviation or median (interquartile range)

When all the patients were pooled and compared based on gender (males and females), it was observed that the median levels of TSH, T3 and T4 were similar between the 2 groups. However, male patients were found to be significantly older and had higher BMI than the female patients (Table 2).

Table 2: Demographic characteristics, thyroid stimulating hormone and thyroid hormones levels in male and female MDR-TB patients without HIV infection and MDR-TB patients with HIV infection

	Male (n = 76)	Female (n = 39)	*P*-value
Age (years)	37.30 ± 11.04	30.54 ± 8.64	0.001*
Height (m)	1.65 ± 0.28	1.61 ± 0.10	0.395
Body weight (kg)	51.62± 13.03	43.33 ± 9.37	0.001*
BMI (kg/m^2)	17.44 ± 5.12	16.65 ± 3.26	0.385
TSH (IU/ml)	1.80 (1.20 – 3.40)	1.90 (1.20 – 3.50)	0.908
fT_4 (nmol/L)	87.00 (67.10 – 101.50)	93.00 (70.00 – 112.00)	0.116
fT_3 (ng/ml)	1.00 (0.75 – 1.75)	1.20 (0.73 – 1.50)	0.895

*Significant at $P<0.05$, BMI= body mass index, TSH=thyroid stimulating hormone, fT_4 =free thyroxine, fT_3 = free triiodothyronine, values are presented in mean ± standard deviation or median (interquartile range)

There was no difference in the median levels of TSH, T3 and T4 when male patients with MDR-TB/HIV co-infection were compared with male patients with MDR-TB only (Table 3).

Table 3: Demographic characteristics, thyroid stimulating hormone and thyroid hormones levels in male MDR-TB patients without HIV infection and male MDR-TB patients with HIV infection

	MDR-TB (n = 65)	MDR-TB/HIV (n = 11)	*P*-value
Age (years)	33.83 ± 8.44	40.64 ± 17.44	0.231
Height (m)	1.64 ± 0.30	1.72 ± 0.04	0.397
Body weight (kg)	51.22 ± 13.94	53.91 ± 5.28	0.532
BMI (kg/m^2)	17.30± 5.48	18.26 ± 1.78	0.570
TSH (IU/ml)	1.80 (1.18 – 3.83)	2.10 (1.60 – 2.40)	0.823
fT_4 (nmol/L)	91.00 (67.80 – 104.00)	80.00 (62.00 – 92.00)	0.226
fT_3 (ng/ml)	1.00 (0.75 – 1.83)	1.14 (0.65 – 1.70)	0.688

BMI= body mass index, TSH=thyroid stimulating hormone, fT_4 =free thyroxine, fT_3 = free triiodothyronine, values are presented in mean ± standard deviation or median (interquartile range)

Similarly, the median levels of TSH, T3 and T4 were similar in female patients with MDR-TB/HIV co-infection and female patients with MDR-TB only (Table 4).

Table 4: Demographic characteristics, thyroid stimulating hormone and thyroid hormones levels in female MDR-TB patients without HIV infection and female MDR-TB patients with HIV infection

	MDR-TB (n = 28)	MDR-TB/HIV (n = 11)	*P*-value
Age (years)	35.04 ± 12.26	36.27 ± 10.17	0.769
Height(m)	1.62 ± 0.09	1.60 ± 0.13	0.737
Body weight (kg)	42.04 ± 8.88	46.64 ± 10.19	0.171
BMI (kg/m^2)	16.12 ± 3.15	18.00 ± 3.28	0.106
TSH (IU/ml)	2.35 (1.10 – 3.53)	1.70 (1.25 – 3.75)	0.955
fT_4 (nmol/L)	92.00 (69.50 – 112.00)	101.00 (63.50 – 115.00)	0.985
fT_3 (ng/ml)	1.20 (0.71 – 1.50)	1.10 (0.79 – 1.45)	0.806

BMI= body mass index, TSH=thyroid stimulating hormone, fT_4 =free thyroxine, fT_3 = free triiodothyronine, values are presented in mean ± standard deviation or median (interquartile range)

In Table 5, there was no significant association between HIV status and levels of TSH, T3 and T4.

Table 5: Association between MDR-TB/HIV co-infection, thyroid stimulating hormone and thyroid hormones in MDR-TB patients without HIV infection and MDR-TB patients with HIV infection

	HIV				
	Yes	No	N	X^2	P-value
TSH					
Below reference range	1 (4.54%)	1 (1.08%)	2	1.257	0.533
Within reference range	17 (77.27%)	75 (80.65%)	92		
Above reference range	4 (18.18%)	17 (18.28%)	21		
fT_3					
Below reference range	2 (9.09%)	4 (4.30%)	6	1.227	0.540
Within reference range	16 (72.73%)	65 (69.89%)	81		
Above reference range	4 (18.18%)	24 (25.81%)	28		
fT_4					
Below reference range	4 (18.18%)	9 (9.68%)	13	1.863	0.394
Within reference range	16 (72.73%)	79 (84.95%)	95		
Above reference range	2 (9.09%)	5 (5.38%)	7		

Discussion

The need for detection of thyroid disease in patients with MDR-TB cannot be under-estimated since reports have shown that subclinical hypothyroidism increases the risk of depression and reduces adherence to MDR-TB and HIV treatment[16,17].

An independent association between chronic illnesses such as tuberculosis and thyroid disease has been reported[18,19]. This might explain the observed SES, subclinical hypothyroidism and subclinical hyperthyroidism in our patients.

Reports have shown that HIV and TB infections cause alteration in thyroid function[5,6]. In this study, there was no significant difference in the median levels of thyroid stimulating hormone and thyroid hormones in patients with MDR-TB only and those with MDR-TB/HIV co-infection. This observation suggests that MDR-TB/HIV co-infection and MDR-TB infection have similar effects son thyroid function.

Modongo and Zetola[20] reported that there is an association between male gender and the development of hypothyroidism in patients with MDR-TB on treatment. The median levels of thyroid stimulating hormone and thyroid hormones were similar between the male and female patients. Our observation shows that the effect of the illness on thyroid stimulating hormone and thyroid hormones levels might not be gender specific. However, male MDR-TB patients were observed to be older and with higher body weight than female patients. Comparing the male patients with MDR-TB only with male patients with MDR-TB/HIV co-infection, there was no significant difference in the median levels of thyroid stimulating hormone and thyroid hormones. A similar pattern was also observed when female patients with MDR-TB only were compared with female patients with MDR-TB/HIV co-infection. These observations further support our earlier observation that the effect of the illnesses on the thyroid function might not be gender specific.

The observed lack of association between HIV status and thyroid stimulating hormone/thyroid hormones levels is in line with our observed non-significant difference in the median levels of thyroid stimulating hormone and thyroid hormones in patients with MDR-TB only and patients with MDR-TB/HIV co-infection. This observation shows that the presence of HIV infection does not seem to alter the thyroid function in MDR-TB patients before the commencement of MDR-TB drugs.

It could be concluded from this study that patients with MDR-TB/HIV co-infection have similar thyroid function compared with patients having MDR-TB without HIV infection before the commencement of MDR-TB drugs. However, the presence of SES and subclinical thyroid dysfunction in some of the patients indicates the need to assess thyroid function in MDR-TB patients with or without HIV infection before commencing MDR-TB therapy as it could identify patients that might benefit from appropriate clinical intervention with a view to preventing aggravation of the thyroid disease during the course of the MDR-TB therapy.

Conflict of Interest

All authors have no conflict of interest to declare

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