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A physician's perspective on correlation of thyroid abnormalities in HIV patients

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Abstract
Backgroundand Aims: There is report of increasing association of thyroid disorders in HIV positive patients. Currently there are insufficient data to recommend routine screening for thyroid disorders in asymptomatic HIV patients, hence this study was undertaken to resolve these issues.
Methods: This is a comparative descriptive study of 90 seropositive HIV patients which was taken for convenience conducted at MGM Medical college Kishanganj Bihar.
Results: Overt hypothyroidism was found in 3.33% patients, subclinical hypothyroidism was found in 8.89% patients, isolated low FT4 was found in 3.33% patients while sick euthyroid syndrome was found in 26.67% patients, none of the patient was found to be had hyperthyroidism.
As the disease progresses FT4 and FT3 level were decreased while TSH level was increased. A direct positive correlation between FT4, FT3 and CD4 count was established while a negative correlation between S.TSH and CD4 count was found. Mean FT3 and FT4 levels were lower in patients on HAART while mean TSH level was higher in patients on HAART.
Conclusion: Thyroid dysfunction in HIV patients were largely asymptomatic.There was a direct correlation between WHO clinical stage and FT3 and FT4 levels. Thyroid Stimulating Hormone level increased as CD4 count decreased. Patients on HAART had a higher prevalence of subclinical hypothyroidism.

Keywords: HIV human immunodeficiency Virus, TSH, HAART, FT3

Introduction
The prevalence of human immunodeficiency virus (HIV) infection in India is estimated to be 2.4 million [1] HIV infection can lead to involvement of various organs and systems including endocrine glands. Alteration in endocrine functions may be due to the possible relationship between the immune and endocrine systems, direct involvement of the glands by the HIV itself, opportunistic infections or malignancies, highly active anti-retroviral therapy (HAART) and drugs used to treat the opportunistic infections [2]. Although the prevalence of overt thyroid disease does not appear to be significantly increased as compared to general population, subtle thyroid dysfunction is common, believed to occur in as many as 35% of all HIV infected individuals [3-6] Earlier studies have evaluated the possible relationship of thyroid dysfunction in HIV. In our Country there are very few reports on thyroid dysfunction seen in HIV patients. The prevalence and relationship of thyroid auto-antibodies in various stages of disease and therapy has not been studied. There was no report of hyperthyroidism in these publications despite reports of resurgence of autoimmunity leading on to Graves' disease in immune reconstitution inflammatory syndrome. So further studies are required to confirm this.Hence the present study is designed to answer the above uncertainties. This study also assess whether universal screening of thyroid function could be enforced in HIV patients.

Aims and Objective
1. To study the thyroid abnormalities in both clinical and biochemical in HIV positive patients.
2. To correlate the thyroid function changes in these patients with their CD4 cell count, WHO clinical stage and duration of HAART.

Material and Methods
This is a comparative descriptive study of 90 seropositive HIV patients which was taken for convenience conducted at MGM MEDICAL COLLEGE KISHANGANJ BIHAR. Duration of this study was from Nov. 2020 to Oct. 2021. The institutional ethics committee approval was taken, informed consent was obtained from all patients and patient confidentiality was maintained.

Inclusion Criterion
1. Subjects with Human Immunodeficiency virus serology positive by ELISA test,
2. Subjects are more than 18 years of age.
3. Subjects who gives their consent to take part in study.
4. Subjects who are clinically stable with all their vitals within normal limits.

Exclusion Criteria

1. Subjects who are known cases of thyroid disorder.
2. Patients on drugs altering thyroid hormones metabolism and stavudine based anti-retroviral drugs.
3. Diabetic patients.
4. Abnormal Liver function tests with SGOT/SGPT levels greater than 3 times normal range, and Abnormal Renal function tests with serum Creatinine greater than 1.6mg%. Based on inclusion and exclusion criteria patients were grouped in to

Group A- Treatment naive. (n=30)
Group B - taking HAART for less than a year (n=30)
Group C - taking HAART for a year or more (n=30)

All patients were evaluated with history taking, physical examination and biochemical investigations, CD4 count was done in all the patients and patients were categorized as per WHO clinical stage. FT3, FT4 & TSH were measured at the endocrinology laboratory of our hospital by chemiluminometic immunoassay. The coefficient of variance for FT3 was 1.71 – 3.71 pg/dl, for FT4 was 0.70 – 1.48 ng/dl and that for TSH was 0.3500 – 4.9400 μIU/ml.

Statistical Analysis

Data analysis was done with help of SPSS software version 15 and sigma plot version 11.Quantitative data is presented with help of mean and standard deviation, comparison between study groups was done with the help of unpaired T-test or Mann whitney test as per the result of normality test. Pearson correlation coefficient test was used to describe correlation between continuous variables like TFT & CD4 count. Qualitative data is presented with the help of frequency and percentage table, association among study groups is assessed with the help of chi-square test. Probability value <0.05 is taken as significant.

Results

Majority patients in the study were males (74%) with age group 21-40 years (77%), most of the patients were in the weight group 40-60 kg (97%), only 1 patient enrolled in the study had weight >60kg while 3 patients had weight <40kg. Number of patients in each group was 30.

Out of 90 patients 44 (49%) had HIV duration less than 1 year while 46 (51%) had HIV duration more than 1 year. 50 patients (56%) had CD4 count <350/mm^3 while 22 patients (25%) had CD4 count between 351-700/mm^3 and 18 patients (19%) had CD4 count >700/mm^3.

Majority of patients enrolled for the study were in WHO clinical stage III (37%) while 24% patients were in WHO stage II, 21% patients were in stage IV and 18% patients were in WHO stage I. Sick euthryoid syndrome was the most common thyroid function abnormality in HIV positive patients 24(26%) followed by subclinical hypothyroidism 8(8.89%). In males none of the patient was having hyperthyroidism (74%). [Table 1]

Table 1: Prevalence of thyroid dysfunction in the study

Thyroid disorder	No. of patients	Males	Females
Overt hypothyroidism	3(3.33%)	1	2
Subclinical hypothyroidism	8(8.89%)	5	3
Isolated low F-T4	3(3.33%)	2	1
Sick Euthyroidism (Isolated low FT3)	24(26.67%)	18	6
Hyperthyroidism	0	0	0
Euthyroidism	52(57.78%)	40	12
Total	n=90	66 (74%)	24 (26%)

Most of the HIV patients who had thyroid dysfunction have CD4 count < 350. [Table2] and thyroid function abnormalities were more common in patients on ART when compared with patients not on ART.[Table3]

Table 2: Distribution of thyroid dysfunction according to CD4 count

CD4 count (mm^3)	Overt hypothyroidism	Subclinical hypothyroidim	Isolated low FT4	Sick Euthyroidism (isolated low FT3)
<350	2 (67%)	7 (88%)	1 (33%)	23 (95%)
351-700	1 (33%)	1 (12%)	2 (67%)	1 (5%)
>700	0	0	0	0
Total	n=3	n=8	n=3	n=24

Table 3: Distribution of thyroid dysfunction according to ART group

ART Group	Overt Hypothyroidism	Subclinical hypothyroidism	Isolated low F-T4	Sick Euthyroidism (isolated low FT3)
A (n=30)	0	0	0	3 (12.5%)
B (n=30)	1 (33%)	3 (36%)	1 (33%)	10 (43%)
C (n=30)	2 (67%)	5 (64%)	2 (67%)	11 (46%)
Total	n=3	n=8	n=4	n=24

Thyroid disorders were more prevalent in group B (patients on HAART < 1 year) and group C as compared to group A (treatment naïve patients) and the difference was clinically significant (p value <0.05).[Table 4 and 5]

Table 4: correlation of thyroid dysfunction between groupA & group B

Thyroid function test (Mean ± SD)	Group A (n=30)	Group B (n=30)	Unpaired T test p value
TSH	1.6461 ± 0.8099	2.8172 ± 1.6795	p=0.001
FT3	2.5382 ± 0.4521	2.0304 ± 0.5356	p=0.001
FT4	1.1518 ± 0.20182	1.0354 ± 0.2104	p=0.008

Table 5: correlation thyroid dysfunction between group A & group C

Thyroid dysfunction (Mean ± SD)	Group A (n=30)	Group C (n=30)	Unpaired T test p value
TSH	1.6461 ± 0.8099	3.7062 ± 1.9796	p=0.001
FT3	2.5382 ± 0.4521	1.9006 ± 0.4930	p=0.001
FT4	1.1518 ± 0.20182	0.8801 ± 0.1749	p=0.001

Figure 1 shows that all of the 5 patients who had overt hypothyroidism were in WHO clinical stage IV and majority of patients with thyroid function abnormalities belong to WHO stage III and IV.

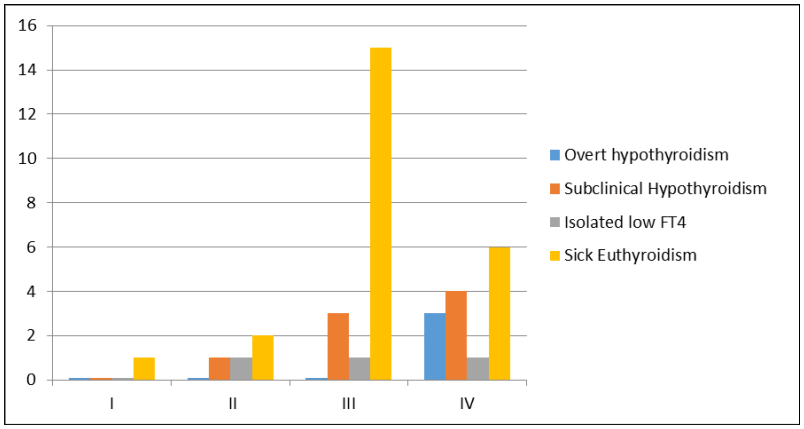

Fig 1: Distribution of thyroid dysfunction according to WHO clinical stage

All the 5 patients who were overt hypothyroidism had HIV duration > 1 year while 10/14 (71%) patients had subclinical hypothyroidism had HIV duration > 1 year, 3/4 (75%) patients with isolated low FT4 had HIV duration > 1 year and 23/39 (59%) patients with sick euthyroid syndrome had HIV duration > 1 year.(Figure 2)

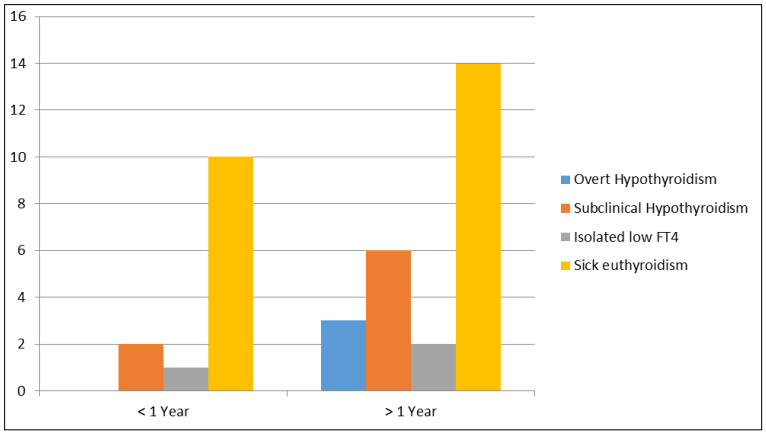

Fig 2: Distribution of thyroid dysfunction according to duration of HIV

Above observation shows that thyroid disorders in HIV patients become more common as duration of disease increases.

On correlating the level of FT3, FT4 and TSH with the WHO stage shows that the level of FT3, FT4 goes on decreasing from stage I to Stage IV (p value = 0.000) and the level of TSH goes on increasing from stage I to Stage IV (p value =0.000). Thus as the clinical severity of HIV infection increases the level of FT3 and FT4 decreases and TSH increases.

On correlating FT3, FT4 and TSH level with CD4 count, a positive correlation between FT3 level and CD4 count is found (Pearson correlation coefficient= 0.4249 p value = 0.000), a positive correlation between FT4 level and CD4 count (Pearson correlation coefficient = 0.2972, p value = 0.0001) is also found, while a negative correlation between S.TSH level and CD4 count (Pearson correlation coefficient = - 0.4741 p value = 0.000) is also established. Above results show that as the CD4 count decreases in HIV positive patients the FT3 and FT4 level also decreases while S.TSH level increase.

On correlating thyroid function abnormalities in patients on HAART and patients not on HAART significant difference (p value = 0.001) is found in mean FT3, FT4 and TSH level between the two groups, which shows that thyroid function abnormalities are more prevalent in patients on HAART [table 6].

Table 6: Correlation between thyroid dysfunction according to HAART

Study Parameter	Study Group		Unpaired T-test p value
	on HAART (Mean±SD)	Not on HAART (Mean±SD)	
FT3	1.96±0.51	2.55±0.44	0.0001
FT4	0.95±0.21	1.16±0.20	0.0001
TSH	3.2894±1.86169	1.5902±0.7763	0.0001

Discussion

The present study enumerates the prevalence of various thyroid function disorders in HIV positive patients and their association with various factors like CD4 count, WHO clinical stage, duration of HIV and HAART. In the present study, the prevalence of overt hypothyroidism was 3.33%, subclinical hypothyroidism was 8.89%, isolated low FT4 in 3.33 % patients, while sick euthyroid syndrome was found in 26.67% patients.

Some other studies such as a study Varanasi [7] reported 30% prevalence of subliminal hypothyroidism and 10.66% prevalence of overt hypothyroidism. In this study patients having acute illness which can alter the thyroid function were also included the difference in results may also be due to ethnical difference and differences in the sample size. None of the patients were found to be hyperthyroid in the present study. Similarly earlier studies from India and western countries also did not reported hyperthyroidism in any of the patients. We also noted a positive correlation between FT3, FT4 level and the CD4 count while a negative correlation between TSH and CD4 count, a study done by Mala V. Kaneria *et al* [8] reported a similar correlation.

The present study also shows that as the HIV patients deteriorate clinically, as reflected by WHO clinical staging, the prevalence of thyroid function abnormalities increases, earlier studies also reported similar results and thyroid function abnormalities were more common in patients receiving HAART than patients not receiving HAART this may be due to the direct effect of antiretroviral drugs on thyroid metabolism.

The role of HAART was also confirmed by a recent report that interruption of HAART was associated with a normalization of thyroid function test [9]. Immune reconstitution autoimmune thyroid disease (AITD) (Grave's disease, thyrotoxicosis and hypothyroidism) to be 3% for women and 0.2% for men. The median duration of immune reconstitution was 17 months [10-12].

Patients with lower CD4 count at baseline who experienced greater increments in the CD4 counts following HAART were more likely to develop AITD. But none of the patients in present study was found of have immune reconstitution syndrome. We also found that thyroid function abnormalities become more prevalent as duration of disease increases this may be due to increasing incidence of opportunistic infections and decreasing CD4 count as the duration of the infection increases.

Certain limitations of our study were

1. As study design was a cross-sectional we could not derived pathogenesis of thyroid dysfunction.
2. As this study was conducted in a tertiary care hospital, the study group does not show the population characteristics and the patients the study could not be equally distributed for HIV associated conditions like stage of infection, CD4 count, HAART etc.
3. TFT was measured at one point in time, limiting the robustness of the relationship being considered between the variable and the thyroid function tests.

Hence studies with larger sample size from general population with longitudinal follow up of the patients are needed to confirm the results of the present study.

Conclusions

Abnormal thyroid function tests are common in HIV infected patients. Sick euthyroid syndrome, subclinical hypothyroidism and overt hypothyroidism are most common thyroid function disorders in HIV positive patients and these disorders are more prevalent in patients who have more severe disease and are on antiretroviral therapy.

Thus patients having HIV duration > 1 year, CD4 count < 350/mm^3 in WHO clinical stage III and IV and patients on HAART may require regular monitoring of thyroid function tests. Currently there is insufficient evidence in favour of screening of thyroid abnormalities in asymptomatic HIV infected patients. Larger studies are needed to examine the epidemiology and health consequences of thyroid dysfunction in HIV patients and to better inform screening and treatment guidelines.

Conflict of Interest

Authors have none to declare.

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