

## Original Research Article

# Thyroid dysfunction in Human immunodeficiency virus infected patients and their correlation with CD4 count

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### ABSTRACT

**Background:** The aim of this study was to evaluate the prevalence of thyroid abnormalities in a subset of human immunodeficiency virus positive patients.

**Methods:** This was a cross-sectional prevalence study conducted on adult HIV positive patients. The patients presenting with hypertension, diabetes mellitus, coronary artery disease or thyroid disorder were excluded from the study. An exhaustive medical history and investigation using biochemical, microbiological and radiological tests were performed to confirm the diagnosis. Additionally, tests were done to determine the free T3, T4, thyroid stimulating hormone and CD4 cell count in all the patients.

**Results:** The prevalence of thyroid dysfunction in our study was 45.7%. Various types of thyroid dysfunctions obtained were euthyroid sick syndrome in 18.6%, subclinical hypothyroidism in 11.4%, secondary hypothyroidism in 10% and primary hypothyroidism and hyperthyroidism each in 2.9% cases. As the stage of HIV advanced, there is alteration in the level of thyroid stimulating hormone, FT3 and FT4. A direct correlation was found between FT3 and CD4 counts but no correlation was found between thyroid stimulating hormone and FT4 levels and CD4 counts.

**Conclusions:** A higher prevalence of thyroid dysfunction that was largely asymptomatic was observed in HIV infected patients with significant change in the hormonal levels in patients with low CD4 count. A direct correlation was observed between FT3 hormone level and CD4 count.

**Keywords:** Thyroid dysfunction, HIV, Euthyroid sick syndrome, Subclinical hypothyroidism, Hyperthyroidism

### INTRODUCTION

Human immunodeficiency virus (HIV) infection is an exceptional infectious disease affecting nearly 38 million people worldwide.<sup>1</sup> It majorly results into functional imbalance in every endocrine organ system of human body, primarily affecting the thyroid, gonadal, and adrenal glands.<sup>2</sup> A global epidemic of HIV infection and acquired immunodeficiency syndrome (AIDS) and the survival benefit of highly active antiretroviral therapy (HAART) have led to high prevalence of endocrinopathies in HIV infected patients.<sup>3</sup> The field of HIV endocrinology is a budding research corner in the arena of modern medicine and endocrinology as well.

The endocrinopathy occurs due to direct HIV effect or structural destruction of endocrine glands or medications causing endocrine dysfunction.<sup>2</sup> Patients not receiving ART have increased production of inflammatory cytokines due to active disease, AIDS wasting, and the presence of opportunistic infections can all contribute to the development of endocrine disorders.<sup>4</sup>

The prevalence of abnormal thyroid function tests (TFTs) increases with age and disease severity in HIV infected patients. The typical thyroid function profile among AIDS patients exhibit increased thyroid binding globulin and reduced free and reverse tri-iodothyronine (T3) levels. The most common immune reconstitution

syndromes include Graves’ disease, Hashimoto’s thyroiditis and hypothyroidism.<sup>5</sup> Predominantly, autoimmune thyroid disease (AITD) occurs more in women, the reason for this is unclear but predicted to be due to inactivation of X chromosomes.<sup>6</sup> Subsequent to the administration of HAART, CD4 cell count rises, leading to the development of AITD.<sup>7</sup> Testing for thyroid disease among symptomatic patients should begin with the measurement of thyroid stimulating hormone (TSH) level.<sup>8</sup> There is a paucity of data on the incidence of thyroid dysfunction in Indian patients infected with HIV. Nevertheless, lack of scientific evidence deters the routine thyroid screening in asymptomatic patients. Hence, this study was primarily undertaken to evaluate the prevalence of thyroid abnormalities in a subset of HIV positive patients. Moreover, thyroid dysfunction was correlated at different levels of CD4 cell counts in HIV infected patients.

**METHODS**

This was an observational study of HIV positive patients diagnosed as per National AIDS control organization (NACO) guidelines from out-patient department (OPD) and in-patient department (IPD) under observation for the treatment in the department of medicine in R. D. Gardi medical college and C. R. Gardi hospital, Ujjain (Madhya Pradesh) over a period of one year. Patients with a previous history of any endocrine disorders, on therapy known to interfere with hormone metabolism other than anti-retroviral therapy or hormone replacement therapy, having abnormal liver function, abnormal renal function tests and diabetes mellitus were excluded from the study.

The study was carried out in accordance with declaration of Helsinki. It was undertaken on symptomatic/asymptomatic HIV sero-positive patients of both sexes confirmed by a series of three ELISA tests as per NACO guidelines (comb AIDS, retro check and micro ELISA). CD4 cells count was done by the Becton Dickinson FACS flow cytometer. All the enrolled patients were personally interviewed.

A meticulous history was taken, detailed clinical examination was done and relevant investigations were sent. For hormone assay blood samples were collected between 8 am to 9 am in fasting state. Serum was separated immediately and stored at -20°C. Serum free T3, serum free T4, TSH were measured using enhanced chemiluminescence method with the help of micro slide technology using VITROS Eci chemistry system by Johnsons and Johnsons. Normal reference range for the hormonal values was taken as cutoff from the same laboratory reference range. Definitions of various endocrine dysfunctions are presented in (Table 1).

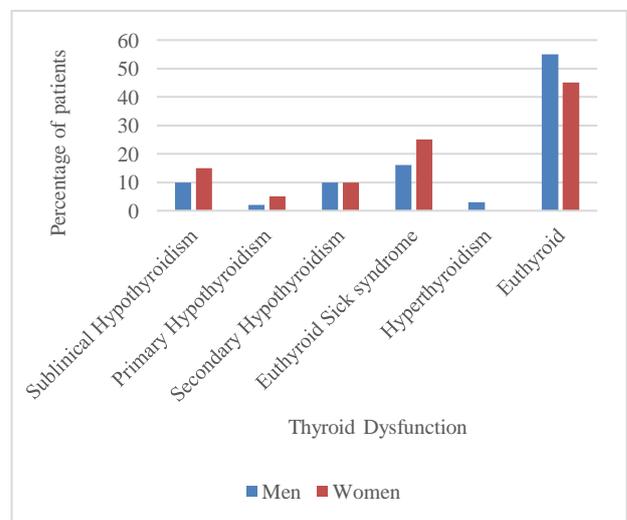
**RESULTS**

In total 70 HIV positive adult men and women, who were admitted to the hospital for various indications, were

included in the study. There were 50 men and remaining women (N=20) having a mean age of 38.84 years with maximum number of cases (43.3%) in the fourth decade. Men predominance (71.4%) was observed and men to women ratio was 2.5:1. The mean body mass index (BMI) of the participants was 20.15±3.23 kg/m<sup>2</sup>. The prevalence of thyroid dysfunction was 45.7% (men, 45.0%; women 55.0%) and predominantly observed in women. Among the types of thyroid dysfunction, the commonest type was euthyroid sick syndrome (18.6%) followed by subclinical hypothyroidism (11.4%), secondary hypothyroidisms (10.0%) and primary hypothyroidism and hyperthyroidism each observed in 2.9% cases. The euthyroid sick syndrome (25.0%) and subclinical hypothyroidism and primary hypothyroidism (5.0%) were highest in women (15.0%) as compared to 16.0%, 10.0% and 2.0% in men, respectively. The secondary hypothyroidism was found to be equally distributed in men and women (10.0%). Hyperthyroidism was observed in 2.0% men and absent in women (Figure 1)

**Table 1: Definitions of various endocrine dysfunctions.**

Endocrine dysfunctions	Definition
<b>Subclinical hypothyroidism</b>	Normal free T3 and free T4 with TSH between 5 and 10 µIU/l
<b>Primary hypothyroidism</b>	High TSH, usually above 10 mIU/l, low free T3, low free T4 level
<b>Secondary hypothyroidism</b>	Normal or low TSH, low free T3 and low free T4 level
<b>Euthyroid sick syndrome</b>	Low FT3 level, variable FT4 level, and relatively normal or decreased TSH level
<b>Hyperthyroidism</b>	Low TSH, high free T4, high free T3 level



**Figure 1: Gender wise distribution of various thyroid dysfunctions in the patients.**

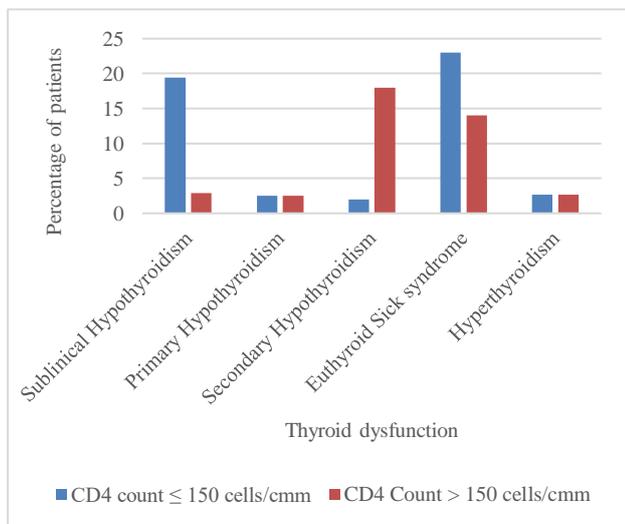
**Gender wise distribution of various thyroid dysfunctions in the study participants**

Depending upon CD4 cell count the HIV positive groups were compared. It was observed that in group A (CD4 count  $\leq 150$ ); thyroid dysfunction was seen in 50.0% cases and remaining 50.0% were normal. Similarly, in group B (CD4 count  $>150$ ); thyroid dysfunction was seen in 41.2% cases and normal in 58.8 % cases. There was no statistically significant association of CD4 count with thyroid dysfunction in group A and B.

Out of 36 patients from group A, 22.2% patients had euthyroid sick syndrome followed by subclinical hypothyroidism in 19.4% patients, secondary hypothyroidism, primary hypothyroidism and hyperthyroidism observed in 2.8% patients from each. Normal thyroid functions were seen in eighteen (50.0%) cases. Likewise, in group B secondary hypothyroidism was the most common thyroid dysfunction, observed in 17.6% patients followed by euthyroid sick syndrome seen in 14.7%, hyperthyroidism, subclinical hypothyroidism, primary hypothyroidism seen in 2.9% of patients each.

**Association of CD4 count with TSH, FT3 and FT4**

In group A, low level of TSH, free (F) T3 and T4 was observed in 19.4%, 55.6% and 25% respectively while a higher level was seen in 25%, 8.3% and 13.9% patients (Figure 2). In group B, low levels of TSH, free T3 and T4 was observed in 8.8% each while higher level of T3 in 2.9% and none of the patients from this group showed high levels of free T3 and T4. A statistically significant association was observed in the severity and degree of immunosuppression. (group A;  $p=0.007$ ,  $p=0.000$  and group B chi square=9.479 with  $p=0.009$  respectively).



**Figure 2: Association of CD4 count with thyroid hormones.**

The thyroid hormone level in group A and B along with the normal reference range is shown in (Table 2). The

student T test did not show significant difference in their mean TSH, free T3 and free T4 levels ( $p>0.5$ ). The Spearman's rho correlation showed no significant correlation between TSH and free T4 level and CD4 count ( $p=0.083$ ,  $p=0.672$  respectively). However, there was significant direct correlation between free T3 level and CD4 count ( $p=0.007$ ).

**DISCUSSION**

Endocrine system is one of the important systems influenced in HIV infection, of which, thyroid gland involvement is most commonly described. Subtle abnormalities in thyroid function are common in HIV-positive patients. The cause of this is multifactorial viz. opportunistic infections or tumors occurring in patients at the symptomatic stage of infection, defective function of the immune system, antiretroviral drugs used or a direct effect of HIV itself.

**Table 2: Thyroid hormone levels.**

Hormone	Normal reference range	Group A (CD4 count $\leq 150$ )	Group B (CD4 count $>150$ )
Free T3 (pg/ml)	2.77-5.27	2.895 $\pm$ 2.141	3.559 $\pm$ 0.951
Free T4 (ng/dl)	0.78-2.19	1.61 $\pm$ 1.004	1.46 $\pm$ 0.470
TSH (mIU/l)	0.465-4.68	3.869 $\pm$ 4.451	3.030 $\pm$ 1.604

\*Data presented as mean $\pm$ standard deviation.

In the present study the prevalence of thyroid dysfunction was 45.7%. Among them euthyroid sick syndrome was the most common thyroid dysfunction seen in 18.6% followed by subclinical hypothyroidism, secondary hypothyroidisms, primary hypothyroidism and hyperthyroidism. Similar findings were also reported by Madge et al, Hoffman et al and Tripathy et al who observed that euthyroid sick syndrome (non-thyroidal illness) was the most common thyroid dysfunction in HIV infected cases.<sup>2,9,10</sup> In this investigation, the proportion of patients with abnormality in TSH, Free T3 and free T4 levels were higher in group A (CD4 count  $\leq 150$ ) as compared to group B (CD4 count  $>150$ ) and was statistically significant indicating a substantial association of thyroid hormone level abnormality with degree of immunosuppression. However, Tripathy et al reported a frequent endocrine dysfunction in HIV-infected patients but absence of correlation between hormone levels and CD4 count.<sup>2</sup> The opportunistic infection is an independent risk factor for thyroid abnormality. Spearman's rho correlation does not show a significant correlation between TSH, FT4 level and CD4 count but there was significant direct correlation between FT3 level and CD4 count. Jain et al found there was a direct correlation between CD4 count and FT3 and FT4 level ( $r=0.357$  with  $p<0.05$ ;  $r=0.650$  with  $p<0.05$  respectively) and there was an inverse correlation of CD4

counts with serum TSH levels ( $r=-0.470$  with  $p<0.050$ ).<sup>11</sup> Mandal et al observed a poor correlation of TSH ( $r=0.14$ ;  $p>0.05$ ), FT3( $r=0.15$ ;  $p>0.05$ ) and FT4 ( $r=0.14$ ;  $p>0.05$ ), when matched with CD4 counts. In current study, group A ( $CD4 \leq 150$ ) showed, euthyroid sick syndrome was the most common type of thyroid dysfunction followed by

subclinical hypothyroidism, secondary hypo-thyroidism, primary hypothyroidism and hyper-thyroidism; whereas in group B ( $CD4 >150$ ) secondary hypothyroidism was the most common thyroid dysfunction, followed by euthyroid sick syndrome followed by hyperthyroidism, subclinical and primary hypothyroidism.

**Table 3: Similar studies reported in literature.**

Reference number	N	Thyroid dysfunction	Non thyroid illness (Euthyroid sick syndrome)	Subclinical hypothyroidism	Hypothyroidism		Hyperthyroidism
					Primary	Secondary	
Tripathy et al <sup>2</sup>	43	60.4	25.6	11.6	3.5	16.2	2.3
Jain et al <sup>11</sup>	70	9.0	-	7.0	2.0	-	2.0
Meena et al <sup>14</sup>	150	40.6	-	30.0	10.6	-	-
Madge et al <sup>9</sup>	3584	24.5	17.0	4.0	2.5	-	<1.0
Ketsamathi et al <sup>15</sup>	200	16.0	6.0	6.0	1.5	6.0	0.5
Beltran et al <sup>16</sup>	343	17.5	6.8	8.1	2.6	-	-
Present study	70	45.7	18.6	11.4	2.9	10.0	2.9

\*Data is presented as % unless otherwise specified

Another Indian study performed in 527 HIV infected patients reported subclinical hypothyroidism as the commonest thyroid dysfunction (14.76%) followed by sick euthyroid syndrome (5.29%).<sup>13</sup> Gafencu et al reported a case of AITD with thyrotoxicosis in a Caucasian woman with stage C3 HIV infection and administered HAART for more than 7 years. She did not show any symptoms of thyroiditis in absence of antiretroviral therapy.<sup>7</sup>

**Limitations**

Current study was limited by the small sample size from a single geographical location and retrospective cross-sectional nature. Only the prevalence of thyroid dysfunction was estimated without assessing the etiology of the endocrinopathy. However, further prospective longitudinal studies with larger sample size belonging to different groups of CD4 counts and more thyroid function parameters are warranted.

**CONCLUSION**

Current study shows that the biochemical abnormality of thyroid function is quite common in patients with HIV. euthyroid sick syndrome was the most common thyroid dysfunction seen in HIV infected patients followed by secondary hypothyroidism. A direct correlation was seen between FT3 and CD4 count indicating an abnormal trend of thyroid function as the disease progresses.

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