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Correlation of CD4 count with Thyroid function test values in treatment naive HIV-infected patients.

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Abstract:

Introduction: Abnormalities in thyroid function tests have been described in HIV patients since the early days of the HIV pandemic. There have been only a handful of studies correlating the CD4 count with different aspects of commonly done thyroid function tests. **Methodology**: The current study was conducted on 100 (one hundred) treatment-naive newly diagnosed HIV patients without any co-infections or therapy for any other disease, over one year. **Results:** 64 % of the patients in the study group were euthyroid with subclinical hypothyroidism being the commonest thyroid abnormality. Thyroid dysfunction was commoner in the later stages of the disease. There was no statistical significance between CD4 count and Free T4 and Free T3 values; however low CD4 count had a negative correlation with TSH values in patients with overt primary hypothyroidism which was statistically significant only in the subgroup of patients with CD4 values < 200/µl ($p<0.00001$). **Conclusion**: Treatment naive HIV patients are mostly euthyroid but thyroid hypo function is common in the advanced form of the disease with the subgroup of CD4 count <200/µl having higher TSH values of statistical significance in patients with overt primary hypothyroidism. This probably reflects an attempt by an intact pituitary-thyroid axis to maintain homeostasis in a severe immunodeficiency state with the production of active hormones in the thyroid gland being affected by multiple factors including infections, malignancies, and micronutrient deficiency.

Keywords: HIV, CD4 count, Hypothyroidism

INTRODUCTION:

Human immunodeficiency virus has been reported to involve the endocrine glands [1] Thyroid dysfunction is among the commonest endocrinopathies[2] in HIV patient. Subtle abnormalities in thyroid functions have been observed in 35% of HIV patients in some studies [3]though overt thyroid dysfunction is considerably uncommon - 1-2 % of cases at any point of time [4] Though the entire spectrum of thyroid dysfunction has been described in HIV patients, in multiple studies, the predominant abnormality detected is hypothyroidism [3] –both subclinical and overt. Multiple studies have been done on the thyroid function tests in HIV patients since the onset of the pandemic. The entire spectrum of thyroid dysfunction overt hyperthyroidism and hypothyroidism, thyroiditis, subclinical hypothyroidism and hyperthyroidism and sick euthyroid syndrome have been described in HIV patients. However, there was no unanimity in the findings of the studies.

The CD4 count remains an important surrogate marker of the immune system in HIV infected patients. Many of the HIV related morbidities including infectious and non infectious complications have an association with

CD4 count. Lower CD4 counts are associated with multiple opportunistic infections and other non-infectious complications. On the other hand, immune dysfunction is involved in the pathogenesis of multiple thyroid disorders even in the general population. Though studies almost since the onset of HIV pandemic have studied the thyroid functions, very few studies have explored the relation between CD4 count and thyroid function in HIV patients. Though this relation may not be factored in the initiation of treatment of HIV patient with Highly Active Antiretroviral therapy, we felt that the association between thyroid function and CD4 count needed to be explored as CD4 count is a marker of the immunologic status of HIV patients and many thyroid disorders is immune related.

The aim of this study, therefore, is to correlate the different thyroid function test abnormalities and diseases with CD4 count in HIV patient.

Materials and Methods:

The present hospital-based cross-sectional study involving 100 patients was conducted in the Department of General Medicine, Silchar Medical College, and Hospital, Assam, India with patients of both sexes aged 18 years and above. The sample size was chosen on the basis of annual newly diagnosed treatment naive HIV patients attending Silchar Medical College and Hospital (approx. 400/ year) with a margin of error ±8% and confidence level 95%. The patients included those attending the out-patient department and in patients admitted to the hospital with a diagnosis of HIV. The study was for a period of one year and the first one hundred patients meeting the inclusion criteria were included in the study.

Informed consent was taken from the eligible patients before taking the history of the illness and conducting a thorough physical examination. The data collected comprised of the name, hospital number, age, sex, personal and occupational history, duration of the disease, history suggestive of opportunistic diseases and coinfections, other comorbid conditions, and drug history. The relevant laboratory tests were done as per protocol and National Aids Control Organisation (NACO) of India guidelines including CD4 count. The patients were then staged as per WHO clinical staging. The thyroid function tests included testing for TSH, FT3, and FT4. USG of the neck was done if indicated. Patient confidentiality was maintained.

Institutional ethical committee clearance was obtained. Exclusion criteria included those who did not give informed consent, pregnant or lactating mothers, present or past history of a thyroid disorder, patients on drugs altering thyroid hormone metabolism, diabetics, and patients on oral contraceptive pills. Patients with tuberculosis on anti tubercular therapy were excluded from the study as thyroid function tests have been found to be affected in patients with tuberculosis receiving Rifampicin based antitubercular drugs [16].Patients with AIDS defining conditions like different opportunistic infections, malignancies like lymphomas and Kaposi's sarcoma were not included in the study.

The values of Serum TSH, FT3, FT4 were estimated by Electrochemiluminescence method. The laboratory reference range were TSH 0.4-4.0 mI U/L, FT3: 2.5-3.9 pg/mL**,** FT4: 0.61-1.12 ng/dL. The flow cytometry method was used to estimate the CD4 cell count. The patients were divided into 2 groups based on CD4 count -- <200 /µL and ≥200 /µL. The cut off CD4 count of 200/µL was based on the data that complications – both infectious and noninfectious were more common in patients with CD4 count < 200 /µL. Based on thyroid function status, patients were grouped into Subclinical hypothyroidism (TSH↑, FT3-N, FT4-N), Subclinical hyperthyroidism (TSH↓, FT3-N, FT4-N),overt primary hypothyroidism(

TSH↑, FT3↓, FT4↓ and Hyperthyroidism (↑FT4, ↑ FT3, ↓ TSH,) . TPoAb was done in select cases of subclinical hypothyroidism. Patients with normal or low TSH with low FT4 and / or low FT3 were considered to be having Sick Euthyroid Syndrome (Non-thyroidal illness; NTI)

Statistical methods:
The results for each parameter for discrete data were represented in numbers, percentages, and average (mean, standard deviation) which were represented in tables and figures and qualitative/categorical variables were expressed as the number of cases and percentages. Man Whitney test was done to analyse the nonparametric data. All comparisons were two-sided, and p-value < 0.01 was the cut-off value for statistical significance. Spearman's Rho (r) was used to measure the strength and direction of relationship between two variables. Statistical analysis and all the statistical graphs were prepared using Microsoft Excel 2010 and IBM SPSS statistics 20.

Results:

In this study, the Mean Age was 34.8±8.70 years. Out of the 100 cases, 44% belonged to the age group 31-40 years and 36% to the age group 18-30 years. 73% of the patients were male and 27% were female. In the present study, 64% of the HIV patients were Euthyroid while 5% of patients had Sick Euthyroid Syndrome (Table 1). All types of thyroid disorders were more common in Stage 3 and 4. Of the 100 patients included in the study, 68% of the patients were in WHO Stage 3 and 4. 64 patients were euthyroid and, 38 of them were in Stage 3 and 4. Hypothyroidism overt and subclinical was the commonest thyroid abnormality and was more common in Stage 3 and 4. Among the patients who had thyroid dysfunction in the study group, 47.22% patients had subclinical hypothyroidism and 27.7% patients had overt primary hypothyroidism. The number of patients with hyperthyroidism and sick euthyroid syndrome (NTI) were 4% and 5% respectively and this was seen only in the advanced stages of HIV infection.

Table 1 : *Relation of thyroid disorder with HIV WHO Stage*

Thyroid disorder	WHO STAGE 1	WHO STAGE 2	WHO STAGE 3	WHO STAGE 4	Total
Subclinical hypothyroidism	1	3	7	6	17
Overt hypothyroidism	0	2	6	2	10
Euthyroid	9	17	22	16	64
Subclinical hyperthyroidism	0	0	1	1	2
Overt hyperthyroidism	0	0	1	1	2
Sick euthyroid syndrome	0	0	1	4	5

Table 2*: Relation of CD4 count with TSH, FT4 and FT3 values*

CD4/µl.		TSH Range mIU/L				FT4 range ng/dl				FT3 range pg/ml			
	mean	<0.4	0.4-4	> 4	mean	< .61	0.61-1.12	> 1.12	mean	< 2.5	2.5 – 3.9	> 3.9	mean
<200	105.9 ±46.49	4	15	13	3.91±3.48	4	25	3	0.8 ± 0.356	7	22	3	2.65± 0.78
>200	605.88 ± 369.51	3	57	8	2.72±2.34	4	63	1	0.9 ± 0.23	7	60	1	2.7 ± 0.52

35patients had CD4 count ≤ 200/ µl (mean 105.9 ±46.49/µl **) (Table 2).** Correlation of thyroid dysfunction with CD4 count showed that 76.56% of euthyroid patients had CD4 count ≥ 200/µl (mean 514.61 ± 406.66/µl). Subclinical hypothyroidism was more common than overt hypothyroidism in patients with CD4 ≥ 200/µl (mean 259.06 ±249.28/µl).

As per the diagnostic criteria , patients with overt and subclinical hypothyroidism had increased TSH. In the entire group of 100 patients, mean TSH values (3.91±3.48 mIU/L) were higher in patients with CD4 < 200/µl but this was not statistically significant (p< 0.05). However, sub group analysis showed that patients with overt hypothyroidism and with CD4 < 200/µl (mean 97.44±25.09/µl) had significantly higher TSH - mean 7.23 ± 3.38mIU/L against 6.74 ± 3.53 mIU/L (p <0.00767 r_s =-0.92763,) than patients with CD4> 200 /µl (mean 605.88 ±369.51/ µl).

Table 3 : Relationship between hypothyroidism with range of CD4 count.

	TSH(mIU / L)	CD4 / µl		
Subclinical hypothyroidism	TSH mean 7.48±2.48	CD4 259.06 ±249.28		p-value is . 0345.
Overt hypothyroidism	7.23 ± 3.38	<200	Mean 97.44±25.09	, p < 0.01
	6.74 ± 3.53	>200	Mean 507 ±218.68	p-value is 1.(NS)

High TSH values did not attain statistical significance in correlation with CD4 count in patients with subclinical hypothyroidism (p< 0.05). Correlation of FT3 and FT4 values with CD4 count in the sample population did not have statistical significance.(**Table 3**)

DISCUSSION:

In the present study of thyroid function in one hundred treatment naive HIV patients, 36% of the patients had thyroid dysfunction which was commoner in the more advanced stages of the disease – WHO stage 3 and 4. This finding corroborates to the findings of Shujing Ji et al[5] who found 33.1% of patients with thyroid dysfunction in their study. Hypothyroidism subclinical and overt hypothyroidism were the commonest thyroid abnormalities found in the study. Hyperthyroidism – subclinical and overt and sick euthyroid syndrome were seen in 9% of cases.

Patients with CD4 count < 200/µl had higher TSH levels which did not attain statistical significance when

correlated with the TSH values in patients with CD4 count> 200/ µl. However, patients with overt primary hypothyroidism and CD4 count < 200 / µl had statistically higher significant TSH levels (7.23 ± 3.38 mI U/L p < 0.01)) as compared to patients with CD4 >200/µl.

Several studies done early in the course of the HIV epidemic found subtle alterations in thyroid function tests in HIV patients. This was seen even in patients without opportunistic infections or co-existing tumors like lymphoma or Kaposi's sarcoma and before receiving Highly Active Anti Retroviral Therapy (HAART). Though there has been no clear explanation of the reasons behind the alterations in thyroid function tests, suggestions had been made that these could be due to the direct effect of HIV on the endocrine system.

The spectrum of thyroid dysfunction had differed between studies. Mathias Abiodun Emokpae and Imwonghomwen Mercy Akinnuoye had found sick euthyroid syndrome to be the commonest thyroid abnormalities[6] while overt hypothyroidism was the commonest abnormality in the study conducted by Shujing Ji et al [7]. The most common thyroid dysfunction observed in this study was Subclinical hypothyroidism (16%), which was similar to Midha NK et al. study [8] (13.84%) and Noureldeen A et al. (6%) [9]

Subclinical hypothyroidism has been defined as an increase of TSH above the reference range with normal FT3 and FT4. The incidence of subclinical hypothyroidism in HIV patients had been found to be higher than in the normal population.[10]

The number of patients with overt hyperthyroidism and subclinical hyperthyroidism were few and it was not possible to extrapolate any conclusions from the low numbers. Other studies had found a lower incidence of overt hyperthyroidism in HIV patients.[5]

The total Mean TSH was found to be 2.98±2.68mIU/L in the study. There was no statistical significance between the TSH values of all patients with CD4 count which could be due to the reason that 64% of patients were euthyroid. This finding is different from the study of Madeddu et al. who found TSH levels having a negative correlation with CD4 count. [11]

Our study showed no significant relationship between FT3 and CD4 cell count (p-value: 0.12), which was similar to Midhaet al.[8] (p-value: >0.05) study; However, a positive correlation was observed in study by Jain G et al.[10] on the same observation. Midhaet al.[8] in their study showed a positive correlation between FT4 and CD4 cell count (p-value: 0.01) which was not found in the present study (p-value: 0.24).

However, subgroup analysis showed that patients with overt pituitary hypothyroidism had a statistically significant relationship with CD4 ≤ 200/µl and higher TSH values (p < .00001). The possibility of a lowered immunity as evident by low CD4 count with higher TSH levels has been variously linked to disordered immune function in HIV patients and its effect on the thyroid gland.

The etiopathogenesis of thyroid dysfunction in treatment naïve HIV patients is complex. Multiple reasons have been cited including opportunistic infections, co-infections, caloric deprivation, and associated systemic diseases. The higher TSH levels in HIV infected patients have been explained as a bodily adaptive response to reduce metabolic rate induced by thyroid hormone at the tissue level in the face of overwhelming systemic infection caused by HIV involving multiple organs.

CD4 count is still considered as the best indicator for initiating treatment of HIV and prophylaxis of opportunistic infections. CD4 count is also a reliable

indicator of the immunologic function of HIV patients. A CD4 count of < 200/µl is an indicator of severe immunodeficiency and in general indicates a high viral load. Autopsy findings of the thyroid gland in patients who had HIV/AIDS revealed anatomo-pathological lesions in 61.7% of cases with mycobacterial involvement of the gland being the commonest opportunistic infection[12]. Mycobacterial infection is commonest in patients with low CD4 count and in the later stages of the disease as is an AIDS-defining condition. Other infections of the thyroid gland described in the later stages of the disease include Pneumocystis jiroveci, Coccidiodes, *and* Cryptococcus which cause thyroiditis[13]

Anatomic damage of the thyroid gland may interfere with the synthesis and secretion of thyroid hormones leading to an increase in the secretion of TSH from the pituitary gland to maintain homeostasis. The thyroid – pituitary axis has been found to be intact in the study by Hommes et al who found TSH responsiveness in HIV patients who were administered TRH [14]. Autoimmune hypothyroidism is the commonest form of primary hyperthyroidism in the general population. However, in patients with HIV antibodies like anti-TPO are rarely identified suggesting that autoimmunity may not be the cause of hypothyroidism[15].

Hypoalbuminemia which might result from caloric deprivation arising from multiple causes has been implicated in the abnormal intracellular transport and conversion of T4 into T3 producing organs like liver [16]. The deficiency of micronutrients like selenium has been described as it can have a negative effect on the deiodinase activity leading to a decrease in FT3[17].

Medications used in HIV infections for opportunistic infections may have an impact on thyroid function. Rifampicin by its action on hepatic micro somal enzymes have been found to reduce peripheral thyroid hormones [18,19].

Essentially our knowledge about the etiology of hypofunction of thyroid gland at low CD4 counts is not substantial. Research on the above subject has been limited as the patients are initiated on Highly Active Antiretroviral therapy (HAART) immediately on diagnosis of HIV as per current guidelines thereby precluding further investigations[20].

The low CD4 Count (<200 /µl) and its correlation with statistically significant high TSH might, therefore, be explained.

Limitations of the study

The study involved 100 (one hundred) patients who were not on HAART or therapy for co infections. The duration of the disease in the patients was not known. Also the number of investigations done on the patients were limited by resource constraints.

Conclusion:

- The majority of patients with HIV infection were euthyroid with subclinical hypothyroidism being the commonest thyroid dysfunction observed in the study.
- All types of thyroid dysfunction were more common in the advanced form of the disease.
- In patients with overt pituitary hypothyroidism, high TSH levels had a statistically significant correlation only in subset of patients with CD4 count < 200/ µl.

Conflict of interests : None

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