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Thyroid Function as Surrogate Marker of Advancing HIV Infection and its Correlation with CD4 Count

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Abstract: ***Objective: In this study we evaluated thyroid function tests in patients infected with human immunodeficiency virus (HIV) infection at various stages of the illness and correlation of thyroid function tests with CD4 count in patient infected with human immunodeficiency virus (HIV). Methods: This study was done in total 100 HIV positive patients. Correlation between CD4 count and serum Free.T3, FreeT4 and serum TSH was studied. Then correlation between CD4 count and serum Free.T3, FreeT4 and serum TSH was studied in both group A and B separately.Pearson correlation coefficient/Spearman rank correlation coefficient was used to assess the association of various quantitative parameters. A p value of <0.05 was considered statistically significant. Results: The study depicts that there was a strong negative correlation between CD4 count (cu.mm) and STSH (uIU/ml) value and this correlation was statistically significant (rho = -0.74, p = <0.001). In Group B the mean S.Free T3 is about 2.81 ± 0.58, the mean S.Free T4 is about 0.85 ± 0.18. The mean STSH is about 2.57 ± 1.51 and and the mean CD4 is about 395.62 ± 103.76. The study showed that there was a moderate positive correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL) this correlation was statistically significant (rho = 0.35, p = 0.014 and). There was a weak positive correlation between CD4 Count (cu.mm) and S.Free T4 (ng/mL), and this correlation was statistically significant (rho = 0.28, p= 0.048). There was a moderate negative correlation between CD4 Count (/cu.mm) and S.TSH (uIU/mL), and this correlation was statistically significant (rho = -0.35, p = 0.014). The study showed that thyroid dysfunction is more frequent in advanced stage (cdc stage- 3) as compared to early stage (stage 1, 2) and there is hypothyroid like stage that occurs in patients with HIV infection. Conclusion: The results showed that thyroid dysfunction is more frequent in female HIV positive patients as compared to male patients. The results also showed that thyroid dysfunction is more frequent in advanced stage (cdc stage 3) as compared to early stage(stage 0,1,2) and there is hypothyroid like stage that occurs in patients with HIV infection. From the findings of our study we can conclude that thyroid function test can be used as a surrogate marker of advancing HIV infection.***

1. Introduction

Acquired immunodeficiency syndrome (AIDS) resulting from infection with HIV may affect any Organ system. Increasing experience suggest that many HIV related endocrine disorder can occur during both the early and late stages of the disease.

Subtle alterations in thyroid function tests are more common in HIV infection and are sometimes already detectable in the early phase of disease. The changes in thyroid function tests are HIV specific and are consistent with an abnormal response to acute illness. Various mechanisms have been proposed to explain such abnormalities in Thyroid function test. These include direct infection of thyroid gland by opportunistic organisms such as Pneumocystis Jirovecii, infiltration of the gland by tumor such as Kaposi sarcoma, effect of humoral factors such as IL-1β and TNF-α, side effect of the drugs used in the course of HIV infection for e.g. rifampicin, ketoconazole, steroids etc. and direct infection of gland by HIV[1].

Thyroid function may be altered in 10-15% of patients with HIV infection. Both hypo- and hyperthyroidism is seen. The predominant abnormality is subclinical hypothyroidism. In the setting of HAART up to 10% of patients have been noted to have elevated thyroid stimulating hormone levels, suggesting that this may be a manifestation of immune reconstitution. Immune reconstitution Graves disease may occur as a late (9-48 months) complication of HAART. In advanced HIV disease, infection of the thyroid gland may occur with opportunistic pathogens, including P. Jirovecii, CMV, mycobacteria, Toxoplasma gondii, and Cryptococcus neoformans. These infections are generally associated with a nontender, diffuse enlargement of the thyroid gland. Diagnosis is made by fine- needle aspirate or open biopsy[2].

2. Materials and Methods

This Cross sectional study was conducted in SRN hospital Prayagraj. HIV+ patients were selected, screened, matched and investigated from the medicine emergency/OPD/IPD of SRN hospital Prayagraj. Ethical Committee approval was taken from Institutional Ethics Committee. Consent was taken as per protocol. The study was done in 100 HIV positive patients. Patients were divided into 2 groups based on CDC stages.

Group A- It consisted of 50 HIV Positive patients in CDC Stage 3.

Group B- It consisted of 50 HIV Positive patients in CDC Stage 1, 2.

This study was done in total 100 HIV positive patients. Correlation between CD4 count and serum Free.T3, FreeT4 and serum TSH was studied. Then correlation between CD4 count and serum Free.T3, FreeT4 and serum TSH was studied in both group A and B separately.

Inclusion criteria- Subject having HIV serology positive by ELISA test and HIV Tri-dot antigen kits. Patients of age >18 year were included in this study.

Exclusion criteria-History s/o thyroid illness, clinically evident thyroid enlargement, or signs of thyroid disease. Use of drugs known to interfere with thyroid hormone metabolism for e.g. rifampicin, steroids, ketoconazole, antiepileptic etc.

Statistical methods-Pearson correlation coefficient/ Spearman rank correlation coefficient was used to assess the association of various quantitative parameters.

A p value of <0.05 was considered statistically significant.

3. Results

Results (in total patients, n=100)

Table: Baseline parameters in total patients (n=100)

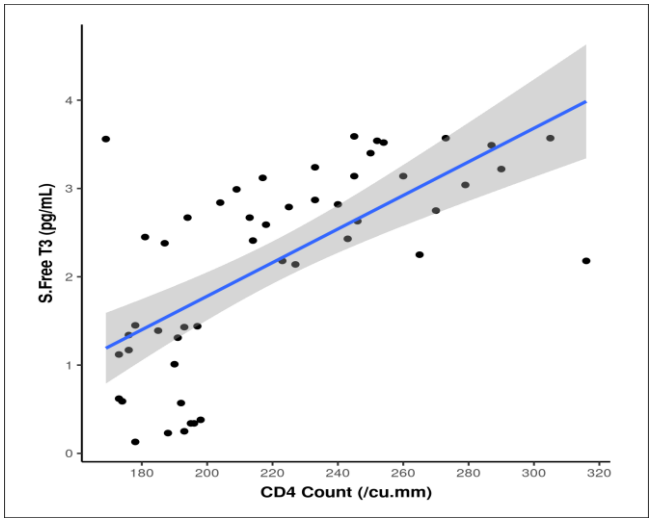
All Parameters	Mean ±SD || Median
Total Patients	100 (100%)
Age (Years)	36.69 ±9.09 || 35.00
Gender Male Female	 71(71%) 29(29%)
S.Free T3(pg/ml)	2.49 ± 0.94 || 2.75
S.Free T4(ng/ml)	0.71 ± 0.36 || 0.81
S.TSH(uIU/ml)	3.33 ± 2.32 || 2.38
CD4 Count(/cu.mm)	307.94 ± 117.62 || 273.00
CD4 Count <200/cu.mm 200-500/cu.mm >500/cu.mm	 22 (22.0%) 68(68.0%) 10(10.0%)

Baseline parameters in Group A and B

Table

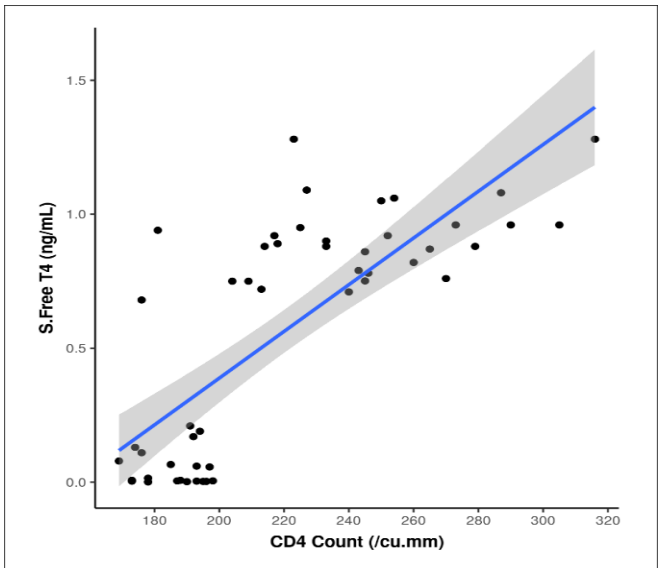
Parameters	Group	
	Group A (n=50)	**Group B** (n=50)
Age(Years)	37.36 ± 8.91	36.02 ± 9.31
Gender Male Female	 34(68.0%) 16(32.0%)	 37(74.0%) 13(26.0%)
CD4 Count (/cu.mm)	220.26 ± 38.69	395..62 ±103.76
CD4 Count <200/cu.mm 200-500/cu-mm >500/cu.mm	 22(44.0%) 28(56.0%) 0(0.0%)	 0(0.0%) 40(80.0%) 10(20.0%)

Correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL) in Group A (n = 50)



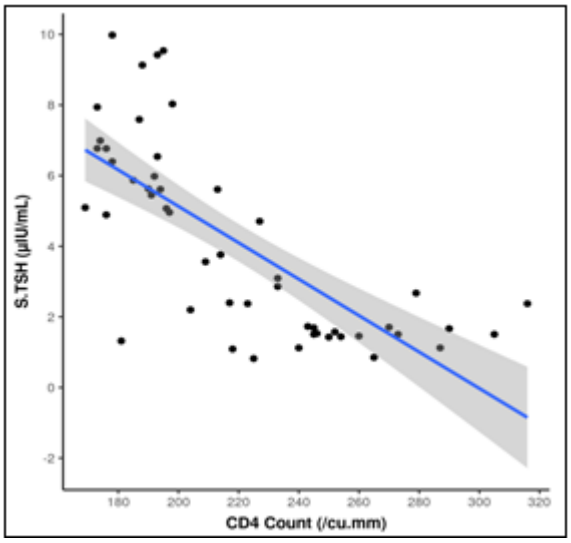
There was a strong positive correlation between CD4 Count (cu.mm) and S.Free T3 (pg/mL), and this correlation was statistically significant (rho = 0.66, p = <0.001).

Correlation between CD4 Count (/cu.mm) and S.Free T4 (ng/mL) in Group A (n = 50)



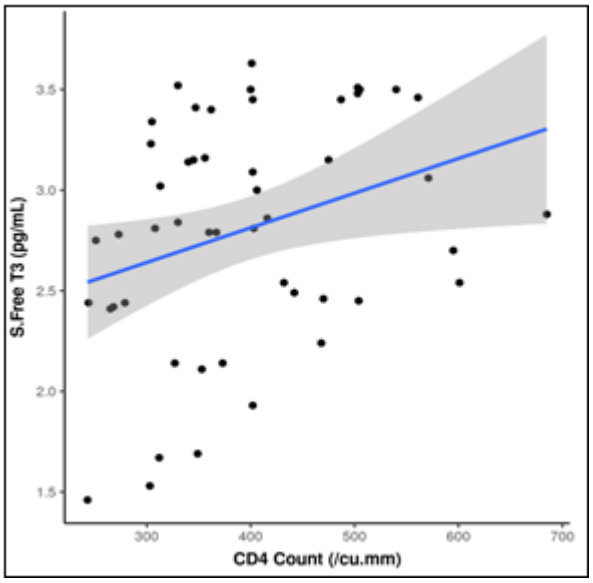
There was a strong positive correlation between CD4 Count (/cu.mm) and S.Free T4 (ng/mL), and this correlation was statistically significant (rho = 0.75, p = <0.001).

Correlation between CD4 Count (/cu.mm) and S.TSH (uIU/mL) in Group A (n = 50)



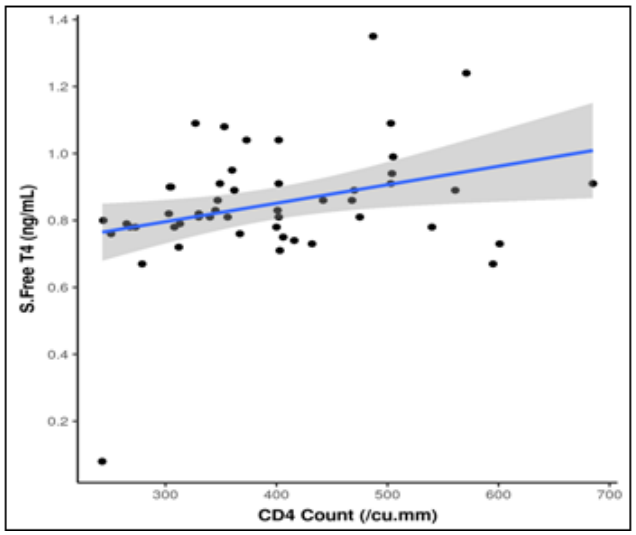
There was a strong negative correlation between CD4 Count (/cu.mm) and S.TSH (uIU/mL), and this correlation was statistically significant (rho = -0.74, p = <0.001).

Correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL) in Group B (n = 50)



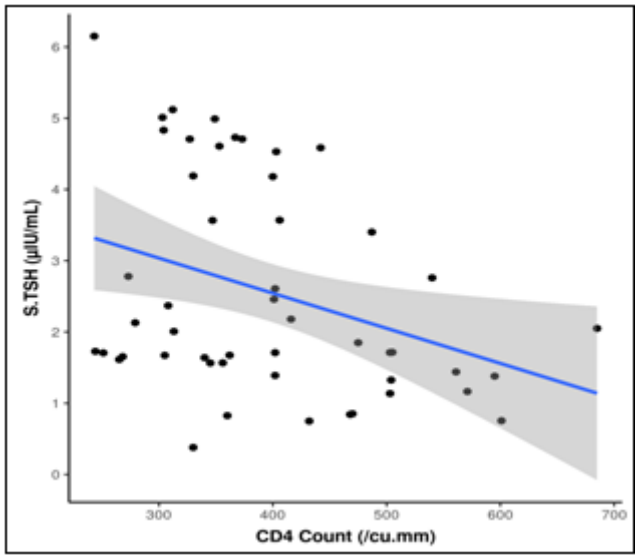
There was a moderate positive correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL), and this correlation was statistically significant (rho = 0.35, p = 0.014)

Correlation between CD4 Count (/cu.mm) and S.Free T4 (ng/mL) in Group B (n = 50)



There was a weak positive correlation between CD4 Count (/cu.mm) and S.Free T4 (ng/mL), and this correlation was statistically significant (rho = 0.28, p = 0.048).

Correlation between CD4 Count (/cu.mm) and S.TSH (uIU/mL) in Group B (n = 50)



There was a moderate negative correlation between CD4 Count (/cu.mm) and S.TSH (uIU/mL), and this correlation was statistically significant (rho = -0.35, p = 0.014).

4. Discussion

The present study was undertaken to explore the association of thyroid function test abnormalities in HIV patients and its correlation with CD4 count at various stages of disease.In our study we have taken 100 patients and divided into 2 Groups, Group A (HIV positive, CDC Stage 3) and Group B (HIV positive, CDC Stage 1 and 2). In Group A the mean S.Free T3 is about 2.17 ± 1.11, the mean S.Free T4 is about 0.56 ± 0.44. The mean STSH is about 4.09 ± 2.72 and the mean CD4 is about 220.26 ± 38.69. The study showed that there was a strong positive correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL) and S.Free T4 (ng/ml) values, and this correlation was statistically significant (rho = 0.66, p = <0.001 and rho = 0.75, p = <0.001 respectively).

The study depicts that there was a strong negative correlation between CD4 count (cu.mm) and STSH (uIU/ml) value and this correlation was statistically significant (rho = -0.74, p = <0.001). In Group B the mean S.Free T3 is about 2.81 ± 0.58, the mean S.Free T4 is about 0.85± 0.18. The mean STSH is about 2.57 ± 1.51 and and the mean CD4 is about 395.62 ± 103.76.

The study showed that there was a moderate positive correlation between CD4 Count (/cu.mm) and S. Free T3 (pg/mL) this correlation was statistically significant (rho = 0.35, p = 0.014 and). There was a weak positive correlation between CD4 Count (cu.mm) and S.Free T4 (ng/mL), and this correlation was statistically significant (rho = 0.28, p= 0.048). There was a moderate negative correlation between CD4 Count (cu.mm) and S.TSH (uIU/mL), and this correlation was statistically significant (rho = -0.35, p = 0.014).

The study showed that thyroid dysfunction is more frequent in advanced stage (cdc stage- 3) as compared to early stage (stage 1, 2) and there is hypothyroid like stage that occurs in patients with HIV infection. Gagan Jain *et al*[1] in year 2006 studied thyroid disfunction in HIV patients and result were analyzed for 50 patients. Patients were studied in two groups: Group 1- It consisted of 25 HIV+ patients having AIDS. A HIV+ patient was said to be having AIDS if the patient belonged to 1993 revised CDC classification for HIV infection. Category A-3, B3, C1-3. Group 2 had consisted of 25 HIV+ patients belonging to 1993 revised CDC classification for HIV infection Category A1-2, B1-2. On the basis of CD4 count distribution; 4 (8%) patients had CD4> 500/µL, 21 (42%) patients had CD4 between 200-500/µL and 25 (50%) patients had CD4<200/µL. Mean CD4 count in HIV positive non-AIDS patient was 358.20 + 138.305, while in AIDS patients it was 97.20 + 56.178.

Thyroid function tests were compared in both HIV+ non-AIDS and AIDS patients. Mean Free T-3 and mean FreeT-4 values were 2.826+0.702 pg/ml and 1.352+0.371 ng/ml in non-AIDS patients while it was 2.518+0.868 pg/ml and 0.925+0.264 ng/ml respectively in AIDS patients. S. TSH was 2.134+1.127 µIU/ml and 4.135+3.231 µIU/ml in non-AIDS and AIDS patient respectively. Among 25 HIV+ patients who were not having AIDS, 3 (12%) patients had FT-3 levels below the normal range, 1 (4%) patient had FT-4 level below the normal range and 1 (4%) patient had FT-4 level above the normal range. Two (8%) patients had s. TSH levels above the normal range. Serum TSH was decreased in one (4%) patient. In 25 patients having AIDS, FT-3 levels were below the normal in 6 (24%) patients, FT-4 levels were below the normal in 9 (36%) patients and TSH levels were above normal in 10 (40%) patients. When the results were statistically analysed, there was a direct correlation between CD4 count and Free T3 and Free T4 values (r=0.357 with p<0.05; r=0.650 with p<0.05 respectively). There was an inverse correlation of CD4 counts with serum TSH levels (r=-0.470 with p<0.05).They concluded that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a primary hypothyroid like stage that occurs in patients with HIV infection . During HIV infection abnormalities in thyroid include both pathological changes and disturbances in its function. Our present study shows that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a subclinical hypothyroid like stage that occurs in patients with advancing HIV infection. Various thyroid function tests such as S.Free T3 /S.Free T4 /S.TSH can be used as a surrogate marker as these correlate with the progression of the disease. The findings in our present study show that there was a direct correlation between CD4 count and S.Free T3 and S.Free T4 values (r=0.357 with p<0.05; r=0.650 with p<0.05 respectively). There was an inverse correlation of CD4 counts with serum TSH levels (r=-0.470 with p<0.05).The present study shows that thyroid dysfunction is frequent in HIV infection and with progression of disease there is a subclinical hypothyroid like stage that occurs in patients with advancing HIV infection. In our study we have studied to explore the association of thyroid function test abnormalities in HIV patients and its correlation which CD4 count at various stage of disease.We calculated that in Group A there was a strong positive correlation between CD4 Count (/cu.mm) and S.Free T3 (pg/mL) and S.Free T4 (ng/ml) values, and this correlation was statistically significant (rho = 0.66, p = <0.001 and rho = 0.75, p = <0.001 respectively).We calculated that there was a strong negative correlation between CD4 count (/cu.mm) and STSH (uIU/ml) value and this correlation was statistically significant (rho = -0.74, p = <0.001).The study showed that thyroid dysfunction is more common in advance stage of HIV infection.

LP Meena *et al*[3]in year 2011 studied studied endocrine changes in male HIV patients in BHU Varanasi. A total of 150 male HIV positive subjects were included in study. The aim of study was to determine the frequency of adrenal, thyroid and gonadal dysfunction in HIV positive male patients and to evaluate the endocrine function at different level of CD4 cell counts. The patients were divided in three groups on the basis of CD4 cell counts. “Group A”: HIV positive with CD4 count <200/mm “Group B”: HIV positive with CD4 count 200-350/mm³ and “Group C”: HIV positive with CD4 count>350/mm³.

Detailed clinical, systemic and anthropometric evaluation was done besides relevant laboratory investigations, In all patients serum was collected for estimation of basal cortisol, TSH, serum testosterone, serum LH/FSH between 8-9 am. In “group A” 15 patients had subclinical hypothyroidism while 11 patients had overt hyperthyroidism. In “group B” 18 had subclinical hypothyroidism while 4 had overt hypothyroidism. In “group C” 12 patients had subclinical and one had overt hypothyroidism. Serum TSH levels in patients of group A, B and C was 8.84±10.41 µg/ml,6.24±3.89 µg/ml,3.95±2.75 µg/ml respectively. The values were significantly elevated in Group A as compared to Group B (p 0.002) and Group C (p<0.0001).There was negative correlation between CD4 count and serum TSH (r=-0.257, p=0.002).They concluded high incidence of thyroid dysfunction in HIV positive patients.In this study 40.66% patients showed abnormal thyroid function (30% subclinical hypothyroidism, 10.66% primary hypothyroidism), However all patients were asymptomatic. None of the patients showed any evidence of biochemical or clinical features of hyperthyroidism. In patients with CD4 < 200, 26/50 (52%) had elevated TSH. High incidence of

biochemical hypothyroidism 10/25 (40%) has also been reported in another Indian study in patients with CD 4 < 200.10 However, in non AIDS patients elevated TSH was found in only 2/25 patients in this study. This pilot study has demonstrated a high incidence of endocrine dysfunction in HIV infected patient in this part of country. In the present study, high incidence of endocrinopathies was observed. The gonadal dysfunction was in line with other studies described in the literature but thyroid dysfunction was quite high in the present study. The findings in present study show that TSH values were significantly elevated in Group A (CD4 count <200/c.mm) as compared to Group B (p 0.002) and Group C (p<0.0001). There was negative correlation between CD4 count and serum TSH (r=- 0.257, p=0.002). Our present study also showed that there is strong negative correlation between CD4 count and TSH (rho = -0.74, p = <0.001) in Group A.

Neera Sharma *et al*[4] in year 2015 studied prevalence and predictors of thyroid dysfunction in patients with HIV infection and AIDS. From initially screened 527 patients 359 patients (61.44 ± 39.42 months disease duration) having good immune function [CD4 count >200 cell/mm³ ± 90.25%, highly active antiretroviral therapy (HAART) 88.58%] were analyzed. Subclinicalhypothyroidism was the commonest thyroid dysfunction (14.76%) followed by sick eu-thyroid syndrome (SES) (5.29%) and isolated low TSH (3.1%). Anti-TPO antibody was positive in 3.90%. An inverse correlation was observed between baseline CD4 count (p=0.031) and anti TPO titers.

Similarly an inverse correlation was observed in CD4 count at present with TSH levels, both at baseline (p=0.043) and after adjusting for age and body mass index (p=0.049).They concluded that subclinical hypothyroidism is the commonest type of thyroid dysfunction followed by sick euthyroid syndrome. The study showed that the burden of thyroid dysfunction in patients with chronic HIV infection with stable immune function (secondary to use of HAART) is lower compared to the pre-HAART era and newly diagnosed HAART naive HIV infected patients.

The findings in present study show that subclinical hypothyroidism was the commonest thyroid dysfunction (14.76%) followed by sick eu-thyroid syndrome (SES) (5.29%) and isolated low TSH (3.1%). Similarly an inverse correlation was observed in CD4 count at present with TSH levels, both at baseline (p=0.043) and after adjusting for age and body mass index (p=0.049).They concluded that subclinical hypothyroidism is the commonest type of thyroid dysfunction followed by sick euthyroid syndrome.

Our present study also showed that in total 100 HIV positive patients there a moderate negative correlation between CD4 Count (cu.mm) and S.TSH (uIU/mL), and this correlation was statistically significant (rho = -0.53, p = <0.001).

Satya Kumar Thongam *et al*[5] in year 2015 studied on thyroid dysfunction in HIV infected children and its correlation with CD4 T lymphocyte count. Sixty confirmed cases of HIV-infected children as per NACO guidelines of 2006 were included (i) 30 HIV Children with a minimum of 6 months with HAART, and (ii) 30 HIV Children without HAART. There are 34 males and 26 females in the study. Thirty each of patients were with and without HAART therapy. In the HAART group, 52.9% were males compared to 47.1% males in those without HAART. Those children who received HAART are significantly taller and heavier significantly than those who did not receive HAART (29.87 ± 5.94 vs. 22.23 ± 3.74, $P < 0.001$). However, there is no difference in body mass index of children between the groups ($P = 0.226$). Of the 30 patients on HAART, 70% are on zidovudine, lamivudine, and nevirapine, while 20% are on lamivudine, nevirapine and stavudine; and 10% are zidovudine, lamivudine, and efavirenz. Thyroid function abnormality was seen in five out of 30 patients in both patients on HAART or without HAART therapy. Clinical studies in HIV-infected children have shown a variable profile of thyroid indices. In the present study, 83.3% of both the groups of patients had normal thyroid function test. In those HAART, sub- clinical hypothyroidism was seen 4 (13.3%) and sick-euthyroid in 1 (3.33%). In the HAART group, there were 3 (10%) cases of frank hypothyroid and 2 (6.66%) cases of sick-euthyroid.

In the present study, there was a highly significant positive correlation between CD4 count and TSH which means that the probability of thyroid dysfunction increases as CD4 decreases or as the disease progresses. In another Indian study, there was a direct correlation between CD4 count and Free T3 (Free T3) and Free T4 values ($r = 0.357$ with $P < 0.05$; $r = 0.650$ with $P < 0.05$, respectively). An inverse correlation of CD4 counts with serum TSH levels was also noted ($r = -0.470$ with $P < 0.050$).The study showed that the biochemical abnormality of thyroid function is quite common among pediatric patients with HIV. An inverse correlation was seen between TSH and CD4 count indicating trend for hypothyroidism as HIV disease progress. The findings in present study show that the biochemical abnormality of thyroid function is quite common among pediatric patients with HIV. An inverse correlation was seen between TSH and CD4 count indicating trend for hypothyroidism as HIV disease progress.

Our study also showed that thyroid dysfunction is more common in advance stage of HIV infection and there is strong negative correlation between CD4 count and TSH (rho = -0.74, p = <0.001) in advanced stage Group (group A).

5. Conclusions

The results showed that thyroid dysfunction is more frequent in female HIV positive patients as compared to male patients. The results also showed that thyroid dysfunction is more frequent in advanced stage (cdc stage 3) as compared to early stage(stage 0,1,2) and there is hypothyroid like stage that occurs in patients with HIV infection.From the findings of our study we can conclude that thyroid function test can be used as a surrogate marker of advancing HIV infection. These patients who became hypothyroid may need treatment.

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