A STUDY OF THYROID DYSFUNCTION IN HIV SEROPOSITIVE PATIENTS

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ABSTRACT

BACKGROUND

There has been significant increase in the prevalence of HIV and with use of HAART there has been significant increase in the survival of HIV infected individuals, leading to increased detection of comorbid conditions associated with HIV. HIV infection can lead to involvement of various organs including endocrine glands. Among the endocrine disorders a high prevalence of abnormalities in thyroid function tests is reported. Thyroid functions may be altered in 10-15% of patients.

MATERIALS AND METHODS

The study has been carried out in 100 patients diagnosed with HIV infection according to NACO guidelines fulfilling inclusion and exclusion criteria, getting admitted to the Department of General Medicine, KIMS, Hubli. The data was collected using pretested proforma meeting the objectives of the study. All patients were investigated for thyroid dysfunction by measuring serum TSH, total T3 and T4.

RESULTS

Among the 100 patients studied, mean age was 37.84±11.05 years, 50 were male. 22% had overt hypothyroidism, 16 (72.73%) males and 6 (27.27%) females. The thyroid function tests in 100 patients compared with CD4 count and the p value found to be 0.907 not statistically significant. Hence no correlation found between CD4 count with the thyroid dysfunction.

CONCLUSION

Thyroid function test abnormalities are common among HIV patients, particularly men, most common being overt hypothyroidism and no correlation noted with the CD4 count and hence with severity of HIV disease.

KEY WORDS

Thyroid Function Abnormality, HIV, CD4 Count, T3, T4, TSH, TFT, Hypothyroidism

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BACKGROUND

Human immunodeficiency virus (HIV) infection results in Acquired Immunodeficiency Syndrome (AIDS) which may directly or indirectly affect any organ system. HIV related endocrine disorders have been recognised with increasing experience with the infection.[1]

Every endocrine organ system has been reported to be affected functionally in HIV infection. These derangements may be attributed to the systemic effects of HIV, opportunistic infections, infiltration by a neoplasm or to the adverse effects of drugs used in the treatment.[2]

Adrenal gland is the most commonly involved endocrine organ in patients with HIV infection in autopsy studies, but clinical adrenal dysfunction is uncommon. Altered thyroid function test results are common even though the clinical thyroid disease is uncommon. Men are found to have gonadal dysfunction commonly compared to women.[2] Abnormalities in thyroid function tests are reported with high prevalence in previous cross-sectional studies.[1]

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However, Indian subcontinent has paucity of data regarding endocrine abnormalities in HIV seropositive patients.[2]

Thyroid function altered in 10–15% of patients with HIV infection. Both hypo- and hyperthyroidism may be seen. The predominant abnormality is subclinical hypothyroidism. In the setting of ART, 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 ART. In advanced HIV disease, infection of the thyroid gland may occur with opportunistic pathogens.[3] Abnormalities of lipid, glucose and bone metabolism are increasingly being recognized, including hyperlipidaemia, hyperinsulinaemia, impaired glucose tolerance, diabetes mellitus, lipodystrophy syndrome and reduced bone mineral density.[4]

Aims and Objectives

1. To study the thyroid dysfunction in seropositive HIV patients.
2. To correlate the Thyroid function changes in these patients with their CD4 cell count.

MATERIALS AND METHODS

Study Design

Descriptive study.

Source of Data
Patients diagnosed as having HIV infection according to the NACO guidelines, fulfilling inclusion and exclusion criteria, admitted to the Department of General Medicine, Karnataka Institute of Medical Sciences, Hubli.

Method of Collection of Data
Information was collected through a pretested and structured proforma for each patient. The study was carried out on HIV serology positive patients fulfilling the inclusion and exclusion criteria.
Qualifying patients underwent detailed history, clinical examination and the below mentioned investigations. The Ethical Committee of KIMS, Hubli has given the ethical clearance for the study.

Sample Size
100 HIV serology positive patients admitted to the Department of General Medicine, Karnataka Institute Of Medical Sciences, Hubli. Sample size was taken for convenience

Sampling Method
Simple random sampling.

Inclusion Criteria
1. Confirmed cases of seropositive HIV.
2. Adults aged more than 15 years.
3. Subjects consenting to take part in study.

Exclusion Criteria
1. Known cases of thyroid disorder.
2. Patients on drugs altering thyroid hormone metabolism like stavudine.
3. Diabetes mellitus.
4. Abnormal Liver function test's with SGOT/SGPT levels greater than 3 times normal range.
5. Abnormal Renal function test's with Serum Creatinine greater than 1.6 mg%.

Investigations
1. HIV (Serology) as per NACO guidelines.
2. CD4 Count (Flow cytometry).
3. Thyroid function tests-TSH, T4, T3.
4. Lipid profile.
5. Electrocardiogram, Chest X-ray
6. Complete Hemogram with ESR.
7. Liver Function Test.
8. Renal function test.
9. Random blood sugar
10. Ultrasonography of neck and FNAC of the thyroid nodule in selected cases.

In our study TSH done by Ultra-Sensitive Sandwich Chemi Luminescent Immunoassay, T3 and T4 done by Competitive Chemi Luminescent Immunoassay.

Statistical Methods
Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

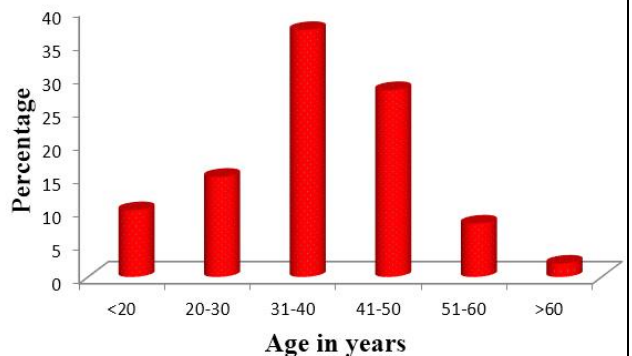
Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant Figures
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value: 0.01<P ≤ 0.05)
** Strongly significant (P value: P≤0.01)

Statistical Software
The Statistical software SPSS 15.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

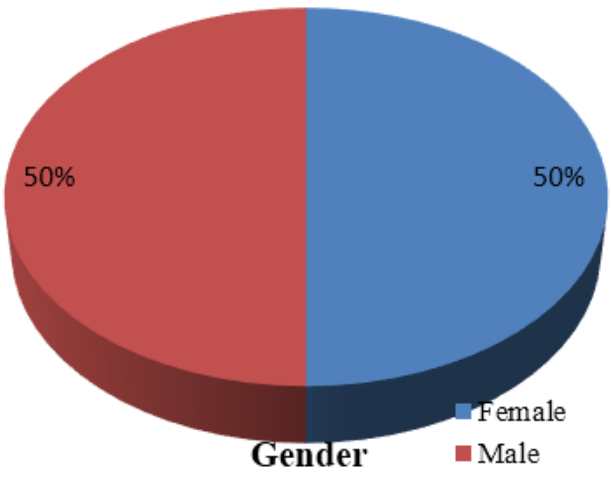
Age in Years	No. of Patients	%
<20	10	10.0
20-30	15	15.0
31-40	37	37.0
41-50	28	28.0
51-60	8	8.0
>60	2	2.0
Total	**100**	**100.0**
Table 1. Age Distribution of Patients Studied		
Mean ± SD: 37.84 ± 11.05		



Graph 1. Age Distribution of Patients Studied

Most of the patients in the study group belonged to the age group 31-40 years (37%). with mean age 37.84±11.05 years.

Gender	No. of Patients	%
Female	50	50.0
Male	50	50.0
Total	**100**	**100.0**
Table 2. Gender Distribution of Patients Studied		



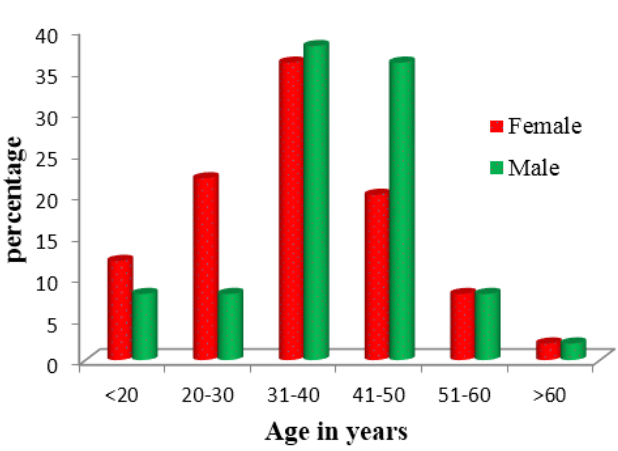
Graph 2. Gender Distribution of Patients Studied

Equal number of male and female patients present in the study group with 50 patients in each category.

Age in Years	Gender		Total
	Female	Male	
<20	6 (12%)	4 (8%)	10 (10%)
20-30	11 (22%)	4 (8%)	15 (15%)
31-40	18 (36%)	19 (38%)	37 (37%)
41-50	10 (20%)	18 (36%)	28 (28%)
51-60	4 (8%)	4 (8%)	8 (8%)
>60	1 (2%)	1 (2%)	2 (2%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 3. Age Distribution of Patients Studied

P=0.269, Not Significant, Fisher Exact test



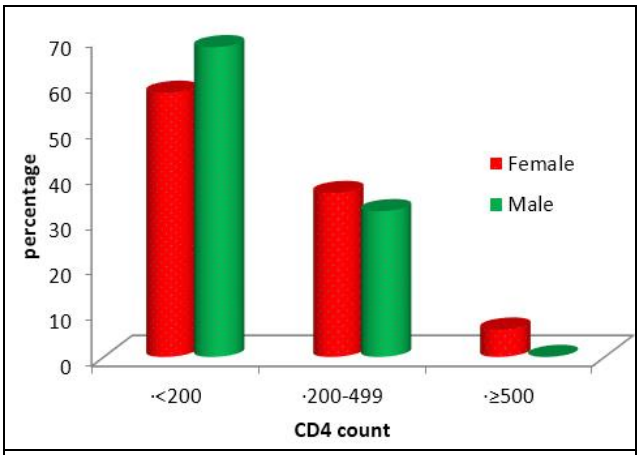
Graph 3. Age Distribution of Patients Studied

Most of the female patients in the study belonged to the age group 31-40 years (36%) and male patients 31-40 years (38%), 41-50 years (36%).

CD4 Count	Male	Female	Total	p-Value
<200	29 (58%)	34 (68%)	63 (63%)	0.198
200-499	18 (36%)	16 (32%)	34 (34%)	
≥500	3 (6%)	0 (0%)	3 (3%)	

Table 4. Distribution of Patients According to CD4 Count–CDC Category

Chi-Square test/Fisher Exact test



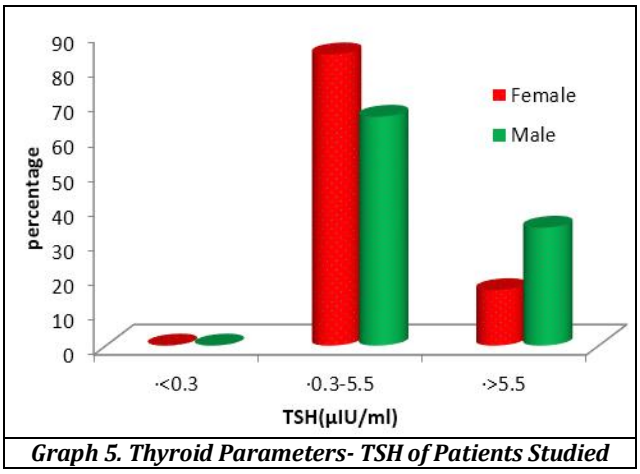
Graph 4. Distribution of Patients According to CD4 Count–CDC Category

Out of the 100 patients 63% had CD4 count <200/µL, 34% between 200-499/µL and 3% >500/µL.

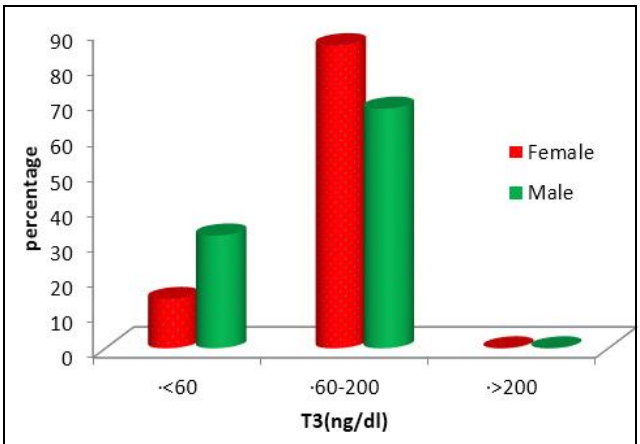
	Gender		Total (n=100)	p-Value
	Female (n=50)	Male (n=50)		
TSH (µIU/ml)				
<0.3	0 (0%)	0 (0%)	0 (0%)	0.063+
0.3-5.5	42 (84%)	33 (66%)	75 (75%)	
>5.5	8 (16%)	17 (34%)	25 (25%)	
T3 (ng/dl)				
<60	7 (14%)	16 (32%)	23 (23%)	0.056+
60-200	43 (86%)	34 (68%)	77 (77%)	
>200	0 (0%)	0 (0%)	0 (0%)	
T4(µg/dl)				
<4.5	8 (16%)	14 (28%)	22 (22%)	0.098+
4.5-12	39 (78%)	36 (72%)	75 (75%)	
>12	3 (6%)	0 (0%)	3 (3%)	

Table 5. Thyroid Parameters of Patients Studied

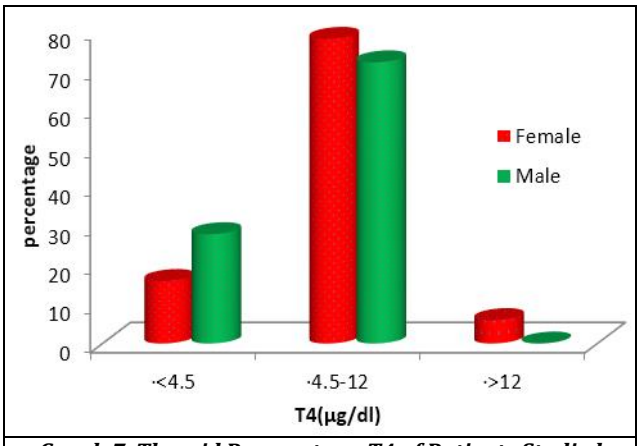
Chi-Square Test/Fisher Exact Test



Graph 5. Thyroid Parameters- TSH of Patients Studied



Graph 6. Thyroid Parameters- T3 of Patients Studied



Graph 7. Thyroid Parameters- T4 of Patients Studied

Of the 100 patients studied 75 patients had normal (0.30-5.5 µIU/ml) TSH, 25 patients had TSH of >5.5 µIU/ml. Of which 22 patients had TSH of >10 µIU/ml – overt hypothyroidism and remaining 3 had subclinical hypothyroidism.

Out of the 100 patients 77 had normal (60-200 ng/dl) T3 and 23 patients had T3 value of <60 ng/dl, of which 22 were overt hypothyroid and 1 patient had isolated low T3 value.

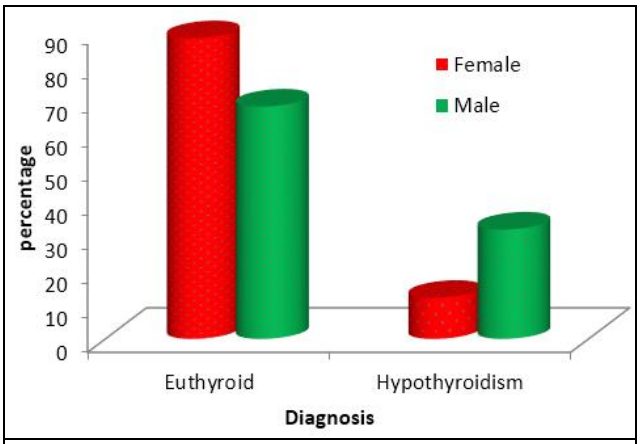
Out of the 100 patients studied 75 patients had normal (4.5-12 µg/dl) T4 levels, of the remaining patients 22 were overt hypothyroid and 3 patients had isolated high T4 value of >12 µg/dl.

TSH, T3 and T4 were found to have p value which is of suggestive significance.

Diagnosis	Gender		Total
	Female	Male	
Euthyroid	44 (88%)	34 (68%)	78 (78%)
Hypothyroidism	6 (12%)	16 (32%)	22 (22%)
Total	**50 (100%)**	**50 (100%)**	**100 (100%)**

Table 6. Diagnosis of Patients Studied

P=0.016*, Significant, Chi-Square Test



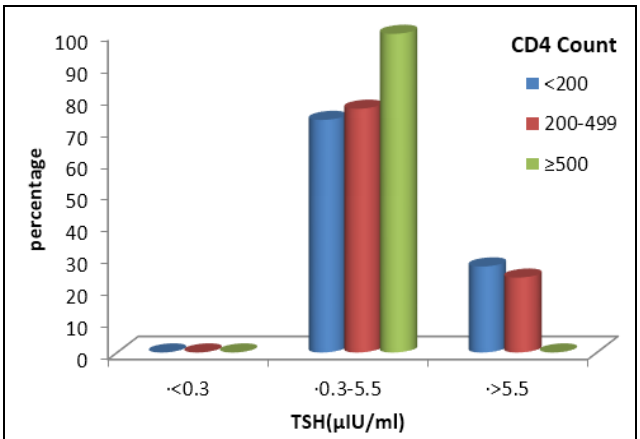
Graph 8. Diagnosis of Patients Studied

In the study 22 (22%) patients found to have overt hypothyroidism, p value was found to be 0.016, which is moderately statistically significant.

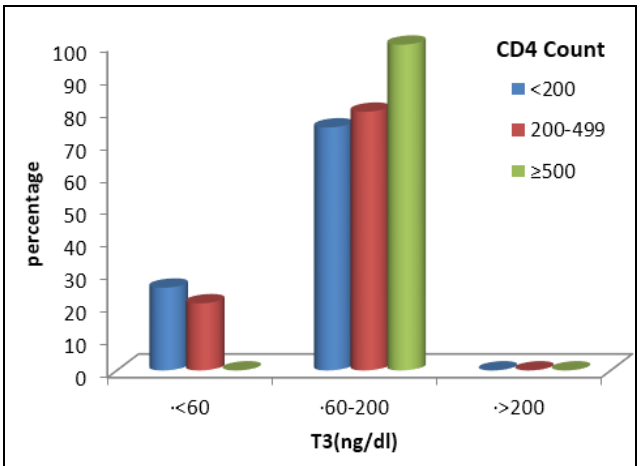
Thyroid Profile	CD4 Count			Total (n=100)	p-Value
	<200 (n=63)	200-499 (n=34)	≥500 (n=3)		
TSH (µIU/ml)					
<0.3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.759
0.3-5.5	46 (73%)	26 (76.5%)	3 (100%)	75 (75%)	
>5.5	17 (27%)	8 (23.5%)	0 (0%)	25 (25%)	
T3 (ng/dl)					
<60	16 (25.4%)	7 (20.6%)	0 (0%)	23 (23%)	0.829
60-200	47 (74.6%)	27 (79.4%)	3 (100%)	77 (77%)	
>200	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
T4 (µg/dl)					
<4.5	16 (25.4%)	6 (17.6%)	0 (0%)	22 (22%)	0.802
4.5-12	45 (71.4%)	27 (79.4%)	3 (100%)	75 (75%)	
>12	2 (3.2%)	1 (2.9%)	0 (0%)	3 (3%)	

Table 7. Thyroid Profile According to CD4 Count

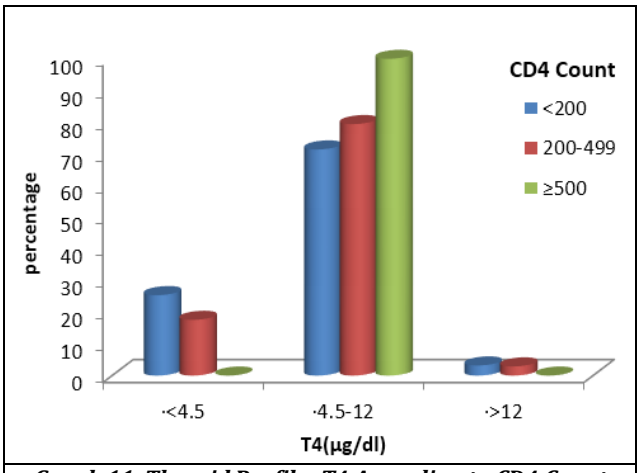
Chi-Square Test/Fisher Exact Test



Graph 9. Thyroid Profile- TSH According to CD4 Count



Graph 10. Thyroid Profile- T3 According to CD4 Count



Graph 11. Thyroid Profile- T4 According to CD4 Count

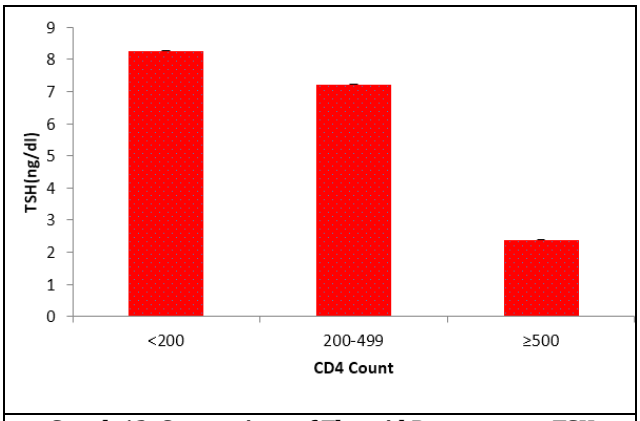
Out of the 25 patients with high TSH 17 of them had CD4 count of <200/µL, out of 23 patients with low T3 16 of them had CD4 count <200/µL and of the 22 with low T4 16 had CD4 of <200/µL. p value was found to be statistically not significant. No correlation could be established between thyroid dysfunction and CD4 count.

Thyroid	CD4 Count			Total	P value
	<200	200-499	≥500		
TSH (µIU//ml)	8.26 ± 13.34	7.22 ± 9.90	2.39 ± 1.18	7.73 ± 12.05	0.685
T3 (ng/dl)	67.10 ±24.91	74.89 ± 23.48	90.33 ± 10.69	70.44 ± 24.51	0.118
T4 (µg/dl)	6.63 ± 2.99	7.58 ± 2.55	7.17 ± 0.32	6.97 ± 2.82	0.283

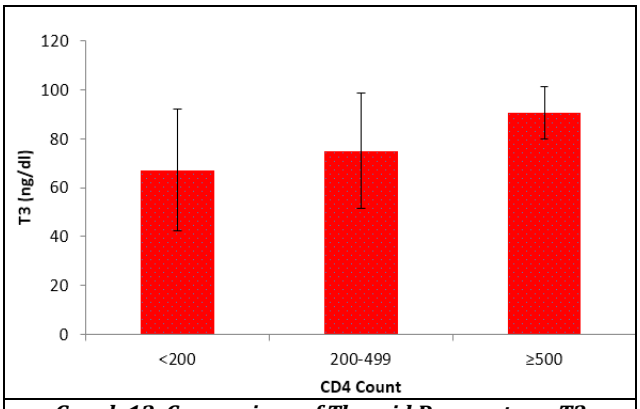
Table 8. Comparison of Thyroid Parameters According to CD4 Count

ANOVA test

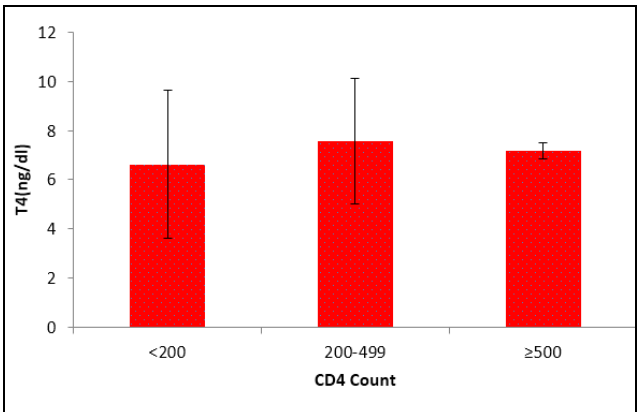
Depending on the CD4 count, with CD4 count of <200/µL the mean TSH, T3 and T4 were 8.26 ± 13.34 µIU/ml, 67.10 ± 24.91 ng/dl and 6.63±2.99 µg/dl respectively. With CD4 count of 200-499/µL it was 7.22 ± 9.90 µIU/ml of TSH, 74.89 ± 23.48 ng/dl T3 and 7.58 ± 2.55 µg/dl T4. With CD4 >500/µL the TSH, T3 and T4 were 2.39 ± 1.18 µIU/ml, 90.33 ± 10.69 ng/dl and 7.17 ± 0.32 µg/dl respectively.



Graph 12. Comparison of Thyroid Parameters- TSH According to CD4 Count



Graph 13. Comparison of Thyroid Parameters- T3 According to CD4 Count

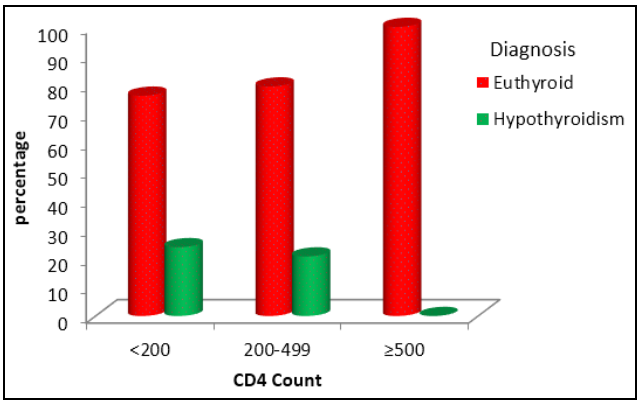


Graph 14. Comparison of Thyroid Parameters- T4 According to CD4 Count

Diagnosis	CD4 Count			Total
	<200	200-499	≥500	
Euthyroid	48 (76.2%)	27 (79.4%)	3 (100%)	78 (78%)
Hypothyroidism	15 (23.8%)	7 (20.6%)	0 (0%)	22 (22%)
Total	**63 (100%)**	**34 (100%)**	**3 (100%)**	**100 (100%)**

Table 9. Diagnosis According to CD4 Count

P=0.907, Not Significant, Fisher Exact Test



Graph 15. Diagnosis According to CD4 Count

Of the 22 hypothyroid patients 15 patients had CD4 count of <200/µL and the p value was found to be not significant.

DISCUSSION

This study conducted in Karnataka Institute of Medical Sciences Hubli. Hundred patients were randomly taken up for the study, after considering the inclusion and exclusion criteria. All the patients were thoroughly examined and investigated as per the proforma. Among these patients, thyroid dysfunction was looked.

Study	L P Meena et al[2]	Nirdesh jain et al[5]	Madge S et al[6]	Palani-samy et al[7]	Beltran et al[8]	Present study
Mean Age (Years)	35.81 ± 8.85	34.10 ± 8.3	37	49	44	37.84 ± 11.05

Table 10. Comparison of Age Group

In our study mean age group was 37.84 ± 11.05 years. Out of the 100 individual patients studied 37% belonged to 31-40 years age group, 28% belonged to 41-50 years age group and 15% belonged to 20-30 years age group.

Of the 100 patients studied 50 were males and 50 were females.

	L P Meena et al[2]	Nirdesh jain et al[5]	Madge S et al[6]	Palanisamy et al[7]	Present Study
Male	150 (100%)	90 (76.92%)	1233 (79%)	50 (100%)	50 (50%)
Female		27 (23.08%)	332 (21%)		50 (50%)

Table 11. Gender Distribution

In 2003 Beltran et al study, included 343 case patients where sex ratio of male to female was 2:1[8].

Percentage distribution of males and females in our study not comparable with other studies, the reason behind this is earlier studies mainly concentrated on male population. In the present study equal number of male and female patients are present. It has the advantage of studying thyroid dysfunction in both males and females and gives better view of thyroid dysfunction in HIV patients.

Sex Wise Distribution of Thyroid Dysfunction in HIV Positive Patients

Among the 100 patients studied, 22 of them had thyroid dysfunction, out of these 22 patients, 16 were males (72.73%) and 6 were females (27.27%). Thyroid Dysfunction was more common in male patients than female patients. This is in contrast to the general occurrence of thyroid dysfunction commonly among females in general population.

Categories Depending upon CD4 Count

Patients categorized according to CD4 count. 63% of patients had CD4 count of less than 200/µL and 34% of the patients had CD4 count ranging between 200 -499/µL. 3% of the study group had CD4 count of >500/µL. The results were comparable with Gagan Jain et al study[1].

In L P Meena et al study, 150 male HIV seropositive patients were included in study. The HIV seropositive patients were divided into three groups on the basis of CD4 cell counts. "Group A": patients with CD4 count < 200/mm^3, "Group B": patients with CD4 count 200-350/mm^3 and "Group C": patients with CD4 count > 350/ mm^3. 50 patients in each group[2].

Gagan Jain et al, study group divided into two groups group 1: belonging to category A-3, B-3, C1-3 consisting of 25 patients. And group 2 belonging to category A1-2, B1-2 consisting of 25 patients**.** On the basis of CD4 cell count distribution; 4 (8%) patients found to have CD4> 500/µL, 21 (42%) patients with CD4 between 200-500/µL and 25 (50%) patients with CD4 cell count <200/µL[1].

In the present study patients were also categorized according to the WHO staging of HIV. 41% of the patients belonged to stage 4, 31% to stage 3, 13% to stage 2 and 15% to stage 1.

	L P Meena et al[2]	Madge S et al[6]	Nirdesh Jain et al[5]	Christopher et al	Present Study
Euthyroid	59.34%	75.5%	89%	63%	78%
Hypothyroid	40.66%	6.5%	9%	37%	22%
Hyperthyroid	0	1%	2%	0	0

Table 12. Comparison of Thyroid Dysfunction in HIV Patients

L P Meena et al study results were, serum TSH 4.5-10 µIU/ml (subclinical hypothyroidism) found in 45(30%) patients and TSH value > 10 µIU/ml (overt hypothyroidism)[2] detected in 16(10.66%) HIV seropositive patients.

Nirdesh Jain et al study, thyroid function test was done in 100 patients, of them, 9 (9%) had raised TSH; however, only 2% were overtly hypothyroid. Only 2% patients had low TSH; however, their T4 and T3 values were within normal range.[5]

Madge S et al study, overall 3584 samples were analysed. Of the patients included in the study, 1233 (79%) were male. Nine hundred patients (58%) were on HAART at the start of the study. Thirty-nine (2.5%) were found to have overt hypothyroidism, and eight (<1%) had overt hyperthyroidism. Sixty-one (4%) had subclinical hypothyroidism, five (<1%) had subclinical hyperthyroidism and 263 (17%) had a nonthyroidal illness. A normal TFT was obtained for 1118 patients (75.5%). Multivariate analysis suggested that no independent variables were significantly associated with overt hypothyroidism, including HAART and stavudine use specifically. Repeated measurements over 3 years were available for 825 patients and only eight new cases (1%) of overt thyroid disease occurred. Concluding that the prevalence of overt thyroid disease was low in this cohort, suggesting that screening is not warranted.[6]

Gagan jain et al study showed that, thyroid function abnormalities were observed in substantial number of patients in a study of 50 HIV seropositive patients. Serum FT-3 levels found to be below the normal range in 9 (18%) patients, decreased serum FT-4 levels in 10 (20%) and serum TSH levels above the normal range in 12 (24%) HIV seropositive patients.[1]

Present study showed that 22% had overt hypothyroidism and 0% hyperthyroidism, 3% subclinical hypothyroidism, 1% isolated low T3 and 3% isolated increase in T4 levels. Which was comparable with L P Meena et al study and Christopher et al study. The results of the study were not comparable to Madge S et al and Nirdesh Jain et al study. Thus, the commonest abnormality found in all the studies was hypothyroidism.

In the present study patients categorized based on the CD4 count, <200/µL, 200-499/µL and >500/µL. The mean TSH, T3 and T4 values in the study group were found as below.

Thyroid	CD4 Count		
	<200	**200-499**	**≥500**
TSH (µIU/ml)	8.26 ± 13.34	7.22 ± 9.90	2.39 ± 1.18
T3 (ng/dl)	67.10 ± 24.91	74.89 ± 23.48	90.33 ± 10.69
T4 (µg/dl)	6.63 ± 2.99	7.58 ± 2.55	7.17 ± 0.32

Table 13. Correlation of CD4 Count with Thyroid Status

Among the 22 patients diagnosed as having hypothyroidism 15(68.18%) had CD4 count of <200/µL and 7(31.81%) patients had CD4 count between 200-499/µL. But upon applying Fisher exact test p value found to be 0.907 not significant. Hence no correlation between thyroid dysfunction and CD4 count.

In L P Meena et al study, in HIV seropositive patients "group A, B and C" TSH level was 8.84± 10.41 µIU/ml, 6.24±3.89 µIU/ml, 3.95±2.75 µIU/ml respectively. The values were significantly elevated in "group A" as compared to "group B" (p 0.002) and "group C" (p< 0.0001). Thus, with the progression of disease mean TSH value increased. Negative correlation between the CD4 counts and serum TSH was observed. In the study 61(40.66%) HIV seropositive patients had hypothyroidism [2].

In Gagan Jain et al study, in both HIV+ non-AIDS and AIDS patients thyroid function tests were compared. 2.826±0.702 pg/ml and 1.352±0.371 ng/ml were mean FT3 and mean FT4 values in non-AIDS patients while it was 2.518±0.868 pg/ml and 0.925±0.264 ng/ml were mean FT3 and FT4 values in AIDS patients. 2.134±1.127 µIU/ml and 4.135±3.231 µIU/ml were S. TSH values in non-AIDS and AIDS patient respectively.[1]

Among 25 HIV patients who did not have AIDS, 3 (12%) 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. 2(8%) patients had TSH values above the normal range. Serum TSH was found to be reduced in one (4%) patient. Among 25 patients having AIDS illness, FT-3 values were reduced in 6 (24%) patients, FT-4 levels were decreased in 9 (36%) patients and s. TSH levels were increased in 10 (40%) patients. As 50 patients were distributed during course of the disease from less severe to more severe according to CD4 cell count, the results were statistically analyzed for all 50 HIV seropositive patients enrolled in the study using Pearson's correlation coefficient. It was found that there was a direct correlation between CD4 cell count and serum FT3 and serum FT4 values ($r=0.357$ with $p<0.05$; $r = 0.650$ with $p<0.05$ respectively). There was an inverse correlation of CD4 cell counts with serum TSH levels ($r = -0.470$ with $p < 0.050$).[1]

CONCLUSION

1. Thyroid dysfunction is observed frequently among HIV patients.
2. Hypothyroidism is the most common thyroid abnormality seen among HIV patients.
3. Thyroid Dysfunction was more common in male patients than female patients. This is in contrast to the general occurrence of thyroid dysfunction commonly among females in general population.
4. Thyroid dysfunction in HIV patients did not correlate with lower CD4 count and hence the severity of the disease.

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