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THYROID DYSFUNCTION IN PATIENTS WITH HIV INFECTION

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ABSTRACT

The aims of the study were to investigate the prevalence of overt and subclinical thyroid dysfunction of HIV-infected patients in Goa Medical College, identify the patterns of thyroid dysfunction prevalent in the study population, determine risk factors associated with the development of thyroid dysfunction in HIV-infected patients and to assess the applicability of thyroid function tests as biochemical indicator of advanced HIV disease. The antiretroviral drug regimens the patients in this study received comprised three of the following antiretroviral drugs; zidovudine, stavudine, lamivudine, nevirapine and efavirenz. In the present study, there was no statistically significant association between receipt of the above mentioned antiretroviral drugs and thyroid dysfunction or hypothyroidism. In the present study, the mean CD4 count was lower in patients with abnormal thyroid function tests (205.6 cell/mm^3) compared to those with normal thyroid function (344.3 cell/mm^3). The difference was found to be statistically significant. The study range included subjects between 22-62 years. The mean age of the study population was 40.7 ± 9.7 years. The patients with thyroid infection were older than the euthyroid patients (mean age 43.8 ± 7.8 v/s 39.8 ± 10.1 months), however there was no statistically significant association between age and development of thyroid dysfunction in HIV-infected individuals (p value =0.143).

KEYWORDS: Thyroid dysfunction, HIV infection, T3 and FT3, CD4 cell counts, highly active antiretroviral therapy (HAART).

INTRODUCTION

Infection with the human immunodeficiency virus (HIV) results in a chronic systemic illness with multi-organ involvement.[1] As acute complications of HIV decrease, the focus has to shift to chronic complications of the decrease and chronic adverse effects of current treatment regimes.[2]

A number of endocrine abnormalities develop in patients with HIV infection both during the early and late stages of the disease. These abnormalities may contribute to the clinical presentation and therefore appropriate treatment would theoretically improve the patient's condition.[1,3] The endocrine dysfunction in these cases may be because of the possible relationship between the immune system and the endocrine system, or through the direct involvement of glands by HIV itself, opportunistic infections or malignancies.[3]

Increasing prevalence of thyroid function abnormalities has been reported in HIV-infected patients in various cross-sectional studies.[4] These include overt hypothyroidism, subclinical hypothyroidism, the low T3 syndrome, the sick euthyroid syndrome, hyperthyroidism including Graves disease, subclinical hyperthyroidism, isolated low FT4 and isolated high FT3. Subtle alteration of thyroid function tests are more common in HIV infection and are sometimes already detectable in the early phase of the disease. Unique abnormalities of thyroid function indices have also been recently documented. A progressive elevation in serum TBG accompanying the decline of the CD4 lymphocyte count and a concomitant increase in the serum T4 value has been reported.[5]

The exact mechanisms of thyroid dysfunction in HIV-infected patients are still unknown.[6] The proposed mechanisms include thyroid gland destruction by opportunistic infections (Pneumocystis jirovaci infection, cytomegalovirus infection, tuberculosis, cryptococcosis and visceral leishmaniasis) or malignant diseases (Kaposi's sarcoma, lymphoma), drug-related adverse effects especially with relation to HAART or side effects of the drugs used in the course of HIV infection (e.g. rifampicin, ketoconazole, steroids etc.), effects of humoral factors such as cytokines and direct infection of gland by HIV itself. The thyroid dysfunction patterns consistent with non-thyroidal illness are less makred in HIV infection and are mainly present in the final stages of the disease.[5-8]

The use of highly active antiretroviral therapy (HAART) in current clinical practice has been associated with benefits in the management of HIV infection, with a dramatic reduction in

HIV-related morbidity and mortality.[9-10] There is an increasing awareness of a growing number of patients receiving HAART who present with symptoms of thyroid dysfunction.[11-13] Hypothyroidism is the most common thyroid function abnormality occurring in HIV-infected patients, especially after treatment with HAART.[4,6]

Some studies have correlated worsening thyroid dysfunction with advancing HIV infection and proposed that various thyroid function tests such as TBG (thyroglobulin), FT3, FT4, TSH can be used as a surrogate markers, as these correlate with the progression of the disease.[14]

In view of the varying results of the previous studies concerning thyroid dysfunction in HIV infected individuals and the absence of comparable data with respect to the Indian and Goan population, it was decided to undertake a study of the prevalence and patterns of thyroid dysfunction in HIV-infected patients in varied clinical settings in Goa Medical College.

MATERIALS AND METHODS

The study was conducted in Goa Medical College and Hospital, Bambolim, Goa in patients attending the Outpatient Department (OPD) of the Department of Medicine and the Anti-Retrovirus (ART) Centre during the period 2011 to 2012.

The study included a total number of 70 patients, 45 male and 25 female, with a mean age of 40 years and 42 respectively.

The study was approved by the Institutional Ethics Committee of the Goa Medical College. All the participants were informed and explained about the study being undertaken and an informed consent was obtained.

The study design was a single-centre observational cross-sectional study followed by a case control study.

Inclusion Criteria

1. Diagnosed case of HIV infection.
2. Age between 18 years to 70 years.

Exclusion Criteria

1. History of previous thyroid illness.

2. Use of drugs known to interfere with thyroid hormone metabolism. (Phenytoin, phenobarbitone, carbamazepine, carbimazole, warfarin, rifampicin, lithium, propranolol, amiodarone, glucocorticoids).[15,16]
3. Abnormal renal function test.[17]
4. Abnormal liver function test.[18]
5. Pregnancy.[16]
6. Acute severe illness.

METHODOLOGY

A total of 70 HIV-infected subjects were included in the study. Data on age, gender, weight, height, duration of HIV infection, WHO clinical stage, receipt of HAART including treatment regimen and duration of HAART was collected in a pretested proforma meeting the objectives of the study. A detailed history, clinical examination and necessary investigations were recorded. Body mass index (BMI) was calculated as weight in kg/(height in meters)[2].Thyroid dysfunction was clinically evaluated based on common symptoms and clinical findings of hypothyroidism and hyperthyroidism. 'Clinical features of overt thyroid disease' was defined as a Wayne score of ≥ 20 or a Billewicz score of > 30. Goitre was graded according to the WHO/ UNICEF/ ICCIDD recommendations.[19] Treatment and outcomes were not included in this study. Since the study was a cross-sectional study there was no follow-up.

Detection of HIV infection: For the detection of HIV infection we employed the following three tests. The diagnosis of HIV infection was made when all the three tests were positive.

1. **HIV ½ Triline Card Test:** Immuno-chromatographic based assay for detection of antibodies to HIV-1 and HIV-2 in human serum or plasma. It demonstrates a sensivity and specificity of 100%.
2. **SD Bioline HIV ½ 3.0:** It is an immune-chromatographic (Rapid) test for the qualitative detection of antibodies to HIV-1 and HIV-2. It demonstrates a sensitivity of 100% and specificity of 99.8%.
3. **HIV ½ Rapid Test Kit (Trispot):** It is an immuno-concentration based assay which employs r- proteins for the detection of antibodies to HIV-1 and HIV-2 in human serum or plasma. These proteins correspond to the highly antigenic structural and non structural proteins of HIV and offer the advantage of high degree of sensitivity and specificity due to multiple epitopes. It demonstrates a sensitivity and specificity of 100%.

- The patients diagnosed to have HIV were divided into 4 clinical stages using the 'WHO clinical staging for HIV/ AIDS for adults and adolescents (2006)'.[20]

TSH: TSH was measured by the 'Architect TSH assay' which is a Chemiluminescent Microparticle Immunoassay (CMIA) for the qualitative determination of human thyroid stimulating hormone in human serum and plasma. A normal range for this test was 0.35µIU/ml to 4.94 µIU/ml. The assay had an analytical sensitivity of ≤ 0.0025 µIU/ml and an analytical specificity of <10% cross-reactivity with FSH, LH and hCG at a concentration of ≤500 µIU/ml, ≤500 µIU/ml and ≤200000 µIU/ml respectively. The ARCHITECT TSH assay is designed to have a functional sensitivity of ≤0.01 µIU/ml, which meets the requirement of a third generation TSH assay.

Free T3: Free T3 (FT3) was measured by the 'ARCHITECT Free T3 assay' which is a two step immunoassay to determine the presence of free (unbound) T3 in human serum and plasma using Chemiluminescent Microparticle Immunoassay (CMIA) technology. A normal range for this test was 1.71pg/ml to 3.71pg/ml. The assay had an analytical sensitivity of ≤1.0 pg/ml and an analytical specificity of ≤0.001% cross-reactivity with T4 at a concentration of 1000000 pg/ml.

Free T4: Free T4 (FT4) was measured by the 'ARCHITECT Free T4 assay' which is a two step immunoassay to determine the presence of free thyroxine in human serum and plasma using Chemiluminescent Microparticle Immunoassay (CMIA) technology. A normal range for this test was 0.70ng/dL to 1.48ng/dL. The assay had an analytical sensitivity of ≤0.4 ng/dL and an analytical specificity of ≤0.0035% cross-reactivity with T3 at a concentration of 12000 ng/dL in a sample containing 0.5 ng/dL of free T4.

Euthyroid state was defined as T3, FT3, T4, FT4 and TSH levels within the normal range.[16] Overt hypothyroidism was defined as a high TSH level and low FT4 level;[21] subclinical hypothyroidism was defined as a high TSH level and normal FT4 level.[21] and the category "Low FT4 syndrome" as an FT4 level <0.70 ng/dL and a normal TSH level. Subclinical hyperthyroidism was defined as a low TSH level and a normal FT4 level and overt hypothyroidism was defined as a low TSH level and elevated FT4 level.[22] Sick euthyroid syndrome/ Non-thyroidal illness was defined as low T3, FT3, T4 or FT4 in the presence of a low or normal TSH level.[16]

'Abnormal renal function test' was defined as a increased serum creatinine level and estimated glomerular filtration rate (eGFR) less than 30 ml/min calculated using the Cockroft-Gault formula. Serum creatinine was measured by Jaffe's method. Normal values for males was 0.6-1.2mg/dl and females was 0.5-1.1mg/dl.

'Abnormal liver function test' was defined as SGOT and/ or SGPT levels greater than three times the upper limit of the normal range or total serum bilirubin level greater than 1.2 mg/dL. SGOT and SGPT were measured by the NADH method and the normal values were between 5-34 U/L and 0-55 U/L respectively. Total bilirubin was measured by the 'Diazonium salt' method and the normal values were between 0.2-1.2 mg/dL.

'Acute severe illness' was defined as any illness not included in the 'WHO clinical staging for HIV/AIDS for adults and adolescents (2006).'

A case-control study was conducted afterward in which patients with hypothyroidism (overt hypothyroidism and subclinical hypothyroidism) were included as case patients and euthyroid patients as control subjects. Patients with other patterns of thyroid dysfunction (i.e. Low FT4 level and sick euthyroid syndrome) were included in the prevalence study but excluded from the case control study.

To study the usefulness of TFTs as a biochemical of advanced HIV disease, the cohort population was divided into two groups. Group 1(n=34) were HIV infected patients in WHO clinical stage 1 and 2, representing the early stages of HIV infection. Group 2 (n=36) were HIV infected patients with WHO clinical stages 3 and 4, representing the advanced stages of HIV infection.

RESULTS

Statistical analysis: Statistical analysis was performed using SPSS software 14.0 version (USA). Data with normal distribution were expressed as mean ± standard deviation. For statistical analysis Pearson correlation test, Chi Square test, Student's t-test and Mann-Whitney U test were used wherever appropriate. Pearson correlation test was applied to determine correlation between CD4 cell counts and thyroid function tests. $P<0.05$ was considered to be statistically significant.

Demographic variables of the study population

The study group consisted of patients with HIV infection attending the Outpatient Department (OPD) of the Department of Medicine and the Anti-Retroviral (ART) Centre at Goa Medical College.

Table 1: Age and sex distribution of the study group

Age (years)	Sex		Total
	Male	Female	
20-29	5	4	9
30-39	18	7	25
40-49	15	5	20
50-59	7	7	14
60-69	0	2	2
Total = 70	**45 (64.3%)**	**25 (35.7%)**	**70 (100%)**

Table 2: Distribution of thyroid profile in the study population

Thyroid Status	No. of Patients	%
Euthyroid	54	77.1
Subclinical Hypothyroidism	7	10.0
Overt Hypothyroidism	2	2.9
Subclinical Hyperthyroidism	0	0.0
Overt Hyperthyroidism	0	0.0
Sick Euthyroid Syndrome	6	8.6
Low FT4 Syndrome	1	1.4
Total	**70**	**100**

Table 3: Serum concentration of the thyroid function tests

Thyroid Profile	T3	T4	TSH	FT3	FT4
Normal Range	0.58 - 1.59	0.58 - 1.59	0.35 – 4.94	1.71 – 3.71	0.70 – 1.48
Study Range	0.25 - 1.53	3.18 - 10.21	0.45 – 11.29	1.00 – 3.71	0.40 – 1.42
Mean	0.92	6.60	2.70	2.74	0.99
Standard Deviation	0.30	1.52	2.02	0.72	0.18

Association between age and thyroid dysfunction: The study range included subjects between 22-62 years. The mean age of the study population was 40.7 ± 9.7 years. The patients with thyroid infection were older than the euthyroid patients (mean age 43.8 ± 7.8 v/s 39.8 ± 10.1 months), however there was no statistically significant association between age and development of thyroid dysfunction in HIV-infected.

Table 4: Association between BMI and thyroid dysfunction

	Thyroid Function Test	N	Mean	Std. Deviation	Std. Error Mean
BMI	Normal	54	20.346	2.8935	.3938
	Abnormal	16	19.056	3.0611	.7653

The participants with thyroid dysfunction had a lower BMI compared to euthyroid subjects (mean BMI = 19.05 ± 3.06 v/s 20.34 ± 3.06 kg/m^2).

Table 5: Independent samples t-Test

		Levene's Test for Equality of Variances		t-Test for Equality of Means				
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
BMI	Equal variances assumed	.411	.523	1.546	68	.127	1.2901	.8344
	Equal variances not assumed			1.499	23.527	.147	1.2901	.8606

There was no statistically significant association between BMI and development of thyroid dysfunction. (p value = 0.127).

Table 6: Association between receipt of HAART and thyroid dysfunction:

Chi-Square Test

Receipt of HAART	Thyroid Function Tests		Total
	Normal	Abnormal	
Yes	39	12	51
No	15	4	19
Total	**54**	**16**	**70**

There was no significant association between the receipt of HAART and thyroid dysfunction in HIV-infected patients (p value=0.826).

Association between receipt of specific antiretroviral drug and thyroid dysfunction

The antiretroviral drugs evaluated in our study included zidovudine (AZT), stavudine (d4T), lamivudine (3TC), nevirapine (NVP) and efavirenz (EFV). The study population was under the following triple drug regimes: AZT + 3TC + NVP, d4T + 3TC + NVP, AZT + 3TC + EFV, d4T + 3TC + EFV. The predominant drug regimen was AZT + 3TC + NVP in both the euthyroid and hypothyroid group. All the participants received lamivudine and hence no statistics were computed as it was a constant.

Zidovudine

Table 7: Chi-Square Test

Receipt of Zidovudine	Thyroid Function Tests		Total
	Normal	Abnormal	
Yes	25	9	34

No	29	7	36
Total	**54**	**16**	**70**

There was no significant association between the receipt of zidovudine and thyroid dysfunction in HIV-infected patients (p value=0.484).

Stavudine

Table 8: Chi-Square Test

Receipt of Stavudine	Thyroid Function Tests		Total
	Normal	Abnormal	
Yes	14	3	17
No	40	13	53
Total	**54**	**16**	**70**

There was no significant association between the receipt of stavudine and thyroid dysfunction in HIV-infected patients (p value=0.557).

Nevirapine

Table 9: Chi-Square Test

Receipt of Nevirapine	Thyroid Function Tests		Total
	Normal	Abnormal	
Yes	35	12	47
No	19	4	23
Total	**54**	**16**	**70**

There was no significant association between the receipt of nevirapine and thyroid dysfunction in HIV-infected patients (p value=0.4446).

Efavirenz

Table 10: Chi-Square Test

Receipt of Stavudine	Thyroid Function Tests		Total
	Normal	Abnormal	
Yes	4	0	4
No	50	16	66
Total	**54**	**16**	**70**

There was no significant association between the receipt of efavirenz and thyroid dysfunction in HIV-infected patients (p value=0.262). However, since only 4 patients in our study population received efavirenz, statistical analysis of this variable was imprecise.

Table 11: Association between duration of HAART and Thyroid Dysfunction

	Thyroid Function Test	N	Mean	Std. Deviation	Std. Error Mean
Duration of HAART (months)	Normal	39	23.49	23.38	3.744
	Abnormal	12	27.42	24.07	6.951

51 participants among our study population were receiving HAART.

The participants with thyroid dysfunction had a greater mean duration of treatment with HAART compared to euthyroid subjects.

Table 12: Independent samples t-Test

		Levene's Test for Equality of Variances		t-Test for Equality of Means				
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
Duration of HAART (months)	Equal variances assumed	0.03	0.953	-.506	49	.615	-3.929	7.770
	Equal variances not assumed			-.498	17.87	-.625	-3.929	7.895

There was no statistically significant association between duration of treatment with HAART and development of thyroid dysfunction (p value=0.615).

Association between duration of HAART and thyroid dysfunction

Table 13: Mann-Whitney U Test

TFTs	T3	CD4 Mean	Std. Deviation	CD4 Median	Range
Normal	54	344.30	221.75	314	16 – 927
Abnormal	16	205.06	109.27	201	53 – 430

There was a significant difference in the CD4 count between euthyroid HIV-infected patients and those with thyroid dysfunction (p-value = 0.027, <0.05).

To analyse the association between low CD4 count and thyroid dysfunction

Table 14: Chi-Square Test

CD4 Count (cells/mm^3)	Thyroid Function Tests		Total
	Normal	Abnormal	
≤200(Low)	15	8	23
>200	39	8	47
Total	**54**	**16**	**70**

The association between thyroid dysfunction and low CD4 count did not attain statistical significance at the 0.05 level (p value = 0.096).

DISCUSSION

The present study included 70 patients with HIV infection, 45 males (64.3%) and 25 females (35.7%) with a mean age of 40 years and 42 years respectively. The mean age of patients in this study was 40.7 ± 9.7 years which was comparable to study groups Quirino et al,[23] Beltran et al[6] and Grappin et al.[24]

Majority of patients in our study were found to have normal thyroid parameters. The prevalence of thyroid dysfunction in our study was 22.9%. A similar prevalence of 24.5% was documented by Madge et al.[25] in their study population. Madeddu et al.[13] and Grappin et al[24] reported a lower prevalence of 12.6% and 12.3% respectively.

There is no uniform pattern of association between thyroid dysfunction and HIV infection. Subclinical hypothyroidism has often been recognized in HIV-infected population with a higher prevalence compared to HIV-negative individuals. Subclinical hypothyroidism was the most common thyroid function abnormality in the present study. The prevalence of subclinical hypothyroidism in our population was 10%. This observation was consistent with several previous studies. Grappin et al.[24] found that 8.5% of their study populations had subclinical hypothyroidism. Merenich et al.[8] reported an 8% prevalence of subclinical hypothyroidism among HIV-infected patients receiving HAART, Calza et al.[26] reported a high prevalence (12.2%) of subclinical hypothyroidism. Beltran et al.[6] reported a prevalence of 6.6%, while Collazos et al.[27] and Madge et al.[25] reported a lower prevalence of 3.5% and 4% respectively. The prevalence of isolated low FT4 levels in our study was 1.4%. The prevalence of isolated low FT4 has varied in each of the population studied. While generally the mean FT4 is on the lower side of normal, isolated low FT4 incidence is reported in a widely distributed spectrum of values. Collazos et al[27] found 1.3% of the determinations of free thyroxine to be below the normal limits which is comparable with our population result.

It was observed that none of the patients in our study group had subclinical or overt hyperthyroidism. This observation was consistent with the findings of Collazos et al.[27] and Grappin et al.[24] Graves' disease is the leading cause of hyperthyroidism both in the general population and in HIV-infected individuals. It is considered a late manifestation of immune reconstitution inflammatory syndrome (IRIS) and is most commonly diagnosed 12-36 months after initiation of HAART. The proposed mechanisms include thyroid gland destruction by opportunistic infections or malignant diseases, drug-related adverse effects especially with relation to HAART, effects of humoral factors such as cytokines, non-thyroidal illness and

changes in thyroid hormone secretion or action due to direct infection of gland by HIV itself. In our study, we evaluated the following risk factors for the development of thyroid dysfunction; age, sex, BMI, duration of HIV infection, receipt of HAART, duration of treatment with HAART, treatment with specific antiretroviral agent, low CD4 count and WHO clinical stage of infection.

Age was not a risk factor for development of thyroid dysfunction or hypothyroidism in HIV-infected patients. This observation was consistent with the previous studies of Beltran et al,[6] Madge et al,[25] Quirino et al.[23] and Afhami et al.[4]

In our study population, the distribution of thyroid dysfunction between the sex groups showed no statistical correlation. Similar results were observed in the studies by Madge et al,[25] Nelson et al.[28] and Afhami et al.[4] Hypothyroidism has been reported to be more prevalent in HIV-infected men than women, different from the gender distribution in women. This finding was not replicated in our study. Quirino et al.[23] and Beltran et al.[6] documented that the prevalence of subclinical hypothyroidism was higher in male patients with HIV infection as compared with men in the general population. The prevalence of subclinical hypothyroidism among the make subjects in our study was 8.9%, similar to that reported by Beltran et al (8.1%).[6]

Longer duration of disease in HIV-infected patients treated with HAART might allow the development of autoimmune thyroiditis as seen by Beltran et al.[6] There was no significant association between the duration of illness and thyroid dysfunction or hypothyroidism in the present study. This observation was concordant with the finding of Afhami et al.[4] and Quirino et al.[23]

CONCLUSION

Abnormal thyroid function tests are common among HIV-infected individuals.The prevalence of thyroid dysfunction in the study population was 22.9%. Subclinical hypothyroidism was the most common abnormality identified in the study population, followed by thyroid function test patterns consistent eith non-thyroidal illness (NTI). Overt and subclinical hyperthyroidism is uncommon among HIV infected patients. Statistical significance was not seen in the association between age, sex, BMI, duration of illness, receipt of HAART, receipt of specific antiretroviral drug, duration of HAART, low CD4 count ($\leq$ 200 cell/mm^3) and thyroid dysfunction or hypothyroidism. There was a statistically

significant association between 'WHO clinical stage of HIV disease' and the development of thyroid dysfunction and hypothyroidism in HIV-infected patients. T3 and FT3 can be used as biochemical indicators of advanced HIV disease as they correlate with CD4 cell counts and the progression of disease. The majority of the thyroid abnormalities detected in our cohort would not be routinely treated and hence the role of screening for thyroid dysfunction in HIV-infected patients is debated.

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