Original Article

Thyroid Function Tests as a Surrogative Marker of Progression of the Disease in AIDS

D. V. Mulay* P. V.Bhalshankar**

Abstract :

.Background:

It has been demonstrated that elevation of thyroid stimulating hormone (TSH) and thyroid binding globulin) (TBG concentration in conjunction with low free thyroxin (FT_4) occurs frequently and correlates with CD_4 + cell depletion.Recent reports have outlined a high frequency of thyroid dysfunction in HIV infected adults treated with highly active anti-retroviral therapy (HAART).

Aims & Objectives:

This observational present study was undertaken to study thyroid function in HIV positive patients and correlate the results obtained with CD_4+ counts.

Material & Methods:

100 consecutive HIV positive cases were studied in two groups. Group A – 50 patients with AIDS [8] and Group B – 50 HIV positive patients with CD_4 + cell count ≥200/μL without any opportunistic infection or complication.'CD4+ count & Thyroid functions were done.

Observations:

The CD_4+ count in these patients ranged from 5 - 773/□L with a mean of 223±190.9/□L. BY using Pearson's correlation coefficient ,study of TFTs and CD_4+ count revealed a direct correlation between CD4+ count and $FT_3$and FT_4 values ($r = 0.4261$ with $p < 0.05$ and $r = 0.2266$ with $p < 0.005$ respectively).An inverse correlation was observed between CD_4+ counts using TSH levels ($r = -0.4683$ with $p < 0.05$).

Conclusion:

Present study shows that thyroid dysfunction is frequent in HIV infection and with progression of disease there is subclinical hypothyroid like state that occurs in patients with advancing HIV infection as is also observed in different studies. [2, 13,20] It can be concluded that FT_3, FT4, and S.TSH can be used as a surrogate marker of the progression of the HIV disease.

KeyWords: Thyroid function, Surrogative marker, HIV/AIDS

Introduction

Acquired immunodeficiency syndrome (AIDS) was first recognized in United States in the summer of 1981.Since the identification of Human Immunodeficiency Virus (HIV) in 1983 and the confirmation of its role as an etiological agent of AIDS in 1984, AIDS has become a global epidemic. [1]

AIDS may affect directly or indirectly any organ system in the body. Increasing experience with this syndrome has led to recognition of a variety of endocrine disorders that occur during both the early and late stages of the disease. [2]

Even in the absence of true endocrine dysfunction, deregulation of endocrine system in patients with AIDS is reflected by the numerous abnormalities detected when endocrine functions are formally tested . Hormones have been shown to effect HIV replication and to modulate the evaluation of HIV associated disorders.[3] The administration of various drugs in HIV and AIDS also can cause endocrinal disturbances.[4]It has been demonstrated that elevation of thyroid stimulating hormone (TSH) and thyroid binding globulin (TBG) concentration in conjunction with low free thyroxin (FT_4) occurs frequently and correlates with CD_4 + cell depletion. In addition to this, thyroid dysfunction correlated with degree of immuno supression and viral replication and preceded worsening of the disease.[5,6] Recent reports have outlined a high frequency of thyroid dysfunction in HIV infected adults treated with highly active anti-retroviral therapy (HAART).[7]

Aims And Objectives:

The present study was undertaken to study thyroid function in HIV positive patients and correlate the results obtained with CD_4+ counts.

Professor* Assistant Professor Medicine**
Department of Medicine, GMC, Aurangabad

Address for correspondence

D. V. Mulay
Email: mulay.dv@gmail.com

Material And Methods

The present study was carried out at Govt. Medical College, Aurangabad. All newly diagnosed adult and adolescent HIV positive patients were enrolled in the study. Informed consent was obtained .The study was approved by the ethical committee of the Hospital. Patients with past history of thyroid illness, clinically evident thyroid enlargement or signs of thyroid disease, those on drugs known to interfere with thyroid metabolism as rifampicin, steroids, ketokonazole, antiepileptics etc., those with abnormal LFT'S (SGOT, SGPT > 3 times the upper normal limit) and deranged renal function (S.creatinine > 1.6 mg%) were excluded from the study.[2] 100 consecutive HIV positive cases were studied in two groups. Group A – 50 patients with AIDS [8] and Group B – 50 HIV positive patients with CD_4 + cell count ≥200/μL without any opportunistic infection or complication.

CD_4+ count was determined by flow cytometry with fluorescence activated cell sorter (FACS) caliber counting system (Beckston Dickson, USA).[9]

Three rapid test kits were used for diagnosing HIV infection 1) Screen kit (SD Bioline), 2) Triline kit and 3)Spot kit.[10]

Thyroid function tests (TSH, FT_3 and FT_4) were determined by chemileuscence immune assay (CLIA) using ADVIA centaur equipment. Definitions used are as per recommendations from AACE, ATA and the endocrine society.[11]

Observations:

In the present study 100 HIV serology positive patients were included. There were 66males and 34 females. The age of these patients ranged from 15 to 66 yrs with a mean of 36.22±9.07 yrs. The CD_4+ count in these patients ranged from 5 - 773/□L with a mean of 223±190.9/□L. They were grouped in to two groups. Group A comprising 50 patients with AIDS and Group B comprising 50 HIV positive patients with CD_4 +count >200/μL without any opportunistic infection or complication. In group A ,CD_4 + count ranged from 5-197/□L with a mean of 69.82 ±49.11/□L. In group B, CD_4+ count ranged from 203-773/□L with a mean of 377.5±151/□L. With decrease in CD4+ count the number of patients with thyroid dysfunction increased and the difference was found to be statistically significant($p<0.05$).Out of 100 patients,18 had low FT_3,12 had low $FT_4$and 1 had increased FT_4.TSH was found to be low in 1 patient while 25 had increased TSH. (**Table1**). Mean FT_3 and FT_4 values were found to be significantly lower in Group A(2.131±0.9826, 1.179±0.4484) than Group B(2.827±0.6406, 1.310±0.3183) $p<0.001$ and <0.05 respectively. TSH values were found to be significantly higher in Group A (5.622±3.616) than Group B (2.430±1.115). $p<0.0001$. **(Table 2.)**

Subclinical hypothyroidism was observed in 19 patients, hypothyroidism in 6 patients, and subclinical hyperthyroidism in one patient, low FT_3 in 12 patients and low FT_4in 5 patients. None of the patient had clinical signs or symptoms of hypo or hyper functioning of thyroid gland. When TFTs were compared, in group A 16 patients had low FT_3, 11 patients had low FT_4 and 23 patients had high TSH. In group B 2 patients had low FT_3, 1 patient had low FT_4, 2 patients had high TSH and 1 patient had low TSH. Statistically significant difference was observed in number of euthyroid patients in the two groups ,13 in group A and 44 in group B ($p<0.0001$). Subclinical hypothyroidism was observed in 17 patients in group A and 2 patients in group B. The difference observed was statistically significant ($p<.0001$). 6 patients in Group A were having hypothyroidism. Subclinical hyperthyroidism was observed in 1 patient in group B. Isolated low FT_3/FT_4 was found in 14 patients in group A and 3 patients in group B. The difference observed was found to be statistically significant ($p<.0001$)**. (Table3).**

BY using Pearson's correlation coefficient ,study of TFTs and CD_4+ count revealed a direct correlation between CD4+ count and $FT_3$and FT_4 values ($r = 0.4261$ with $p < 0.05$ and $r = 0.2266$ with $p < 0.005$ respectively).An inverse correlation was observed between CD_4+ counts using TSH levels ($r = -0.4683$ with $p < 0.05$).(**Table 4)**

Discussion:

Infection from HIV may directly or indirectly affect any organ system in the body. HIV related endocrine disorders occur during both the early and late stages of the disease. Thyroid hormone have been shown to affect HIV replication and to modulate evaluation of HIV associated disorders.[12]

It was observed that CD_4+ count decreased with progression of the disease.[12] Mean CD_4+ count was found to be less in Group – A (69.82±49.11/μl) than Group – B (377.5±151.3/μl).The difference observed was found to be statistically significant. ($p<0.05$) Similar observations have been made previously.[2,13]

Multiple alterations in the serum concentration of iodothyronines have been recognized in patients with systemic non-thyroidal illnesses(NTI).Most prominent are $T_3$and elevated reverse T_3 concentrations leading to the generally used 'low T_3 syndrome', however a more appropriate description would be 'sick euthyroid syndrome', where not only T_3 concentrations but all the

thyroid parameters including TSH are often affected.[14] low serum T_3 concentrations have also been found in patients with liver disease ,[15]after stress or surgery,[16]in patients with chronic renal failure,[17]in elderly sick[18]and after ingestion of drugs.[4] Of course these changes have to be attributed to illness only in absence of an underlying disorder of the hypothalamic pituitary – thyroid axis and there complete reversal must accompany recovery from the casual illness.

Thyroid manifestations associated to HIV infection are due to a variety of mechanisms including opportunistic infections, alterations in glucose and lipid metabolism,[19] effects of drugs used to treat the wide spectrum of HIV related diseases[4] and a possible direct or indirect effect of HIV itself on thyroid function. Many studies indicate that thyroid hormone values may be altered in AIDS due to nonthyroidal illnesses and much less frequently due to impaired hypothalamic pituitary or thyroid gland function, as in other nonthyroidal illnesses.[14]However few workers believe that in HIV there is hypothyroid like regulation of the pituitary-thyroid axis which is different from euthyroid sick syndrome.[12]

In the present study FT_3 values were found to be significantly lower ($p<0.0001$) in AIDS patients (Group-A) than non AIDS patients (Group-B).Similar findings have been reported earlier. [2,5,11]

Changes in protein binding of T_4 could be responsible for the abnormal thyroid hormone indices observed in patients with nonthyroidal illnesses. Decreased concentrations of one or more of the binding proteins could explain low levels of T_4 and or an increased FT_4 fraction. However in HIV patients presence of higher level of Thyroid binding globulin (TBG) affect levels of mean FT_3 and FT_4.[15]In the present study mean FT_4 values were found to be significantly lower ($p<0.05$) in non AIDS patients than those with AIDS. Similar observations have been noted earlier.[2,5,6,12]

Mean TSH was found to be significantly higher ($p < 0.0001$) in AIDS patients (Group-A) than non AIDS patients (Group-B).Similar observations have been reported earlier. [2,5,6,12,20]

Conclusion:

Present study shows that thyroid dysfunction is frequent in HIV infection and with progression of disease there is subclinical hypothyroid like state that occurs in patients with advancing HIV infection as is also observed in different studies.[2, 13,20] It can be concluded that FT_3, FT4, and S.TSH can be used as a surrogate marker of the progression of the HIV disease.

Limitations:

The cause of thyroid dysfunction was not determined and may represent either coincidental occurrence of hypothyroidism or may be due to AIDS related thyroid gland dysfunction. The present study may not be giving the true picture of thyroid abnormality in HIV-AIDS as structural correlates of Thyroid dysfunction could not be done in patients with hypothyroid like state. Besides this Serum reverse triiodothyronine (RT3), thyroxin binding globulin (TIBG) and thyrotropin releasing hormone (TRH) stimulation test, thyroid peroxidase (TPO) and TIBG antibodies could not be done because of non availability of these tests in our setup. Further studies are needed to solve the issue of management of thyroid dysfunction in HIV-AIDS.

Table 1: Showing TFT compared with CD $_4$+ counts

TFT	RESULT	GROUP – A CD_4+< 200/μ L	GROUP – B CD_4+> 200/μ L	Total 100	p value
FT_3	Normal (1.8 -4.2pg /dl)	34(68%)	48(96%)	82(82%)	<0.05
	Increased (>4.2pg /dl)	0	0	0	
	Decreased (< 1.8pg /dl)	16(32%)	2(4%)	18(18%)	
FT_4	Normal (0.8 -1.9 ng /dl)	39(78%)	48(96%)	87(87%)	<0.05
	Increased (>1.9 ng /dl)	0	1(2%)	1(1%)	
	Decreased (<0.8ng /dl)	11(22%)	1(2%)	12(12%)	
TSH	Normal (0.4 -4.0 μIU/ml)	27(54%)	47(94%)	74(74%)	<0.05
	Increased (>4.0μIU/ml)	23(46%)	2(4%)	25(25%)	
	Decreased (<0.4 μIU/ml)	0	1(2%)	1(1%)	

Table 2: Showing comparison of TFT between Group -A and Group - B			
	Group A CD_4+<200/µ L	Group B CD_4+≥200/µL	p value
Mean FT 3pg/dl	2.131± 0 .9826	2.827± 0.6406	0.0001
Mean FT_4 ng/dl	1.179± 0.4484	1.310±0.3183	<0.05
Mean TSH µIU/ml	5.622±3.616	2.43 ±1.115	0.0001

Table 3: Showing pattern of thyroid abnormalities according to CD_4+ count.				
Type of Thyroid abnormality	CD_4+ count < 200 Group A (n=50)	200 Group B (n=50)	Total(n=100)	p value
Euthyroidism	13(13%)	44(44%)	57(57%)	0.0001
Subclinical Hypothyroidism	17(17%)	2(2%)	19(19%)	0.0001
Hypothyroidism	6(6%)	0	6(6%)	
Subclinical Hyperthyroidism	0	1(1%0	1(1%)	
Hyperthyroidism	0	0	0	
Isolated low FT_3	10(10%)	2(2%)	12(12%)	
Isolated low FT_4	4(4%)	1(1%)	5(5%)	
Isolated low FT_3/FT_4	14(14%)	3(3%)	17(17%)	0.0001
Total	50	50	100	

Table4: Showing correlation between CD_4+count and Thyroid function tests in study group.		
Parameter	r value	p value
CD_4 v/s FT_3	0.4261	< 0.05
CD_4 v/s FT_4	0.2266	< 0.05
CD_4 v/s STSH	-0.4683	< 0.05

Refrences:

1) Fauci and Lane in "Harrison's Principals Of Internal Medicine,17th ed,2008 New Delhi, Mc Graw Hills,1137-40
2) Jain G,Devpura G,Gupta B.Abnormalities in thyroid function tests as surrogate marker of advancing HIV infection in infected adults .JAPI,2009;(57)508-510.
3) Masharani U, SchamelanM. The endocrine complications of Aquired Immune Deficiency Syndrome.Adv Intern Med 1993; :323-36.
4) Merenich JA;McDermott MT et al. Evidence of endocrine involvement in the course of human immunodeficiency virus infection. J Clin Endocrinol Metab 1990;70 :566-71
5) Oliveri A,Sorcini M et al.Thyroid hypofunction related with the progression of HIV infection.J Endocrinol Invests.1993;16 : 407-13.
6) Hirshfeld S;Laul L et al.Thyroid abnormalities in children infected with human immunodeficiency virus. J Pediatr 1996;128:70-74.
7) Grappin M, Piroth L, Verges B et al. Increased prevalence of subclinical hypothyroidism in HIV patients treated with highly active antiretroviral therapy. AIDS 2000;14:1070-72 .
8) CDC Revision of the CDC surveillance case definition for Aquired Immunodeficiency Syndrome. MMWR 1992;41:(RR-17)
9) Becton, Dickinson.

http//wwwbdbiosciences.com/clinical/globalhealth/efforts/new technologies. JSP.

10) NAACO Antiretroviral therapy. Guidelines for HIV infected adults and adolescents including post exposure. Govt.of India May 2007.
11) Gharib H, Tuttle RM, Baskin J,Fish LH, Singer PA, McDermott MT. Consensus statement: Subclinical thyroid dysfunction : A joint statement from the American Thyroid Association and The Endocrine Sosciety. J.Clin Endocrinol Metab 2005;90(1):581-585
12) Beltran S, Lescure FX, Desailloud R etal. Increased prevalence of hypothyroidism among human immuno deficiency virus infected patients: a need for screening. Clin Infect Dis 2003;37:579-583.
13) Pasupathi P,Manivannan P,Manivannan U,Mathiyallagan D. Thyroid function, cardiac risk assessment profile and haematological changes during HIV infection and AIDS patients. J Medicine.2010;11:131-136.
14) Carter JN, Eastman CJ, Corcoran Jmetal. Effect of chronic severe illness on thyroid function.Lancet,II,1974:971-974.
15) Nomura S,Pittman CS,Chanibers JB,Buck MW and Shimezu T. Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis.J Clin Invest.1975;56:643-652.
16) Burr WA, Griffiths RS, Black EG, Hoffenberg R, Meinhold H and Wenzel KW.Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operations. Lancet II;1975:1277-1279.
17) Finucane JF, Griffiths RS, Black EG and Hall CL. Effects of chronic renal disease on thyroid hormone metabolism. Acta Endocrinologica; 84:750-758.
18) Burrows AW, Cooper E, Shakespear RA, Aickin CM, Fraser S, Hesch RD, Burke CW.Low serum L-T3 levels in the elderly sick. Protein binding, thyroid and pituitary responsiveness and reverse T3 concentrations. Clincal Endocrinology.1977;7:289-300.
19) Grunfeld C,Pang M etal.Indices in thyroid functions and weight loss in human Immunodeficiency Virus infection and the Immunodeficiency syndrome. Metabolism. 1993;2:1270-1276.
20) Meena LP, Rai M,Singh A et al. Endocrine changes in male HIV patients .J Assoc Physicians India. 2011;59:365-371.