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Research Article

STUDY ON ENDOCRINOLOGICAL PROFILE OF HIV INFECTED MALE PATIENTS FROM EASTERN INDIA

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ABSTRACT

Human Immunodeficiency virus (HIV) infectionis associated with a variety of endocrine problems. Hypoadrenalism, hypothyroidism and hypogonadism are commonly found singly or in combination. Especially, male hypogonadism is very common in this population and may lead to weight loss, lethargy and other co morbidities. We undertook this cross sectional observational study to evaluate endocrine profile in HIV infected males in a sample Eastern Indian population. We also studied for any correlation of the endocrine dysfunctions with their immune status. We studied the blood hormone profiles along with blood CD4 counts. The bloods were drawn in fasting state and analysed using suitable high sensitivity assays. Standard statistical methods were used. We had 48 patients in our study. Among them, 33% had hypogonadism, 20% had hypothyroidism and 15 patients had diabetes. The hypogonadism was mainly hypogonadotropic. In other studies across the globe also, hypogonadism in HIV positive males is found to be significant. Our diabetic patients were not on protease inhibitors. We found some patients who had multiple endocrine dysfunctions. HIV infection is often associated with endocrine abnormalities. This aspect of the disease must be addressed during routine care of these patients. Hormone replacement must be individualized and may be needed for prolonged periods.

Keywords: HIV, Endocrine, Hypogonadism, Diabetes, Hypothyroidism

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is a risk factor for a variety of endocrine problems[1]. The gamut of endocrine problems in HIV infected persons range from adrenal insufficiency and hypogonadism to pituitary and thyroid disorders[1]. This can occur due to different opportunistic infections of the glands or HIV virus mediated damage. But in most cases, the exact pathophysiology of endocrine dysfunction in HIV infection is unknown.

Although adrenal insufficiency was once the most studied endocrine dysfunction in HIV, other hormonal problems have also been recognized[1]. Especially hypogonadism in males is now recognised as a significant association with HIV infection[2]. This hypogonadism is often hypogonadotropic and it causes different problems like weight loss and lethargy[1, 3]. This hypogonadism may be irreversible even after anti-retroviral therapy (ART) and thus, regular hormone replacement may be needed[3].

Hypogonadism is less common in HIV positive women. However, in women, measuring of hormone levels is often difficult due to different reference ranges in different times of the menstrual cycle and thus, mild deficits may be missed. Different studies have shown conflicting results regarding sex hormone levels in HIV positive women, with many studies showing normal levels[4]. Hypopituitarism due to infections etc. can cause hypogonadism in both sexes[1]. Thus, hypogonadism is more important in male subset of HIV patients, although other hormone dysfunctions also occur in both sexes.

Thyroid dysfunction is also a recognised entity in HIV infection[5]. Different patterns of dysfunction are recognised and often advanced HIV infection can have sick euthyroid syndrome[5]. Some thyroid disorders like Grave's disease can also occur as a part of immune reconstitution syndrome[5]. Hence, with other endocrine dysfunctions, thyroid disorders are also important to rule out in this group of patients.

In India, the number of persons living with HIV/AIDS (PLHA) is rising rapidly. However, the endocrine aspect of this new epidemic has not been adequately studied. In our resource limited setting, it may not always be possible to do all hormone assays in every patient. A pilot study from U.P. has shown that in male HIV patients, hypogonadism and hypothyroidism is quite common[6].

We therefore undertook this study to evaluate the hormonal status of HIV positive male patients. This was a small pilot study to understand the extent of endocrine changes in HIV infection. We wanted to find out which hormonal assays are most important in our setting, when all tests cannot be done due to financial reasons. This study can also help to formulate a policy of hormone replacement in HIV care.

PATIENTS AND METHODS

We undertook this study in a tertiary care hospital of Eastern India with a special referral clinic for HIV positive patients. The male patients attending this clinic or admitted indoors were selected after proper counselling and consent. Ethical approval was obtained beforehand. This was an observational hospital based cross sectional study.

Patients with sepsis, pregnancy, drug therapy like ketoconazole or steroids, or patients on any hormone therapy were excluded from the study. After proper selection, the patients were tested for hormone levels in serum. Morning blood samples were drawn in fasting state. For cortisol level measurement, 8 am sample was drawn from central venous line in atraumatic way. Simultaneously, blood for CD4 count was also drawn.

The Serum TSH was assayed by immunoassay using commercially available kit (Eliscan™, Aelvis, Hannover) and absorbance was noted in Tecan ELISA reader. Assay was

done in duplicate. The kit provides sensitivity of 0.078 µIU/ml.

Serum free iodothyronine (FT3) and free thyroxin (FT4) were assayed by Eliscan immunoassay kit. Absorbance value was read in each well at 450 nm (using reference wavelength of 630 nm to minimize well imperfections) by Tecan ELISA reader. By utilizing calibrators of absorbance was recorded by Tecan ELISA reader. Estimation of serum LH and FSH were done by Eliscan immunoassay kit and reading was recorded by Tecan ELISA reader. The cortisol level measured here is 8 am blood level without prior administration of steroids. Cortisol level is measured by chemiluminescence immunoassay (Abbott, USA). Low or borderline cortisol levels were not further checked by ACTH stimulation due to financial constraints.

Since this was a cross sectional study, we drew blood of the patient only once. So, we have measured fasting blood glucose (FBS) and HbA1C levels only to diagnose diabetes. Fresh blood anticoagulated with Potassium EDTA was used for estimation of HbA1C percentage. HbA1C was quantitatively analysed by Randox HbA1C assay kit in auto analyser (Randox- Daytona). The determination of HbA1C is based on latex agglutination inhibition assay.

Standard statistical methods were used. The data was first copied in Microsoft Excel worksheet. The data is presented as mean± S.D. (continuous) or proportions and percentages (categorical). Correlation is studied with Pearson coefficient. Online freeware like Graphpad or MedCalc is used for calculations. P value<0.05 is considered significant. The hormone levels are expressed as less than, inside or above reference range in a categorical way (Table 1).

The normal hormone levels for males are as under[7]: - (standard reference range and literature in packages of the kits used, as mentioned)

Table 1: **Normal ranges for the hormones in blood**

Hormone	Normal levels
LH	2—18 mIU/ml
FSH	1—18 mIU/ml
Testosterone [total]	2.4—12 ng/ml
TSH	0.39--6.16µIU/ml
FT3	1.4—4.2pg/ml
FT4	0.8—2ng/dl
Cortisol 8 AM	<5 µg/dl: low; 5-10 µg/dl: borderline; >10 µg/dl: normal

Table 2: **Hormone and other blood parameter levels in our patients**

Name of hormone	Levels	No. of patients (N ;%)
LH(mIU/ml)	<2	5;10.4
	2-18	39;81.2
	>18	4;8.3
FSH(mIU/ml)	<1	3;6.3
	1-18	41;85.4
	>18	4;8.3
Total testosterone(ng/ml)	<2.4	16; 33%
	2.4-12	32; 67%
	>12	0
TSH(µIU/ml)	<0.39	2;4.2
	0.39-5.5	36;75
	>5.5	10;20.8
fT4(ng/dl)	<0.8	8; 16.7
	0.8-2	40; 83.3
	>2	0
fT3(pg/ml)	<1.4	1;2.1
	1.4-4.2	47;98
	>4.2	0
Cortisol (8 AM) (µg/dl)	<5	1; 2
	5-10	3; 6.2
	>10	44;91.8
FBS (mg/dl)	<110	31;64.6
	110-125	7;14.6
	≥126	10;20.8
HbA1C (%)	≤5.6	28;58.3
	5.7-6.4	8;16.7
	≥6.5	12;25

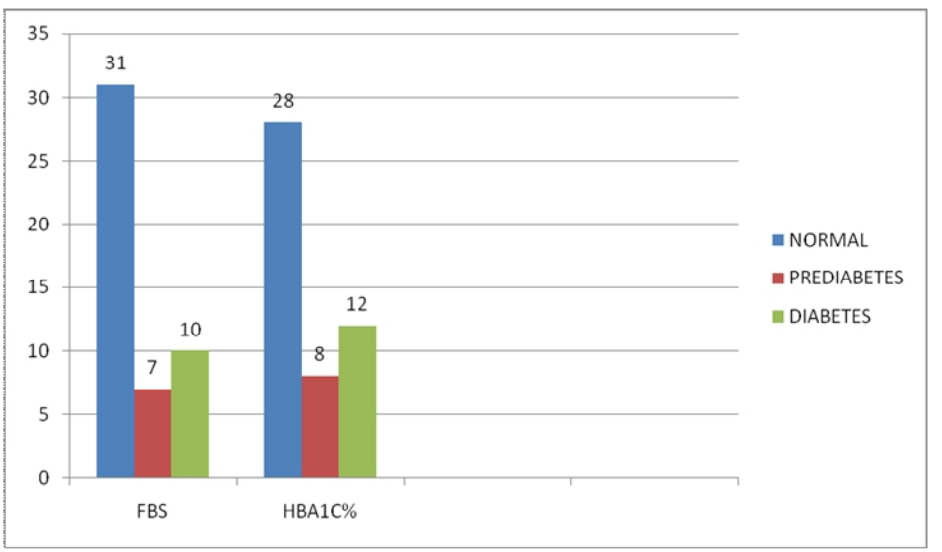

Figure 1: **Glycaemic status, according to FBS and HbA1C %**

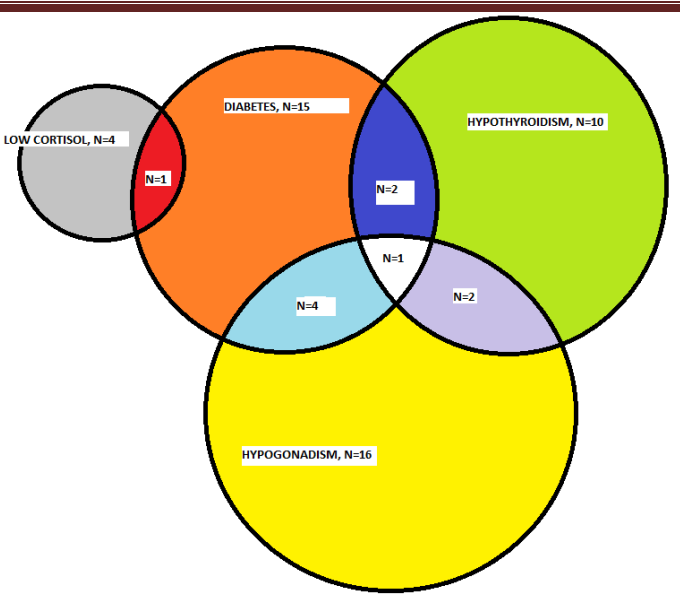

Figure 2: Different hormonal disorders in our patients

RESULTS

We at first selected 64 patients. However, some of them opted out of study and some of them could not get the tests done due to various reasons. Finally, we had 48 patients in our study. The average age of our patients was 35±6.9 years (Range 26 to 50 years). Thus, there was no confounding effect on hormone levels due to senility. The CD4 count of our patients varied from 43 to 189/cmm. Altogether, 24 (50%) of patients had CD4 count less than 100/cmm. Of them, 4 (16.67%) had CD4 counts less than 50/cmm.

The various hormone and other blood parameter levels are shown in table 2.Low levels of total testosterone was found in 33% (n=16) patients. Low levels of LH and FSH were found in 10.4 and 6.3 % of cases respectively; low level of both LH and FSH was found in 2 (4.2%) patients. Patients with low LH/FSH invariably had low testosterone levels. However, the reverse was not true. 10 patients had isolated testosterone deficiency with normal LH/FSH. Low levels of cortisol (< 10 µg/dl) were found in 4 cases (8.3%). Hypothyroidism, as diagnosed by high TSH levels was found in 10 (20.8%) patients. However, of them, 8 (80%) had low fT4 levels and only 1 person had low levels of both fT4 and fT3. Isolated low fT3 was not found. Although borderline low TSH is found in 2 patients, we did not find any evidence of high thyroid hormones, i.e. fT3 or fT4.

Figure 1 shows the glycaemic status of the patients. Overall, 15 (31.2%) of the patients were diagnosed to be diabetic. 7 of them were diagnosed by both FBS and HbA1C criteria. 3 were diagnosed by FBS criteria alone and 5 were diagnosed by HbA1C criteria alone. None of the patients diagnosed to be diabetic were on protease inhibitors. Prediabetic status was found in 8 patients.

There were more than one endocrine dysfunctions in some patients. Of the 15 diabetics, 3 had associated hypothyroidism and 5 (33%) had associated low testosterone levels (Fig. 2).

HbA1c level was inversely related to the CD4 count. The coefficient of correlation with CD4 counts for HbA1c was –0.67 (p=0.04). However, TSH, FT3 and FT4 achieved poor correlation when matched with the CD4 counts (coefficients of correlation, r: 0.14, 0.15 and 0.15 respectively; p value in each case>0.05). The FSH, LH and total testosterone were all found to decrease proportionally with the CD4 counts, attaining correlation coefficients of 0.43 (p=0.07), 0.51 (p=0.32) and 0.39 (p=0.03) respectively. Similar to the thyroid function parameters, serum Cortisol levels achieved poor correlation with CD4 counts, with a correlation coefficient of 0.24 (p=0.15).

DISCUSSION

In our cross sectional observational study in male patients, we found significant levels of hypogonadism, hypothyroidism and diabetes. Presence of more than one endocrine dysfunction in the same patient was also found in some cases. Blood CD4 counts were found to correlate with glycemic status and male sex hormone levels.

In 2011, Meena Et al published a similar study from U.P., India where they found substantial percentage of hypogonadism in male HIV positive cases. The prevalence increased with decreasing CD4 counts[6]. In our study too, we found negative correlation of total testosterone levels with CD4 counts (r=0.39; p=0.03). Another study found evidence of hypogonadism in 45% of their male patients[8]. However, they found hypergonadotropic hypogonadism in many of their patients.In our study, we found mainly hypogonadotropic state.

The exact cause of male hypogonadism in HIV is not known. Decreased gonadotrophin release from the pituitary is one of the mechanisms[9]. It is seen that PLHA with concomitant other infections like hepatitis C are more prone to develop hypogonadism[10]. In our study, none of the patients had any other infection. It must be noted that hypogonadism is often subclinical and if we wait for symptoms like decreased libido to test for sex hormone levels, a large number of patients may be missed[8, 10]. Undernutrition, other illness or use of drugs may also be associated with hypogonadism in PLHA. Treatment is with testosterone replacement and features like emaciation or weakness may respond more with hormone replacement than improvement of sexual function[11].

31.2% of our study subjects came to be diabetic and 21% were found to be hypothyroid. In one study from France, 16% of the HIV positive patients were found to be hypothyroid, although mostly it was subclinical[12]. Also, male HIV positive cases were found to have more prevalence of

hypothyroidism compared tofemales. Low CD4 cell count was a risk factor for presence of hypothyroidism[12]. In our study, we found poor correlation of CD4 count with thyroid hormone levels; but this may be due to small number of patients. The thyroid disorders may be due to infiltrative conditions like lymphoma or infections like pneumocystis jiroveci[5]. Also, sick euthyroid syndrome and isolated deficiency of thyroxin is commonly found in HIV positive patients, which may improve with anti-retroviraltherapy (ART) [5].

Butt et al found no increased prevalence of diabetes in HIV infection itself, but presence of HCV co infection or ART use increased the risk of diabetes[13]. However, another study has found the prevalence of metabolic syndrome to be 14-18% in PLHA[14]. This was more common in protease inhibitor users and the prevalence of type 2 diabetes was also higher in this group[14]. Insulin resistance is the main mechanism in pathophysiology of diabetes in PLHA, but autoimmune destruction of islet cells has also been found[15]. Concurrent drug abuse, like heroin addiction may also contribute to insulin resistance. Presence of associated endocrine problems like growth hormone deficiency may also be a causative factor in insulin resistance in PLHA[15]. In different studies, use of ART like stavudine has been found to be the strongest risk factor in development of diabetes in HIV patients[16]. In our hospital, we generally start with Zidovudine based regimen, unless contraindicated. Of the 15 patients diagnosed to be diabetic in our study, only 2 were on stavudine.

We found low cortisol levels in 4 patients. Hypoadrenalism is a recognised association with advanced HIV infection[17]. However, low cortisol levels should always be evaluated with ACTH stimulation test. We could not do it due to financial reasons. If hypocortisolism is suspected, adrenal infections should be ruled out.

The following table shows the prevalence of endocrine dysfunction in HIV positive patients in different studies from across the world.

Table 3: **Prevalence of endocrine dysfunction in PLHA (in %) {ND—not done}**

Organ affected	Meena et al. India, 2011[6]	Raffi et al. 1991[18]	Present study
Thyroid	40.6	16	20.8
Gonads	33	29	33
Pancreas	ND	ND	31.2
Adrenal gland	2.7	9.1	8.2

CONCLUSION

HIV positive patients should be screened for endocrine disorders. Diabetes and hypogonadism are the main disorders and in resource limited settings, these should be ruled out first, especially in male patients. The decision of hormone replacement should be considered on individual basis.

Thus, besides opportunistic infections and malignancy, HIV induced hormonal disorders are also to be ruledout in daily clinical settings for better patient care.

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