

Endocrinopathies in HIV Infected Patients

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Received

26th April 2020

Received in revised form

15th July 2020

Accepted

11th August 2020

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ABSTRACT

Introduction: Hormonal abnormality is one of many clinical manifestations of HIV infections that is not well understood. However, the consequences could affect quality of life and are potentially treatable. Thus, this study aimed to determine the prevalence and associated factors of thyroid, adrenal and gonadal dysfunctions among HIV-infected patients. **Methods:** This is a single centre cross-sectional study involving 150 HIV-infected patients attending the HIV clinic. Each subject was required to answer specific symptoms questionnaire and their medical records were reviewed for relevant clinical and biochemical data. Blood for was collected and thyroid hormones, cortisol, ACTH, FSH, LH, testosterone and estradiol were analysed using electrochemiluminescent immunoassay. Thyroid, adrenal and gonadal axes abnormalities were identified. **Results:** Hypogonadism had the highest prevalence amongst the endocrine abnormalities, which was detected in 23 patients (15.3%), followed by thyroid dysfunction in 18 patients (12%) and hypocortisolism in 2 patients (1.3%). There was significant correlation between CD4 count, BMI and age with the hormone levels. **Conclusion:** Prevalence of endocrine abnormalities was low in these well-treated HIV-positive patients, with hypogonadism being the most common. However, significant correlations between CD4 count, age and BMI with the hormonal levels were detected. Clinical symptoms in relation to endocrinopathy are not specific as a screening tool thus underscoring the need for biochemical tests to identify these treatable conditions.

KEYWORDS: Hormone abnormalities, hypogonadism, thyroid dysfunction, adrenal dysfunction, HIV-infected patients

INTRODUCTION

Endocrine abnormalities in the form of adrenal, thyroid and gonadal abnormalities have been reported amongst patients with HIV infections in both early and advanced stages of the disease [1]. These abnormalities may manifest as mild biochemical changes or overt glandular failure, resulting in loss of muscle mass, sexual dysfunction, abnormal fat distribution and reduction in quality of life [1]. There are multiple mechanisms that contribute to this hypothalamic-pituitary-hormonal axis dysregulation. Primary endocrine dysfunction refers to direct effect of HIV on the various organs [1]. Secondary endocrine dysfunction occurs due to release of viral protein and

cytokines during viral infection, which progresses to chronic inflammatory state and results in activation or inhibition of the hormonal systems [2]. There are substantial data and epidemiological studies on hormone abnormalities among HIV-infected patients along with associated factors contributing to the endocrinopathies. However, most of these studies had been conducted among the Caucasian populations and there is scarcity of data on the Asian population who are phenotypically different compared to the Caucasians. Furthermore, the varying prevalence in previous reports and conflicting results on associated factors make it difficult to come up with general recommendations regarding interventions with hormone replacements in HIV-infected patients with hormone imbalance.



Although the majority of endocrine disorders reflect chronic infection, stress and mal-infection, some disorders are characteristic of HIV infection or AIDS and deserve particular clinical attention. Identification of HIV-infected patients at risk of frank endocrine disorders, rapid and correct diagnosis, and appropriate management are essential steps to minimize morbidity and mortality. Thus, this study aimed to determine the prevalence and associated factors of hormonal abnormalities in HIV-infected patients

MATERIALS AND METHODS

This is a cross-sectional, observational study conducted at a single tertiary main national referral centre for infectious diseases. Subjects were recruited by convenient sampling (n=150), including patients who were attending the infectious diseases clinic from December 2016 until February 2018. Inclusion criteria included, patients aged between 18 and 65 years, with a confirmed diagnosis of HIV by 2 different tests at 2 different times, and able to give informed consent to participate in the study. Subjects with pre-existing endocrine disorders with or without hormonal therapy, history of taking traditional medications or patients who were on long term steroid therapy were excluded. The patients' medical records were reviewed for relevant data including HIV infection details, co-morbidities and latest CD4 count. Blood samples for estimation of FT4, TSH, cortisol, FSH, LH, testosterone and estradiol were taken between 8 and 11 am to avoid circadian variations. Blood samples were collected in plain tubes, promptly centrifuged and stored at -20° C. For ACTH, blood samples were collected in a refrigerated EDTA tube, after which the samples were placed in a pre-cooled centrifuge and centrifuged to separate the plasma. All hormone levels were estimated using electrochemiluminescent immunoassay on a Roche immunoassay analyser. Normal reference range for the hormonal values were taken as cut off levels from our laboratory reference range. A standardised data collection form was used to collect demographic data, clinical history, diagnosis, and laboratory test results. Other laboratory tests include fasting serum lipid (FSL) and blood sugar (FBS). Patients with significantly abnormal results were subsequently referred to the

Endocrine Clinic for further assessments and treatment. This study was approved by the Research Ethics Committee, Universiti Teknologi MARA- UiTM Shah Alam (ref: REC79/15). The study was also approved by the Medical Research and Ethics Committee (MREC).

Data were analysed using SPSS version 24. The categorical data is expressed in frequency and percentage using a frequency table. The numerical variables are expressed as mean (SD) or median (IQR). For continuous data, the correlation between associated factors (duration of HIV illness, CD4 counts, age, and BMI) and hormone profile (thyroid, adrenal and gonads) was analysed using Spearman correlation. For categorical data, the association between the contributing factors and hormone profiles was analysed using Chi square test. Independent T test was used to analyse both categorical and continuous data. The level of significance was set at $p < 0.05$

RESULTS

The sociodemographic data and baseline characteristics of the subjects are summarized in Table 1. The subjects were predominantly males, with more Chinese males, followed by Malay, Indian and other races. Age, BMI and blood pressure are expressed as mean \pm SD, while duration of illness, CD4 counts are expressed as median. Slightly higher number of subjects had a duration of illness of more than 4 years, with majority of them demonstrating CD4 counts of more than 200 cells/mm³. Biochemical characteristics including testosterone, estradiol, FSH, LH and thyroid function test are summarized in Table 2. Normally distributed hormonal data are presented as mean (SD) whereas those that were not normally distributed are presented a median (IQR).

Hypogonadism had the highest prevalence amongst the endocrine abnormalities, followed by thyroid dysfunction and hypocortisolism (Table 3). Among male patients with hypogonadism, absence of early morning erection accounted for the majority of the reported symptoms (60%), followed by reduction in libido (34%). Non-specific symptoms like lethargy was reported by 6% of the subjects within the group. However, due to the small sample size, these were not statistically significant.

Table 1 Sociodemographic and baseline characteristics

Variable	N (%)	Mean (SD)	Median (IQR)
Age (years)		40.1(10.1)	
Gender			
Male	125 (83.3)		
Female	25 (16.7)		
Ethnicity			
Malay	72 (48.0)		
Chinese	58 (38.7)		
Indian	11 (7.3)		
Others	9 (6.0)		
BMI (kg/m ²)		23.2 (5.2)	
Normal (<23)	74 (48.1)		
Abnormal (≥23)	76 (49.4)		
Systolic BP (mm/Hg)		140.0 (24.4)	
Diastolic BP (mm/Hg)		83.3 (14.2)	
Duration of illness			48 (95)*
<4 years	74 (48.1)		
≥4 years	76 (49.4)		
CD4 counts (cells/mm ³)			462.5 (299)*
<200	17 (11.3)		
≥200	133 (88.7)		

Table 2 Biochemical characteristics

Variable	Mean (SD)	Median (IQR)
Testosterone (male) (nmol/L)	18.6 (7.2)	
Estradiol (female) (pmol/L)		173.7 (304)*
FSH (IU/L)		
Male		8.0 (5.2)*
Female		7.8 (23.6)*
LH (IU/L)		
Male		7.7 (4.6)*
Female		6.8 (18.5)*
FT4 (pmol/L)	14.8 (2.7)	
TSH (mIU/L)		1.43 (1.18)*
Cortisol (nmol/L)	412.8 (173.6)	

*skewed to the right

Table 1 Prevalence of endocrine abnormalities

Variable	N (%)
Hypogonadism	
Yes	23 (15.3)
No	127 (84.7)
Thyroid dysfunction	
Yes	18 (12)
No	132 (88)
Hypocortisolism	
Yes	2 (1.3)
No	48 (98.7)

Thyroid hormone dysfunctions that was observed included hypothyroidism, isolated low FT4, isolated high FT4, subclinical hyperthyroidism and subclinical hypothyroidism. Among these patients, subclinical hyperthyroidism had the highest prevalence, detected in 8 of 18 patients (44.4%) with thyroid dysfunction. The 2 patients with abnormally low early morning cortisol were male subjects with CD4 counts of 204 and 423 cells/mm³.

Univariate analyses were performed to identify statistically significant associations between anthropometric measurements, duration of illness and serological markers with the various hormonal abnormalities and these are summarised in Table 4. There was a significant negative correlation between CD4 counts and cortisol level with no other correlations with the other measured hormones. There was a significant negative correlation between BMI and testosterone level among the males. However, there

were no significant correlations between BMI and estradiol in females or between BMI and the other measured hormones. There was however a significant negative correlation between age and estradiol. Although there was no significant correlation between age and testosterone in male, there was a trend towards declining testosterone level with age. In addition, there was a statistically significant positive correlation between age and FSH level. There was no correlation between age and LH level. There was a significant negative correlation between age and FT4 level, but there was no correlation with TSH level. There were no correlations between duration of illness with any of the hormone levels. Simple linear regressions were conducted among variables with significant univariate analysis results ($p < 0.05$) with the outcome of interest as summarised in Tables 5 to 10. However, multiple linear regression analysis was not done since there was only one significant predictor for each outcome.

Table 4 Correlation between CD4 counts, age, BMI, duration of illness and other hormone level

			FT4	TSH	Cortisol	ACTH	FSH	LH	Testosterone	Estradiol
CD4	Correlation Coefficient (r)	<u>CD4</u> 1.000	.107	.036	-.198*	-.035	-.117	-.062	-.162	.167
	p-value	.	.192	.661	.015	.735	.153	.454	.071	.424
Age	Correlation Coefficient (r)	<u>Age</u> 1.000	-0.250**	0.090	-0.69	-0.124	0.325**	0.212**	0.053	-0.459**
	p-value	.	0.002	0.272	0.401	0.232	0.001	0.009	-0.174	0.021
BMI	Correlation Coefficient (r)	<u>BMI</u> 1.000	.050	.017	-.048	-.020	-.117	-.062	-.344**	.167
	p-value	.	.543	.833	.564	.852	.153	.454	0.001	.424
Duration of illness	Correlation Coefficient (r)	<u>Duration of illness</u> 1.000	0.061	-0.024	-0.084	-0.099	0.004	0.064	0.001	-0.231
	p-value	.	0.456	0.772	0.307	0.341	0.963	0.439	0.989	0.266

Table 5 Simple linear regression analysis between age and estradiol

Variable	b (95% CI)	t statistic	p-value	r ²
Age	-0.259(-159.22, 37.06)	-1.288	0.03	0.067

Table 6 Simple linear regression analysis between age and FSH

Variable	b (95% CI)	t statistic	p-value	r ²
Age	0.573 (1.13, 4.78)	3.356	0.03	0.329

Table 7 Simple linear regression analysis between age and LH

Variable	b (95% CI)	t statistic	p-value	r ²
Age	0.563 (0.58, 2.58)	3.271	0.003	0.317

Table 8 Simple linear regression analysis between BMI and testosterone

Variable	b (95% CI)	t statistic	p-value	r ²
BMI	-0.311(-0.719, -0.21)	-3.623	<0.001	0.096

Table 9 Simple linear regression analysis between CD4 and cortisol

Variable	b (95% CI)	t statistic	p-value	r ²
CD4	-0.191 (-0.246, -0.22)	-2.368	0.019	0.036

Table 10 Simple linear regression analysis between age and FT4

Variable	b (95% CI)	t statistic	p-value	r ²
Age	-0.159 (-0.08, 0.00)	-1.958	0.052	0.025

DISCUSSION

This study showed a relatively low prevalence of endocrine abnormalities, which could possibly be due to the good treatment (HAART) these patients were receiving. There were 99.3% of patients who were on HAART with a mean CD4 count of 462.5 cell/mm³. The overall findings of low prevalence of endocrine abnormalities, and hypogonadism as the main endocrine abnormality, are consistent with several other studies elsewhere, which also found hypogonadism as the most common finding followed by thyroid dysfunction and hypocortisolism [1, 3-5].

There was a negative correlation between CD4 count and cortisol level. The elevated cortisol could be a response to the HIV infection itself (disease burden) or with associated opportunistic infection that the patients might be suffering from [6, 7]. Therefore, when CD4 count improves with treatment, the stress response too decreases with lower cortisol levels. The increase in cortisol level while CD4 count is falling could also be explained by decreased cortisol catabolism caused by an abnormal fatty acid profile and

alterations in the concentrations and binding properties of corticosteroid-binding globulin in HIV-infected patients [8]. There was no significant correlation between CD4 count and ACTH, which suggests stress mechanism is only at the adrenal level. The increased serum cortisol concentration observed in patients with HIV infection, most often without concomitant increase in circulating ACTH, suggests that the adrenal cortex is directly stimulated by other factors [8]. Cytokines, such as interleukin-1 (IL-1) and interferon alpha (IFN α), acting indirectly or directly, could well modulate adrenal steroid production via their influence on the hypothalamic-pituitary-adrenal (HPA) axis. However our findings, which demonstrated no correlation between CD4 count and cortisol, differed from previous studies, possibly due to our smaller sample size [9]. There were no significant correlations between CD4 count and levels of gonadal hormones. This finding is in contrast to the findings in a study by Bajaj et al., (2017), which found that hypogonadism was significantly associated with the age of HIV patients, their CD4 count, and duration of HAART. Duration of

HAART was not recorded in this study. The reason for this discrepancy, though unclear, could perhaps be due to the different study designs, where some had included a non-retroviral arm as control.

Although there was no correlation between age and testosterone, there was a trend towards declining testosterone level with age. Consistent with other studies, the presented data show that the prevalence of testosterone deficiency increases with age (although not statistically significant), as it happens in the general population [10]. Testosterone production by testicular Leydig cells is closely regulated by the hypothalamic–pituitary–gonadal (HPG) axis *via* production of luteinizing hormone (LH). Total serum testosterone levels decrease with age, due to rising sex hormone binding globulin (SHBG) level [11]. In addition, there was a statistically significant positive correlation between age and FSH (not LH), which suggests a response towards normalising testosterone. LH levels can vary in older men based upon decreased numbers and function of Leydig cells, decreased sensitivity of the HPG axis to feedback inhibition, and/or decreased LH pulse amplitude despite normal pulse frequency. Decreased LH pulse amplitude may potentially be related to reductions in neuronal cell secretion of GNRH [11].

There was a significant negative correlation between BMI and testosterone, suggesting that the decline in BMI might lead to a compensatory mechanism for increased secretion by the gonads, rather than at pituitary level. Our results are consistent with studies done by Klein et al. and Gomes et al. [12] showing a negative correlation between BMI and testosterone levels. Serum total testosterone levels decrease with increasing body mass because of declining SHBG level [12]. Gomes et al (2016b) found that 18.1 % of patients with testosterone deficiency presented with visceral obesity (as measured by waist circumference >102 cm), in contrast to 7.5% of eugonadal individuals. The authors' explanation was the increase in tissue sensitivity to glucocorticoids as the underlying pathophysiology. Other underlying mechanisms include reduction of adipokines, and a reduction of peroxisome proliferator-activated receptor (PPAR- γ) activity, which were not included within the scope of the study.

CONCLUSION

Prevalence of endocrine abnormalities are low among these well-treated HIV-infected patients. Hypogonadism had the highest prevalence compared to the other hormonal profiles. Although the prevalence of endocrine abnormalities is generally low, there were nevertheless significant correlations between CD4 counts, age and BMI with the hormone levels. Questionnaires on clinical symptoms relating to the endocrinopathies are not reliable as they are not specific enough to identify the endocrine abnormalities. Therefore, biochemical tests remain as an important screening tool for the treatable hormonal abnormalities among these HIV-infected patients.

Conflict of Interest

Authors declare none

REFERENCES

1. Tripathy SK, Agrawala RK, Baliarsinha AK. Endocrine alterations in HIV-infected patients. *Indian Journal of Endocrinology and Metabolism*. 2015;19(1):143-7.
2. Bhangoo A, Desai N. Endocrinopathies in HIV, AIDS and HAART. *Rev Endocr Metab Disord*. 2013;14(2):101-3.
3. Raffi F BJ, Planchon B, Remi JP, Barrier JH, Grolleau JY. Endocrine function in 98 HIV infected patients: A prospective study. *AIDS*. 1991;5(6):729-33.
4. Mandal SK, Paul R, Bandyopadhyay D, Basu AK, Mandal L. Study on Endocrinological Profile of Hiv Infected Male Patients from Eastern India. *International Research Journal of Pharmacy*. 2013;4(3):220-3.
5. Jain N MM, Dandu H, Verma SP, Gutch M, Tripathi AK. An observational study of endocrine disorders in HIV infected patients from North India. *J HIV Hum Reproductive* 2013;1:20-4.
6. Meena LP RM, Singh SK, Chakravarthy J, Singh A, Goel R, Pathak A, Sundar S. . Endocrine changes in male HIV patients. *Journal of The Association of Physicians of India*. 2011;59:1-3.

7. Uma Sinha NS, Prasanta Mukhopadhyay, and Keshab Sinha Roy. Human immunodeficiency virus endocrinopathy. *Indian J Endocrinol Metab.* 2011;15(4):251-60.
8. Odeniyi IA, Fasanmade OA, Ajala MO, Ohwovoriole AE. CD4 count as a predictor of adrenocortical insufficiency in persons with human immunodeficiency virus infection: How useful? *Indian journal of endocrinology and metabolism.* 2013;17(6):1012.
9. Wen Y, bo Ding H, Chen W, Zhou Y, Wang W, Wang Y, et al. Correlation of baseline hormonal disorders with immunological failure and mortality in male HIV patients during follow-up. *Medicine.* 2016;95(52).
10. Gomes AR, Souteiro P, Silva CG, Sousa-Pinto B, Almeida F, Sarmiento A, et al. Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy. *BMC infectious diseases.* 2016;16(1):628.
11. McBride JA, Carson III CC, Coward RM. Testosterone deficiency in the aging male. *Therapeutic advances in urology.* 2016;8(1):47-60.
12. Klein RS, Lo Y, Santoro N, Dobs AS. Androgen levels in older men who have or who are at risk of acquiring HIV infection. *Clinical infectious diseases.* 2005:1794-803.