

Should Clinician Suspect Hormonal Disturbances at Early Stages of HIV Infection in Males?- A North Indian Study

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ABSTRACT

Despite decades of research, HIV seropositive subjects continue to suffer from myriad complications. Endocrinopathies is one area which has emerged after the advent of HAART for HIV infection. As the life span of these patients has increased and number of HIV positive children is increasing, hormonal imbalances continues to affect patient management. This study was planned to assess whether reproductive hormonal disturbances are present in HAART naive HIV seropositive male subjects attending ART center, PGIMS, Rohtak. A correlation between Hormone levels- Testosterone, Estrogen and Progesterone with CD4+ cell counts was also studied. Fifty three cases were compared with fifty three healthy age matched controls. Cases were segregated into three groups depending upon CD4 cell counts as: Group A-CD4 cell counts $<200/\text{mm}^3$, Group B-CD4 cell counts $200-350/\text{mm}^3$, Group C-CD4 cell counts $>350/\text{mm}^3$. Controls were placed in Group 4. Mean testosterone level was significantly decreased in male cases in all groups than controls. Significant decrease in testosterone levels in males was seen in comparison between Group 1 vs 4, Group 2 vs 4, Group 3 vs 4. Estrogen levels were not decreased non-significantly between cases and controls. 78.9% males in group A and 72.2% in group B had Progesterone levels $<0.28 \text{ ng/ml}$ as compared to 12.5% in group C and 7.5% in controls ($p < 0.001$). Conclusion: reproductive hormones should be assessed in HIV positive males on disease detection for better management.

Keywords: HIV, endocrinopathy, testosterone, estrogen, progesterone, AIDS, hypogonadism

INTRODUCTION

Hypogonadism refers to insufficient secretion of sex steroids by the gonads to maintain normal physiologic function dependent on these hormones, including reproductive function, secondary sexual characteristics, body composition, mood and behavioural actions. Hypogonadism is low testosterone in men and it can lead to a variety of symptoms including fatigue, anemia, depression, loss of libido, impaired

sexual function, and decreased fertility. [1]

Many of these symptoms of androgen deficiency in men are nonspecific and overlap with those of depression or chronic illness. More specific symptoms of hypogonadism, including changes in the pattern of hair growth (loss of pubic or axillary hair), testicular atrophy, decreased libido, and gynecomastia, may not be present. [2] Both testosterone and estrogen protect the bones, and the risk of bone loss

(osteopenia or osteoporosis) increases as levels of these hormones decrease. [3]

AIMS AND OBJECTIVES

- To measure the Testosterone, Estrogen and Progesterone levels in 53 HAART naïve HIV seropositive males and 53 age matched controls
- To find any correlation between these hormone levels with CD4 cell counts.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the Department of Biochemistry in association with Department of Microbiology; Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak.

We enrolled fifty three HAART naïve HIV seropositive male patients visiting integrated counselling and testing center (ICTC) for diagnosis of HIV infection and those attending ART center for CD4 monitoring. Fifty three age matched healthy male controls were taken. Written informed consent was obtained from all participants after explaining nature of study and procedures. Cases and controls underwent physical examination according to patient's proforma along with relevant history. Three serological rapid tests were used to diagnose a person as HIV seropositive. Flow cytometry was deployed for CD4+ cell counts and Chemiluminescence on ADVIA Centaur CP for hormone estimation. Cases were segregated into three groups depending upon CD4 cell counts as: Group A-CD4 cell counts < 200/mm³, Group B-CD4 cell counts 200-350/mm³, Group C-CD4 cell counts > 350/mm³. Controls were placed in Group 4.

Age group of 15 to 45 years was chosen for study to minimize the effect of physiological andropause. Patients on HAART, drugs affecting hypothalamo-pituitary-gonadal axis and steroids were excluded. Those with any recent opportunistic infection within 4 weeks,

significant liver disease and chronic infection like DM, asthma and chronic renal failure were rejected.

SAMPLE COLLECTION AND STORAGE

Fasting early morning venous blood sample was taken in a plain red capped evacuated blood collection tube under all aseptic precautions for routine investigations and hormones including Estrogen, Progesterone and Testosterone. Samples were processed within one hour of collection. Serum was separated by centrifugation at 2000 rpm X 10 minutes after clotting. Separated serum was stored at -20⁰C (maximum 3 months) for evaluating hormone levels.

Estrogen reference range

males: ND* – 52 pg/mL (ND* – 191 pmol/L)

Progesterone reference range

males: 0.28 – 1.22ng/mL (0.89 – 3.88nmol/L)

* ND: not detectable

Testosterone Reference Interval

males: 241 – 827ng/dL (8.4 – 28.7nmol/L)

RESULTS

Mean age was 32 ± 7 years in males with a range between 17-45 years. 35.8% Males were asymptomatic and 64% had weight loss. BMI in Group A was 18.63 ± 3.46, Group B was 19.32 ± 2.50, Group C was 22.57 ± 1.61 and Controls was 22.57 ± 1.61. TG and VLDL were significantly raised in both male and female cases. Cholesterol was significantly decreased in males. HDL and LDL was also decreased significantly in males. Glucose was increased significantly in males. Mean testosterone level was significantly decreased in male cases in all groups than controls. (Figure 1) Significant decrease in testosterone levels in males was seen in comparison between Group 1 vs 4, Group 2 vs 4, Group 3 vs 4. Estrogen levels were not decreased non-significantly between cases and controls. (Figure 2) 78.9% males in group A and 72.2% in group B had Progesterone levels <0.28 ng/ml as

compared to 12.5% in group C and 7.5% in controls ($p < 0.001$). (Figure 3) Significant Correlation was seen between BMI and CD4, CD4 and testosterone, and BMI and Estrogen.

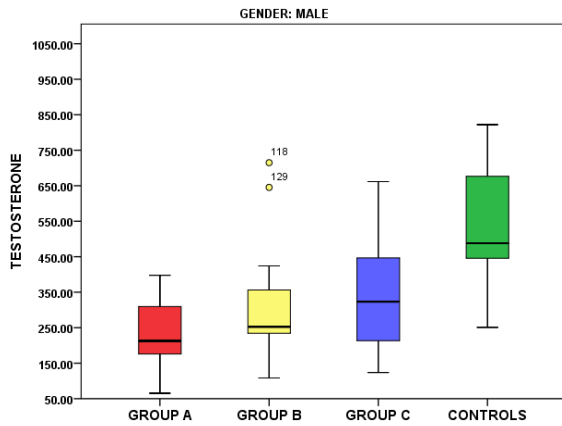


Figure 1: Testosterone levels in cases and controls

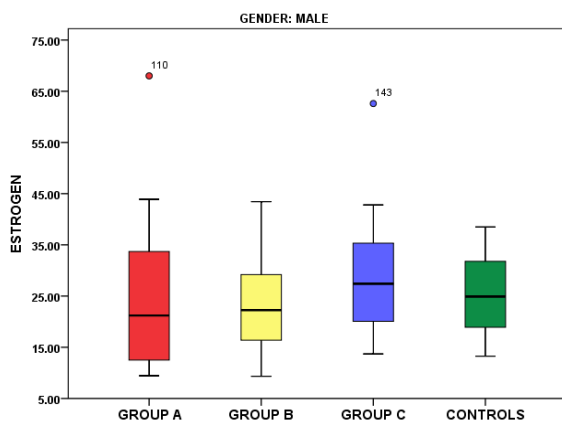


Figure 2: Estrogen levels in male cases and controls

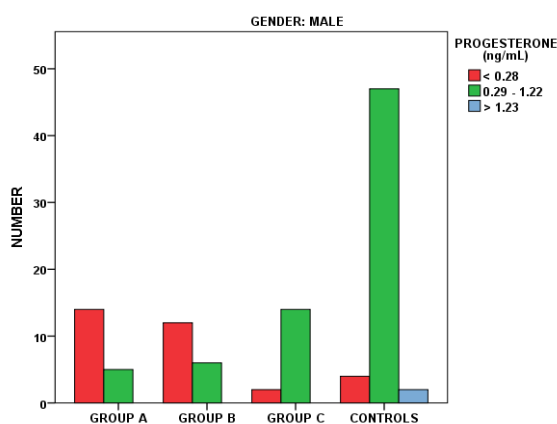


Figure 3: Progesterone levels in male cases and controls

DISCUSSION

This cross-sectional study was conducted in HIV seropositive males to assess reproductive hormone levels and correlate these levels with CD4+ cell counts.

Body Mass Index:

BMI in cases was significantly lower than controls in both males and females. Group A had significantly lower BMI than controls ($p < 0.001$). This is in agreement with previous studies which have shown wasting to be highly prevalent (34%). Weight loss is a significant predictor of mortality in HIV infection. Body mass index (BMI) of less than 18.4 kg/m^2 shows 2.2-fold increased mortality and BMI less than 16 kg/m^2 shows associated 4.4-fold increased mortality in HIV-infected patients. Currently, AIDS wasting syndrome is defined as weight less than 90% of ideal weight or weight loss of more than 10% of body weight over 3 months. A disproportionate loss of lean body mass with relative sparing of body fat with disease progression in both sexes characterizes the condition. Other important features include muscle wasting, weakness, increased resting energy expenditure and hypertriglyceridemia. Cytokine related increased energy expenditure and decreased appetite, malabsorption and hypogonadism remain central to the potential mechanisms behind such wasting. [4] In our study correlation was found between BMI and CD4 cell counts. Mean BMI was 17.71 ± 1.71 in group A, 18.11 ± 2.22 in group B, 19.71 ± 2.84 in group C and 22.45 ± 1.70 in controls. BMI also correlated with estrogen in both male and female cases. In contrast Jain et al found no correlation between BMI and endocrine function. [5]

Lipids

Triglycerides were significantly raised in cases than controls in both females and males. Cholesterol and HDL-C was significantly decreased in male cases. Previous studies have also shown that lipid metabolism is characterized by increased triglyceride and decreased cholesterol and

high-density lipoprotein levels in patients with AIDS. Hypertriglyceridemia appears to be independent of the degree of wasting. The mechanism of elevated triglyceride level relates to decreased lipoprotein lipase activity and decreased hepatic clearance of triglyceride. Increased triglyceride levels correlate with serum interferon levels. Females in our study had comparatively higher cholesterol at low CD4 cell counts but HDL was decreased similarly to males. HDL was similar in all groups in female cases. [6]

Testosterone levels in males:

The prevalence of Hypogonadism among HIV-infected men in the present study is 39.6%, [p value<0.001]. Sunchatawirul et al found rate of hypogonadism in 25% cases. [7] This rate of hypogonadism in the HAART era is lower than the rates in the previous studies conducted in the pre-HAART era by Dobs et al (50%) and Grinspoon et al (49%). [8,9] The former mentioned study diagnosed hypogonadism by determining total testosterone levels have underestimated the prevalence of hypogonadism but Grinspoon et al used free testosterone levels which were recommended according to increased SHBG levels in HIV-infected patients. The prevalence of hypogonadism in the present study is higher than the findings of other studies in the HAART era, including studies by Berger et al. (17%), Fisher et al. (20%), and Rochira et al (16%). [10] Hypogonadism remains a significant problem even among the patients in the early stages of HIV infection, particularly when the prevalence is still higher than the average rate for the general population. Previous studies have indicated that the prevalence of hypogonadism in HIV-infected men was higher than that of the general population at the same age. These findings propose that serum testosterone might begin to decrease at an early age in HIV-infected men. [11] In the general population, the most widely accepted parameter to establish the presence of hypogonadism is the measurement of serum total testosterone (TT). But serum TT

level does not correlate well with diagnosis of hypogonadism in HIV-infected men. This is because of high SHBG levels in HIV patients. [10]

CD4 and Testosterone

An association was seen between CD4 cell counts and testosterone in our study. Mean testosterone level in group A was 233.69±100.89 ng/dl, group B was 296.45±165.04 ng/dl, group C was 335.83±156.92 ng/dl and 534.97±152.54 in controls. There was no association between CDC clinical category, CD4 cell count or HIV-related illness and hypogonadism. This result is similar to the other studies in the HAART era. [10]

Estrogen levels in males

Mean of estrogen levels in group A was 25.06±15.65 pg/mL, group B was 23.94±9.58 pg/mL, 28.89±12.14 pg/mL in group C and 25.04±7.15 pg/mL in controls. Rochira et al reported that Serum estradiol was significantly higher in HIV-infected men with eugonadism and compensated hypogonadism compared with men with secondary or primary hypogonadism, but the E2/T ratio was significantly higher in men with secondary hypogonadism than in subjects with eugonadism and compensated hypogonadism. [10]

Similarly rise in estrogen levels in HIV cases was also reported by Ezeugwunne et al. [12]

Teichmann et al evaluated the pituitary and testicular endocrine markers in 14 HIV-positive men in a longitudinal study with a follow up to of 18 months period. Testosterone levels were normal with a slight reduction at the end of the 18-months observation period (p <0.05). Both estrone and estradiol were significantly increased with a further rise at the end of the study (p <0.05). They suggested that the elevation of the serum estrone and estradiol in HIV-afflicted patients correlates with the progress of the HIV-disease, being paralleled by a decrease in testosterone. [11] An interesting finding in our study was that estrogen in males correlated with the BMI.

Lower estrogen levels were seen at lower BMI.

Progesterone levels in males

In our study we found progesterone levels were decreased in male cases than in controls. 78.9% cases in group A, 72.2% cases in group B, 12.5% cases in group C and 7.5% controls had progesterone level less than 0.28 ng/ml. Similarly percentage of cases with progesterone level between 0.29 to 1.22 ng/mL decreased from 87.5% in group C, 27.8% in group B to 21.05% in group A. This is in contrast to study of Lortholary et al and Ezeugwunne who reported significant increased progesterone levels in cases than controls. ^[13]

CONCLUSION

Endocrinal disturbances appear in early stages in HIV seropositive patients so reproductive hormones should be monitored periodically for better management of patients. Early detection of hormonal perturbations may prevent many complications.

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