HYPOGONADISM AMONG HIV INFECTED MALES AND ITS CORRELATION WITH CD4 COUNT

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ABSTRACT

BACKGROUND
After introduction of Highly Active Anti-Retroviral Therapy (HAART), the prevalence of hypogonadism among Human Immunodeficiency Virus (HIV) infected males is decreasing.

MATERIALS AND METHODS
Cross-sectional study was undertaken at ART centre of a medical Institute. The study recruited HIV infected males aged 18 to 65 years receiving ART. Patients with any debilitating chronic illness, diabetes mellitus, chronic smokers or alcoholic, currently on opioids or methadone were excluded. Androgen deficiency in aging male (ADAM) questionnaire was used to screen patients for possible presence of hypogonadism. Patients underwent biochemical evaluation for serum total testosterone (TT), luteinising hormone (LH) and CD4 count. Chi-squared test was used to compare different parameters. Pearson's correlation coefficient was used to assess any relationship between CD4 count, LH and testosterone. A p-value of <0.05 was considered statistically significant.

RESULTS
In the study 120 patients were evaluated. The mean age of the patients was 41.61 years. The mean BMI of the patients was 22.47 kg/m2. The mean duration of ART was 6.13 years and mean CD4 count was 442.63 cells/mm3. Hypogonadism was seen in 20 (23.3%) and majority (85.7%) had secondary hypogonadism. There was significant association between hypogonadism and CD4 count but no association was found with body mass index (BMI) and duration of ART.

CONCLUSION
Hypogonadism is seen in 23.3% of HIV infected males. Majority (85.7%) had secondary hypogonadism. There was significant association of hypogonadism with lower CD4 count.

KEYWORDS
CD4 Count, HIV, Testosterone.

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BACKGROUND
A wide spectrum of endocrine abnormalities is seen in HIV patients.[1-3] In older studies 29-50% of the men with HIV infection had low total testosterone.[4-7] But after the introduction of HAART more recent studies have reported a lower prevalence of around 9 to16%.[8-11] Studies from India have reported prevalence ranging from 13.3% to 33%.[12-14] But with a small sample Tripathy et al., reported a prevalence of 89.7%.[15] All the prevalence reported are much

higher than 6% in the age group of 40-69 years from Massachusetts Male Aging Study.[16] As men live longer and are generally healthier than they were before the introduction of ART, the role testosterone plays in sexual function as well as in general well-being is becoming increasingly important.[17] There are no such data from North-East India on the prevalence of hypogonadism among HIV infected males. So the present study was planned to estimate the prevalence of hypogonadism in HIV male patients and to determine the correlation between hypogonadism and CD4 count.

Aims and Objectives
- To estimate the prevalence of hypogonadism among HIV infected males and
- To determine the correlation between hypogonadism and CD4 count.

MATERIALS AND METHODS

This cross-sectional study was undertaken in a Centre of Excellence, ART, under National AIDS Control Organization, Government of India attached to Department of General Medicine of a teaching institute. Ethical clearance was obtained from the institutional ethics committee. Informed consent was obtained from all participants. The study recruited HIV infected males aged 18 to 65 years receiving ART. We excluded patients with any debilitating chronic illness, chronic smokers or alcoholic, currently on opioids or methadone. HIV infected patients with diabetes mellitus, co-infected with hepatitis B and C were also excluded.

Each enrolled patient underwent through a thorough clinical evaluation. ADAM questionnaire was used to screen patients for possible presence of hypogonadism.[18] They also underwent venepuncture in the morning between 8 to 10 am. All blood samples collected in a sterile plain vial and stored at -20 degree Celsius until analysed. Serum total testosterone and LH was assayed using immuno-chemiluminescence automated analyser (Vitros Microwell ECIQ assay, Ortho-Clinical Diagnostic, Bridgend, United Kingdom). CD4 cell count was estimated by using automated analyser, Fluorescence Activated Cell Sorter (FACS) manufactured by BD Biosciences, 2350, Qume Drive, San Jose, CA 95131-1807, USA. The reference range of total testosterone was 132-813 ng/dl and normal range of LH was 1.4-8.9 ng/dl. Hypogonadism was diagnosed using the Endocrine Society practice guideline cut-off of ≤300 ng/dl.[19] BMI of the patients was categorized using WHO Asian classification.[20]

Data collected was checked for completeness and consistency. Data was analysed using SPSS Statistics 21 for Windows, IBM Corp. 1995, USA 2012. Data were summarized using frequencies, percentage, mean and standard deviation. Chi-squared test was used to compare different parameters among HIV infected patients with and without hypogonadism. Pearson's correlation coefficient was used to assess any relationship between CD4 count, LH and testosterone. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 120 HIV male patients screened for adult onset hypogonadism using ADAM questionnaire and hormonal evaluation of TT and LH. The age of the patients ranged from 22 years to 64 years with a mean of 41.61 ± 9.14 years. The BMI of the patients ranged from 17 kg/m^2 to 31kg/m^2 with mean of 22.47 kg/m^2. Most of the patients had normal BMI (n= 59). Duration of ART ranged from 1 to 20 years. The mean duration of ART was 6.13 ±3.81 years. Maximum (56.6%) patients had been on ART for less than 5 years. The mean CD4 count was 442.63±276.97 cells/mm^3. The mean total testosterone level was 432.73 ±207.169 ng/dL and hypogonadism was seen in 20 (23.3%) of those who underwent biochemical screening for total testosterone. The prevalence of hypogonadism according to age groups is shown in figure 1. Even patients below the age of 45 years were affected with a prevalence of 25.3%.

There was significant correlation between TT and CD4 count but no correlation was found between TT and BMI and Duration of ART. (Table 1, 2, 3)

BMI (kg/m2)	Testosterone Level N (%)		p Value
	≤300 ng/dl	>300 ng/dl	
Underweight (<18.5)	1	10	
Normal (18.5-22.9)	16	41	0.550
Overweight (23-24.9)	6	23	
Obese (>30)	5	18	
Table 1. Association between BMI and Hypogonadism			

BMI- body mass index.

Duration of ART (Years)	Testosterone Level		P Value
	≤300 ng/dl	>300 ng/dl	
≤5	16	52	
6-10	7	30	0.312
11-15	5	7	
16-20	0	3	
Table 2. Association between duration of ART with hypogonadism			

ART – anti-retroviral therapy.

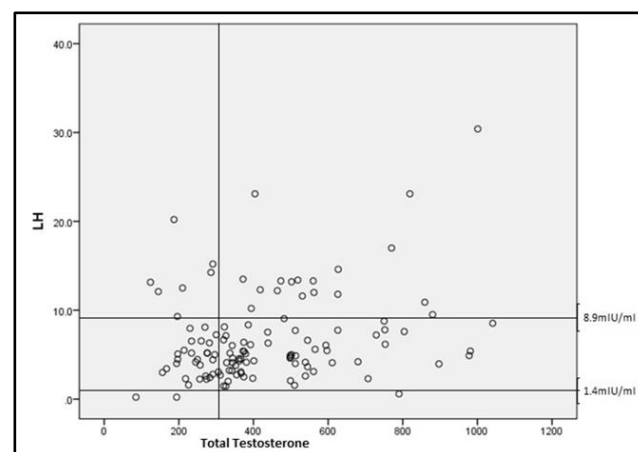| CD4 Count (cells/mm)	Testosterone Level n(%)		P Value
	≤300 ng/dl	>300 ng/dl	
≤250	13 (38.2)	21(61.8)	
251-350	6(30)	14(70)	0.037
351-500	4(17.4)	19(82.6)	
>500	5(11.6)	38(88.4)	
Table 3. Association between CD4 Count and Hypogonadism			

Figure 1. Showing the Correlation between LH and Total Testosterone Level among HIV Infected Males
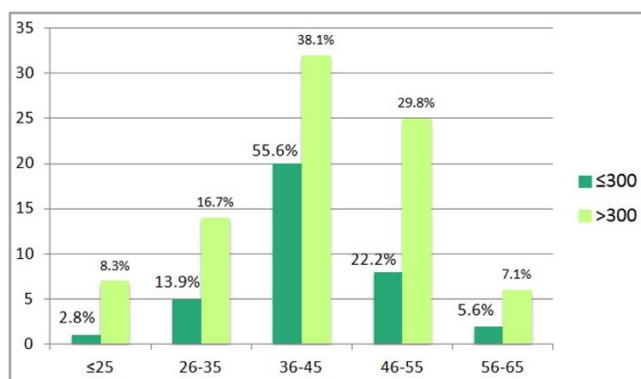
Figure 2. Showing the Prevalence of Hypogonadism (Testosterone ≤300ng/dL) among the Different Age Groups of HIV Infected Males

Test of strength of linear dependence of CD4 count with TT and LH levels was done using Pearson's correlation coefficient. For all the hormone the coefficient of correlation (r) was nearer to zero (r= -0.042, -0.145 respectively) and P value for each hormone >0.05. This indicates that there was negligible or no correlation between CD4 count and serum hormone level.

Among those with low testosterone majority (85.7%) had either low or inappropriately normal LH suggesting secondary hypogonadism as shown in figure 2.

DISCUSSION
In the present study 120 HIV male patients were screened for adult onset hypogonadism using ADAM questionnaire and hormonal evaluation for TT and LH. Hypogonadism was seen in 23.3% of patients. This finding is comparable with those of other studies in the HAART era reporting prevalence ranging from 16% to 33%.[9,12,13,21,22,23,24] Meena et al., reported a prevalence of 33.3% using a testosterone cut-off of 200ng/dl so their prevalence would be much higher the current cut-off of 300ng/dl.[12] During the pre-ART era, studies have shown high prevalence of hypogonadism approximately 50% with AIDS which is associated with increased severity of the disease.[5] Recent study published from India showed a prevalence of 13.3% among 45 patients on HAART.[14] Our study is limited to the fact that total testosterone was used to diagnose hypogonadism which can give a falsely lower prevalence. In the Multicenter AIDS Cohort Study (MACS), reliance on total testosterone missed 33% of patients with hypogonadism.[11] In another study, Mureno-Perez et al., reported that total testosterone has a poor sensitivity of 25% to diagnose hypogonadism among HIV-infected patients.[8] This is because sex hormone binding globulin (SHBG) levels are increased with HIV infection.[21,25]

In our study, the prevalence of hypogonadism was 25.3% among patients below 45 years. In a large Italian cohort highest rate of hypogonadism was seen in men aged 40-49 and 50-59. Remarkably, 10.6% of patients in the age group 30-39 years also had hypogonadism.[9]

Among those patients with hypogonadism, secondary hypogonadism was much more frequent than primary hypogonadism. Crum-Cianflone et al., demonstrated that all patients with low testosterone had secondary hypogonadism.[22] In the Swiss HIV cohort low or inappropriately gonadotropin level was seen in 91% of patients during initiation of HAART.[26] Similarly in the study Arver et al., 81% of hypogonadal patients with HIV infection were hypogonadotropic.[24] Finding similar to our study is reported by several authors.[6,9,12-15]

As secondary hypogonadism is most common among the patients, a primary impairment of pituitary gonadotropin secretion could be postulated. The virus itself and the HAART medications could be implicated in the suppression of the hypothalamic-pituitary-gonadal axis. Secondary hypogonadism might be due a decrease in gonadotropin secretion during severe illness and involvement of hypothalamic or pituitary tissue by opportunistic infections or malignancies.[27]

Primary gonadal failure may be due to opportunistic infections such as Cytomegalo virus, Mycobacterium avium complex, Cryptococcus neoformans or infiltration by a neoplasm like Kaposi's sarcoma.[28,29] Cytokines such as IL1 and tumor necrosis factor (TNF) may decrease leydig cell steroidogenesis.[30]

Association with BMI
BMI was negatively correlated with testosterone although statistically not significant. Crum- Cianflone et al., demonstrated a higher body mass index (BMI) were positively associated with hypogonadism.[22] In studies done by Meena et al.,[12] and Jain et al.,[31] the incidence of low testosterone was directly correlated with the body mass index. This may be because of the differences in BMI in the studies. In our study most of the patients had normal BMI whereas in theirs, majority of them were underweight patients. The higher BMI recorded in our study could be due to regional variations and also the fact that patients with debilitating chronic diseases/unstable patients were excluded from the study. Klein et al, also did not find any significant association between low androgen level with BMI.[32] Some other studies did not find any correlation with weight.[6,21]

Association with CD4 Count
There was no significant correlation between CD4 count and testosterone level. Klein et al., did not find any significant association between low androgen level with CD4 count among older males 49-81 years old.[32] Other studies also did not found any correlation between hypogonadism and CD4 count.[6,15,21] However studies by Meena et al.,[12] and Mandal et al.,[13] found a negative correlation of total testosterone with CD4 count.

Association with duration of ART
Our study did not show any significant relationship between the duration of ART of the patients and gonadal dysfunctions which is consistent with a study by Jain et al.[31] Rietschel et al.,[21] Klein et al.,[32] and also did not find any significant association between low androgen level with ART. But these findings cannot be assured as we did not compare the level

of testosterone before the initiation of ART and while on ART. We recommend that a long follow-up to be done. Impotency and low levels of testosterone observed in HIV infected patients may be related to the progression of the HIV infection or maybe the result of compound effect of debilitating illnesses and secondary infections along with psychological effects.

Implication of Hypogonadism

Wunder et al reported that there is no or little improvement of hypogonadism before and after ART. But testosterone replacement among hypogonadal HIV patients increase fat-free mass.[24] Grinspoon et al demonstrated an increased depression score in association with hypogonadism in men with AIDS wasting, independent of weight, virologic status, and other disease factors. Administration of testosterone results in a significant improvement in depression inventory score.[33] Sexual function and depression scores improved and antidepressant medication use decreased with testosterone therapy. Body composition profiles remained stable in men with HIV/AIDS during 12 months of follow-up.[34]

CONCLUSION

In this study, almost one fourth (23.3%) of the patients on ART was found to have hypogonadism, with 25.3% of patients below 45 years affected. Among those patients with hypogonadism, around 86% had inappropriately normal or low LH suggestive of secondary hypogonadism. As secondary hypogonadism is most common among the patients, hypothalamic-pituitary axis should be regarded as the main element involved in the development of hypogonadism in HIV patients. There was negligible or no correlation between serum testosterone with BMI, CD4 count and duration of ART.

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