Original Article

A study on hypogonadism in male HIV patients in northeastern part of India

Nungsangla Pongener, Ranabir Salam, Robinson Ningshen, Vizovonuo Visi, Tamphasana Wairokpam, L. Shaini Devi[1]

Departments of General Medicine and [1]Biochemistry, Regional Institute of Medical Sciences, Imphal, Manipur, India

Address for correspondence:

Dr. Robinson Ningshen, Department of General Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India.

E-mail: dr.ningshen@yahoo.com

Abstract

Context: After the introduction of highly active antiretroviral therapy (ART), the prevalence of hypogonadism among human immunodeficiency virus (HIV)-infected males is decreasing. **Aims:** The aim of this study was (i) to estimate the prevalence of hypogonadism among HIV-infected males and (ii) to determine the risk factors for hypogonadism. **Settings and Design:** This was a cross-sectional study undertaken at ART center of a medical Institute. **Subjects and Methods:** The study recruited HIV-infected males aged 18–65 years receiving ART. Patients with any debilitating chronic illness, diabetes mellitus, chronic smokers or alcoholic, currently on opioids, or methadone were excluded from the study. Androgen Deficiency in Aging Male (ADAM) questionnaire was used to screen patients for the possible presence of hypogonadism. For those screened positive on ADAM questionnaire underwent biochemical evaluation for serum total testosterone, luteinizing hormone (LH), and CD4 count. **Statistical Analysis Used:** The Chi-square test was used to compare different parameters. Pearson's correlation coefficient was used to assess any relationship between CD4 count, LH, and testosterone. $P < 0.05$ was considered statistically significant. **Results:** In the study, 426 were initially screened and 120 patients who had probable hypogonadism were further evaluated. The mean age of the patients was 41.61 years. The mean body mass index (BMI) of the patients was 22.47 kg/m^2. The mean duration of ART was 6.13 years and the mean CD4 count was 442.63 cells/mm^3. 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 BMI and duration of ART. **Conclusions:** 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.

Key words: CD4 count, human immunodeficiency virus, testosterone

INTRODUCTION

A wide spectrum of endocrine abnormalities is seen in human immunodeficiency virus (HIV) patients.[1-3] In older studies, 29%–50% of the men with HIV infection had low total testosterone (TT).[4-7] However, after the introduction of highly active antiretroviral therapy (HAART), more recent studies have reported a lower prevalence of around 9%–16%.[8-11] Studies from India have reported the prevalence ranging from 13.3% to 33%.[12-14] However, with a small sample, Tripathy *et al.* reported a prevalence of 89.7%.[15] All these prevalence reported are much higher than 6% in the age group of 40–69 years

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from the Massachusetts Male Aging Study.[16] As men live longer and are generally healthier than they were before the introduction of ART, the role of testosterone plays in sexual function as well as in general well-being is becoming increasingly important.[17] There are no such data from Northeast India on the prevalence of hypogonadism among HIV-infected males. Hence, the present study was planned to estimate the prevalence of hypogonadism in HIV male patients and its determinants.

The study was conducted with the aim as follows:

i. To estimate the prevalence of hypogonadism among HIV-infected males and
ii. To determine the risk factors for hypogonadism.

SUBJECTS AND METHODS

This cross-sectional study was undertaken in a Centre of Excellence, ART, under the National AIDS Control Organization, Government of India, attached to the Department of General Medicine of a teaching institute. Ethical clearance was obtained from the Institutional Ethics Committee. Informed consent was obtained from all the participants. The study recruited HIV-infected males aged 18–65 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, coinfected with hepatitis B and C were also excluded from the study.

Each enrolled patients underwent through a thorough clinical evaluation. Androgen Deficiency in Aging Male (ADAM) questionnaire was used to screen patients for the possible presence of hypogonadism.[18] For those screened positive on ADAM questionnaire underwent venipuncture in the morning between 8 and 10 am. All blood samples collected in a sterile plain vial and stored at −20°C until analyzed. Serum TT and luteinizing hormone (LH) were assayed using immunochemiluminescence automated analyzer (Vitros Microwell ECIQ assay, Ortho-Clinical Diagnostic, Bridgend, United Kingdom). CD4 cell count was estimated using automated analyzer and fluorescence-activated cell sorter manufactured by BD BioSciences, 2350, Qume Drive, San Jose, CA 95131-1807, USA. The reference range of TT 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 cutoff of ≤300 ng/dl.[19] Body mass index (BMI) of the patients was categorized using the WHO Asian classification.[20]

Data collected were checked for completeness and consistency. Data were analyzed using SPSS Statistics 21 for Windows, IBM Corp. 1995, USA 2012. Data were summarized using frequencies, percentage, mean, and standard deviation. Chi-square 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. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 426 HIV male patients screened for adult-onset hypogonadism using the ADAM questionnaire, out of which 120 patients who had probable hypogonadism were further evaluated. The age of the patients ranged from 22 years to 64 years with the mean of 41.61 ± 9.14 years. The BMI of the patients ranged from 17 to 31 kg/m^2 with the 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 <5 years. The mean CD4 count was 442.63 ± 276.97 cells/mm^3. The mean TT level was 432.73 ± 207.169 ng/dL, and hypogonadism was seen in 20 (23.3%) of those who underwent biochemical screening for TT. The prevalence of hypogonadism according to the 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 association between TT and CD4 count, but no association was found between TT and BMI and duration of ART [Tables 1-3].

Test of strength of linear dependence of CD4 count with TT and LH levels was done using the Pearson's correlation coefficient. For all the hormones, the

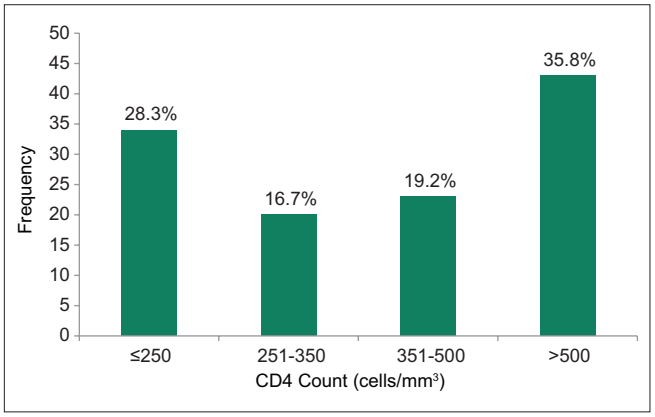

Figure 1: Distribution of patients by CD4 count

Table 1: Association between body mass index and hypogonadism

BMI, kg/m²	Testosterone level, *n* (%)		*P*
	≤300 ng/dl	>300 ng/dl	
Underweight (<18.5)	1	10	0.550
Normal (18.5-22.9)	16	41	
Overweight (23-24.9)	6	23	
Obese (>30)	5	18	

BMI=Body mass index

Table 2: Association between duration of antiretroviral therapy with hypogonadism

Duration of ART (years)	Testosterone level		*P*
	≤300 ng/dl	>300 ng/dl	
≤5	16	52	0.312
6-10	7	30	
11-15	5	7	
16-20	0	3	

ART=Antiretroviral therapy

Table 3: Association between CD4 count and hypogonadism

CD4 count (cells/mm³)	Testosterone level, *n* (%)		*P*
	≤300 ng/dl	>300 ng/dl	
≤250z	13 (38.2)	21 (61.8)	0.037
251-50	6 (30)	14 (70)	
351-500	4 (17.4)	19 (82.6)	
>500	5 (11.6)	38 (88.4)	

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, 426 HIV male patients were screened for adult-onset hypogonadism using the ADAM questionnaire, out of which 120 patients who had probable hypogonadism were further evaluated. Hypogonadism was seen in 23.3% of the 120 who underwent biochemical evaluation. This finding is comparable with those of other studies in the HAART era reporting the prevalence ranging from 16% to 33%.[9,12,13,21-24] Meena *et al.* reported a prevalence of 33.3% using a testosterone cutoff of 200 ng/dl; hence, their prevalence would be much higher the current cutoff of 300 ng/dl.[12] During the pre-ART era, studies have shown high prevalence of hypogonadism approximately 50% with AIDS

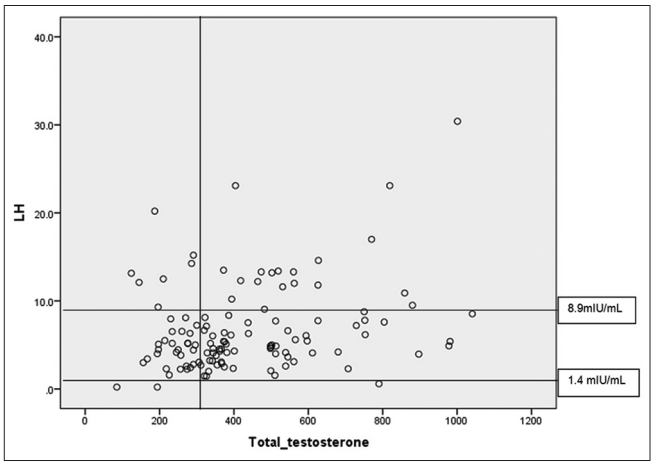

Figure 2: Gonadal status according to serum total testosterone threshold of 300ng/dL and LH normal range

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 TT was used to diagnose hypogonadism which can give a falsely lower prevalence. In the Multicenter AIDS Cohort Study, reliance on TT missed 33% of patients with hypogonadism.[11] In another study, Moreno-Pérez *et al.* reported that TT has a poor sensitivity of 25% to diagnose hypogonadism among HIV-infected patients.[8] This is because sex hormone-binding globulin levels are increased with HIV infection.[21,25]

In this 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 years. 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 the initiation of HAART.[26] Similarly, in the study by 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 the 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 to 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 *Cytomegalovirus*, *Mycobacterium avium* complex, *Cryptococcus neoformans*, or infiltration by a neoplasm-like Kaposi's sarcoma.[28,29] Cytokines such as interleukin 1 and tumor necrosis factor may decrease Leydig cell steroidogenesis.[30]

Association of hypogonadism with body mass index

BMI was negatively correlated with testosterone, although statistically not significant. Crum-Cianflone *et al.* demonstrated a higher 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 BMI. 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 of hypogonadism 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 TT with CD4 count.

Association of hypogonadism with duration of antiretroviral therapy

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] and Klein *et al.*,[32] and also did not find any significant association between low androgen level with ART. However, 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 the 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. However, testosterone replacement among hypogonadal HIV patients increases fat-free mass.[26]

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]

CONCLUSIONS

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 hypogonadism, around 86% had inappropriately normal or low LH suggestive of secondary hypogonadism. As secondary hypogonadism is the 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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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Grinspoon SK, Bilezikian JP. HIV disease and the endocrine system. N Engl J Med 1992;327:1360-5.
2. Aron DC. Endocrine complications of the acquired immunodeficiency syndrome. Arch Intern Med 1989;149:330-3.
3. Marks JB. Endocrine manifestations of human immunodeficiency

virus (HIV) infection. Am J Med Sci 1991;302:110-7.
4. Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. Am J Med 1988;84:611-6.
5. Raffi F, Brisseau JM, Planchon B, Rémi JP, Barrier JH, Grolleau JY, *et al.* Endocrine function in 98 HIV-infected patients: A prospective study. AIDS 1991;5:729-33.
6. Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard J, Katznelson L, *et al.* Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 1996;81:4051-8.
7. Schürmeyer TH, Müller V, von zur Mühlen A, Schmidt RE. Endocrine testicular function in HIV-infected outpatients. Eur J Med Res 1997;2:275-81.
8. Moreno-Pérez O, Escoín C, Serna-Candel C, Portilla J, Boix V, Alfayate R, *et al.* The determination of total testosterone and free testosterone (RIA) are not applicable to the evaluation of gonadal function in HIV-infected males. J Sex Med 2010;7:2873-83.
9. Rochira V, Zirilli L, Orlando G, Santi D, Brigante G, Diazzi C, *et al.* Premature decline of serum total testosterone in HIV-infected men in the HAART-era. PLoS One 2011;6:e28512.
10. Pérez I, Moreno T, Navarro F, Santos J, Palacios R. Prevalence and factors associated with erectile dysfunction in a cohort of HIV-infected patients. Int J STD AIDS 2013;24:712-5.
11. Monroe AK, Dobs AS, Palella FJ, Kingsley LA, Witt MD, Brown TT, *et al.* Morning free and total testosterone in HIV-infected men: Implications for the assessment of hypogonadism. AIDS Res Ther 2014;11:6.
12. Meena LP, Rai M, Singh SK, Chakravarty J, Singh A, Goel R, *et al.* Endocrine changes in male HIV patients. J Assoc Physicians India 2011;59:365-6, 371.
13. Mandal SK, Paul R, Bandyopadhyay D, Basu AK, Mandal L. Study on endocrinological profile of HIV infected male patients from Eastern India. Int Res J Pharm 2013;4:220-3.
14. Pathak A, Lalit P, Chakravarty J, Rai M, Sundar S. A pilot study to evaluate the effect of HAART on gonadal dysfunction in male HIV patients. Natl J Physiol Pharm Pharmacol 2015;5:33-5.
15. Tripathy SK, Agrawala RK, Baliarsinha AK. Endocrine alterations in HIV-infected patients. Indian J Endocrinol Metab 2015;19:143-7.
16. Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, *et al.* Prevalence and incidence of androgen deficiency in middle-aged and older men: Estimates from the Massachusetts male aging study. J Clin Endocrinol Metab 2004;89:5920-6.
17. Ashby J, Goldmeier D, Sadeghi-Nejad H. Hypogonadism in human immunodeficiency virus-positive men. Korean J Urol 2014;55:9-16.
18. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, *et al.* Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000;49:1239-42.
19. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, *et al.* Testosterone therapy in men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.
20. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
21. Rietschel P, Corcoran C, Stanley T, Basgoz N, Klibanski A, Grinspoon S, *et al.* Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. Clin Infect Dis 2000;31:1240-4.
22. Crum-Cianflone NF, Bavaro M, Hale B, Amling C, Truett A, Brandt C, *et al.* Erectile dysfunction and hypogonadism among men with HIV. AIDS Patient Care STDS 2007;21:9-19.
23. Sunchatawirul K, Tantiwongse K, Chathaisong P, Thongyen S, Chumpathat N, Manosuthi W. Hypogonadism among HIV-infected men in thailand. Int J STD AIDS 2012;23:876-81.
24. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S, *et al.* Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. J Androl 1999;20:611-8.
25. Monroe AK, Dobs AS, Xu X, Palella FJ, Kingsley LA, Post WS, *et al.* Low free testosterone in HIV-infected men is not associated with subclinical cardiovascular disease. HIV Med 2012;13:358-66.
26. Wunder DM, Bersinger NA, Fux CA, Mueller NJ, Hirschel B, Cavassini M, *et al.* Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. Antivir Ther 2007;12:261-5.
27. Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. Clin Infect Dis 2001;33:857-64.
28. Welch K, Finkbeiner W, Alpers CE, Blumenfeld W, Davis RL, Smuckler EA, *et al.* Autopsy findings in the acquired immune deficiency syndrome. JAMA 1984;252:1152-9.
29. De Paepe ME, Waxman M. Testicular atrophy in AIDS: A study of 57 autopsy cases. Hum Pathol 1989;20:210-4.
30. Sellmeyer DE, Grunfeld C. Endocrine and metabolic disturbances in human immunodeficiency virus infection and the acquired immune deficiency syndrome. Endocr Rev 1996;17:518-32.
31. Jain N, Mittal M, Dandu H, Verma SP, Gutch M, Tripathi AK. An observational study of endocrine disorders in HIV infected patients from North India. J HIV Hum Reprod 2013;1:20-4.
32. Klein RS, Lo Y, Santoro N, Dobs AS. Androgen levels in older men who have or who are at risk of acquiring HIV infection. Clin Infect Dis 2005;41:1794-803.
33. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A, *et al.* Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. J Clin Endocrinol Metab 2000;85:60-5.
34. Blick G, Khera M, Bhattacharya RK, Kushner H, Miner MM. Testosterone replacement therapy in men with hypogonadism and HIV/AIDS: Results from the TRiUS registry. Postgrad Med 2013;125:19-29.