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Research Article

ASSESSMENT OF CLINICAL FACTORS AND SERUM TESTOSTERONE ABOUT ERECTILE DYSFUNCTION IN HIV-INFECTED MEN

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ABSTRACT

Objective: The objective of this study was to assess and correlate serum testosterone (ST) levels with erectile dysfunction (ED) and associated risk factors in human immunodeficiency virus (HIV)-positive men.

Methods: The present correctional study was conducted among 75 HIV-positive patients. The study subjects were analyzed for ST levels and evaluated for ED using the international index of erectile function (IIEF-5). IIEF score was compared across depression severity assessed using a patient health questionnaire. Other variables, including age, the cluster of differentiation 4 (CD4+) count, antiretroviral treatment therapy, body mass index, and HIV duration, were also correlated with ED concerning ST levels.

Results: The prevalence of ED among HIV-positive patients was 96%. The majority (54.67%) of patients had mild-moderate ED. Hypertension was found in 14.67% of the study population. The mean IIEF score was 16.15±2.93. The relationship between depression severity and IIEF score was statistically significant ($p<0.001$). A weak positive correlation between CD4+ count and ED was found when ST was average (rs: 0.316, $p=0.163$). There was no correlation between age and abnormal ST and ED **[**rs: −0.459, $p=0.003$]

Conclusion: The prevalence of ED and its effect on ST levels could help in better management among HIV-infected males. Mild-moderate depression played a significant role in causing ED in association with ST levels. The study suggests that testosterone supplementation, along with optimum treatment of depression in HIV patients, can be fruitful in treating ED.

Keywords: Erectile dysfunction, HIV, International index of erectile function, Serum testosterone.

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INTRODUCTION

Sexual health (SH) or dysfunction has always been a concern in patients infected with the human immunodeficiency virus (HIV) [1]. As per the global data, around 38 million individuals are affected with HIV [2]. India stands third in this largest HIV epidemic in the world, comprising 2.1 million HIV patients [3]. The prevalence of HIV in men was found to be 0.25% and 0.19% in women [4]. It has been observed that the SH has risen from 30% to 74%, mostly in HIV-infected men than in non-HIV-infected men [4,5].

Erectile dysfunction (ED) is one such sexual problem experienced in this subset of the population [6]. This could result from comorbidities such as hypertension, stress, depression, and cardiac disease in older men. Conversely, in younger men, factors such as psychogenic causes, hormonal imbalances, medication use, drug or alcohol abuse, or systemic conditions may be contributing factors [7]. Hypogonadism might contribute to ED among HIV-infected men. A previous study reported that ED was significantly improved in a group of HIV-negative men when supplemented with a combination of testosterone and sildenafil and assumed that lower levels of testosterone may confer sexual dysfunction (SD) in HIV patients [8]. However, highly active antiretroviral therapy (HAART) and its impact on SD are still a subject of debate. Some studies have opined that type and duration of HAART do not affect the semen parameters of sperm concentration, volume ejaculate, etc., nine while one study observed a reduced percentile of spermatozoa in patients treated with efavirenz, another study found a relation of protease inhibitors with SD [9,10].

HIV patients on HAART have a common phenomenon of lipodystrophy, and due to the increasing number of fibroblasts and macrophages in lipotropic areas, testosterone gets converted to estrogen by intracellular aromatization [8]. The role of testosterone is significantly established for improving/correcting ED and other STDs in the general population. However, its part and the causes of the serum decline of testosterone in HIV-infected men are still under debate. Hence, the present study attempted to correlate ED with clinical factors and serum testosterone (ST) in HIV-infected male patients.

METHODS

Study design and population

A hospital-based observational cross-sectional study was conducted on an HIV-infected male patient attending the General Medicine Department of our tertiary care hospital. Patients aged more than 18 years and willing to participate in this study with informed consent approval were included in the study. Exclusion criteria included patients with chronic liver disease, renal failure, diabetes, psychiatric disorders, genital abnormalities, and hypertensive patients on beta-blockers, elderly who were aged >65 years, and patients on medication that could influence erectile function like ketoconazole, ganciclovir, methadone, anti-depressants, and beta-blockers. The sample size was 75 patients, and consecutive patients were recruited in the study using convenient sampling. The study was given the all-clear by the institution's ethics board.

Data collection

Clinical data, including age, body mass index (BMI), complete blood count, liver function test, renal function test, serum free testosterone (FT), ultrasonography abdomen, chest X-ray, and the cluster of Differentiation 4 (CD4) count, were collected. Patient health questionnaire (PHQ) PHQ-9 was used to assess the mental status of the patients [11]. ED was evaluated using the international index of erectile function (IIEF-5) [12].

Outcome variables

IIEF-5 score was considered the primary outcome variable, whereas PHQ PHQ-9, serum FT, CD4 count, and hemoglobin were secondary outcome variables. Age and BMI were other explanatory variables.

Statistical analysis

IBM SPSS version 25 was used for statistical analysis. Categorical data were presented as frequency and proportion, and continuous data were presented as mean and standard deviation. Shapiro will test with $p \geq 0.05$ was considered as a normal distribution. The values $p \leq 0.05$ was considered statistically significant.

RESULTS

The mean age was 46.12±8.49 years, and the mean BMI was 23.2±2.58 Kg/m^2. Most of the patients had mild-moderate ED (54.67%) with minimal depression (34.67%) and were not suffering from hypertension (85.33%), and were on TLE antiretroviral regime (70.67%) with a mean duration of the antiretroviral administration of 4.76±2.31 months, as presented in Table 1. The mean depression was noted to be 7.13±4.06 using PHQ-9, indicating mild depression existed among the patients.

Other investigations are reported in Table 2. Among both age groups, most of the patients had mild-moderate ED, which was noted to be 46% for the 20–49 year and 72% for the ≥50 age group. Most of the hypertensive (63.64%) and non-hypertensive (53.13%) patients belonged to the IIEF score of mild-moderate ED. A relatively similar distribution was noted for patients on antiretroviral treatment (ART) regime, ST, and hemoglobin levels, as shown in Table 3. IIEF score of ED significantly differed with depression severity ($p<0.001$) (Table 3). A moderate positive statistically significant correlation was found between ST and ED with $p<0.001$.

A strong positive correlation was noted between age, antiretroviral regime, and HIV duration when ST was within the normal range ($p<0.05$; Table 4). A strong positive correlation was noted between age, CD4 count, and HIV duration when ST was not within the normal range ($p<0.05$).

Most of the patients had mild ED across different groups when ST was within the normal range, as shown in Table 5. A similar scenario was noted in that most of the patients had mild ED across different groups when ST was not within the normal range.

In table no 6. Found ,the moderate ED group had the lowest median IIEF score of 121.50 (IQR 43.75 to 240.5), which was significantly lower than the mild-moderate ED group (median 213, IQR 128 to 342), the mild ED group (median 451, IQR 268 to 682), and the no ED group (median 656, IQR 565 to 854). The P value for the comparison was less than 0.001.

The group with ED (N=72) had a significantly lower median IIEF score of 656 (IQR 565 to 854) compared to the group without ED (N=3), which had a median IIEF score of 268 (IQR 156 to 565). The P value for this comparison was 0.021.

In table no 7 we found For participants with mild-moderate ED, those with abnormal ST levels had a significantly lower median CD4 count of 173 (IQR 128 to 264.8) compared to those with normal ST levels. However, there was no significant difference in the median IIEF score between these groups. For participants with mild ED, those with abnormal ST levels had a significantly lower median CD4 count of 282 (IQR 246 to 358) compared to those with normal ST levels. There was no significant difference in the median IIEF score between these groups. For participants with no ED, all participants had normal ST levels, and there were no significant differences in the median IIEF score or CD4 count between participants.

A statistically significant difference in the median IIEF score between CD4 counts was observed ($p<0.001$). Furthermore, CD4 count was significantly higher in patients with ED when compared to those without ($p<0.021$).

The difference in the median of IIEF score between CD4 count was observed when ST levels were not within normal limits ($p<0.018$).

Table 1: Demographic and clinical characteristics of the patients (n=75)

Parameter	Number of patients (%)
Age (years)#	46.12±8.49
BMI#	23.2±2.58
IIEF questionnaire	
Q1	
3	26 (34.67)
4	40 (53.33)
5	9 (12.00)
Q2	
2	9 (12.00)
3	39 (52.00)
4	26 (34.67)
5	1 (1.33)
Q3	
2	22 (29.33)
3	38 (50.67)
4	15 (20.00)
Q4	
2	14 (18.67)
3	35 (46.67)
4	24 (32.00)
5	2 (2.67)
Q5	
2	10 (13.33)
3	45 (60.00)
4	19 (25.33)
5	1 (1.33)
IIEF score group	
Moderate ED	4 (5.33)
Mild-moderate ED	41 (54.67)
Mild ED	27 (36.00)
No ED	3 (4.00)
IIEF scores#	16.15 (2.93)
Depression severity	
Minimal	26 (34.67)
Mild	24 (32.00)
Moderate	25 (33.33)
Hypertension	
Yes	11 (14.67)
No	64 (85.33)
ART regimen	
TLE	53 (70.67)
ZLE	10 (13.33)
Not on ART	12 (16.00)
PHQ-9#	7.13±4.06
Serum free testosterone#	8.62±6.99
CD4 count#	349.75±240.52
Duration (months)#	94.67±36.01
ART regimen duration (months)#	4.76±2.31

#Data is presented as mean±SD. ART: Anti-retroviral treatment, BMI: Body mass index, ED: Erectile dysfunction, IIEF: International Index of Erectile Function, PHQ-9: Patient health questionnaire-9, ZLE: Zidovudine, lamivudine, efavirenz, TLE: Tenofovir, lamivudine, efavirenz, Q: Question, CD4: The cluster of differentiation 4

DISCUSSION

The incidence of ED among HIV men has been rising, affecting the many clinical factors among them. ST also has a significant role to play in causing SD in HIV patients. The present study showed that ED was significantly correlated with age, ART regimen, and HIV duration when the TT was standard. When TT levels were abnormal, it was significantly associated with age and HIV duration. Further, CD4 count

Table 2: Distribution of patients based on age, clinical, and biochemical values across international index of erectile function score group

Parameters (n)	IIEF score group			
	Moderate ED, n (%)	Mild-moderate ED, n (%)	Mild ED, n (%)	No ED, n (%)
Age (years)				
20–49 (50)	3 (6)	23 (46)	21 (42)	3 (6)
≥50 (25)	1 (4)	18 (72)	6 (24)	0
Presence of hypertension				
Yes (11)	1 (9.09)	7 (63.64)	3 (27.27)	0
No (64)	3 (4.69)	34 (53.13)	24 (37.5)	3 (4.69)
ART regimen				
TLE (53)	3 (5.66)	30 (56.6)	19 (35.85)	1 (1.89)
ZLE (10)	1 (10)	6 (60)	3 (30)	0
Not on ART (12)	0	5 (41.67)	5 (41.67)	2 (16.67)
Serum testosterone				
Normal (34)	0	11 (32.35)	20 (58.82)	3 (8.82)
Abnormal (41)	4 (9.76)	30 (73.17)	7 (17.07)	0
Hemoglobin				
Anemia (40)	4 (10)	25 (62.5)	10 (25)	1 (2.5)
Normal (35)	0	16 (45.71)	17 (48.57)	2 (5.71)

ART: Antiretroviral treatment, n: Number of patients, ZLE: Zidovudine, lamivudine, efavirenz, TLE: Tenofovir, lamivudine, efavirenz, IIEF: International Index of Erectile Function

Table 3: Comparison of international index of erectile function score across depression severity

Parameter	Depression severity, median (IQR)			p-value
	Mild (n=24)	Minimal (n=26)	Moderate (n=25)	
IIEF score	16 (14.25–18.75)	18 (16.75–20)	14 (12.50–15)	<0.001***

***Significance. Test used was Kruskal–Wallis test. IQR: Interquartile range, IIEF: International Index of Erectile Function

Table 4: Correlation between erectile dysfunction and clinical variables concerning testosterone levels

Parameter	ST normal		ST abnormal	
	Spearman correlation (*r*)	p-value	Spearman correlation ®	p-value
Age	−0.568	<0.001***	−0.459	0.003**
Age CD4+count (years)				
20–49	0.316	0.163	0.482	0.008**
≥50	0.155	0.612	0.013	0.969
ART regimen duration	−0.458	0.014*	−0.288	0.093
BMI	0.037	0.834	0.097	0.546
HIV duration in month	−0.456	0.010*	−0.348	0.028*

*, ***Signifies the p<0.05 and<0.001. HIV: Human immune virus, ART: Anti-retroviral treatment, BMI: Body mass index, ST: Serum testosterone, CD4: The cluster of differentiation 4

was also significantly correlated with ED in patients aged 20–49 years with abnormal TT levels.

When a man reaches his reproductive prime between the ages of 20 and 40, his androgen levels peak and begin to decrease after that [13]. The reduced androgen levels affect physiological, somato-vegetative, and SH, and the symptoms include hyposexuality, ED, and reduction of orgasmic function, ejaculation amount, and force [14]. Similarly, HIV individuals >50 years had a greater prevalence of ED as compared to patients aged 20–49 years, which is consistent with previous studies [15,16]. The prevalence of ED in the present study was 96%, while other studies reported ED prevalence of 21.6% and 58.5% [17,18]. The high prevalence in our study could be due to the small sample size.

Hypertension (13.4%) cases among HIV-positive men in Gomes *et al*. study were like our study [15]. However, psychological reasons and

Table 5: Distribution of patients across International Index of Erectile Function score group when serum testosterone was normal

Parameters (n)	IIEF score group		
	Mild- moderate ED, n (%)	Mild ED, n (%)	No ED, n (%)
Normal ST			
ART regimen			
TLE (25)	9 (36)	15 (60)	1 (4)
ZLE (3)	1 (33.33)	2 (66.67)	0
Not on ART (6)	1 (16.67)	3 (50)	2 (33.33)
Depression severity			
Mild (12)	6 (50)	5 (41.67)	1 (8.33)
Minimal (20)	3 (15)	15 (75)	2 (10)
Moderate (2)	2 (100)	0	0
Hemoglobin			
Anemia (12)	4 (33.33)	7 (58.33)	1 (8.33)
Normal (22)	7 (31.82)	13 (59.09)	2 (9.09)
Age (years)			
20–49 (21)	4 (19.05)	14 (66.67)	3 (14.29)
≥50 (13)	7 (53.85)	6 (46.15)	0
Abnormal ST			
ART regimen			
TLE (25)	3 (10.71)	21 (75)	4 (14.29)
ZLE (3)	1 (14.29)	5 (71.43)	1 (14.29)
Not on ART (6)	0	4 (66.67)	2 (33.33)
Depression severity			
Mild (12)	0	9 (75)	3 (25)
Minimal (6)	1 (16.67)	2 (33.33)	3 (50)
Moderate (23)	3 (13.04)	19 (82.61)	1 (4.35)
Hemoglobin			
Anemia (28)	4 (14.29)	21 (75)	3 (10.71)
Normal (13)	0	9 (69.23)	4 (30.77)
Age (years)			
20–49 (21)	3 (10.34)	19 (65.52)	7 (24.14)
≥50 (13)	1 (8.33)	11 (91.67)	0

IIEF: International index of erectile function, ST: Serum testosterone, ED: Erectile dysfunction

Table 6: Comparison of median international index of erectile function score with the cluster of differentiation 4 count

IIEF score (*n*)	CD4 count, median (IQR)	p-value
Moderate ED (4)	121.50 (43.75–240.5)	<0.001[kw]
Mild-moderate ED (41)	213 (128–342)	
Mild ED (27)	451 (268–682)	
No ED (3)	656 (565–854)	
Presence/absence of ED		
Yes (72)	656 (565–854)	0.021[mw]
No (3)	268 (156–565)	

mw: Mann–Whitney *U*-test, kw: Krushal–Wallis test; IIEF: International Index of Erectile Function, ST: Serum testosterone, ED: Erectile dysfunction, IQR: Interquartile range, CD4: The cluster of differentiation 4

Table 7: Comparison of median International Index of Erectile Function score with the cluster of differentiation 4 count concerning serum testosterone levels

IIEF score (n)	Normal ST		Abnormal ST		
	CD4 count, median (IQR)	P (K–W)	IIEF score (n)	CD4 count, median (IQR)	p (K–W)
Moderate ED (0)	0 (0–0)	0.207	Mild ED (4)	121.5 (43.75–240.5)	0.018*
Mild-moderate ED (11)	468 (213–624)		Mild-moderate ED (30)	173 (128–264.8)	
Mild ED (20)	565 (350–715)		Mild ED (7)	282 (246–358)	
No ED (3)	656 (565–854)		No ED (0)	0	

The difference in the median of IIEF score between CD4 count was observed when ST levels were not within normal limits (p<0.018). ED: Erectile dysfunction, K-W: Krushal–Wallis test, ST: Serum testosterone, CD4: The cluster of differentiation 4, IQR: Interquartile range, IIEF: International Index of Erectile Function

low socioeconomic status are the leading causes of ED [15]. In our study, the majority (63.64%) of hypertensive HIV patients showed mild-moderate ED. Hypogonadism results due to low levels of FT (<300 ng/dL) from the early morning samples, which are accompanied by other clinical features such as SD, muscle mass, weight loss, tiredness, depression, and anemia [8,19]. ED in HIV patients was present even when testosterone levels were normal and low. However, ED was found to be more in patients with low testosterone levels (n=41), along with moderate depression. Our study found that most patients had mild-moderate anemia. There is minor literature on the association of anemia by itself as a factor for ED in HIV men. HAART is associated with a greater prevalence of lack of sexual desire and elevated serum estradiol levels in men [20]. Correspondingly, we found that 62/63 HIV patients who were on ART regimen showed ED.

The mean IIEF score (16.15±2.93) was similar to the study by Shindel *et al*. (25.3±6.1) in a cohort of HIV-positive men [16]. Majority of them had mild-moderate ED as per the IIEF score. While Fumaz *et al*. reported that most HIV-infected men showed mild ED (51.5%).[1] Furthermore, depression severity was significantly associated with IIEF scores. Numerous studies have related depression to ED, delayed ejaculation, and no desire for sex [21,22]. Fewer studies [23,24] have shown antiretroviral drugs to cause SD, whereas some have shown no association [4,8,24,25].

The previous studies reported no significant correlation between the duration of ART and gonadal dysfunction [26-28]. Similarly, we found a weak negative correlation between ART regimen duration and ED when ST was abnormal (*P*=0.093). However, the finding must be further studied as we did not compare the testosterone levels before the start and on treatment. Low sexual desire and deficient testosterone levels in HIV subjects could be associated with the advancement of HIV illness or could be attributed to morbid conditions or mental status.

Rochira *et al*. found that total ST levels <300 ng/dL (10.4 nmol/L) were observed in 16% of the subjects, with a maximum rate of total low testosterone in men aged between 40 and 60 years [29]. This study also found significantly low testosterone levels in younger men (10.6%) aged 30–39 years. Several studies have shown no association of TT with and its severity [30-32], but low TT in older individuals had related to ED [33]. Few studies have shown FT and not TT to be associated with ED. In the present investigation, we found that ST was significantly associated with ED among the population (P0.001). The lower level of FT was correlated to ED, which was following a study by Huang *et al*., where low FT among young HIV individuals associated with ED [34].

The prevalence of hypogonadism, which occurs due to testosterone deficiency, depends on the CD4 counts [19]. Meena *et al*. demonstrated a significant correlation between FT and CD4 counts (r=0.175, p=0.037) [35]. Study by Fumaz *et al*. reported that the median CD4 count was higher in patients without ED (631 [480, 832]) than those with ED (597 [451, 811]) [1]. Similarly, we found that the median CD4 has significantly differed with respect to the severity of ED in IIEF score in patients with abnormal ST. This indicates that a low CD4 count can predict ED in patients with odd TT. High mean CD4 scores in patients without ED infer good immune response.

The study was one of its kind, and the comparison between FT with ED and other clinical factors by taking a larger. The study's limited sample size and its methodology were two of its major flaws, which meant that the conclusions should not be taken at face value. Although we found anemia to be associated with ED, the type of anemia was not elicited, and hence, future research on the association of anemia in HIV men with ED is required. As this is a cross-sectional study, it did not allow us to identify the causality, only the associations. In the future, studies should be taken up that would appropriately correlate with HAART treatment, comorbidities, levels of testosterone, and ED in HIV men.

CONCLUSION

The prevalence of ED in HIV patients was 96%. The prevalence of ED and its effect on ST levels could help in better management among HIV-infected males. Mild-moderate depression played a much more significant role in causing ED in association with testosterone levels. The study suggests that testosterone supplementation, along with optimum treatment of depression in HIV patients, can be fruitful in treating ED.

AUTHORS' CONTRIBUTIONS

Equal contribution.

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Nil.

CONFLICTS OF INTEREST

Nil.

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