Tadalafil, a Phosphodiesterase-5 Inhibitor, Improves Erectile Dysfunction in Patients With Liver Cirrhosis

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Background: Erectile dysfunction (ED) is common in patients with chronic liver disease (CLD). Although it significantly worsens the quality of life, caregivers and researchers often neglect it. **Aim:** Evaluating the prevalence of ED in patients with CLD, associated factors, and response to therapy with tadalafil, a phosphodiesterase-5 inhibitor. **Methods:** A total of 60 males with Child-Pugh score between 5 and 10 and no overt hepatic encephalopathy were studied. ED was assessed based on the 15-question International Index of Erectile Function (IIEF) questionnaire. Patients were classified as ED+ if score was <25. Patients with ED were given 10 mg of tadalafil for 4 weeks. **Results:** The mean age was 45.2 $\pm$ 7.8 years. The mean Child-Turcotte-Pugh (CTP) score was 6.4 $\pm$ 1.7, and model for end-stage liver disease (MELD) score was 12.1 $\pm$ 4.5. Twenty-seven (45%) patients had compensated cirrhosis, and 45 (75%) had alcohol as etiology. Twenty-five (42%) had an IIEF score <25, suggestive of ED. The IIEF score had significant correlation with the presence of ascites ($r = -0.27$, $P = 0.04$) and serum creatinine ($r = -0.26$, $P = 0.05$); however, there was no correlation with CTP, MELD, or alcohol as etiology. Among ED group, IIEF scores improved significantly with 4 weeks of tadalafil therapy (15.1 ± 5.6 vs 22.0 ± 3.4 , $P < 0.001$), and 11 (44%) had resolution of ED. **Conclusion:** ED is common in patients with cirrhosis. Tadalafil administration significantly improves ED in these patients. (J CLIN EXP HEPATOL 2019;9:312–317)

Erectile dysfunction (ED) is defined as the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.¹ It is known to affect up to a third of the general population and has a considerable impact on the quality of life.² ED is much more common in men with chronic illnesses such as diabetes, dyslipidemia, coronary heart disease, and chronic liver disease (CLD).³

The pathogenesis of ED in patients with CLD, although not well elucidated, appears multifactorial. Hypogonadism secondary to reduced synthetic function, altered reproductive hormone profiles, presence of malnutrition, coexisting depression, concomitant alcohol intake, and drugs such as

diuretics and beta-blockers may all contribute to development of ED in this population.^{4–6}

It is known to affect patients across the spectrum of disease severity and leads to a substantial decline in the quality of life of these patients.⁷ Still, ED is often overlooked in this population by both patients and doctors alike. Only a handful of studies have evaluated the burden of ED in patients with CLD and its impact on the patients' well-being. Moreover, evidence on the efficacy and safety on the use of specific drug therapies to treat ED in this population is scant at best.

Tadalafil is a phosphodiesterase-5 (PDE5) inhibitor commonly used for the treatment of ED. Its metabolism is not significantly altered in patients with mild-to-moderate hepatic impairment, i.e. Child-Turcotte-Pugh (CTP) class A and B. We evaluated the impact of tadalafil on improving ED in patients with compensated and decompensated cirrhosis.

PATIENTS AND METHODS

We prospectively enrolled consecutive patients with cirrhosis from the Liver Clinic of the Postgraduate Institute of Medical Education and Research, Chandigarh, with Child-Pugh score between 5 and 10. Diagnosis of cirrhosis was based on a combination of clinical findings, endoscopic findings (presence of esophageal varices),

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Abbreviations: CLD: Chronic Liver Disease; CTP: Child-Turcotte-Pugh; ED: Erectile Dysfunction; HE: Hepatic Encephalopathy; HRQOL: Health-Related Quality of Life; IIEF-15: International Index for Erectile Function; MELD: Model for End-Stage Liver Disease; MMSE: Mini-Mental State Examination; PDE: Phosphodiesterase

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radiological parameters (irregular liver outline, portal vein ≥ 14 mm, splenomegaly), liver stiffness ≥ 12.5 kPa by transient elastography (FibroScan®, Echosens, Paris, France), and/or histopathological evidence of cirrhosis. Patients with ascites, hepatic encephalopathy, or history of variceal bleeding were classified as having decompensated cirrhosis. Patients with recent alcohol intake (<12 weeks), known cardiorespiratory diseases, renal failure, malignancy, neurological disease (Alzheimer's, Parkinson's, stroke), and anatomical deformities of the penis were excluded. Presence of hepatocellular carcinoma was ruled out using an ultrasound and/or triple-phase contrast-enhanced computed tomography. The participants were subjected to a Mini-Mental State Examination (MMSE), and only patients with MMSE >24 were included in the study. ED was assessed using the International Index of Erectile Function (IIEF)-15 questionnaire.

Patients in the ED group received 10 mg of tadalafil once daily for 4 weeks. These patients were followed up either in the liver clinic or by the telephonic interview within 7–10 days for compliance of treatment and for development of any side effects. All patients were called up in the liver clinic for the final evaluation at the end of 4 weeks (Figure 1), which included a detailed clinical evaluation and a repeat IIEF-15 score assessment (see Figure 2).

INTERNATIONAL INDEX OF ERECTILE FUNCTION-15

IIEF is a valuable and validated tool for clinical assessment of sexual dysfunction.⁸ It is a self-administered measure of ED, which can be used to establish a baseline value and monitor the effect of treatment. It includes 15 questions related to five domains of sexual function—ED, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. Patients with an IIEF score <25 were classified as ED. Stratification of the IIEF score according to the severity of ED was as follows: 0–6 severe dysfunction, 7–12 moderate dysfunction, 13–18 mild-to-moderate dysfunction, 19–24 mild dysfunction, and 25–30 no dysfunction. Resolution of ED was defined as IIEF score ≥ 25 at 4 weeks in patients with ED. To rule out the influence of a familiarization or learning effect, IIEF questionnaire was also given to the patients of the non-ED group at 4 weeks.

STATISTICAL ANALYSIS

Continuous data were expressed as mean $\pm$ standard deviation and categorical data as count or frequency (percentage). Descriptive analysis was performed for all variables. Normality of data was checked using Kolmogorov-Smirnov test. Continuous variables with normal distribution were analyzed using *t*-test; variables that were not normal were analyzed using the Mann-Whitney U test. Comparison between two groups was performed by inde-

pendent *t*-test. Discrete variables were analyzed using χ^2 test. Pearson's correlation was used to check the correlation between the variables with normal distribution, and Spearman correlation was used for variables that were not normally distributed. Multivariate logistic regression analysis was conducted to assess the independent variables that affected ED. Comparisons were made among the patients of the ED group and non-ED group. All statistical analysis was performed two sided and performed at a significance level of 0.05. Statistical package for the social sciences (SPSS), version 22, (IBM Corporation, Chicago, IL) was used for statistical computations.

RESULTS

Demographic Profiles and Baseline Parameters

A total of 80 male patients with liver cirrhosis from the Liver Clinic of Postgraduate Institute of Medical Education and Research, Chandigarh, India, were evaluated. Sixty patients were included in the study (20 excluded—six active alcoholism, five recent variceal bleed, four hepatocellular carcinoma, two renal insufficiency, one infection, one stroke, one on antidepressants). On the basis of their IIEF scores, they were divided into ED and non-ED groups. Both groups were largely similar in terms of demographic, hematological, and biochemical parameters and had comparable severity of liver disease as assessed by CTP and model for end-stage liver disease (MELD) scores (Table 1). There was also a trend toward a higher proportion of smokers among those with ED (56% vs 31.4%, $P = 0.07$), although it did not reach statistical significance (Table 1).

Alcohol was the most common etiology of cirrhosis in the study population, responsible for more than half of the cases. There was no significant difference in the etiologies of cirrhosis in the ED and non-ED groups (Table 2). We also compared the patients with compensated cirrhosis with those with decompensated disease. There was no difference in the frequency (32.4% vs 56.6%, $P = 0.10$) or the severity of ED (mean IIEF score 23.14 ± 7.17 vs 20.91 ± 7.16 , $P = 0.25$) between the two groups (Table 3).

Factors Associated With ED

The baseline IIEF score was found to have a significant inverse correlation with the presence of ascites ($r = -0.27$, $P = 0.04$) and serum creatinine ($r = -0.26$, $P = 0.05$); however, there was no correlation with CTP ($r = -0.08$, $P = 0.53$) or MELD ($r = -0.08$, $P = 0.55$).

On univariate analysis, smoking, ascites, serum creatinine, and serum sodium were all found to have significant association with ED. However, on multivariate analysis, smoking emerged to be the sole significant factor influencing the presence of ED in this population (odds ratio [OR] = 3.75, $P = 0.01$) (Table 4).

Figure 1 Flow of Patients into the Study. ED, Erectile Dysfunction

Figure 2 IIEF score in patients who received tadalafil. ED, Erectile Dysfunction; IIEF, International Index of Erectile Function.

Efficacy of Tadalafil in ED

All patients who were given tadalafil demonstrated improvement in the IIEF score at 4 weeks of treatment (15.08 vs 22.00 , $P \leq 0.001$). Eleven (44%) patients showed resolution of ED at the end of 4 weeks of therapy. Overall increase in the IIEF scores was 6.9 ± 1.6 in those who took tadalafil as compared with 0.17 ± 0.15 in the non-ED group. The increase in IIEF scores after tadalafil administration was similar in both compensated and decompensated cirrhosis (7.1 ± 4.3 vs 6.8 ± 3.4 , $P = 0.84$). The improvement was more in patients with a lower IIEF score (baseline IIEF vs Δ IIEF; $r = -0.93$, $P < 0.001$) (see [Table 5](#)).

Safety of Tadalafil

Treatment with tadalafil was well tolerated. Of the 25 patients who received the treatment, adverse effects were reported in three patients (dyspepsia, 2; headache, 1). None of these were dose limiting. No major serious adverse effect was reported.

DISCUSSION

This study showed that ED is common in patients with liver cirrhosis, irrespective of etiology. The frequency and severity do not vary with the severity of liver disease in

Table 1 Demographic Profiles and Baseline Parameters of all Patients.

Predictors	All patients (N = 60)	ED (N = 25)	Non-ED (N = 35)	P value
Age (years)	45.2 ± 7.8	46.5 ± 7.2	44.3 ± 8.1	0.61
CTP score	6.5 ± 1.7	6.7 ± 1.7	6.3 ± 1.7	0.68
MELD score	12.1 ± 4.5	12.5 ± 3.9	12.3 ± 15.5	0.18
PHES score	−4.50 ± 4.70	−5.2 ± 4.9	−4.0 ± 4.5	0.15
Hemoglobin (g/dL)	11.8 ± 2.8	10.8 ± 4.9	11.5 ± 4.5	0.39
TLC (10 ³ cells/mm ³)	7.6 ± 6.1	7.0 ± 4.5	7.5 ± 7.5	0.62
Platelets (10 ⁵ cells/mm ³)	1.3 ± 0.7	1.2 ± 0.8	1.2 ± 0.8	0.69
Serum Na ⁺ (mmol/L)	137 ± 3.8	137.6 ± 4.2	137.46 ± 3.6	0.08
Serum K ⁺ (mmol/L)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.6	1.00
Serum creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.4	0.9 ± 0.2	0.03*
Total bilirubin (mg/dL)	1.9 ± 2.2	1.5 ± 1.5	2.2 ± 2.7	0.26
AST (U/L)	77 ± 52	79 ± 46	76 ± 57	0.80
ALT (U/L)	57 ± 48	55.6 ± 38	58 ± 55	0.69
Total protein (gm/dL)	7.37 ± 0.78	6.8 ± 2.9	7.33 ± 0.69	0.19
Serum albumin (gm/dL)	3.6 ± 0.3	3.2 ± 1.4	3.7 ± 0.8	0.32
INR	1.3 ± 0.3	1.4 ± 0.3	1.3 ± 0.4	0.95
Diabetes	7(11.6%)	4 (16.0%)	3 (8.5%)	0.43
Beta-blocker	7 (11.6%)	5 (20.0%)	2(5.7%)	0.12
Diuretics	11 (18.3%)	8 (28.0%)	3 (11.4%)	0.03*
Ascites	10 (16.6%)	8 (32.0%)	2 (5.7%)	0.04*
Smoking	25 (41.6%)	14 (56.0%)	11 (31.4%)	0.07

TLC, Total Leukocyte Count; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease; PHES, Psychometric Hepatic Encephalopathy; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; NASH, Nonalcoholic Steatohepatitis; AST, Aspartate Transaminase; ALT, Alanine Transaminase; INR, International Normalized Ratio.

Data are presented as mean (95% confidence interval) or as number (percentage).

patients with CTP scores ≤10. Smoking is an important factor associated with the presence of ED. Tadalafil is effective and safe in treating ED in patients with cirrhosis.

ED is common in patients with liver cirrhosis and known to negatively affect the quality of life. Still, its significance is often neglected by most practitioners and researchers. This ignorance probably stems from the acceptance of ED as a part of liver failure, multiple medical issues drawing away the focus of the practitioner, and the

dearth of data on efficacy and safety of therapeutic modalities. In our study, 25 patients (41.7%) had evidence of ED based on the IIEF score. A Korean population group of 69 patients with hepatitis B-related CLD, of whom 34 had cirrhosis, found the prevalence of ED to be 24.6%; however, among those with cirrhosis, the prevalence was 41.2%. This subgroup had a mean age of 50.5 to 6.3 years, which too was similar to our study population.⁹

Evidence is conflicting on whether the frequency of ED varies with the severity of liver disease. A Turkish cohort of 94 patients with hepatitis B- and hepatitis C-related CLD (10 cirrhotic) found the prevalence of ED to be 50.6% for all patients and 50, 50, and 51.1% for cirrhosis, chronic hepatitis, and carriers, respectively.¹⁰ However, most other studies report a higher prevalence of ED in cirrhosis as compared with noncirrhotic chronic hepatitis. Among patients of cirrhosis, a Japanese study found a higher frequency of ED in patients of higher Child-Pugh class.⁶ None of the other available studies make a similar comparison. We did not find a significant relation between the IIEF score and the frequency of ED with CTP score in our study. The fact that our patients were much younger

Table 2 Etiology of Cirrhosis.

Predictors	All patients (N = 60)	ED (N = 25)	Non-ED (N = 35)	P value
Alcohol related	33 (55%)	14 (56%)	19 (54.3%)	1.00
HCV related	10 (16.6%)	3(12%)	7 (20%)	0.49
NASH related	1 (1.6%)	0	1 (2.9%)	1.00
HBV related	2 (3.3%)	1(4%)	1 (2.9%)	1.00
Others	14 (23.3%)	7 (28%)	7(20%)	0.54

HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; NASH, Nonalcoholic Steatohepatitis.

Data are presented as number (percentage).

Table 3 Prevalence and Severity of ED.

Predictors	Total (N = 60)	Compensated cirrhosis (N = 37)	Decompensated cirrhosis (N = 23)	P value
IIEF score	22.28 + 6.40	23.14 + 7.17	20.91 + 7.16	0.25
ΔIIEF	2.98 + 4.15	2.4 + 4.07	3.9 + 3.57	0.17
Frequency of ED	25 (41.7%)	12 (32.4%)	13 (56.5%)	0.10
ED grade				
No ED (25–30)	35 (58.3%)	25 (67.6%)	10 (43.5%)	0.24
Mild (19–24)	8 (13.3%)	4 (10.8%)	4 (17.4%)	
Mild-moderate (13–18)	10 (16.7%)	4 (10.8%)	6 (26.1%)	
Moderate (7–12)	5 (8.33%)	3 (8.1%)	2 (8.7%)	
Severe (0–6)	2 (6.6%)	1 (2.7%)	1 (4.3%)	

IIEF, International Index of Erectile Function; ED, Erectile Dysfunction.

Data are presented as mean (95% confidence interval) or as number (percentage).

Table 4 Multivariate Logistic Regression for the Relative Risk of Erectile Dysfunction.

Predictors	Odds ratio	95% CI	P value
CTP score	1.44	0.93–2.24	0.10
Ascites	0.70	0.14–3.61	0.67
Serum sodium (mEq/L)	1.10	0.91–1.34	0.35
Serum creatinine (mg/dL)	0.12	0.01–1.09	0.06
Diabetes	2.93	0.47–18.05	0.24
Smoking	3.75	1.27–11.10	0.04*
Use of Beta-blocker	7.35	0.58–91.75	0.12
Use of diuretics	2.08	0.35–12.35	0.49

CTP, Child-Turcotte-Pugh; CI, Confidence Interval.

Data are presented as mean (95% confidence interval) and odds ratio.

than the Japanese cohort and had a much lower overall frequency of ED may be one of the reasons for this difference. Age has been shown to be one of the most important risk factors of ED. In the Massachusetts Male Aging Study, ED was found in 8% in patients in their 40s and rises up to 80% in patients older than 70 years.¹¹

The evidence on whether the etiology of cirrhosis affects sexual function has been divided. While an American study

found a much higher frequency of ED in patients with alcohol-related cirrhosis, none of the other studies have found a similar association once active alcoholism was excluded—the presence of ED did not vary with etiology of cirrhosis.^{12,13} Our population too had a similar result, with 14 of 33 (42%) of alcohol-related cirrhosis having ED, as opposed to 11 of 27 (41%) of non-alcohol-related cirrhosis ($P = 0.89$). None of the other etiologies seemed to influence the frequency of ED.

Some studies have shown serum albumin to be an independent predictor of ED.^{6,9} Low levels of albumin alter the ratio of albumin-bound testosterone to free testosterone, thus possibly affecting sexual function. However, this association has not substantiated by other studies, including ours.

Diuretics ($P = 0.03$), presence of ascites ($P = 0.04$), creatinine ($P = 0.03$), and smoking ($P = 0.07$) showed significant association with ED on univariate analysis. However, smoking alone retained significance after multivariate analysis ($OR=3.75$, $P 0.04$), emerging as the sole independent determinant of ED. Smoking is already an established risk factor for ED. The association between smoking and ED was evaluated by Naomi et al. in a cohort of 2115 Caucasian men; compared with men who never smoked,

Table 5 Change in ED Grade From Baseline After 4 Weeks of Treatment.

ED grade	Total (N = 60)		Compensated cirrhosis (N = 37)		Decompensated cirrhosis (N = 23)	
	Baseline	4 weeks	Baseline	4 weeks	Baseline	4 weeks
No ED	35 (58.3%)	46 (76.6%)	25 (67.6%)	30 (81%)	10 (43.5%)	16 (69.6%)
Mild	8 (13.3%)	9 (15%)	4 (10.8%)	4 (10.8%)	4 (17.4%)	5 (21.7%)
Mild to moderate	10 (16.7%)	5 (8.3%)	4 (10.8%)	3 (8.1%)	6 (26.1%)	2 (8.6%)
Moderate	5 (8.33%)	0	3 (8.1%)	0	2 (8.7%)	0
Severe	2 (6.6%)	0	1 (2.7%)	0	1 (4.3%)	0

ED; Erectile Dysfunction.

Data are presented as number (percentage).

men who smoked at some time had a greater likelihood of ED (OR = 1.42).¹⁴ The meta-analysis of four prospective cohort studies and four case-control studies (28,586 participants) concluded that smoking was a risk factor for ED in current smoker (OR=1.81) and ex-smoker (OR=1.25).¹⁵ It leads to worsening of ED in patients with comorbidities because of its association with cardiovascular disease, atherosclerosis, neuropathy, and endothelial dysfunction. The major mechanisms in smokers, which lead to ED, are endothelial dysfunction, increased oxidative stress, and decreased availability of nitric oxide.

Tadalafil is a PDE5 inhibitor used in the management of ED. Although PDE5 inhibitors have safely been used in Child's A and B cirrhosis,^{16,17} no study had documented the efficacy of this drug in patients with cirrhosis of liver. We demonstrated that tadalafil had a good response in patients with cirrhosis. Forty-four percent of the patients who received the drug had resolution of ED after 4 weeks of therapy. All the patients in the ED group revealed an increase in the IIEF scores and improvement in the severity of ED at least by one severity class. The mean IIEF score in this group improved by 7 points at the end of 4 weeks. Interestingly, the most improvement was seen in patients with more severe ED with lower IIEF scores.

To evaluate the variables associated with response to tadalafil, we correlated the change in the IIEF score (Δ IIEF) with all other variables. We did not find any correlation between the Δ IIEF score and CTP, MELD, smoking, diabetes mellitus, ascites, beta-blocker use, or diuretics use. Beta-blockers have been known to lead to ED independently; however, as only seven patients in our population used these, it is very difficult to draw meaningful conclusions for this aspect.

Tadalafil was well tolerated in all patients, with almost no significant side effects. Two patients reported dyspepsia and one reported headache after taking the drug. No other side effects were reported, and none of the patients discontinued the drug during the study period.

Our study had its limitations. Being a proof-of-concept study, we did not have a placebo group for comparison of efficacy of treatment. Also, most of the patients included in the study were predominantly stable cases in an outdoor setting. So prevalence of ED in advanced disease could not be studied.

In conclusion, ED is common in patients with liver cirrhosis. Although ED leads to a significant deterioration in the quality of life, it is often neglected by most caregivers and researchers. Smoking seems to have a strong association with the presence of ED. Tadalafil is effective in treatment of ED in patients with compensated and decompensated cirrhosis of liver and is quite well tolerated. The improvement is more in patients with more severe ED and is independent of the severity of liver disease. However, larger trials would be required to assess the safety of

the drug, especially in decompensated cirrhosis, before it may be recommended for routine use.

CONFLICTS OF INTEREST

The authors have none to declare.

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