**Name of Journal:** World Journal of Hepatology  
**Manuscript NO:** 76488  
**Manuscript Type:** OPINION REVIEW

**Sexual dysfunctions and their treatment in liver diseases**

Rakesh Kumar Jagdish

**Abstract**

Sexual dysfunction (SD) is much prevalent but a very commonly ignored aspect in the treatment of liver diseases and cirrhosis. Etiology is multifactorial and therefore treatment strategies are also complex, especially in females. Phosphodiesterase (PDE) inhibitors are useful and effective in erectile dysfunction in males but in females, no single pill is available for SD, therefore multimodality of treatment is required depending upon the cause. The foremost and fundamental requirement in both gender is to be stress-free and have adequate control of liver diseases. Improved quality of life is helpful in improving SD and vice versa is also true. Therefore patients should come forward and ask for treatment for SD, suffering from liver diseases and physicians should actively enquire about SD while history taking and evaluating these patients. Sexual Dysfunction results in deterioration in the quality of life, both are modifiable and treatable aspects of liver diseases, which are never addressed actively, due to social taboos and fears of taking help in presence of liver diseases. Diagnosis of SD does not require extra costly investigations, as the diagnosis can be established based on validated questionnaires available for both genders, therefore detailed targeted history taking using questionnaires is essential. Data is emerging in this area but is still in the infantile stage. More studies should be dedicated to this Nobel area.
INTRODUCTION

Introduction

Sexual dysfunctions (SD) in liver diseases have a multifactorial origin, and this is often the most ignored aspect in both gender. This review is to break the myths and social taboos about the sexual aspect, and the quality of life in patients with liver disease of both genders, with simplified diagnostic criteria, the common causes, treatment, and other management options. The purpose is to provide support to the sexual life of liver disease patients as SD can have a negative effect on the quality of life and can cause psychological issues like less emotional satisfaction and general unhappiness and depression. This is to be clarified that, infertility issues related to cirrhosis are separate from the sexual dysfunctions, therefore not discussed here in this review.

Sexual Dysfunction:

In men, SD in men is categorized into disorders of desire (low libido), arousal (erectile dysfunction), or orgasm (premature or delayed ejaculation, or anorgasmia), according to their occurrence in the cycle of sexual response. The most common presentations are premature ejaculation, which is arbitrarily defined as ejaculation within one minute (60 Seconds) of vaginal penetration, or erectile dysfunction, which is the inability to obtain and maintain a penile erection for achieving satisfactory sexual activity. Erectile dysfunction (ED) is considered to be common in cirrhosis; predominantly due to endocrine dysfunction and sarcopenia. There is a paucity of data on the precise prevalence of and predictive factors for ED in cirrhosis. PDE5 inhibitors were found useful in ED in the non-cirrhotic and cirrhotic population recently in an RCT of the use of Tadalafil in cirrhotics.

In females, sexual dysfunctions, are more complex to describe, and predominantly can manifest with low libido, vaginal dryness, dyspareunia, inability to orgasm, or menstrual abnormalities.

Incidence and Prevalence of SD:

Patients with cirrhosis have a high prevalence of ED ranging from 25 to 92% in various studies as shown in table 1. In a recent RCT, we have found it 70.3 %, whereas in
females studies on prevalence are limited, which showed abnormal menstrual cycles in 58%, 42% had decreased sexual interest in 42%, and no sexual activity in 56% of females\(^9\). In a study in women with non-alcoholic liver disease, reduced sexual desire was in 33%, reduced arousal in 18%, not feeling orgasm in 25%, and dyspareunia in 21%, related to decreased vaginal lubrication. Prospective studies needed in this are especially in female patients.

**Risk factors contributing for ED in Liver Diseases in both genders:**

The causation of Sexual Dysfunction in both genders is multifactorial, although there are only a few studies in females as compared to males. The female sexual function involves hormonal, neurological, vascular, psychological, and emotional aspects. Dysfunction may be triggered or maintained by any of these, or by the interplay between them. The hormonal interplay are grossly disturbed in chronic liver diseases along with multiple other non-hormonal factors contributing to the SD in CLD. The Possible contributing factors for SD in both genders\(^{10,13}\) in liver diseases, shown in the figure1.

**Non Hormonal Causes:**

**Disturbing quality of life** with Depression (which can affect all phases of sexual function), Anxiety, and Stress are the important factors. ED in itself is associated with a poor health-related quality of life (HRQOL)\(^{11,12}\) and depressive symptoms in both cirrhotic and non-cirrhotic patients.

**Low serum Albumin** is a significant factor for ED and low IIEF score in liver diseases which is reported in multiple studies\(^4\). Hypoalbuminaemia results in water retention and loss of muscle volume which decreases sexual desire, and physical function. The ratio of albumin-bound to free testosterone might be influenced by decreased production of albumin which might influence sexual desire and sleep-related erection. A study by Paternostro et al\(^{14}\) showed that liver dysfunction, diabetes mellitus, Hypertension, and High Hepatic venous pressure gradient (HVPG), is a key risk factors for ED in male cirrhotic.
Sarcopenia, as measured by appendicular skeletal muscle index (ASMI), was found to be associated with ED in a recent study\(^1\). This appears to be clinically significant because patients with low muscle mass are more likely to have low albumin, low power, frailty, and poor sexual performance. A concept of sexual frailty can be given, similar to frailty in other organ systems. Musculoskeletal health needs to be highlighted in the evaluation of cirrhosis along with sexual health. More randomised trials should be conducted to understand the pathogenesis and underlying mechanisms and possible treatment options in this area.

Clinical features of hypogonadism, such as ED, infertility, decreased libido, and testicular atrophy, are often seen in patients with advanced liver disease, and it has been seen that the severity of liver cirrhosis correlates with the degree of ED.\(^4\)

**Effects of Drugs:** Propranolol has a negative impact on erectile function, which has become widely used to treat portal hypertension\(^{15,16}\), but the doses which are required to cause ED are higher than the doses commonly used in CLD. Although Paternostro et al\(^{14}\) found \(\beta\)-blockers not to be associated with ED, \(\beta\)-blockers generally cause vasodilation, inhibition of release of renin, angiotensin II, and aldosterone production. These result in a decreased adrenergic outflow from the sympathetic nervous system, resulting in SD\(^{17}\). However, a large meta-analysis\(^{18}\) did not support the notion that beta-blocker (BB) therapy is associated with a relevant risk of sexual dysfunction, which was also supported by a recent RCT\(^1\). Spironolactone, an anti-mineralocorticoid and aldosterone antagonist, has anti-androgenic properties and can cause decreased libido and SD\(^{16,17}\).

**Hormonal causes (sex Hormones):**

Studies have shown that free and albumin-bound testosterone, rather than total testosterone concentration, correlated positively with sexual desire and sleep-related erection in healthy subjects\(^{19}\). Therefore, it is possible that the reduced production of albumin may affect the ratio of free testosterone to albumin-bound testosterone, as well as the total amount of testosterone, possibly modifying cell or tissue response to this sex hormone in cirrhotic patients. Sex hormone-binding globulin (SHBG) levels\(^{20,21}\) are elevated in patients with cirrhosis due to increased hepatic production, but the
pathogenesis of this remains unclear. Rising levels of SHBG have been shown to correlate with the severity of fibrosis in patients with chronic liver disease. Due to the binding of testosterone to SHBG, the total serum testosterone value can remain normal or occasionally be raised in this patient group, despite reduced levels of free (presumed biologically active) testosterone.

Assessment of Sexual dysfunctions (SD):

There are various well-validated questionnaires for SD and its risk factor assessment. The Female Sexual Function Index (FSFI) and The International Index of Erectile Function (IIEF) in males are the two most validated objective tools for SD severity assessment, with various domains and questions pertaining to each domain, which are then scored into numerical values (figure 2).

**Females:** The Female Sexual Function Index (FSFI): A total of six domains are assessed, with a total set of 19 questions. All domains have the highest score of 6, and the total maximum score is 36, where a score of 0 represents no sexual activity during the preceding month. An overall score below 26.55 is indicative of female SD. Female sexual dysfunctions (FSD) are classified into three main clinical types. For each diagnosis, the disorder is experienced at least 75% of the time for at least six months (except for medication-induced FSD), resulting in significant distress. The three types, some or all of which may be present, are (1) Sexual interest/arousal disorder, which is defined as reduced or absent sexual interest, responsiveness, erotic thoughts and sexual pleasure, (2) Female orgasmic disorder (absence, infrequency, reduction, delay of orgasm), and (3) Genito-pelvic pain/penetration disorder (difficulty in vaginal penetration, marked vulvovaginal or pelvic pain during penetration, fear or anxiety about pain in anticipation of, during, or after penetration, and tightening or tensing of pelvic floor muscles during attempted penetration).

**Male:** International Index of Erectile Function (IIEF): A 15-item questionnaire that assesses five domains of male sexual function using 5- to 6-point likert scales, with 0 or 1 signifying a low frequency or ability and 5 signifying a high frequency or ability. These domain include erectile function, orgasmic function, sexual desire, intercourse
satisfaction, and overall satisfaction. The erectile function domain possible scores range from 1 to 30. The severity of ED was defined using the IIEF-EF domain’s score: 5 or lower, (no attempts at intercourse at all ); 6 to 10, severe ED; 11 to 16, moderate ED; 17 to 21, mild to moderate ED; 22 to 25, mild ED; and 26 to 30, is normal erectile function. IIEF has been validated in the Indian population also.

Other questionnaires: The quantitative qADAM questionnaire is a new tool in quantifying the severity of hypogonadism, Sexual Encounter Profile (SEP), and Global Assessment Question (GAQ) for assessing sexual performance. The quantitative ADAM questionnaire is a new tool in quantifying the severity of hypogonadism. A total qADAM score between 10 and 50, with 10 being the most symptomatic and 50 being the least symptomatic.

The Sexual Encounter Profile (SEP) diaries record yes/no responses after sexual encounters. There are five questions, but two questions are most frequently used to assess the SD. SEP2 is "Were you able to insert your penis into your partner’s vagina?" and SEP3 is "Did your erection last long enough for you to have successful intercourse?"

Quality of life in erectile dysfunction (ED) and cirrhosis:

About 92% of patients with cirrhosis with sexual dysfunction (SD) have a significant impact on the quality of life as assessed by the SF-36 score. Other scores related to the quality of life are the Generalized Anxiety Disorder 7 (GAD-7) questionnaire, where a GAD-7 score of ≥10 indicates a probable diagnosis of GAD. Patient Health Questionnaire (PHQ) where PHQ-9 score ≥10 was taken as an indication of major depression. Both anxiety and depression are implicated in the causation of ED and sexual dysfunction. In a recent study, we have shown that treatment of ED with tadalafil results in a significant decline in the GAD-7 and PHQ-9 scores; significantly more improvement in scores of five of the eight domains of SF-36 when compared with placebo.

Management, Clinical approach and Treatment:

Adequate management of the primary liver diseases is of paramount importance, as most of the treatment targeting SD may not be feasible or even contraindicated in child
C cirrhosis. Therefore, adequate control of liver diseases and co-morbidities is warranted. The clinical approach and treatment of SD in liver diseases are summarised in figure 3 and 4.

Both male and female:

**Counselling for partners:** Counselling for both partners on understanding the facts and myths, particularly regarding liver diseases and sexual activity.

**Environmental Modifications:** Partners may accordingly be advised to change to a suitable environment, to change positions, or poses, as per the stage of the disease. Pelvic floor exercises and general exercises can be recommended for improving frailty, including sexual frailty.

**Avoid stamina supplements:** Avoid complementary alternative medications (CAM), herbs, and over the counter drugs (OTC) available in many countries to boost stamina. Most of these are not studied drugs and are strictly discouraged for use as they can be harmful in the presence of liver diseases.

**Female:**

Female sexual dysfunction (SD) is a subjective dissatisfaction, the management of which can vary among patients. A single pill cannot be the answer to female sexual dysfunction in contrast to her male counterpart’s erectile dysfunction.

Management of female sexual dysfunction (SD) in cirrhotics is complex and depends on finding and treating the predominant underlying causes, but often requires multimodality involvement for optimal results. Evaluation of the underlying causes includes a detailed history, hormonal analysis, pelvic ultrasound, gynaecological examination, and psychological evaluation, along with the status and stage of liver diseases. A new-onset SD can be a sign of advanced liver disease, coagulopathy, or other metabolic or cardiovascular disease.

Various strategies are shown in figure 3. Modifications in lifestyle are recommended, like possible pelvic floor exercises as per cirrhotic stage, quitting smoking and alcohol. If it’s causing poor performance, even in a passive role in sexual activity, blood transfusion or IV iron therapy can be used to correct anaemia.
Coagulation correction and care of bleeding should be kept in mind. Forcible acts, avoiding love bites, may have the risk of bleeding. Arousal enhancement strategies include relationship couples counselling, sex education using videos and educational literature, sexual positions yoga, romantic songs, romantic dressings, making the environment suitable for sexual pleasure, and increasing foreplay timings. Cognitive behavioural therapy is a type of psychotherapy that helps in removing sexual inhibitions and helps in enhancing interpersonal relationships and sexual involvement. Medical devices like Clitoral Therapy devices for sexual arousal and orgasmic dysfunctions can be helpful in some cases. Oestrogen is effective in the treatment of dyspareunia related to menopause. Strict contraception should be used to avoid pregnancy, as pregnancy should be planned with prior discussion with the treating doctor for the best outcome. Transdermal testosterone was tried in postmenopausal women with hypoactive sexual desire disorder with variable results. To date, there are no FDA-approved treatments available for FSD, so prospective studies and RCTs should be conducted in these patients.

**Sexual dysfunction in women after liver transplantation:**

Studies of liver transplant recipients showed that 72 percent of females became sexually active after LT. 95% of females younger than 46 years had a regular menstrual cycle by the end of the first year of liver transplantation. But, irregular bleeding and amenorrhea were present in 26% and 26%, respectively. An interval of at least 1-2 years after successful LT is recommended before considering pregnancy. Mycophenolate mofetil (MMF) should be stopped before planning a pregnancy due to its teratogenicity.

**Male:**

The basic mechanism of sexual arousal and further physiological changes involves nitric oxide (NO) and related mechanisms. Phosphodiesterase (PDE) inhibitors competitively bind to PDE5 and inhibit c-GMP hydrolysis, thus enhancing the effects of NO. This increase in c-GMP in the smooth muscle cells results in a prolonged erection. In view of the lack of direct effect of PDE5 inhibitors on corpus cavernosum and smooth-muscle relaxation, adequate sexual stimulation is necessary for an erection to
occur. Therefore, foreplay and stress relief are required. The approved agents for the treatment of ED are sildenafil, tadalafil, vardenafil, and avanafil, but tadalafil appears to be the best option due to its long half-life and flexibility in the timing of administration.

A recent RCT demonstrated that 12-week therapy with Tadalafil (10 mg daily) significantly improves erectile function, anxiety, depression, and quality of life, and is well tolerated by men with cirrhosis (CTP score 10) and ED, with no significant side effects. It helps in improving depression and quality of life-related to erectile dysfunction.

Other treatment strategies of ED in CLD:

Intramuscular testosterone supplementation, testosterone has been shown to be beneficial in increasing muscle mass and improving sarcopenia, which can indirectly benefit SD as sarcopenia has been shown to be associated with ED. This may help with sexual frailty in an overall sense. But direct data on sexual function is not available.

Role of Albumin: No direct evidence is available on this hypothesis, but this seems to be logical by adequately controlling the primary liver diseases with the help of albumin, which may help in sexual frailty. Our hypothesis suggests that reduced serum albumin may affect the ratio of free albumin to bound testosterone with a possible altered testosterone response. Therefore, improving albumin concentration might be helpful in ED and testosterone is more likely to be beneficial in patients with high albumin levels. Therefore, regular albumin therapy and high protein intake may be somewhat indirectly helpful in improving sexual dysfunction. This hypothesis needs to be confirmed in prospective trials.

Liver transplantation and sexual functions:

Improvement in SD has not been consistently reported after liver transplantation. This needs more randomised trials for better understanding. There are a few contradictory studies, so there needs to be more randomised trials in both genders in this area. Improvement in erectile function is associated with the absence of hypogonadism before living donor liver transplant (LDLT). However, after transplantation, up to
25% of patients report persistent sexual dysfunction, and approximately one-third of patients describe the appearance of de novo sexual dysfunction. The use of PDE-5 inhibitors has been reported in post-renal transplant recipients with erectile dysfunction without any drug interactions with immunosuppression or side effects.

**Side effects of PDE Inhibitors:**

PDE5 inhibitors are generally well tolerated for the treatment of ED. The most common reported adverse drug reactions include headaches, back pain, myalgia, flushing, nasal congestion, sore throat, and dyspepsia. In general, the pain is of mild to moderate severity, typically occurring 12–24 h post administration and usually resolving within 48 h, with or without medical treatment, like acetaminophen.

**Studies of HVPG changes with PDE-5 inhibitors (shown in table 2):**

In a study, higher MELD scores and higher HVPG values were found in patients with ED. PDE-5 inhibitors have been studied to lower portal pressure in cirrhosis but results are conflicting.1,43-48

**Abbreviations:**

ED-Erectile Dysfunction, SD-Sexual dysfunction, FSD-Female sexual dysfunction, CTP-Child-Turcotte Pugh, CLD-chronic liver disease, IIEF-International Index of Erectile Function, QoL-Quality of life, RCT-Randomized controlled trial, HVPG-Hepatic venous pressure gradient, ASMI-appendicular skeletal muscle index, qADAM-quantitative Androgen Deficiency in the Aging Male, SF 36-Short Form (36) Health Survey, PHQ9-Patient Health Questionnaire 9, GAD7-Generalized Anxiety Disorder 7 questionnaire, SHBG-Sex hormone-binding globulin, SEP-Sexual Encounter Profile, MELD-Model for end-stage liver diseases, beta-blockers (BB), Sexual Encounter Profile (SEP) and Global Assessment Question (GAQ), complementary alternative medications (CAM), herbs, Over the counter drugs (OTC), Mycophenolate mofetil (MMF), Live donor liver transplantation (LDLT)

**CONCLUSION**
Sexual Dysfunction in liver diseases is one of the most ignored health issues and we need more prospective studies in this area which is potentially treatable. In particular, PDE inhibitors, especially Tadalafil, are helpful in erectile dysfunction in males, and in females, treatment is multifactorial. Adequate control of primary liver diseases and causative agents for SD is warranted. All liver diseases and cirrhosis patients should be evaluated, as these are modifiable and treatable aspects and result in an improved quality of life. More prospective and randomized controlled trials are needed in this area, particularly to understand the global epidemiology of the disease burden, possible underlying mechanisms, particularly in non-hormonal aspects and sarcopenia, and possible newer treatment options.
<table>
<thead>
<tr>
<th>#</th>
<th>Source Description</th>
<th>Words</th>
<th>Similarity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Marie Sinclair, Mathis Grossmann, Paul Gow, Peter Angus. &quot;In reference to higher serum testosterone is associated with increased risk of advanced hepatitis c-related liver disease in males&quot;, Hepatology, 2012</td>
<td>67</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>patient.info</td>
<td>67</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>Shereen Shoukry Hunter, Amr Gadallah, Maan Khalaf Azawi, Wahid Doss. &quot;Erectile dysfunction in patients with chronic hepatitis C virus infection&quot;, Arab Journal of Gastroenterology, 2014</td>
<td>64</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>care.diabetesjournals.org</td>
<td>60</td>
<td>2%</td>
</tr>
<tr>
<td>5</td>
<td>onlinelibrary.wiley.com</td>
<td>50</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>assets.researchsquare.com</td>
<td>47</td>
<td>1%</td>
</tr>
<tr>
<td>7</td>
<td><a href="http://www.pubfacts.com">www.pubfacts.com</a></td>
<td>44</td>
<td>1%</td>
</tr>
<tr>
<td>8</td>
<td>aasldpubs.onlinelibrary.wiley.com</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Matthew C Babcock, Lyndsey E DuBose, Teresa L Witten, Brian L Stauffer et al. "Oxidative Stress and Inflammation Are Associated With Age-Related Endothelial Dysfunction in Men With Low Testosterone", The Journal of Clinical Endocrinology & Metabolism, 2022

www.aerzteblatt.de