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Sexual dysfunction and dissatisfaction in chronic hepatitis C patients

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ABSTRACT

Introduction: The prevalence of sexual dysfunction (SD) and dissatisfaction with sexual life (DSL) in patients with chronic hepatitis C virus infection (CHC) was jointly investigated via a thorough psychopathological analysis, which included dimensions such as fatigue, impulsiveness, psychiatric comorbidity, health-related quality of life (HRQL) and sociodemographic and clinical characteristics. **Methods:** Male and female CHC patients from an outpatient referral center were assessed using the Brief Fatigue Inventory, the Barrat Impulsiveness Scale, the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale, the Hamilton Anxiety Scale (HAM-A), and the World Health Organization Quality of Life Scale-Brief Version (WHOQOL-BREF). Structured psychiatric interviews were performed according to the Mini-International Neuropsychiatric Interview. SD was assessed based on specific items in the BDI (item 21) and the HAM-A (item 12). DSL was assessed based on a specific question in the WHOQOL-BREF (item 21). Multivariate analysis was performed according to an ordinal linear regression model in which SD and DSL were considered as outcome variables. **Results**: SD was reported by 60 (57.1%) of the patients according to the results of the BDI and by 54 (51.4%) of the patients according to the results of the HAM-A. SD was associated with older age, female gender, viral genotype 2 or 3, interferon-α use, impulsiveness, depressive symptoms, antidepressant and benzodiazepine use, and lower HRQL. DSL was reported by 34 (32.4%) of the patients and was associated with depressive symptoms, anxiety symptoms, antidepressant use, and lower HRQL. **Conclusions**: The prevalence of SD and DSL in CHC patients was high and was associated with factors, such as depressive symptoms and antidepressant use. Screening and managing these conditions represent significant steps toward improving medical assistance and the HRQL of CHC patients.

Keywords: Hepatitis C. Sexual dysfunction. Sexual dissatisfaction. Interferon-α. Health-related quality of life.

INTRODUCTION

Sexual dysfunction (SD) and dissatisfaction with sexual life (DSL) are common among men and women and are more frequently observed among those suffering from chronic medical conditions[1]. Chronic infection with hepatitis C virus (CHC) is a worldwide health problem that affects approximately 160 million people[2]. Sexual transmission of the hepatitis C virus (HCV) has been thoroughly investigated; however, studies of SD and satisfaction with sexual life among CHC patients are scarce[3].

Sexual dysfunction appears to be more frequent among CHC patients than among the general population[4]. Data suggest an association between interferon (IFN)-α, the standard treatment for CHC, and SD[5-7]. In addition, IFN-α is frequently associated with psychiatric adverse events, such as depressive disorders that occur in approximately 30% of patients[8]. Depressive disorders and antidepressant use are commonly associated with SD in the general population[9]. Most studies of SD in CHC patients have focused on male patients[3,5-7,10-13]. Few studies have systematically investigated SD in women with CHC. Soykan et al. performed a cross-sectional study of 46 IFN-α-naive CHC patients and found higher rates of SD in women (50%) than in men (21%)[14]. More recently, Elshimi et al. evaluated SD in women with CHC before IFN-α treatment and in controls[15]. They found a significantly higher prevalence of SD in the women with CHC than in the controls (79% and 21%, respectively).

In the general population, SD typically impairs quality of life, but few studies have systematically evaluated the impact of SD on quality of life among CHC patients[4,5]. Most studies that have investigated the psychopathological and psychiatric factors that are associated with SD in CHC patients used only depressive or anxiety inventories[4,14]. Several studies focused on the effects of IFN-α on sexual function[5-7]. Other psychopathological dimensions, such as fatigue, impulsiveness, psychiatric comorbidities assessed using structured interviews, and health-related quality of life (HRQL), have not been jointly evaluated in the context of SD. Finally, no systematic study of SD has been conducted on Brazilian CHC patients.

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Therefore, the objective of this study was to investigate the prevalence of SD and DSL in CHC patients and to evaluate the sociodemographic, clinical and psychopathological characteristics that may be associated with these conditions.

METHODS

Study design, setting and participants

From May 2009 to April 2013, a cross-sectional study of CHC patients was performed at a public university-based outpatient clinic for infectious diseases (Centro de Treinamento e Referências em Doenças Infecciosas e Parasitárias Orestes Diniz - Secretaria Municipal de Saúde de Belo Horizonte e Universidade Federal de Minas Gerais/CTR DIP Orestes Diniz-SMSA-BH/UFMG) in Belo Horizonte, Brazil. All of the patients in this study were older than 18 years of age, displayed anti-HCV antibody positivity for more than six months according to a third-generation enzyme-linked immunosorbent assay (ELISA) and expressed hepatitis C virus (HCV) ribonucleic acid (RNA) as detected by polymerase chain reaction (PCR) (AMPLICOR, Roche Molecular Systems). Patients were excluded from the study if they exhibited co-infection with the hepatitis B virus or human immunodeficiency virus (HIV) or a low score on the Mini-Mental Status Examination, which was suggestive of a cognitive deficit. This report is a component of a major project investigating the psychopathological characteristics of CHC patients and the clinical and laboratorial correlates of these characteristics[16,17].

Procedures

All of the patients were assessed on the same day as a routine clinical consultation. Sociodemographic, clinical and laboratory data, including liver biopsy and corresponding METAVIR scores and the alanine aminotransferase and hemoglobin levels, were obtained. Additionally, the presence of comorbid conditions was assessed via chart review.

The patients were assessed using the Brief Fatigue Inventory (BFI)[18], the Barrat Impulsiveness Scale (BIS)[19], the Beck Depression Inventory (BDI)[20,21], the Hospital Anxiety and Depression Scale (HADS)[22,23], the Hamilton Anxiety Scale (HAM-A)[24,25] and the World Health Organization Quality of Life Scale-Brief Version (WHOQOL-BREF)[26,27]. Structured psychiatric interviews were performed according to the Mini-International Neuropsychiatric Interview[28,29].

Sexual disfunction was assessed based on specific items in the BDI (item 21; loss of libido) and the HAM-A (item 12; loss of libido, premature ejaculation, erectile dysfunction and impotence). In the HAM-A, we distinguished between urinary symptoms and amenorrhea and SD symptoms. However, we did not distinguish between the individual SD symptoms listed in item 12 of the HAM-A. Any degree of symptoms (a score other than zero) in the BDI and the HAM-A was sufficient to consider the presence of SD. The BDI has been used previously for the assessment of SD[30,31]. The use of two instruments to assess SD displays several benefits. Because the BDI is a self-rated questionnaire and the HAM-A is a scale consisting of direct questioning by interviewers, an investigation of SD using these two methods may reduce underreporting of SD. The BDI provides specific information about the loss of libido, whereas the HAM-A provides broader information regarding SD. DSL was assessed based on a specific question in the WHOQOL-BREF (item 21, *How satisfied are you with your sex life?*).

Data analyses

Pearson's chi-squared test was performed for univariate analysis of the categorical variables. The Kolmogorov-Smirnov test was used to determine whether the variables met the criteria of a normal distribution. One-way ANOVA and the Kruskal-Wallis Test were used for univariate analysis of continuous variables and to determine which variables displayed a normal or non-parametric distribution, respectively. Multivariate analysis was performed according to a proportional odds ordinal logistic regression model using a forward stepwise approach, and SD and DSL were considered as outcome variables. Before being entered into the final model of the multivariate analysis, the variables were grouped into the following three categories: sociodemographic, clinical and laboratory, and psychopathological. The preliminary multivariate analysis of each variable category only considered variables displaying significance values equal to or less than 0.20 (according to univariate analysis). After the preliminary multivariate analysis, variables displaying significance values equal to or less than 0.10 were entered into the final model. The tests were two-sided, and the significance threshold was fixed at α=0.05. Goodness of fit and a test of parallel lines were performed to validate model adjustment and assumption, respectively. Statistical Package for the Social Sciences (SPSS) version 20 (SPSS, Inc., Chicago, Illinois, USA) was used to conduct all of the statistical analyses.

Ethical considerations

This study was approved by the local ethics committee, and all subjects provided their written informed consent.

RESULTS

Overall, 113 CHC patients were assessed for eligibility, and a total of 105 patients were enrolled in the study. Four patients refused to participate, and four patients displayed scores on the Mini-Mental Status Examination that were suggestive of cognitive impairment. The 105 enrolled patients were compared with the eight patients who did not enter the study, and no significant differences were found in any sociodemographic or clinical characteristic between these patients.

Table 1 depicts the sociodemographic, clinical and laboratory characteristics of the patients. The mean age of the patients was 51 years (range 26-72 years). The patients were evenly distributed according to gender, relationship status (predominantly married), and education (approximately nine years). Among the patients who were not currently employed (n=55), the majority (n=35) were retired. The majority of patients (n=48) had never used IFN-α. However, 27 patients were currently on IFN-α treatment, and 30 patients

TABLE 1 - Sociodemographic, clinical and laboratory characteristics of 105 CHC patients.

Characteristic	N (%) or mean [median] ± standard deviation
Sociodemographic	
age (years)	50.8 [51.0] ± 11.5
gender (male)	51 (48.6)
years of education	8.4 [8.0] ± 4.6
never married	22 (21.0)
married or in a relationship	60 (57.1)
divorced or widowed	23 (21.9)
currently employed	50 (47.6)
Clinical and laboratory	
current tobacco use	23 (21.9)
BMI	27 [25.7] ± 6.4
history of diabetes	11 (10.5)
history of hypertension	41 (39.0)
history of comorbidity	23 (21.9)
years since CHC diagnosis	5.5 [4.0] ± 4.5
viral genotype 1	78 (76.5)
METAVIR A ≥2*	37 (47.8)
METAVIR F ≥2*	50 (54.3)
ALT (IU/L)	64.4 [46.0] ± 62.5
hemoglobin (g/dL)	13.7 [14.2] ± 2.3
IFN-α naive	48 (45.7)
current IFN-α use	27 (25.7)
past IFN-α use	30 (28.6)
current antidepressant use	13 (12.4)
current benzodiazepine use	18 (17.1)

BMI: body mass index; **CHC:** chronic hepatitis C; **ALT:** alanine aminotransferase; **IU/L:** international unit per liter; **IFN-α**: interferon-α. Liver biopsy results were available for 92 (87.6%) of the patients.

had previously used IFN-α, with the last dose used at least one year before the interview. In the group of patients currently on IFN-α, the mean duration of IFN-α use at the time of the interview was 18.9 weeks, with a standard deviation of 8.7 weeks.

Thirteen (12.4%) patients reported current antidepressant use, and 18 (17.1%) patients reported current benzodiazepine use. The reported antidepressants included selective serotonin reuptake inhibitors (n=9), serotonin-norepinephrine reuptake inhibitors (n=2), and tricyclics (n=2).

Overall, SD was reported by 60 (57.1%) patients according to the results of the BDI and by 54 (51.4%) patients according to the results of the HAM-A. Twenty-six (24.8%) patients were less interested in sex than they used to be. Additionally, 16 (15.2%) patients were much less interested in sex, and 18 (17.1%) patients completely lost their interest in sex. A significant association was found between SD according to the results of the BDI and the SD according to the results of the HAM-A ($p<0.001$).

Among the male patients (n=51), SD was reported by 23 (45.1%) patients: 16 (42.1%) without current IFN-α use and 7 (53.8%) with current IFN-α use (p=0.46). Among the female patients (n=54), SD was reported by 37 (68.5%) patients: 24 (60%) without current IFN-α use and 13 (92.8%) with current IFN-α use (p=0.04). Interestingly, a 43-year-old female patient reported an increase in libido during the last two months of IFN-α treatment. This patient reported that her libido returned to pre-treatment levels three weeks after the end of antiviral treatment.

Satisfaction with sexual life was reported by the following patients: 47 (44.8%) patients were very satisfied or satisfied, 24 (22.9%) patients were neither satisfied nor dissatisfied, and 34 (32.4%) patients were dissatisfied or very dissatisfied. DSL was found more frequently among female (40.7%) patients than among male (23.5%) patients (p=0.04).

The following variables entered into the multivariate analysis as potential factors associated with SD: age, gender, and employment status (sociodemographic); the alanine aminotransferase levels, the hemoglobin levels, viral genotype, IFN-α use, inflammatory activity, and fibrosis based on a liver biopsy (clinical and laboratory data); impulsiveness, fatigue, and depressive or anxiety symptoms (psychopathological); and alcohol use disorders, depressive disorders, and antidepressant and benzodiazepine use (psychiatric).

The following variables entered into the multivariate analysis as potential factors associated with DSL: gender and marital status (sociodemographic); the alanine aminotransferase levels, the hemoglobin levels, clinical comorbidities, body mass index, viral genotype, IFN-α use, and years since CHC diagnosis (clinical and laboratory data); tobacco use (epidemiological); impulsiveness, fatigue, and depressive or anxiety symptoms (psychopathological); alcohol use disorders, depressive and anxiety disorders, and antidepressant and benzodiazepine use (psychiatric).

Table 2 shows the results of the multivariate analysis for SD according to the outcome variables. Overall, the following factors were associated with SD: female gender (OR=5.36, 95% CI=2.24-12.83), current employment (OR=6.20, 95% CI=2.52-15.25), viral genotype 2 or 3 (OR=3.78, 95% CI=1.41-10.09), impulsiveness (OR=1.04, 95% CI=1.01-1.09), depressive symptoms (OR=1.22, 95% CI=1.10-1.35), and antidepressant use (OR=7.74, 95% CI=2.46-24.32) according to the results of the BDI. In addition, older age (OR=1.05, 95% CI=1.01-1.10), viral genotype 2 or 3 (OR=4.09, 95% CI=1.61-10.37), current IFN-α use (OR=4.50, 95% CI=1.59-12.79), depressive symptoms (OR=1.15, 95% CI=1.05-1.28), and benzodiazepine use (OR=3.74, 95% CI=1.23-11.39) were associated with SD according to the results of the HAM-A. DSL was associated

TABLE 2 - SD and DSL among 105 CHC patients according to ordinal linear regression multivariate analysis: odds ratio (95% confidence interval).

	SD (BDI)	SD (HAM-A)	DSL (WHOQOL-BREF)
Age (older)		1.05 (1.01 - 1.10)	
Gender (female)	5.36 (2.24 - 12.83)		
Current employment	6.20 (2.52 - 15.25)		
Virus genotype 2 or 3	3.78 (1.41 - 10.09)	4.09 (1.61 - 10.37)	
IFN-α use		4.50 (1.59 - 12.79)	
Impulsiveness	1.04 (1.01 - 1.09)		
Depressive symptoms	1.22 (1.10 - 1.35)	1.15 (1.05 - 1.28)	1.13 (1.02 - 1.25)
Anxiety symptoms			1.15 (1.04 - 1.28)
Antidepressant use	7.74 (2.46 - 24.32)		4.14 (1.53 - 11.25)
Benzodiazepine use		3.74 (1.23 - 11.39)	

SD: sexual dysfunction; **DSL:** dissatisfaction with sexual life; **CHC:** chronic hepatitis C; **BDI:** Beck Depression Inventory; **HAM-A:** Hamilton Anxiety Scale; **WHOQOL-BREF:** World Health Organization Quality of Life Scale-Brief Version; **IFN-α:** interferon-α. The blank spaces refer to differences that are not significant.

with depressive symptoms (OR=1.13, 95% CI=1.02-1.25), anxiety symptoms (OR=1.15, 95% CI=1.04-1.28), and antidepressant use (OR=4.14, 95% CI=1.53-11.25).

Additional univariate and multivariate analyses were performed, and the sample was stratified by gender (data shown in **Table 3**). These analyses demonstrated that lower hemoglobin levels (OR=1.87, 95% CI=1.12-2.87) were associated with SD in men and that fatigue (OR=1.50, 95% CI=1.21-1.86) was associated with SD in women.

Table 4 shows the results of a comparison of HRQL according to the WHOQOL-BREF in CHC patients with or without reported SD according to the BDI and the HAM-A, and in patients with or without reported DSL. The patients with reported SD according to the BDI and the HAM-A displayed worse HRQL scores in the following domains: physical ($p<0.001$ and $p<0.001$, respectively), psychological ($p<0.001$ and $p<0.001$, respectively), social ($p<0.001$ and $p<0.001$, respectively), environmental ($p<0.002$ and $p<0.020$, respectively), and overall HRQL ($p<0.008$ and $p<0.001$, respectively). In addition, the patients with reported DSL displayed worse HRQL scores in the following domains: physical ($p=0.001$), psychological ($p<0.001$), social ($p<0.001$), environmental ($p=0.003$), and overall HRQL ($p<0.001$).

In an additional analysis that was stratified by gender (**Table 5**), SD and DSL were associated with lower HRQL in both male and female patients. Furthermore, this analysis indicated that SD and DSL were associated with worse HRQL scores in all of the domains.

When the sample was stratified into two groups according to age (<40 and ≥40 years), all of the parameters associated with SD in the multivariate analysis remained the same, excluding viral genotype 2 or 3 and antidepressant use, which persisted only among older (≥40 years) patients.

DISCUSSION

Our study revealed that SD was prevalent in patients with CHC and occurred in more than half of these patients. SD was associated with older age, female gender, current employment, viral genotype 2 or 3, current IFN-α use, impulsiveness, depressive symptoms, and use of antidepressants and benzodiazepines. DSL was reported by one-third of the patients and was associated with depressive symptoms, anxiety symptoms, and antidepressant use.

The prevalence of SD in this study was higher than that reported for the general Brazilian population: 49% for women[32] and 45% for men[33]. Dove et al. studied male patients with CHC before and during IFN-α treatment and found that the prevalence of SD varied from 39% before antiviral treatment to up to 58% at week four of treatment. In addition, they found that the prevalence of DSL varied from 44% before antiviral treatment to up to 51% at week 24 of treatment[5]. In this previous study, only a few patients reported improvement in their sexual life during IFN-α use, which is in agreement with our finding of a female patient who reported an increase in libido during the last two months of antiviral treatment.

We found a lower prevalence of SD among female patients than that observed by Elshimi et al. in Egypt. They found that 79% of patients suffered from SD before the onset of IFN-α treatment[15]; however, in addition to sociocultural differences between Egypt and Brazil, 63.4% of the female patients in this previous study had been subjected to female genital cutting, which may have impaired sexual function. According to these authors, "In a society like Egypt, (…) discussion of sexual desires and function, especially with females, is considered unacceptable by many". Soykan et al. found that the prevalence of SD among male and female

TABLE 3 - SD and DSL among 51 male and 54 female CHC patients according to ordinal linear regression multivariate analysis: odds ratio (95% confidence interval).

51 males	SD (BDI)	SD (HAM-A)	DSL (WHOQOL-BREF)	54 females	SD (BDI)	SD (HAM-A)	DSL (WHOQOL-BREF)
Age (older)		1.20 (1.05 - 1.36)					
Current employment	14.8 (2.88 - 75.57)						
Clinical comorbidity (other)	12.37 (1.63 - 93.65)						
Virus genotype 2 or 3		12.97 (2.11 - 79.55)		Genotype 2 or 3	6.24 (1.67 - 23.30)	3.95 (1.10 - 14.10)	
Hemoglobin (g/dL)		1.87 (1.12 - 2.87)					
Depressive symptoms		1.36 (1.08 - 1.72)	1.34 (1.09 - 1.64)				
Anxiety symptoms	1.29 (1.08 - 1.52)		1.26 (1.06 - 1.50)	Anxiety symptoms			1.14 (1.02 - 1.28)
Fatigue				Fatigue	1.50 (1.21 - 1.86)		
Antidepressant use	26.19 (3.07 - 223.18)	18.60 (1.43 - 241.14)	118.95 (5.15 - 2744.75)	Antidepressant use	8.85 (2.20 - 35.63)		
Benzodiazepine use			33.46 (2.10 - 531.98)	Benzodiazepine use		8.52 (2.18 - 33.33)	3.96 (1.14 - 13.83)

SD: sexual dysfunction; **DSL:** dissatisfaction with sexual life; **CHC:** chronic hepatitis C; **BDI:** Beck Depression Inventory; **HAM-A:** Hamilton Anxiety Scale; **WHOQOL-BREF:** World Health Organization Quality of Life Scale Brief Version. The blank spaces refer to differences that are not significant.

Turkish CHC patients before antiviral treatment was 21% and 50%, respectively[14]. Compared with this previous study, the prevalence of SD in the current study was higher for men and similar for women. These divergent results suggest that socio-cultural aspects should be considered when analyzing issues of sexuality; therefore, regional studies of SD are important[1]. In addition, methodological discrepancies, such as the use of different instruments to assess SD and the exclusion of clinical comorbidities, must be taken into account.

Previous studies in the general population[33,34] and in CHC patients[3,14,31] have demonstrated that older age is a risk factor for SD. This study found that older age was associated with SD only among men.

We were not able to fully explain the association between employment and SD. The burden of stress that is associated with an excessive work load may impair sexual function. Data from the Brazilian Study of Sexual Behavior suggested that an excessive work load and the lack of spare time were significant deleterious factors that affect sexual function in 27% and 19% of men, respectively[35].

Biological or virological factors may contribute to SD in CHC patients. Danoff et al.[4] found that HCV genotypes 2 and 3 were significantly associated with DSL. This result is consistent with our finding that HCV genotypes 2 and 3 were associated with SD. Additionally, Danoff et al. found that SD and DSL were associated with worse HRQL both in the physical and mental subscales. The results of the current study indicated an association between SD, DSL and worse HRQL, which is consistent with their findings. To the best of our knowledge, no prior studies have systematically evaluated the impact of SD on HRQOL in women with CHC. In a secondary analysis, Bonkovsky et al. investigated changes in HRQL and sexual health in a subset of male and female patients with and without a sustained virological response[31]. SD was strongly associated with female gender, older age, higher BDI score, statin use, and concomitant use of antidepressants and anxiolytic drugs. They found that a sustained virological response was associated with an improvement in HRQL and sexual health. Previous studies in men without HCV infection demonstrated that SD was associated with worse HRQL and that HRQL improved in men who were treated for erectile dysfunction[36,37]. Danoff et al[4]. investigated the impact of SD on HRQL in men with CHC and found that this association was independent of depression[4].

Kraus et al. prospectively investigated SD in male CHC patients during conventional IFN-α treatment[7]. They found that androgen reduction and depressive symptoms, most likely caused by IFN-α, independently and negatively affected sexual function. The association between IFN-α use, androgen reduction and SD was found by Malaguarnera et al. in a prospective analysis[6]. In this study, the greatest degree of SD occurred during the third month of IFN-α treatment. At the end of this treatment, all of the mean scores were similar to the pretreatment scores. In comparison, the patients who were on IFN-α in the current study were evaluated at a later time point, i.e., the fourth and fifth months. Despite this time difference, our study confirmed that current IFN-α use was associated with SD.

Depression and anxiety disorders are commonly associated with SD[36,38-40]. The results of the current study revealed that depressive symptoms were associated with SD and DSL in CHC patients. This finding is similar to that observed in the general population[1,32,33]. Similarly, Baranyi et al. suggested that impaired sexual satisfaction was a contributing factor to IFN-α-induced depression[41]. We found that impulsiveness was associated with SD. Classically, impulsiveness has been associated with hypersexuality and compulsive/impulsive sexual behavior[42]. We found that impulsiveness was frequent in CHC patients and was associated with current IFN-α use and several psychopathological changes, such as anxiety symptoms and alcohol use disorder[17].

The results of this study indicated that antidepressant use was associated with SD and DSL. The patients on antidepressants were predominantly using selective serotonin reuptake inhibitors as recommended to prevent and treat IFN-α-induced depression[43-45]. Dove et al. studied male CHC patients and found that SD, more specifically the loss of libido and erectile dysfunction, was associated with depressive symptoms and antidepressant use[5]. Accordingly, guidelines should consider recommending antidepressants displaying different profiles regarding sexual adverse effects, such as mirtazapine and bupropion[46,47]. The association between benzodiazepines and SD has been demonstrated previously in psychiatric outpatients[48].

In a study by Castera et al., sexual life changes were significantly associated with higher perceived disease severity and anxiety, which suggests that diagnosis-related stress could play a prominent role in these behavioral changes[49]. This finding is in agreement with our finding of an association between anxiety symptoms and DSL.

This study contains several limitations. The patients were recruited from a referral center and may not have reflected the overall population of CHC patients. This study did not use structured interviews or specific instruments for the comprehensive assessment of SD because the data were extracted from a broader project investigating the psychopathological characteristics of CHC patients[16,17]. In this context, we did not distinguish between specific SD symptoms, such as the loss of libido, premature ejaculation, erectile dysfunction and impotence. The two instruments (BDI and HAM-A) that were used to investigate SD were correlated but provided complimentary information about sexual life determinants (**Table 2**), which indicates that each instrument assessed different dimensions of SD. Furthermore, only the presence of SD symptoms was considered in the analyses, whereas the severity of these symptoms was not considered. Moreover, the sexual response cycle includes more dysfunctions than those assessed in this study. We did not perform laboratory testing for testosterone, other sex hormones, or serum cryoglobulins. We did not account for the use of oral contraceptives. A potential limitation of this study was the absence of a control group of patients with chronic hepatitis due to another viral agent (e.g., hepatitis B) who may have been matched for age, race/ethnicity, and the severity

TABLE 4 - A comparison of HRQL in 105 CHC patients with or without reported SD according to the BDI and the HAM-A, and with or without reported DSL.

HRQL	Patients without reported SD-BDI (n=45)	Patients with reported SD-BDI (n=60)	*p* value	Patients without reported SD-HAM-A (n=51)	Patients with reported SD-HAM-A (n=54)	*p* value	Patients without reported DSL (n=71)	Patients with reported DSL (n=34)	*p* value
Physical domain	68.02 [67.86] ± 17.50	50.00 [50.00] ± 17.59	<0.001	65.71 [67.86] ± 17.10	47.06 [46.43] ± 17.76	<0.001	62.17 [64.29] ± 18.69	48.42 [46.43] ± 18.49	0.001
Psychological domain	72.69 [79.17] ± 14.31	57.78 [62.50] ± 18.55	<0.001	70.14 [70.83] ± 15.31	56.20 [58.33] ± 19.19	<0.001	69.25 [70.83] ± 15.01	53.55 [52.08] ± 20.29	<0.001
Social domain	72.41 [75.00] ± 20.01	51.25 [50.00] ± 21.25	<0.001	68.33 [66.67] ± 20.23	49.63 [50.00] ± 22.68	<0.001	70.89 [75.00] ± 17.24	38.24 [41.67] ± 17.78	<0.001
Environmental domain	63.13 [62.50] ± 14.65	53.65 [53.13] ± 14.13	0.002	60.89 [59.38] ± 14.30	53.47 [56.25] ± 15.12	0.020	60.83 [59.38] ± 14.37	51.19 [51.56] ± 14.52	0.003
Overall	66.39 [75.00] ± 22.59	55.21 [50.00] ± 22.58	0.008	69.38 [75.00] ± 17.29	47.50 ± [50.00] 24.22	<0.001	65.67 [75.00] ± 20.99	48.16 [50.00] ± 23.26	<0.001

SD: sexual dysfunction; **DSL:** dissatisfaction with sexual life; **BDI:** Beck Depression Inventory; **HAM-A**: Hamilton Anxiety Scale; **HRQL:** health-related quality of life; **CHC:** chronic hepatitis C. The scores for each of the four domains of HRQL ranged from 0-100; higher scores indicated better HRQL. Mean [median] ± standard deviation.

TABLE 5 - A comparison of HRQL in 51 male and 54 female CHC patients with or without reported SD according to the BDI and the HAM-A and with or without reported DSL.

HRQL	Patients without reported SD-BDI (n=28)	Patients with reported SD-BDI (n=23)	p value	Patients without reported SD-HAM-A (n=30)	Patients with reported SD-HAM-A (n=21)	p value	Patients without reported DSL (n=39)	Patients with reported DSL (n=12)	p value
Males (51)									
physical domain	70.03 [69.64] ± 17.98	56.06 [57.14] ± 17.51	0.009	74.11 [73.21] ± 13.60	51.08 [50.00] ± 16.87	<0.001	67.86 [67.86] ± 16.41	50.30 [44.64] ± 21.07	0.009
psychological domain	73.07 [72.92] ± 13.34	58.33 [62.50] ± 16.23	0.002	73.66 [70.83] ± 11.00	57.60 [58.33] ± 17.62	0.001	71.26 [70.83] ± 12.60	50.69 [56.25] ± 17.66	0.001
social domain	68.75 [66.67] ± 18.79	47.46 [50.00] ± 21.97	0.001	67.86 [66.67] ± 18.94	48.55 [50.00] ± 22.84	0.001	67.74 [66.67] ± 16.90	31.25 [33.33] ± 15.94	<0.001
environmental domain	60.27 [59.38] ± 13.71	52.85 [53.13] ± 16.15	0.095	60.83 [60.94] ± 13.35	52.17 [56.25] ± 16.16	0.063	58.89 [56.25] ± 13.84	50.52 [50.00] ± 18.07	0.204
overall	65.18 [68.75] ± 21.88	58.15 [62.50] ± 21.52	0.209	72.32 [75.00] ± 14.97	49.46 [50.00] ± 22.45	<0.001	66.67 [75.00] ± 19.09	46.88 [43.75] ± 23.91	0.007
Females (54)									
physical domain	64.71 [67.86] ± 16.65	46.24 [46.43] ± 16.79	<0.001	58.37 [58.93] ± 16.61	42.85 [42.85] ± 18.08	0.003	55.25 [57.14] ± 19.20	47.40 [48.21] ± 17.36	0.131
psychological domain	72.06 [79.17] ± 16.19	57.43 [62.50] ± 20.06	0.011	67.06 [70.83] ± 17.88	54.73 [52.08] ± 21.02	0.033	66.80 [70.83] ± 17.41	55.11 [50.00] ± 21.82	0.063
social domain	78.43 [83.33] ± 21.05	53.60 [58.33] ± 20.74	<0.001	68.75 [75.00] ± 21.59	50.76 [54.17] ± 22.99	0.008	74.74 [75.00] ± 17.13	42.05 [41.67] ± 17.91	<0.001
environmental domain	67.83 [68.75] ± 15.34	54.14 [53.13] ± 12.93	0.003	60.94 [59.38] ± 15.29	54.83 [54.69] ± 14.20	0.168	63.18 [62.50] ± 14.87	51.56 [51.56] ± 12.64	0.005
overall	68.38 [75.00] ± 24.25	53.38 [50.00] ± 23.32	0.021	66.80 [68.75] ± 18.94	45.45 [50.00] ± 26.32	0.003	64.45 [62.50] ± 23.36	48.86 [50.00] ± 23.44	0.025
physical domain	64.71 [67.86] ± 16.65	46.24 [46.43] ± 16.79	<0.001	58.37 [58.93] ± 16.61	42.85 [42.85] ± 18.08	0.003	55.25 [57.14] ± 19.20	47.40 [48.21] ± 17.36	0.131

HRQL: health-related quality of life; **CHC:** chronic hepatitis C; **SD:** sexual dysfunction; **BDI:** Beck Depression Inventory; **HAM-A:** Hamilton Anxiety Scale; **DSL:** dissatisfaction with sexual life. The scores for each of the four domains of HRQL ranged from 0-100; higher scores indicated better HRQL. Mean [median] ± standard deviation.

of liver disease. This study was a cross-sectional analysis; therefore, it was impossible to determine the causality between several of the variables and the presence of SD. We did not perform a longitudinal analysis to investigate whether SD and DSL persisted in patients who completed antiviral treatment. Because the age-stratified analysis implied minor changes in SD-associated variables and because the overall analysis contained more robust data regarding sample size, we did not focus on the former analysis. A large number of predictive variables relative to the sample size would lead to model overfitting and would impact the predictive performance of the model. Stepwise methods may not represent the optimal model when redundant predictors are present, and the number of candidate predictive variables may affect the number of noise variables that entered into the model. As stated by Greenland[50], "*To maximize the validity of model-based estimates, an investigator should use both the data and prior information to critically evaluate the epidemiologic assumptions implied by the model and the statistical assumptions required by the model.*" Prior information regarding the variables that are associated with SD or DSL in the general population and in CHC patients is in agreement with our findings (excluding the results for impulsiveness and viral genotype 2 or 3); therefore, the model in this study was probably adequate. These limitations indicate that the current study must be regarded as exploratory.

Because female gender is a risk factor for IFN-α-induced depression[8] and because our study found that female gender, IFN-α use and depressive symptoms/disorders were independently associated with SD, more attention regarding sexual satisfaction is warranted in clinical practice, especially when assessing women with CHC. The detection and management of SD represents a significant step toward improving medical care and the HRQL of CHC patients. As a working hypothesis, clinicians can screen the loss of libido using a single question (i.e., item 21 in the BDI) and subsequently assess SD and DSL in any patient displaying a score other than *zero*. Future longitudinal studies may clarify the individual burden of the hepatitis virus (and related biological mechanisms), comorbidities, IFN-α use and psychosocial characteristics on SD and DSL among CHC patients. The impact of novel non-IFN-α-based therapeutic strategies on sexual function must be systematically assessed.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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