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Erectile dysfunction in patients with chronic viral liver disease: its relevance to protein malnutrition

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Background. In patients with chronic liver disease (CLD), quality of life is generally accepted as poor, especially for physical function. However, sufficient data regarding erectile function has not been shown in patients with CLD. The international index of erectile function (IIEF) is widely used to assess erectile function, and a short form of the IIEF was recently developed (IIEF-5). Using this questionnaire, we evaluated erectile dysfunction (ED) in patients with CLD. ***Methods.*** A total of 117 Japanese patients (64 with chronic hepatitis [CH] and 53 with liver cirrhosis [LC]) were analyzed. The etiologies were hepatitis B virus (HBV) in 21, HCV in 94, and non-B non-C in 2. The IIEF-5 and Medical Outcomes Study Short Form 36 (SF-36) were administered to the patients, and biochemical analyses for items serum albumin, prothrombin time, bilirubin, and ammonia were also performed. ***Results.*** The incidence of ED was 85% in the total cohort with CLD, 78% in those with CH, and 92% in those with LC ($P < 0.05$ between CH and LC). ED was found in 50% of CLD patients under age 50 years, in 79% aged 50–59, and in 100% aged over 60 (P, overall <0.001). The scores for ED severity correlated with increasing grades of a modified Child-Pugh classification ($P < 0.05$). Simple regression analysis showed age ($P < 0.01$), physical function ($P < 0.001$), role physical ($P < 0.001$), and social functioning ($P < 0.05$) on the SF-36, and serum albumin ($P < 0.001$) as significant determinants of ED. Multiple regression analysis identified age ($P < 0.001$) and serum albumin ($P < 0.001$) as independent significant factors that determined ED. ***Conclusions.*** These data clearly demonstrate that liver disease is the cause of ED in patients with CLD, and serum protein status could be relevant to this condition in these patients.

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Introduction

Erectile dysfunction (ED) is defined by the National Institutes of Health (NIH) Consensus Development Conference as the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] Its prevalence is estimated to be about 32% among the male population in the United States[2] and about 26% in Japan.[3] Thus, ED is widely prevalent irrespective of ethnic groups, and it has become an increasing problem worldwide. While ED is not a life-threating disorder, its effect on quality-of-life (QOL) issues is significant.[3] However, assessment of ED has not been widely performed by physicians, because the laboratory-based diagnostic procedures are not convenient. In contrast, recent studies have demonstrated that the use of self-reported questionnaires is a valid and easy way to assess ED. The international index of erectile function (IIEF), developed by Rosen et al.,[4] has excellent reliability and sensitivity for assessing male erectile function. It consists of five domains and a 15-item questionnaire. Recently, a five-item version of the IIEF (IIEF-5) was developed to diagnose the presence and severity of ED, and this version has been validated as being as suitable as the original IIEF.[5]

The presence of various conditions affects erectile function. ED is significantly correlated with age, and many diseases, including hypertension,[6] diabetes mellitus,[7] hyperlipidemia,[8] heart disease,[9] chronic renal disease,[10] and neurologic disease[11] could also be in the etiological background of ED. Lifestyle-related factors such as smoking and drinking are also related.[12] In patients with chronic liver disease, QOL is poor due to

the disease itself and its complications, such as encephalopathy, ascites, edema, and muscle cramps.[13–15] Although some reports have referred to disturbed erectile function in patients with alcoholic liver disease,[16] such ED was due to alcohol abuse in most of the patients, and no definitive assessment of ED in patients with chronic viral liver disease has yet been carried out.

The aim of our study was to assess the prevalence of ED in patients with chronic viral liver disease, using the IIEF-5, and to explore its relevance to patients' clinical profiles and other QOL issues.

Patients and methods

Patients

One hundred and forty-eight outpatients with chronic liver disease (CLD), from four local hospitals in Gifu City, Japan, participated in this study. Chronic hepatitis (CH) and liver cirrhosis (LC) were diagnosed by clinical and laboratory profiles, and were confirmed by histological examination of liver biopsy specimens. All of the patients answered questionnaires regarding ED and QOL at their first visit to the liver unit.

We excluded patients complicated with any other major chronic disease that might influence erectile function, such as diabetes, hypertension, hyperlipidemia, alcohol abuse (including alcoholic liver disease), ischemic heart disease, renal disease, neurologic disease, and malignancy (including hepatocellular carcinoma). We also excluded patients with a past history of surgery for urological or bowel disease which might affect sexual potency. Patients who had answered two questionnaires incompletely were not included for further analysis. Medication was recorded as the current treatment, including drugs taken up to 6 months before the study commenced. No patient reported the use of prostaglandin E or sildenafil.

A total of 117 patients were finally eligible, aged from 30 to 79 years; 64 patients had CH and 53 had LC. Their demographic and clinical characteristics are given in Table 1. Although the age tended to be higher in patients with LC than in those with CH, the difference did

Table 1. Clinical characteristics of the patients

Characteristic	Total	Chronic hepatitis	Liver cirrhosis	Statistical significance[a]
No. of patients	117	64	35	—
Age (years)				
Under 50	22 (19%)	17 (27%)	5 (9%)	
50–59	33 (28%)	16 (25%)	17 (32%)	
Over 60	62 (53%)	31 (48%)	31 (58%)	NS
Modified Child-Pughs classification				
A	—	—	30 (57%)	
B	—	—	17 (32%)	
C	—	—	6 (11%)	
Etiology				
HBV	21 (18%)	13 (20%)	8 (15%)	
HCV	94 (80%)	51 (80%)	43 (81%)	
nBnC	2 (2%)	0 (0%)	2 (4%)	NS
Blood analysis				
Total bilirubin (mg/dl)	1.0 ± 0.1	0.8 ± 0.0	1.3 ± 0.1	$P < 0.01$
Albumin (g/dl)	3.9 ± 0.1	4.2 ± 0.0	3.5 ± 0.1	$P < 0.01$
AST (IU/l)	59 ± 4	51 ± 4	70 ± 8	$P < 0.01$
ALT (IU/l)	57 ± 4	59 ± 6	55 ± 5	NS
Total cholesterol (mg/dl)	152 ± 4	170 ± 5	139 ± 5	$P < 0.01$
Prothrombin time (%)	81 ± 2	100 ± 4	75 ± 2	$P < 0.01$
Ammonia (μg/dl)	63 ± 6	34 ± 4	74 ± 7	$P < 0.01$
Creatinine (mg/dl)	0.78 ± 0.02	0.78 ± 0.03	0.79 ± 0.04	NS
Platelets ($\times 10^4$/μl)	13.8 ± 0.6	16.8 ± 0.6	10.0 ± 0.7	$P < 0.01$
Free testosterone[b] (pg/ml)	10.4 ± 1.2	11.4 ± 1.1	9.8 ± 1.8	NS
Total testosterone[b] (ng/ml)	6.83 ± 0.37	6.81 ± 0.51	6.84 ± 0.52	NS
Estradiol[b] (pg/ml)	37.9 ± 1.9	32.0 ± 2.0	41.7 ± 2.6	$P < 0.05$

Values are expressed as means ± SEM
NS, not significant
[a] Between chronic hepatitis and liver cirrhosis by χ^2 test for age and etiology, and by Mann-Whitney *U*-test for blood analysis
[b] $n = 38$ (15 CH and 23 LC)

not reach statistical significance. The etiologies of the patients were hepatitis B virus in 21, hepatitis C virus in 94, and non-B non-C in 2. The modified Child-Pugh classification of cirrhotic patients was A in 30 patients, B in 17, and C in 6 (Table 1). As a control group, 94 healthy male volunteers, age ranging from 23 to 69 years, were examined. All patients and controls were Japanese. Informed consent was obtained from each subject. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in prior approval by each institution's review board for human research.

Methods

The Japanese version of the IIEF-5, which has been verified in terms of validity, reliability, and sensitivity,[5] was used in this study. The questionnaire consists of five items; confidence in maintaining erection, feasible erectile function, intercourse satisfaction, difficulty of erectile preservation, and overall satisfaction for the latest 6 months. Each item's maximal score is 5, giving a full score of 25 for the questionnaire. A patient with a score of less than 21 points is diagnosed as having ED.

We first administered both the IIEF and IIEF-5 to the initial 49 consecutive patients, and found a highly significant correlation between the scores of the two questionnaires (Fig. 1). For the rest of the patients and the controls, ED was assessed with the IIEF-5 alone. ED was classified, according to the score, into five grades of severity: no ED (score 22–25), mild (score 17–21), mild to moderate (score 12–16), moderate (score 8–11), and severe (score 1–7). We also administered the Medical Outcomes Study Short Form 36 (SF-36)[17] to the patients, which is validated to estimate QOL in patients with liver disease.[14] It contains 36 items, divided into eight domains: physical functioning, ability to perform expected physical roles, degree of bodily pain, overall sense of general health, vitality, ability to function in social roles, ability to perform expected emotional roles, and overall sense of mental health. The domain scores for SF-36 range from 0 to 100.

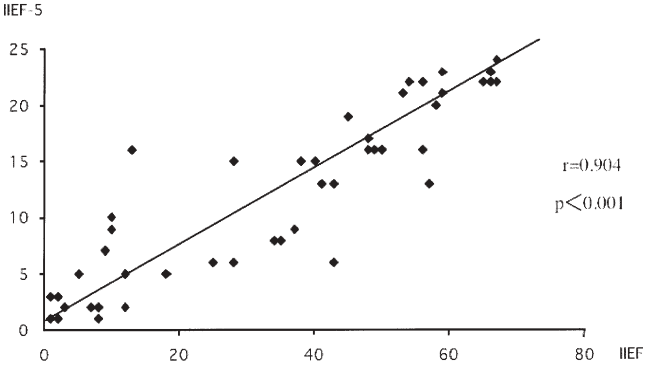

Fig. 1. Correlation between international index of erectile dysfunction (*IIEF*) and five-item version of IIEF (*IIEF*-5) scores in patients with chronic liver disease ($n = 49$)

Blood biochemical analyses, including total bilirubin, albumin, aspartate and alanine aminotransferases, total cholesterol, prothrombin time, ammonia, creatinine, and platelet count were performed using standard techniques. In 38 patients (15 with CH and 23 with LC), we also measured serum hormone levels, including total and free testosterone and estradiol.

Two patients were followed up for more than 6 months to see the changes in IIEF-5 and SF-36 scores after the attenuation of liver disease or the administration of sildenafil.

Statistical analysis

Data values were expressed as means and SEM. Differences in mean values were tested by analysis of variance (ANOVA), followed by the Mann-Whitney *U*-test. The χ^2 test (or contingency table analysis) was used to compare the distribution of individual variables among the patient groups. Simple and multiple regression analyses were used to identify significant determinants of ED. Correlations between two variables were calculated using Spearman's correlation coefficient. Differences were considered significant when *P* values were less than 0.05. All analyses were performed using Stat View 5.0 for Macintosh (SAS Institute, Cary, NC, USA).

Results

The numbers of control subjects sufficient for reliable statistical evaluation were 29 in those aged 40–49 and 23 in those aged 50–59. According to Marumo et al.[18] The incidence of ED of grades higher than "mild–moderate" (score under 16) was calculated in the controls and patients with CLD in each of these age groups (Table 2). The incidence was significantly higher in these with CLD than in controls at age 50–59, but not at age 40–49 years.

In the total of 117 CLD patients, 99 (85%) showed ED of any grade, including "mild" (Table 3). The incidence of ED in patients with LC (49/53; 92%) was sig-

Table 2. Incidence of erectile dysfunction of grades higher than "mild-moderate" (score under 16) in controls and patients with chronic liver disease aged 40–49 and 50–59

Age (years)	Control	Chronic liver disease
40–49	6/29 (21%)	5/16 (31%)
50–59	7/23 (30%)	21/33 (64%)*

* $P < 0.05$ as compared to controls age 50–59 by χ^2 test

Table 3. Incidence of erectile dysfunction (ED) in patients with chronic liver disease according to age

	Total		Chronic hepatitis		Liver cirrhosis	
Age (years)	ED[a]	Average ED score	ED[a]	Average ED score	ED[b]	Average ED score
Under 50	11/22 (50%)	17.8 ± 1.3	8/17 (47%)	19.1 ± 1.3	3/5 (60%)	15.2 ± 4.6
50–59	26/33 (79%)	14.4 ± 1.2[c]	11/16 (69%)	16.8 ± 1.5	15/17 (88%)	12.1 ± 1.6[f]
Over 60	62/62 (100%)	8.6 ± 0.8[d,e]	31/31 (100%)	10.6 ± 1.1[d,e]	31/31 (100%)	6.6 ± 1.1[c,e,g]
Total	99/117 (85%)	11.9 ± 0.7	50/64 (78%)	14.4 ± 1.2	49/53 (93%)[h]	9.0 ± 1.0[g]

ED scores are expressed as means ± SEM
[a] $P < 0.001$ and [b] $P = 0.052$ by χ^2 test
[c] $P < 0.05$ and [d] $P < 0.01$ as compared to under age 50, and [e] $P < 0.01$ as compared to age 50–59 by ANOVA followed by the Mann Whitney *U*-test
[f] $P < 0.05$ and [g] $P < 0.01$ as compared to chronic hepatitis by ANOVA followed by the Mann Whitney *U*-test
[h] $P < 0.05$ as compared to chronic hepatitis by χ^2 test

Table 4. ED severity in patients with chronic liver disease

				Liver cirrhosis		
ED severity	Score	Total	Chronic hepatitis	A	B	C
Severe	1–7	38 (32%)	11 (17%)	13 (43%)	11 (65%)	3 (50%)
Moderate	8–11	17 (15%)	10 (16%)	5 (17%)	0 (0%)	2 (33%)
Mild to moderate	12–16	24 (21%)	15 (23%)	5 (17%)	3 (18%)	1 (17%)
Mild	17–21	19 (16%)	14 (22%)	3 (10%)	2 (12%)	0 (0%)
No ED	22–25	19 (16%)	14 (22%)	4 (13%)	1 (6%)	0 (0%)
Total		117 (100%)	64 (100%)	30 (100%)	17 (100%)	6 (100%)

P overall = 0.028 by χ^2 test (5 × 4 contingency table analysis)

nificantly higher than that in patients with CH (50/64; 78%; $P < 0.05$). The incidence of ED rose significantly in parallel with the patients' ages in the total CLD cohort and in the patients with CH ($P < 0.001$; Table 3). The average ED score fell significantly in parallel with the patients' ages in the total CLD cohort, as well as in the subgroups of CH and LC patients ($P < 0.01$ for each by two-way ANOVA; Table 3). In those aged 50–59 and those over 60, the average ED score was significantly lower in the patients with LC than in those with CH ($P < 0.05$ and $P < 0.01$, respectively; Table 3).

The incidence of severe ED in patients with LC rose in the order of grades A, B, and C of liver dysfunction as assessed by the Child-Pugh classification ($P = 0.028$ by 5 × 4 contingency table analysis; Table 4).

The incidence of ED in HCV-positive patients (83/94; 88%) was significantly higher than that in HBV-positive patients (13/21; 62%; $P < 0.005$). The average ED score in the HCV-positive patients was significantly lower than that in the HBV-positive patients (11.2 ± 0.8 and 16.1 ± 1.6, respectively; $P < 0.01$ by the Mann Whitney *U*-test). However, this difference may have been due to the distribution of age rather than the different virus (50 ± 3 years in those with HBV and 62 ± 1 years in those with HCV; $P < 0.001$).

Simple regression analysis showed that the significant determinants of ED were age, physical function (PF) on the SF-36, role physical (RP) on the SF-36, social functioning (SF) on the SF-36, and serum albumin in laboratory data (Table 5; Fig. 2). Plasma levels of sex hormones did not significantly correlate with ED scores (Table 5). Among the five significant variables, multiple regression analysis identified age ($r = 0.683$; $P < 0.001$) and serum albumin ($r = 0.498$; $P < 0.001$) as significant independent determinants of ED.

The IIEF-5 and SF-36 scores were followed up in two patients. One was a 36-year-old patient with type C cirrhosis. He was suffering from severe ascites, his Child-Pugh classification was C, and his IIEF-5 score was nine. Daily oral administration of 40 mg furosemide and 12 g branched-chain amino-acid (BCAA) granules improved the serum albumin from 2.8 to 3.5 g/dl, and the ascites diminished in 8 months. His IIEF-5 and SF-36 scores were dramatically improved, as shown in Table 6. The other patient was 58 years old, with type C cirrhosis. His Child-Pugh classification was A and his IIEF-5 score was 12. The occasional use of sildenafil (50 mg) in 9 months of follow up raised his IIEF-5 score to 23, but the SF-36 scores remained unchanged (Table 6).

Table 5. Correlation between IIEF-5 score and SF-36 scores or biochemical data in patients with chronic liver disease

	Γ		Γ
Age	0.582**	T-bil	0.032
Modified Child-Pugh classification	0.158	Alb	0.491***
SF-36		AST	0.1
PE	0.390***	ALT	0.13
RP	0.385***	T-cho	0.138
BP	0.141	PT	0.045
GH	0.134	HPT	0.063
VT	0.138	NH_3	0.095
SF	0.195*	Cr	0.164
RE	0.017	Plt	0.161
MH	0.148	BS	0.045
		Free testosterone[a]	0.292
		Total testosterone[a]	0.090
		Estradiol[a]	–0.169

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ by simple regression analysis ($n = 117$)
PF, physical function; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotion; MH, mental health
[a] $n = 38$

Table 6. Changes in IIEF-5 and SF-36 scores before and after treatment in two patients with liver cirrhosis

	Case 1, age 36 years; type C	Case 2, age 58 years; type C
Period	8 Months	9 Months
Child-Pugh classification	C --> B	A --> A
Sildenafil administration	(–)	(+)
IIEF-5 score	9 --> 18	12 --> 23
Physical Function[a]	65 --> 90	60 --> 75
Bodily pain[a]	60 --> 90	100 --> 100
General health[a]	25 --> 40	85 --> 85
Vitality[a]	60 --> 90	45 --> 50
Social functioning[a]	50 --> 88	75 --> 100
Role emotion[a]	100 --> 100	100 --> 100
Mental health[a]	52 --> 84	36 --> 36
Reported health transition[a]	0 --> 75	60 --> 50

[a] SF-36 scores

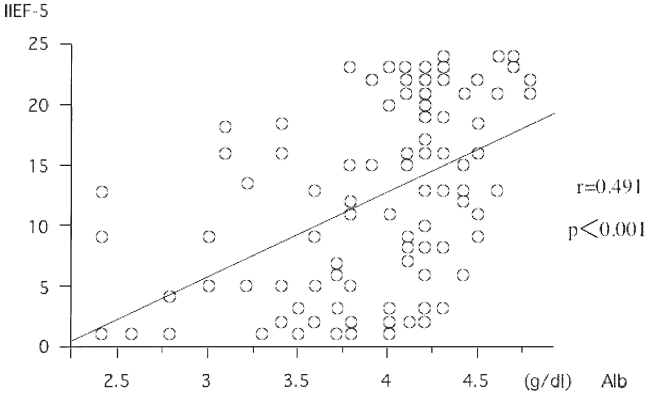

Fig. 2. Correlation between IIEF-5 score and serum albumin (*Alb*) in patients with chronic liver disease ($n = 117$)

Discussion

ED is defined as the inability to achieve and/or maintain penile erection sufficient for satisfactory sexual performance.[1] It is widely prevalent in the general population. The estimated worldwide prevalence of ED in 1995 was 152 million, and it is forecast to increase to 322 million in 2025.[19] In 2000, the Massachusetts Male Aging Study (MMAS) revealed that 52% of the whole population suffered from ED, and the prevalence increased with age, from 38% in the youngest group to 70% in the oldest men.[9] In Japan, Marumo et al.[18] reported that the prevalence of ED in the general population was 9% in those aged 40–49 years ($n = 302$), 20% in those aged 50–59 years ($n = 235$), and 64% in those over 70 years

($n = 152$), as assessed by the international index of erectile function (IIEF). Although we should take into account the different questionnaires used by Marumo et al.[18] and by us, our healthy cohort of age 40–49 and age 50–59 showed incidences of ED similar to those reported by Marumo et al.[18] (Table 2; $\chi^2 = 0.94$ for age 40–49 and $\chi^2 = 0.04$ for age 50–59).

Several studies have previously reported on the prevalence of ED in patients with chronic liver disease (CLD), but most of these patients were heavy drinkers. Cornely et al.[16] showed a high prevalence of sexual dysfunction in alcoholics, particularly in those with cirrhosis, in contrast to a relatively low rate of impotence (10 out of 40 patients) in those with nonalcoholic cirrhosis.[16] Wang et al.[20] reported on the prevalence of ED in patients with hepatitis B virus-related postnecrotic cirrhosis, although the number of patients was, again, small and the relation between the severity of liver disease and ED was not definitive. We have here clarified that ED is highly prevalent in patients with viral liver disease (Table 2).

Surprisingly, a high prevalence of ED was observed not only in patients with liver cirrhosis (LC) but also in those with chronic hepatitis (CH; Table 3). Furthermore, the numbers of patients with moderate or severe ED increased with disease severity, while the number of patients with mild ED was relatively stable (Table 4). These results suggest that liver disease per se is the key factor to influence the erectile function in patients with viral liver disease.

The causes of ED in patients with liver disease are not clear. It has been reported that the plasma level of testosterone is decreased in patients with alcoholic or postnecrotic liver cirrhosis, and that plasma testosterone concentration was correlated with disease severity.[20] Moreover, concomitantly, plasma gonadotropin concentration remained at basal levels, suggesting the existence of a hypothalamic defect in these patients. However, whether or not the reduced level of testosterone is contributory to sexual dysfunction in patients with liver disease is not conclusive, because there was no significant effect of testosterone treatment on improvement of erectile function in patients with alcoholic liver disease.[21] In contrast, abstinence from alcohol is effective, to some extent, for the recovery of gonadal dysfunction, only if the patients have not developed testicular atrophy or poor gonadotropin responses to luteinizing hormone-releasing factor or clomiphene. Van Thiel et al.[22] administered oral exogenous androgen to alcoholics who had not recovered sexual function with abstinence from alcohol, and those patients with no testicular atrophy recovered sexual potency, suggesting the existence of androgen hyposensitivity in alcoholic patients. In our study, plasma levels of sex hormones, except for the free testosterone level ($r = 0.29$, $P = 0.07$), were not directly related to the ED score. However, the power of the free testosterone level to affect ED was weaker than other factors, such as serum albumin level and age.

We have shown a correlation between the ED score and serum albumin in this study. A previous study reported that free and albumin-bound testosterone, rather than total testosterone concentration, correlated positively with sexual desire and sleep-related erection in healthy subjects.[23] 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 amout of testosterone, possibly modifying cell or tissue response to this sex hormone in cirrhotic patients.

Another factor of relevance to ED in cirrhotic patients could be the physical disturbance caused by protein malnutrition in these patients. Hypoalbuminemia leads to fluid retention; namely, edema, ascites, or pleural effusion, and this influences physical function in cirrhotic patients.[24] Moreover, protein malnutrition also induces loss of muscle volume, which leads to decreased muscle strength.[25] Thus, physical function could be relevant to hypoalbuminemia, which was a significant determinant of ED. Such correlations between physical function and protein status could explain why the close relationship of the SF-36, physical function and role physical with ED, shown by simple regression analysis, disappeared after multiple regression analysis in this study. Previously, an association between QOL and impotence was shown in the general population,[26] and, in patients with cirrhosis, impaired sex life was a perceived health problem, as well as other health-related QOL factors.[14] In fact, both the ED score and the SF-36 scores were well improved after the attenuation of disease severity in our case 1 (Table 6). Thus, in this patient the treatment responsible for these changes may have been the use of BCAAs, as BCAAs have been shown to improve serum albumin,[27,28] muscle metabolism,[28] and patient prognosis,[27] as well as improving disease-free survival and QOL in patients with liver cirrhosis.[29,30]

It is difficult to avoid some limitations in this kind of clinical study. The limitation in this study is the lack of interventional challenge such as liver transplantation or interferon treatment. In Japan, neither liver transplantation nor interferon therapy is generally employed for cirrhotic patients. It is possible, however, that antiviral treatment or transplantation may improve erectile function in some patients. Actually, in this study, the IIEF-5 score recovered in one patient in parallel with the attenuation of the severity of liver damage over 8 months. It is established that liver transplantation or interferon treatment attenuates the severity of liver damage and improves QOL. These results suggest that

such interventions may possibly be effective in resolving ED, but this hypothesis should be tested in prospective clinical trials.

Another limitation of our study is the lack of plasma amino-acid analysis. Plasma BCAAs correlate significantly with albumin levels[27] and, thus, could be a possible determinant of ED in a manner similar to albumin. Such a correlation, if present, might support the recommendation of BCAA supplementation to treat ED in patients with CLD, as suggested in our patients (case 1 in Table 6).

In conclusion, the majority of patients with viral liver disease proved to be suffering from ED, and protein malnutrition could be relevant to this condition. Further study is needed to clarify what intervention is effective to improve sexual function as well as QOL in patients with liver disease.

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