Male sexual dysfunction and liver fibrosis : Are there other secret Players?

Original Article

Ghada M. Shams[1], Hoda Ramadan Askar[1], Ahmed Abdel-Wahab Saleh[1], Mohamed Ashraf El-Jaky[2]

[1]Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Benha University, Benha and [2]National Liver Institute, Menoufia University, Egypt.

ABSTRACT

Background: The effect of advanced liver disease on male sexual health is wellestablished, yet data on sexual disturbances in liver fibrosis are scant.

Aim: This work aimed to investigate the sexual dysfunctions in male participants with varying stages of fibrosis.

Patients and Methods: A sample of 400 male patients with varying grades of liver fibrosis were subjected to noninvasive transient elastography (FibroScan) and evaluation of sexual functions using International Index of Erectile Functions (IIEF) and its short form.

Results: Among studied participants, 57.75% had sexual dysfunction, with a significantly reduced IIEF score accompanying rising stage of fibrosis (r=0.513, *P*<0.001). The IIEF score was significantly positively correlated with elevated serum albumin levels (r=0.433, *P*< 0.001) and hemoglobin levels (r=0.334, *P*=0.009).

Conclusion: A high percent of patients with liver fibrosis were found to have erectile dysfunction, the severity of which was directly proportional to the stage of fibrosis. Lower serum albumin and hemoglobin levels appear to be attributes.

Key Words: Erectile dysfunction, international index of erectile function, liver fibrosis, sexual health inventory for men

Received: 05 October 2022**, Accepted:** 13 December 2022

Corresponding Author: Ghada M. Shams, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Benha University, Egypt, **Tel:** 01279497226, **E-mail:** ghadashams84@gmail.com

ISSN: 2090-6048, 2023

INTRODUCTION

The erect penis has classically been used to symbolize a man's masculinity and sexual power. Even though it is not a life-threatening ailment, erectile dysfunction (ED) and its therapies have sparked the curiosity of people throughout time. Dilatation of arteries, relaxation of erectile tissue smooth muscle fibers, as well as restricted outflow caused by compression of subtunical venules are necessary incidents in the erection series of events[1]. Finally, rigidity is obtained by the contraction of striated muscles[2].

'The inability to sustain a rigid penile erection for optimum sexual performance' defines ED, formerly known as impotence. Although no specific timespan is specified in this definition, some have proposed that the condition must last 6 months[3]. It is supposed to affect a large percentage of men, at least at certain time throughout their lives[4]. Previously, most cases of ED were thought to be simply psychological, but credible research reveals that more than 80% of cases involve an organic cause or, at least, a mixed origin[2].

Caused by chronic liver insult, the hallmark of liver fibrosis is the buildup of extracellular matrix proteins[5]. In certain clinical scenarios, including recurrent attacks of severe acute alcoholic hepatitis, subacute hepatitis, and fibrosing cholestasis, liver fibrosis advances promptly to cirrhosis[6].

Comorbidities and risk factors linked up to the development of ED are frequent in patients with liver cirrhosis, includingchanges in the metabolism of sex hormones and frequent use of medications that may affect penile erection on a frequent basis. In addition, advanced chronic liver disease may contribute to the emergence of ED[7].

Up to this point, the available data in this context are insufficient. As evidence exists that ED incidence may increase with advanced liver disease, the goal of the present work was to study how variable stages of liver fibrosis may affect erectile function and to evaluate frequency of ED in patients with varying stages of liver fibrosis.

PATIENTS AND METHODS

The local ethics committee on research involving human participants authorized the protocol for this multicentriccross-sectional study (MS:25-1-2020), which

 DOI: 10.21608/HA.2023.165981.1091

was performed in line with the fundamentals of Helsinki Declarationon 400 male patients with hepatic fibrosis aged more than or equal to 18 years. They were recruited from those attending the Hepatology and Gastroenterology Department in Benha University hospitals and Menoufia National Liver Institute during the period from January 2021 to October 2021.Normal values of white blood cell count and platelet count were prerequisites for enrollment in the study. Patients with active alcohol consumption (within the last 3 months), malignant tumors, or coexistence of recognized factors known to predispose to ED, such as hypertension, type 2 diabetes mellitus, or cardiovascular disease were excluded.

Noninvasive transient elastography (FibroScan) (Echosens , France) was used to categorize patients into four groups based on the stage of liver fibrosis, with 100 patients in each group: group A:stage 1 fibrosis (F1),group B: stage 2 fibrosis (F2), group C: stage 3 fibrosis (F3), and group D: stage 4 fibrosis (F4) (compensated liver cirrhosis), as suggested by de Lédinghen and Vergniol (2008)[8].

After the patients had been informed verbally and in written information about the aim of the research, an informed consent was obtained. Patients were provided a thorough clinical history as well as full clinical examination, including liver and spleen palpation and percussion for ascites, and BMI measurement using the 'weight in kilograms/height in m2' formula.

The validated Arabic versions[9] of International Index of Erectile Function (IIEF)[10] and the Sexual Health Inventory for Men[11] were used for evaluation of sexual functions in studied patients.

Five aspects of male sexual function were evaluated through the 15 questions of IIEF: the erectile function (six questions, with a maximum score of 30, where score <25 was considered as ED), the sexual desire (two questions, with a maximum score of 10, where score <9 was considered decreased sexual desire), the orgasmic function (two questions, with a maximum score of 10, where score <9 was considered decreased orgasmic functions), and intercourse satisfaction (three questions, with a maximum score of 15, where score <13 was considered dissatisfaction), and overall satisfaction (two questions, with a maximum score of 10, where score <9 was considered dissatisfaction).

Disease grades of sexual dysfunction on Sexual Health Inventory for Men/IIEF5 or sexual scores were categorized as follows: 5–7, severe sexual dysfunction; 8–11, moderate dysfunction; 12–16, mild to moderate dysfunction; 17–21, mild dysfunction; and 22–25, no dysfunction.

FibroScan was used by experienced hands to determine the liver stiffness measurements and calculate the degree of hepatic fibrosis. The depth of the measurement was between 25 and 65mm beneath the skin's surface. The software automatically omitted measurements that did not show a proper vibration pattern or vibration propagation follow-up. Each participant received up to 10 successful measurements. The ratio of the number of successful measurements to the total number of acquisitions was used to compute the success rate. The values are given in kilopascals (kPa). The successful measurements' median value was preserved as a proxy for hepatic stiffness. The entire evaluation lasted less than 5min. Only liver stiffness measurement acquired with at least 10 valid measurements and a success rate of at least 30% were deemed credible.

Laboratory investigations included assessment of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, complete blood picture, serum levels of bilirubin (total and direct), albumin, urea, creatinine, and serological tests for hepatitis viruses, namely,HBsAg for hepatitis B virus and hepatitis C virus (HCV) RNA for HCV.

Child–Pugh scoring system[12] was used to assess the class of hepatic fibrosis based on clinical and laboratory data.

Data management and statistical analysis

Received data were processed and analyzed using IBM-SPSS, version 24 (May 2016), IBM, Chicago, Illinois, USA. Tests used included Kruskal–Wallis, $\chi 2$, Wilcoxon's, Spearman's correlation, and logistic regression analysis. The data were presented, and appropriate analysis was performed based on the type of data obtained for each variable. Pvalues of less than 0.05 represented statistical significance.

RESULTS

A total of 400 male patients were divided into four equal groups based on the stage of hepatic fibrosis as assessed using FibroScan. Demographic characteristics of studied patients (n=400) are clarified in Table 1.

The mean BMI was 29.43±3.54 kg/m^2. Among participants, 77.75% of the patients were Child–Pugh class A, whereas 22.25% met the class B criteria. The mean values of ALT and AST were 39.6±40.6 and 38.5±24.6 IU/l, respectively. HCV-positive patients were 38.75% of the sample,whereas hepatitis B virus-positive patients were only 3.75%. Laboratory investigations of the studied participants are presented in Table 2.

Table 1: Demographic characteristics of the studied group (N=400)

Variables	Value
Age (years)	51.13±9.8
Mean ±SD	30–75
Range	n (%)
Education	
Illiterate	160(40.0)
Read and write	40(10.0)
Primary	83(20.75)
Preparatory	67(16.75)
Secondary	33(8.25)
University graduate	17(4.25)
Occupation	
Nonworking	93(23.25)
Worker/farmer	225(56.25)
Trades/business	43(10.75)
Semiprofessional/clerk	25(6.25)
Professional	14(3.5)

Table 2: Laboratory investigations in studied patients (N=400)

Variables	Mean ±SD	Range
Hb	11.34±2.5	8.6–16.4
WBCs	7.40±3.65	3.4–13.00
Platelets	233.4±43.2	150–430
ALT	39.6±40.6	12–174
AST	38.5±24.6	14.3–130
Total bilirubin	4.3±3.8	0.17–9.1
Direct bilirubin	0.42±0.3	0.1–1.8
Albumin	3.43±0.432	2.09–4.53
Creatinine	1.4±6.54	0.51–7.6
Urea	24.34±10.5	11.2–66.3
Variables		No.(%)\
HBV		
No		385 (96.25)
Yes		15 (3.75)
HCV		
No		245 (61.25)
Yes		155 (38.75)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cell.

The results of IIEF show that the mean erection domain value was 20.345±8.71,whereas the mean intercourse and orgasm domain were 8.73±4.25 and 7.45±3.42, respectively. The mean value of desire domain was 7.07±2.59, whereas the overall satisfaction was only 6.9±2.83. The total IIEF score was 50.5±21.1 (Fig. 1).

Accordingly, 57.75% of studied patients were found to have sexual dysfunction. Table 3 shows that there was a highly significant relation between the sexual dysfunction and the stage of fibrosis (P<0.001), with most patients suffering from sexual dysfunction (62.7%) were F3 or F4 fibrosis,whereas 40.82% of patients who had no sexual dysfunction were F1. Similarly, all domains of sexual functions were adversely affected with advancing stage of fibrosis (Tables 4, 5).

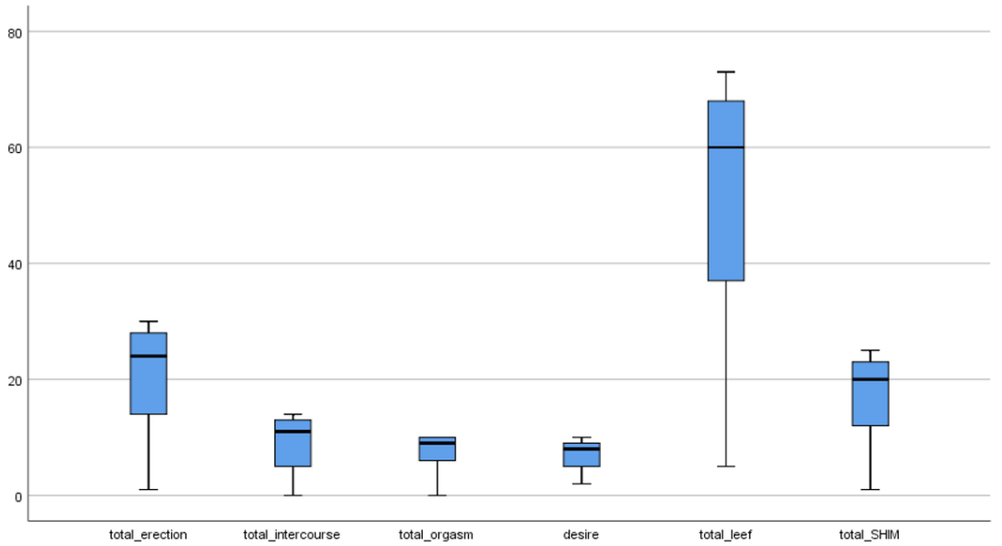

Fig. 1: Boxplot illustrating IIEF domains and total score of the questionnaire and its short form. IIEF, International Index of Erectile Function.

Table 3: Relation between the degree of erectile dysfunction and degree of fibrosis (N=400)

Fibrosis degree	IIEF-5 Grades of sexual dysfunction					X^2 Test	P value
	No ED (n=169)	Mild (n=70)	Mild moderate (n=98)	moderate (n=7)	Severe (n=56)		
	N(%)	N(%)	N(%)	N(%)	N(%)		
F1	69(40.8)	23(32.8)	2(2.0)	3(42.9)	3(5.4)	97.571	<0.001**
F2	45(26.6)	18(25.7)	31(31.6)	0(0.0)	6(10.7)		
F3	30(17.8)	20(28.6)	32(32.7)	1(14.2)	17(30.4)		
F4	25(14.8)	9(12.9)	33(33.7)	3(42.9)	30(53.5)		

χ2,χ2 test; ED, erectile dysfunction; IIEF, International Index of Erectile Function.
**P value less than 0.001 (highly significant).

Table 4: Relation between erectile function domains and degree of fibrosis (N=400)

Variables	Fibrosis degree				F-test	*P* value
	F1	F2	F3	F4		
	Mean± SD	Mean± SD	Mean± SD	Mean± SD		
ERECTION domain	25.33+5.53	21.58+7.6	18.75+8.8	15.72+5.3	26.276	<0.001** P1=0.001 P2<0.001 P3<0.001 P4=0.013 P5<0.001 P6=0.008
Intercourse domain	11.75+3.33	9.2+3.1	7.81+2.5	6.16+2.1	33.751	<0.001** P1<0.001 P2<0.001 P3<0.001 P4=0.016 P5<0.001 P6=0.005
ORGASM domain	8.98+2.8	8.65+3.2	7.04+ 2.3	5.13+2.24	32.778	<0.001** P1=0.449 P2<0.001 P3<0.001 P4<0.001 P5<0.001 P6<0.001
DESIRE domain	8.82+2.85	7.45+2.83	6.52+2.73	5.5+2.13	37.887	<0.001** P1<0.001 P2<0.001 P3<0.001 P4=0.004 P5<0.001 P6=0.002
Satisfaction domain	9.1+3.09	7.84+2.9	6.27+3.0	5.4+2.07	40.354	<0.001** P1=0.001 P2<0.001 P3<0.001 P4=0.015 P5<0.001 P6=0.014

One-way analysis of variance with post-hoc test P1 relation betweenF1 and F2.
P2 relation between F1 and F3.
P3 relation between F1 and F4.
P4 relation between F2 and F3.
P5 relation between F2 and F4.
P6 relation between F3 and F4.
***P* value less than 0.001 (highly significant).

Table 5: Relation between total erectile function score and degree of fibrosis (N=400)

Variables	Fibrosis degree				F test	*P* value
	F1	F2	F3	F4		
	Mean± SD	Mean± SD	Mean± SD	Mean± SD		
Total score IIEF15 (Long form)	62.98+12.02	53.72+16.9	46.39+16.6	37.94+13.65	34.081	<0.001** P1<0.001 P2<0.001 P3<0.001 P4=0.006 P5<0.001 P6=0.002
Total IIEF5 (Short form)	20.82+4.18	17.9+6.15	15.55+7.15	12.98+4.6	26.787	<0.001** P1=0.002 P2<0.001 P3<0.001 P4=0.01 P5<0.001 P6=0.005

One-way analysis of variance with post-hoc test.
IIEF, International Index of Erectile Function.
P1 relation betweenF1 and F2.
P2 relation betweenF1 and F3.
P3 relation betweenF1 and F4.
P4 relation betweenF2 and F3.
P5 relation betweenF2 and F4.
P6 relation betweenF3 and F4.
***P* value less than 0.001 (highly significant).

The IIEF score was significantly lower with older age (r=-0.213, P=0.03), with higher BMI (r=-0.198, *P*=0.04), with increasing stageof fibrosis (r=-0.513, *P*<0.001),and with elevated serum levels of AST (r=-0.415, *P*=0.002), ALT (r=-0.392, *P*=0.005), urea (r=-0.224, *P*=0.03),and creatinine (r=-0.398, *P*=0.003). However, the IIEF score was significantly positively correlated with elevated serum albumin levels (r=0.433, *P*<0.001) and hemoglobin levels (r=0.334, *P*=0.009) Table 6.

Table 6: Correlation between International Index of Erectile Function score and different parameters among studied patients

Variables	IIEF score	
	r	*P*
Age	-0.213	0.03*
BMI	-0.198	0.04*
Hb	0.334	0.009*
WBCs	0.087	0.543
Platelets	0.045	0.723
ALT	-0.415	0.002*
AST	-0.392	0.005*
Albumin	0.433	0.001*
Creatinine	-0.398	0.003*
Urea	-0.224	0.03*
Fibrosis degree	-0.513	<0.001**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IIEF, International Index of Erectile Function; r: Pearson correlation; WBC, white blood cell.
**P* value less than 0.05 (significant).
***P* value less than 0.001 (highly significant).

DISCUSSION

In this work, we tried to investigate how common is ED in varying stages of liver fibrosis, even in its earliest stages. Moreover, the effect on variable sexual domains, including sexual desire, orgasmic function, and the overall sexual satisfaction, was alsotaken into consideration.

Because the hepatic parenchyma collapses and is replaced with a collagen-rich tissue, hepatic fibrosis was once assumed to be a passive and irreversible process. It is currently thought of as a prototype of the wound-healing process to chronic liver injury[5]. To stop, lessen, and reverse the progression of fibrosis to cirrhosis with all its problems and the requirement for liver transplantation are the aims of the current and future therapeutics for any chronic liver disease[13].

Previous attempts were made to evaluate the possible effect of liver disease on male sexual health, unfortunately, most of which were focusing on end-stage liver disease, namely, cirrhosis, with alcoholism as a main impressing factor[14], in opposition to the current work, where alcoholic patients were excluded. Scant literature was found investigating sexual health in patients with fibrosis.

'How can liver disease affect sexual functions in absence of alcoholism?' is a question to be answered. Decreased serum testosterone was suggested, yet exogenous testosterone was not that useful[15]. Another suggested answer is the protein deficiency and albumin levels, hence decreased muscle tone[16], not to mention ascites and edema in advanced liver disease.

In the current work, among the studied participants (n=400), 57.75% were found to have sexual dysfunction, with a significant lower IIEF score with increasing grade of fibrosis (r=-0.513, P<0.001). Not only erectile functions but also sexual desire, orgasmic functions, satisfaction with intercourse, and overall sexual satisfaction were all affected.

Interestingly, in the current study, there was a highly significant association (P<0.001) between ED and the degree of fibrosis, with most patients suffering from ED (62.7%) having F3 or F4 fibrosis, whereas 40.82% of patients who did not have ED had F1. Meanwhile, there was a highly significant relationship (P<0.001) between the degree of ED and the degree of fibrosis, with the majority of patients with severe dysfunction (53.5%) being F4 and the majority of those without dysfunction (40.8%) being F1.

In the same context, Toda *et al.*[16] stated that patients with chronic hepatitis as well as liver cirrhosis both had a significant prevalence of ED. Additionally, as the condition got worse, more patients developed moderate or severe ED, while the proportion of patients with mild ED remained mostly stable.

In opposition to our results, a study by El-Atrebi *et al.*[17] reported that ED was found only in 19.4 and 29.4% patients of early and advanced liver fibrosis, respectively. On the contrary, Maimone *et al.*[7] concluded that even when other chronic comorbidities are present, the reported incidence of ED in patients with compensated liver cirrhosis is comparable to general population.

Cirrhosis patients may experience ED for one of three reasons. First, ED can be caused by hormonal deficits. Cirrhotic patients exhibit apparent feminizationowing to hypogonadism and hyperestrogenism; furthermore, the bioavailability of free testosterone is reduced as the level of sex hormone-binding globulin rises[18]. Still, a clear etiology is not wellestablished.

According to Toda *et al.*[16], an even more concern that may be relevant to ED in hepatic patients is the effects of protein malnutrition. They reported that physical function may be related to hypoalbuminemia, which is a significant predictor of ED. This may explain our findings, wherea significantly positive correlation was found between IIEF score and elevated serum albumin levels (r=0.433, P<0.001).

The fact that ED increases with advancing age is also reported in successive research. According to the Massachusetts Male Aging Study, 52% of the total population had ED in 2000, and the prevalence increased with age, rising from 38% among the youngest men to 70% among the oldest[19]. This also was consistent with the results of our work. Age seems to be a determinant of ED; in other words, ED may be considered an age-related disease[20].

The current work showed a significant positive correlation between IIEF score and hemoglobin levels in studied patients (r=0.334, P=0.009). Bodie *et al.*[21] warranted the routine screening of hemoglobin levels as a part of laboratory evaluation of patients with ED. They found that at least 25% of their studied patients had low hemoglobin. Moreover, Maimone *et al.*[7] suggested that liver disease per se is not a factor in development of ED, but other risk factors including older age and low hemoglobin may have a principal role.Whether anemia causes ED or liver disease contributes to both is yet to be elucidated.

The current work also demonstrated a significant lower IIEF score with higher BMI (r=-0.198, P=0.04). Growing evidence suggests the effect of obesity on sexual and reproductive health[22]. It is hypothesized that obesity can affect erectile functions through two main mechanisms: the deleterious repercussions of fat tissue dysfunction (that includes thechanges in the cellular composition, increased lipid storage and impaired insulin sensitivity in adipocytes, and secretion of a proinflammatory, atherogenic, and diabetogenicadipokine pattern that result from ectopic fat deposition specially visceral fat)[23] and the consequent metabolic disturbances that lead to endothelial dysfunction, and the known hormonal imbalances associated with abundant adipose tissue[20].

In such type of clinical research, some limitations are

difficult to avoid. The lack of assessment of the role of medications and hormonal assay represents limitations to our study, which will be taken into consideration in future studies.

CONCLUSION

A large percentage of patients with liver fibrosis proved to have ED, the severity of which was directly related to the stage of fibrosis. Lower serum albumin and hemoglobin seem to be contributing factors. More research is warranted to determine which interventions are effective in improving sexual function in patients with liver fibrosis.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. GiulianoF. Neurophysiology of erection and ejaculation. J Sex Med2011; 8 (Suppl 4):310–315.
2. DeanRC, LueTF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am2005; 32:379–377.
3. SooriyamoorthyT, LeslieSW. Erectile Erectile dysfunction. In:■■. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Retrieved September 23, 2022 from https://www.ncbi.nlm.nih.gov/books/NBK562253/.
4. KubinM, WagnerG, Fugl-MeyerAR. Epidemiology of erectile dysfunction. Int J Impot Res2003; 15:63–71.
5. BatallerR, BrennerDA. Liver fibrosis [published correction appears. J Clin Invest2005; 115:209–218.
6. AfdhalNH, NunesD. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol2004; 99:1160–1174.
7. MaimoneS, SaffiotiF, OlivaG, Di Benedetto A, Alibrandi A, Filomia R. Erecti le dysfunction in compensated liver cirrhosis. Dig Liver Dis2019; 51:843–849.
8. De Lédinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterol Clin Biol. 2008 Sep;32(6 Suppl 1):5867-
9. ShamloulR, GhanemH, Abou-zeidA. Validity of the Arabic version of the sexual health inventory for men among Egyptians. Int J Impot Res2004; 16:452–455.
10. RosenRC, RileyA, WagnerG, OsterlohIH, KirkpatrickJ, MishraA. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology1997; 49:822–830.
11. RosenRC, CappelleriJC, SmithMD, LipskyJ, PeñaBM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res1999; 11:319–326.
12. PughRN, Murray-LyonIM, DawsonJL, PietroniMC, WilliamsR. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg1973; 60:646–649.
13. CholankerilG, AhmedA. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2018; 16:1356–1358.
14. SimsekI, AslanG, AkarsuM, KoseogluH, EsenA. Assessment of sexual functions in patients with chronic liver disease. Int J Impot Res2005; 17:343–345.
15. DurazzoM, PremoliA, Di BisceglieC, BoS, GhigoE, ManieriC. Male sexual disturbances in liver diseases: what do we know?. J Endocrinol Invest2010; 33:501–505.
16. TodaK, MiwaY, KuriyamaS, *et al.* Erectile dysfunction in patients with chronic viral liver disease: its relevance to protein malnutrition. J Gastroenterol2005; 40:894–900.
17. El-AtrebiKA, El-AtrebiMA, El-BassyouniHT. Sexual dysfunction in males with hepatitis C virus: relevance to histopathologic changes and peginterferon treatment. Saudi J Gastroenterol2011; 17:406–410.
18. SinclairM, GrossmannM, GowPJ, AngusPW. Testosterone in men with advanced liver disease: abnormalities and implications. J Gastroenterol Hepatol2015; 30:244–251.
19. FeldmanHA, JohannesCB, DerbyCA, *et al.* Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med2000; 30:328–338.
20. PizzolD, SmithL, FontanaL, *et al.* Associations between body mass index, waist circumference and erectile dysfunction: a systematic review and META-analysis. Rev Endocr Metab Disord2020; 21:657–666.
21. BodieJ, LewisJ, SchowD, MongaM. Laboratory

evaluations of erectile dysfunction: an evidence based approach. J Urol2003; 169:2262–2264.

22. MoonKH, ParkSY, KimYW. Obesity and erectile dysfunction: from bench to clinical implication. World J Mens Health2019; 37:138–147.

23. BlüherM. Adipose tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes 2009; 117:241–250.