

Prospective Study on Sexual Dysfunction in Male Chinese Liver Transplant Recipients

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Abstract

In patients with end-stage liver disease, hypogonadism and erectile dysfunction are often seen. This study was to determine the incidence of erectile dysfunction before and after liver transplantation (LT) with correlation to change in sex hormone levels from a Chinese cohort. This prospective longitudinal study was registered with The University of Hong Kong Clinical Trials Centre (HKUCTR-1563). The Institutional Review Board approval number is UW-12-273. The study period was from January 2012 to December 2016. Adult male patients with end-stage liver disease enlisted for LT were recruited on informed written consent. All recruited patients were to complete a cross-sectional cohort questionnaire—International Index of Erectile Function, version 5 (IIEF5)—and to receive serum sex hormone checks before and after LT. Twenty-eight patients who underwent LT were included in the analysis. The included patients had significantly reduced prolactin ($p < .001$) and 17-beta-estradiol ($p = .024$) after LT. There was also a significant drop of IIEF5 score at 1 month after LT, but the score returned to pre-LT level at 6 months. This study demonstrated that there was improvement in sex hormone levels after LT, namely, normalization of estradiol level and lowering of prolactin and progesterone levels. However, improvement in sex hormone levels did not translate into improvement of erectile dysfunction.

Keywords

liver transplantation, erectile dysfunction, hypogonadism, end-stage liver disease, sexual dysfunction, treatment outcome

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Sexual dysfunction is characterized by disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle in men and women. It occurs in 10%–50% of men (Burra, 2009). Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse (Lue, 2000). In patients with end-stage liver disease, hypogonadism and signs of feminization can be seen. Testicular atrophy, low testosterone levels, decreased libido, infertility, reduced secondary sex hair, and gynecomastia are reported in men with cirrhosis, and 50% of patients with cirrhosis have reduced spermatogenesis and peritubular fibrosis (Karagiannis & Harsoulis, 2005). Patients with poorer liver function, as reflected by high Model for End-Stage Liver Disease

(MELD) scores, would have worse sexual function (Sorrell & Brown, 2006; Wiesner et al., 2001).

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Studies on Western populations reported that there was improvement in sex hormone disturbances after successful liver transplantation (LT). The proportion of sexually inactive men was reported to decrease from 29% to 15% after LT, but the incidence of ED remained unchanged (Burra, 2009). Risk factors for ED in LT patients are largely unknown. A better understanding of coexisting chronic medical conditions that increase the risk of ED is essential to developing adaptive strategies. Reports on Chinese patients on this area are lacking. It is hoped that the current study will fill the void in the literature.

Patients and Methods

Adult male patients admitted to the Liver Transplant Centre at Queen Mary Hospital, Hong Kong, were considered potential participants of the study. Those with end-stage liver disease who were eligible for LT (deceased-donor LT or living-donor LT) were recruited on written informed consent. Patients with fulminant hepatic failure, in hepatic coma, on anti-ED medication (e.g., Viagra), on testosterone replacement therapy, or younger than 18 years were excluded. Recruited patients were allowed to withdraw from the study at any time. This was a prospective longitudinal study, which was registered with The University of Hong Kong Clinical Trial Centre (HKUCTR-1563). The Institutional Review Board approval number is UW-12-273.

The primary endpoint was to determine the incidence of ED before and after (at 6 months) LT by using the International Index of Erectile Function, version 5 (IIEF5; validated Chinese version; Appendices A and B). The secondary endpoint was to determine the change of sex hormone disturbances by measuring sex hormones assay (17-OH progesterone, prolactin, total and free testosterone, thyroid-stimulating hormone, 17-beta-estradiol, and sex-hormone-binding globulin [SHBG]) before and after (at 6 months) LT.

Data Collection

A dedicated nurse specialist interviewed all recruited patients, and an IIEF5 questionnaire, a validated Chinese version, was completed by direct questioning in a single room. The patients were interviewed on their first outpatient visit and at 1 month and 6 months after LT. At the same time, blood was taken for check of sex hormones after each interview. Frequency of preoperative outpatient visits depended on individual patients' clinical conditions. All patients were followed up at the outpatient clinic weekly after LT for the first 3 months. Frequency of subsequent visits was determined according to clinical needs. The VITROS® 3600 system was used for immunoassay

for testosterone, estradiol, and progesterone, the Centaur® XP system was used for immunoassay for prolactin and thyroid-stimulating hormone, and the IMMULITE® 2000 system was used for immunoassay for SHBG. The following equation was used to calculate free testosterone level (Ho, Stoddart, Walton, Anderson, & Beckett, 2006; Vermeulen, Verdonck, & Kaufman, 1999):

$$\text{Calculated free testosterone} = \left(\frac{T - N - S + \sqrt{(N + S - T)^2 + 4NT}}{2N} \right)$$

where $N = 0.5217A + 1$, and T , S , and A are total testosterone (nmol/L), SHBG (nmol/L), and albumin (g/L) concentrations, respectively.

Data Analysis

Only results of patients who had undergone LT were included for further analysis. Pre- and post-LT total IIEF5 scores and sex hormone assays were compared by paired-sample t test or Wilcoxon signed-rank test where appropriate. Linear regression was used to explore possible factors affecting IIEF5 score upon inclusion. SPSS, version 20, was used for statistical analysis.

IIEF5 score is the sum of the ordinal responses to the five items. Score 22–25: no ED. Score 17–21: mild ED. Score 12–16: mild-to-moderate ED. Score 8–11: moderate ED. Score 5–7: severe ED (Rosen, Cappelleri, Smith, Lipsky, & Peña, 1999).

Results

Fifty patients were recruited during the period from January 2012 to December 2016. Among the 50 patients, 29 had LT done during the study period (18 had deceased donors and 11 had live donors), 3 died while waiting, 13 were delisted due to disease deterioration, and 5 were still waiting (Figure 1). One of the 29 LT recipients received the operation at another center. Five recipients died after the operation. After excluding 1 in-hospital postoperative mortality, 28 LT recipients were included for analysis. The 28 recipients' demographic characteristics, pre-morbidities, and median MELD score at the time of inclusion are listed in Table 1. The median waiting time to LT was 8.3 months (range, 0.03–69.7 months).

Figure 2 is a plot of IIEF5 scores at different time points in the study. The median IIEF5 score of the patients included for analysis was identified to be low preoperatively and postoperatively. Only 12 patients (24%) had a score of 17 or above before the operation. The preoperative median score was 11 (range, 1–24), the score at postoperative 1 month was 4 (range, 1–18), and the score at postoperative 6 months was 9 (range, 1–25). After

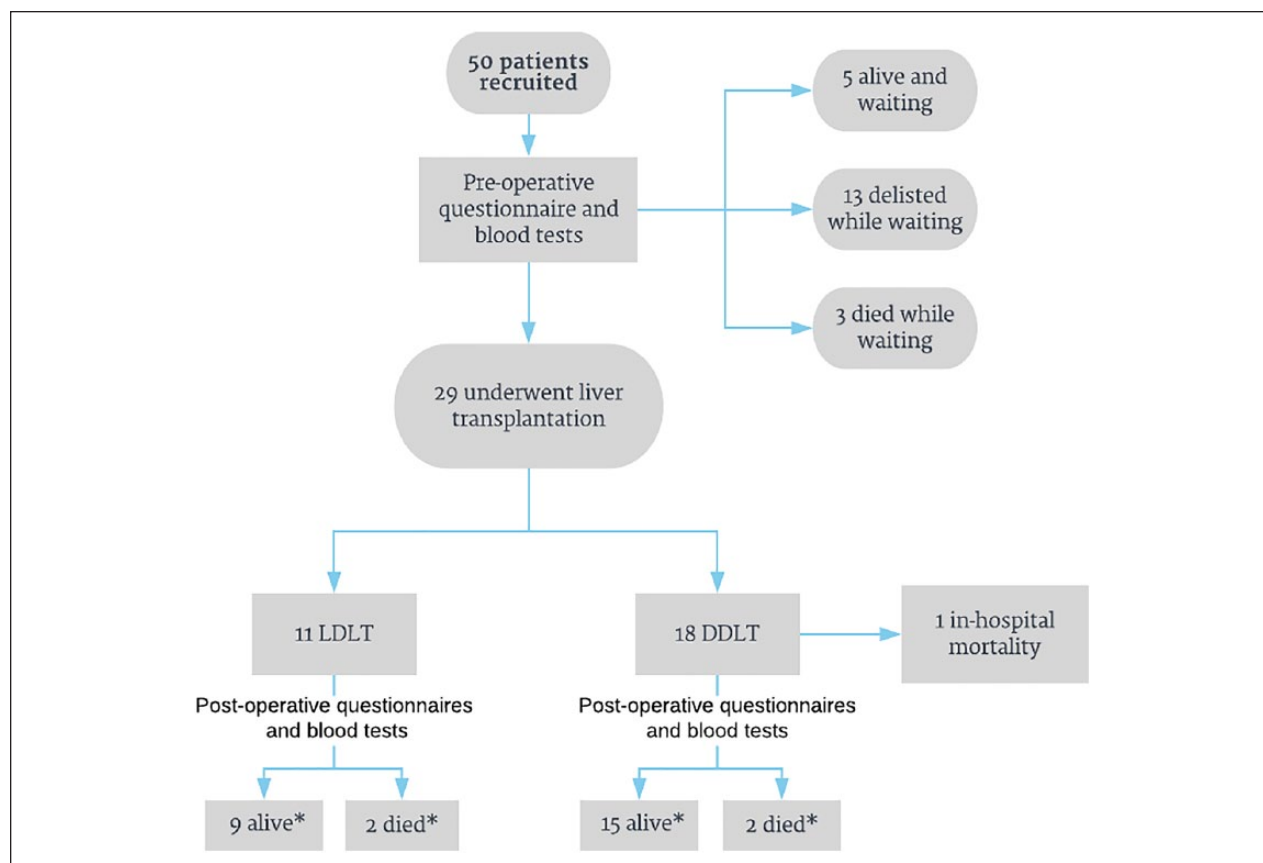


Figure 1. Flow diagram of patient inclusion. LDLT = living-donor liver transplantation; DDLT = deceased-donor liver transplantation.

*Patients included for analysis.

excluding patients who did not have LT done and the one in-hospital death, comparison of sex hormone levels and IIEF5 total scores at three different time points (before LT and at 1 month and 6 months after LT) was made (Table 2). The IIEF5 scores before LT and at post-LT Month 6 were similar ($p = .927$). The only significant change was at the first month after LT, where the score was lowest. When defining IIEF5 score ≤ 16 as moderate-to-severe ED, 34.5% of the LT recipients had persistent moderate-to-severe ED at Month 6. Only 5 patients (17.2% of 29 patients) expressed improvement at Month 6 in an IIEF5 score of over 17 when compared with that before LT. Three patients (10% of 29 patients) actually indicated a deterioration of IIEF5 score at Month 6. Five patients failed to complete the questionnaires at Month 6 because of hospitalization or missing from follow-up.

The median values of preoperative serum sex hormone levels of the 28 LT recipients are listed in Table 2. Eight patients did not have their sex hormone levels measured. Eleven patients (26.2%) had an elevated 17-OH progesterone level (normal range, 0.9–6.6 nmol/L). Prolactin level was elevated in two patients (4.8%; normal range,

45–375 mIU/L). Nine patients (21.4%) had a suppressed total testosterone level (normal range, 10–35 nmol/L) and 14 patients (28%) had a low free testosterone level (i.e., <0.225 nmol/L; Rosen et al., 1999). Almost half of the patients (47.2%, 20 patients) had an elevated SHBG level (normal range, 10–57 nmol/L), and 18 patients (42.9%) had an elevated 17-beta-estradiol level (normal range, 20–160 pmol/L). After LT, there was a significant decrease in prolactin and 17-beta-estradiol levels. The median prolactin level dropped from 224.2 ± 92.3 mIU/L before LT to 141.5 ± 60.4 mIU/L at Month 6 ($p < .05$). The median level of 17-beta-estradiol dropped from 344.3 ± 505.7 pmol/L before LT to 72.2 ± 36.6 pmol/L at Month 6 ($p = .024$). There was no significant change in total testosterone level (15.7 ± 10.3 nmol/L before LT and 11.7 ± 6.4 nmol/L at Month 6; $p = .067$) or SHBG level (54.0 ± 34.0 nmol/L before LT and 37.0 ± 20.9 nmol/L at Month 6; $p = .183$). Finally, 17-OH progesterone level was elevated insignificantly from 5.1 ± 2.1 nmol/L before LT to 5.7 ± 2.8 nmol/L at the first post-LT month ($p = .494$) and then it dropped significantly to 4.1 ± 1.8 nmol/L at Month 6 ($p = .040$), but the overall

Table 1. Demographics, Background, and Premorbid Status of the 28 Liver Transplant Recipients.

Number of patients	28
Mean age at inclusion (years)	55.3 ± 6.5
Patient status	
Alive	24 (86%)
Dead	5 (14%)
Liver transplant (deceased donor: living donor)	17 (61%):11 (39%)
Indications for liver transplant (n)	
Chronic liver failure	7 (25%)
HBV-related cirrhosis	3 (11%)
HCV-related cirrhosis	1 (4%)
Alcoholic cirrhosis	2 (7%)
Cryptogenic cirrhosis	1 (4%)
Hepatocellular carcinoma	15 (54%)
HBV related	11 (39%)
HCV related	3 (11%)
Alcohol related	1 (4%)
HBV-related cirrhosis with acute decompensation	3 (11%)
Acute flare of hepatitis B	2 (7%)
Primary biliary cirrhosis	1 (4%)
Premorbidity	
Diabetes mellitus	8 (29%)
Hypertension	9 (32%)
Ischemic heart disease	2 (7%)
Cerebrovascular accident	0
Spinal cord disease	0
Depression	0
Others	5 (18%)
Median Model for End-Stage Liver Disease score (range)	14.2 (6–40)

Note. Data are presented as number of patients (%) unless otherwise stated. HBV = hepatitis B virus; HCV = hepatitis C virus.

decrease from before LT to Month 6 was not significant ($p = .083$).

Linear regression was performed for various factors to explore any relationship with IIEF5 score. The factors were age, MELD score, waiting time at inclusion, and premorbidity (diabetes mellitus, hypertension, and ischemic heart disease). None of these factors reached statistical significance for IIEF5 score at time of inclusion or for change in IIEF5 score from before LT to Month 6.

Discussion

ED is more prevalent in Asian regions. According to a study by Ng and Cheng (2007), the overall prevalence of ED in Hong Kong was 36.7%, similar to Japan, where it was 34%. In other regions, such as Italy and Brazil, it was only 15%–17% (Nicolosi, Glasser, Moreira, & Villa, 2003; Nicolosi, Moreira, Shirai, Bin Mohd Tambi, & Glasser, 2003; Nicolosi, Moreira, Villa, & Glasser, 2004).

Yet the topic is poorly studied, with very few published papers. In a systematic review, there were a total of 40 studies qualified for review and only 2 of them were from Asian regions (Prins, Blanker, Bohnen, Thomas, & Bosch, 2002).

While many health-care providers focus on survival and complications after LT, sexual health in post-LT patients is often ignored. Sexual health is one of the important aspects contributing to satisfactory quality of life after LT. Evidence is particularly scarce in Asian regions, even for the general population. There was a similar study on changes in IIEF5 score before and after LT, but it did not evaluate hormonal levels (Chien, Chiang, Lin, & Chen, 2015). The current study is one of the first in Asia to explore the change in sex hormone levels before and after LT and the possible correlation with ED.

Prolactin has been known to be one of the hormones affecting sexual function. Hyperprolactinemia from any cause leads to inhibition in central dopaminergic activity and hence the secretion of gonadotropin-releasing hormone (Farthing, Green, Edwards, & Dawson, 1982; Jha & Kannan, 2016; Paick, Yang, Kim, & Ku, 2006). This in turn results in hypogonadotropic hypogonadism (Lue, 2000). In patients with liver failure, there is a disturbance in amino acid metabolism, causing an increase in circulating aromatic amino acids. This leads to inhibition of dopamine release in the central nervous system, and thus hyperprolactinemia (Jha & Kannan, 2016). Therefore, it was not surprising in this study to see a significant decrease in prolactin level when liver function returned to normal after LT.

Hyperestrogenemia is a well-documented hormonal imbalance in patients with liver failure (Madersbacher, Ludvik, Stulnig, Grünberger, & Maier, 1996). With decreased metabolism of estrogen by the liver, the increase in estrogen level inhibits the production of luteinizing hormone by the pituitary gland, and thus the reduction in production of testosterone (Huyghe et al., 2009). In this study, estrogen level decreased significantly after liver function returned, which reflected the normalization of estrogen metabolism.

Despite the significant improvement in prolactin and 17-beta-estradiol levels, there was no significant improvement in total or free testosterone level at Month 6. This contradicts with the results obtained by a study in 2014 (Nitsche, Coelho, de Freitas, Zeni Neto, & Martins, 2014), which saw a significant increase in testosterone levels and a drop in SHBG in patients with a MELD score below 18 at 6 months after LT. Another Austrian group also published similar data in the 1990s (Madersbacher et al., 1996; Madersbacher, Grünberger, & Maier, 1994). The reason behind such difference is still unknown, but it is postulated that the relatively higher rate of LT and

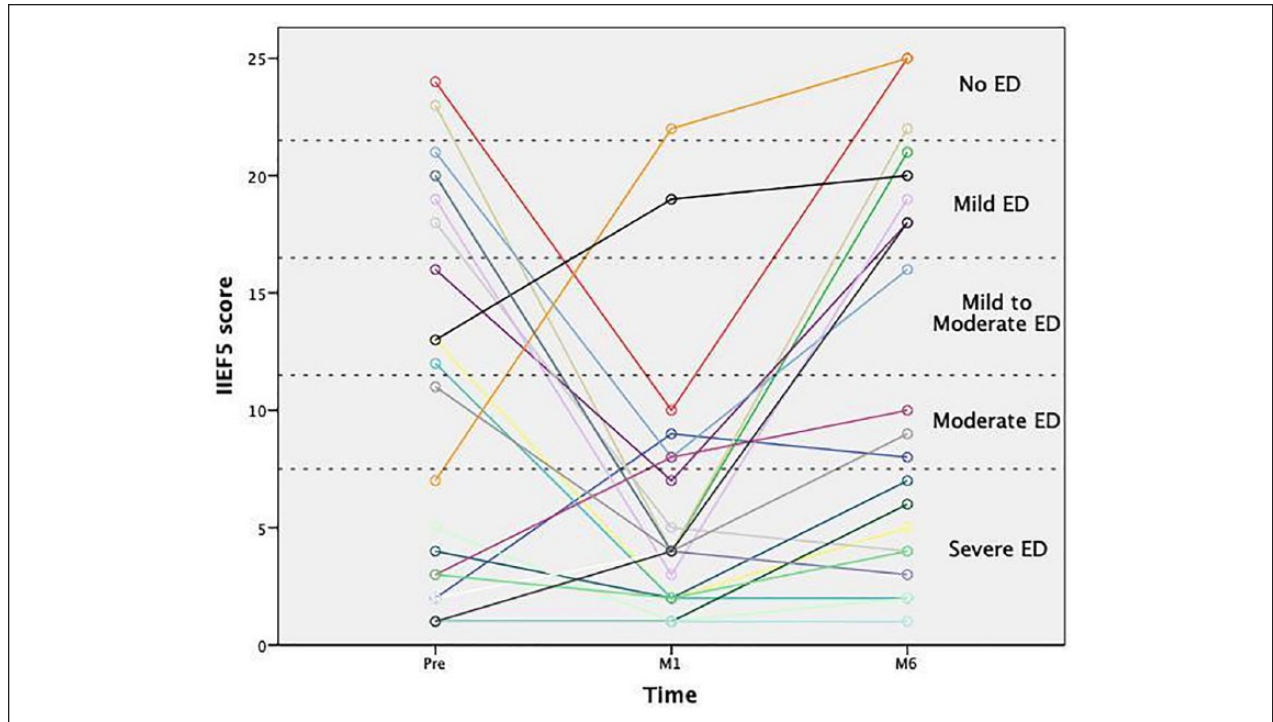


Figure 2. Plot of the International Index of Erectile Function version 5 (IIEF5) questionnaire scores of patients who underwent liver transplantation (each line represents one patient’s IIEF5 scores at different time points). ED = erectile dysfunction; M1 = 1 month after transplant; M6 = 6 months after transplant; Pre = pretransplant.

Table 2. Sex Hormone Levels and IIEF5 Total Scores of the 28 Liver Transplant Recipients at Different Time Points.

	Median (range)			Reference range	p value		
	Pre	M1	M6		Pre vs. M1	M1 vs. M6	Pre vs. M6
17-OH progesterone (nmol/L)	4.7 (2.1–11.0)	4.4 (0.8–12.0)	3.9 (0.8–8.3)	0.9–6.6	.520	.040*	.083
Prolactin (mIU/L)	210.5 (67.0–436.0)	244.0 (118.0–74.0)	137.0 (12.2–298.0)	45–375	.083	<.0001*	<.0001*
Testosterone (nmol/L)	15.5 (1.7–34.0)	11.0 (2.0–24.0)	10.0 (2.7–26.0)	10–35	.108	.092^	.067
Free testosterone (nmol/L)	0.21 (0.05–1.33)	0.21 (0.03–0.57)	0.18 (0.04–0.44)	5.4–21.6 ^a	.247^	.043*^	.093^
Thyroid-stimulating hormone (mIU/L)	1.50 (0.07–3.70)	2.20 (0.21–7.20)	1.55 (0.54–9.30)	0.35–4.78	.002*	.061^	.123^
17-Beta-estradiol (pmol/L)	147.5 (9.0–2256.0)	48.0 (20.0–74.0)	60.0 (34.0–181.0)	20–160	<.0001*^	.003*^	<.0001*^
Sex-hormone-binding globulin (nmol/L)	54.0 (3.4–122.0)	37.0 (9.7–60.0)	37.0 (13.0–111.0)	10–57	.108	.935^	.183
IIEF5 total score	13 (1–24)	4 (1–22)	9 (1–25)	17–24	.011*	.001*	.927

Note. IIEF5 = International Index of Erectile Function version 5 questionnaire; M1 = 1 month after transplant; M6 = 6 months after transplant; Pre = pretransplant.

^aIwamoto et al. (2004).

*Statistically significant. ^Wilcoxon signed-rank test used.

shorter waiting time in European countries (Global Observatory on Donation and Transplantation data, 2016) may contribute to a quicker recovery in gonadal function. Whether preexisting gonadal alteration by toxic

metabolites is fully reversible after LT is a question yet to be answered. The role of immunosuppressive therapy is also important. Possible effects of immunosuppressants on sexual function are also being studied (Kaczmarek

et al., 2004; Lee et al., 2005; Tondolo et al., 2005), and some of these studies suggested that sirolimus may have a negative effect on male gonadal function. Most LT recipients at this center were given tacrolimus monotherapy, and its effect on gonadal function is not clear.

This study is mainly limited by its small number of participants and relatively short observation period after the operation. Unexpectedly, most of the patients had normal preoperative testosterone levels and were included into the study, which might be the reason why there was insignificant change in testosterone level and IIEF5 score. Future research on this topic can consider including measurement at 6 months and 1 year after LT to observe any delayed improvement in sexual function.

ED is a multifactorial condition, where psychological, physical, and social factors all come into play (Lue, 2000; Nicolosi, Glasser, et al., 2003; Nicolosi et al., 2004; Prins et al., 2002). Liver disease affects a patient in many aspects, such as hormonal imbalance, psychological stress of chronic illness, and even family tension while considering organ donation. After LT, despite normalization of liver function and improvement in sex hormone levels, erectile function is still under the influence of a number of factors, including complications from the operation, wound pain, and medications. When facing patients with ED, a physician's responsibility is to exclude any organic cause and, if necessary, provide assistance in psychological and social aspects. Multidisciplinary collaboration is paramount in helping this group of patients.

Conclusion

This study demonstrated that there was improvement in sex hormone levels after LT, namely, normalization of estradiol level and lowering of prolactin and progesterone levels. However, improvement in sex hormone levels did not translate into improvement of ED.

Declaration of Conflicting Interests

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Supplemental Material

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