PHYSICAL PERFORMANCE AND HEALTH-RELATED QUALITY OF LIFE IN MEN ON A LIVER TRANSPLANTATION WAITING LIST

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Twenty-six men on a liver transplant waiting list (12 had alcoholic cirrhosis, 8 suffered from posthepatitic cirrhosis, and 6 from cirrhosis of other etiologies) were eligible for this observation. Nineteen subjects underwent exercise testing to determine oxygen uptake at anaerobic threshold. In all patients dynamometry was performed to determine isokinetic muscle strength of knee extensor muscles, and handgrip. Quality of life was evaluated in all patients with the MOS SF-36 questionnaire. Child-Pugh A patients showed $54 \pm 8\%$, Child-Pugh B patients $36 \pm 2\%$, and Child-Pugh C patients $31 \pm 4\%$ of VO_{2-max} predicted at the anaerobic threshold (Kruskal-Wallis ANOVA, $p < 0.05$). Isokinetic muscle strength of the quadriceps femoris (left/right) was $149 \pm 20/134 \pm 14$ Nm in Child-Pugh A, $108 \pm 16/114 \pm 19$ Nm in Child-Pugh B, and $89 \pm 10/81 \pm 11$ Nm in Child-Pugh C patients (Kruskal-Wallis ANOVA, $p < 0.05$). MOS-SF36 revealed a Child-Pugh class dependent reduced functional status (Kruskal-Wallis ANOVA, $p < 0.05$). No significant differences in target parameters were found when analysed according to the etiology of cirrhosis. Patients on the liver transplant waiting list do have a stage dependent reduction in physical health. These data are the basis for longitudinal studies measuring the effects of preoperative rehabilitation programs in these patients.

Key words: exercise, quality of life, physical performance, cirrhosis, liver transplantation.

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INTRODUCTION

Patients with advanced stage liver disease often suffer from tiredness and a reduced ability to perform the activities of daily living. Even though studies of physical health and the ability to perform tasks of daily living exist for a variety of chronic disease (1–4), no comparable data for patients with cirrhosis of the liver due to chronic viral hepatitis or other etiologies exist to date. The primary goal of health care for patients with chronic conditions is to maximize function in everyday life and to achieve the highest level of well-being (5–7). Accomplishing this goal may reduce health costs (8).

In a recent study in patients with alcoholic liver disease, a significant weakening of isokinetic muscle strength was noted, which was dependent on the severity of malnutrition as assessed by lean body mass calculation but not on the severity of liver disease (9). No studies have investigated isokinetic muscle strength and aerobic capacity in patients with cirrhosis of various etiologies so far. The aim of our study was to investigate physical fitness by measuring isokinetic muscle strength and oxygen uptake at anaerobic threshold by exercise testing in patients on a waiting list for orthotropic liver transplantation (OLT) with liver diseases of various etiologies and severities. These data can serve as baseline values to monitor improvements during follow-up examinations of patients undergoing liver transplantation. At the same time, they could serve as a basis for the development of a rehabilitation program for
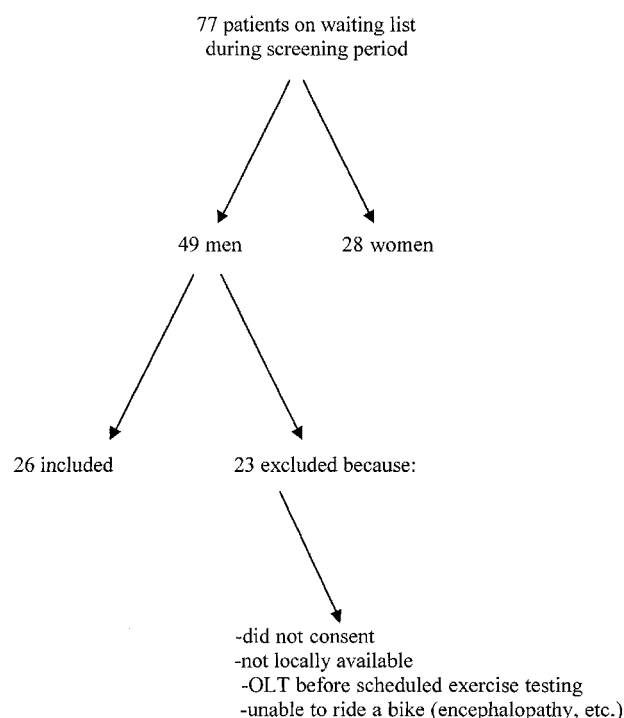

Fig. 1. Flow chart describing selection process. OLT = orthopedic liver transplantation.

Table I. *Patient characteristics and performance according to the etiology of liver disease*

Etiology	Toxic ($n = 12$)	Viral ($n = 8$)	Others ($n = 6$)	Total ($n = 26$)
Age (years)	53 ± 2	51 ± 3.5	57 ± 1.7	54 ± 1.5
Child-Pugh classification A/B/C (n)	1/3/8	2/5/1	1/2/3	4/10/12
ATVO$_2$ (ml/min/kg)	9.5 ± 0.9	9.6 ± 1.1	10.3 ± 1	9.8 ± 0.5
ATVO$_2$ of predicted peak VO$_2$ (%)	32 ± 2.8	37 ± 4.5	43.3 ± 6.2	37 ± 2.6
Knee 60°/second extension left side (Nm)	91.25 ± 11.01	139.12 ± 17.1	89.83 ± 14.9	105 ± 8.95
Knee 60°/second extension right side (Nm)	82 ± 10.93	139.37 ± 18.7	92 ± 18.11	101.96 ± 9.74
Hand grip strength (kg)	49 ± 5.4	66 ± 5.1	49 ± 7.8	54 ± 3.6

Results are presented as means $\pm$ SEM. Kruskal-Wallis ANOVA for all variables listed: $p > 0.05$.

patients with chronic liver disease. To date, no data with regard to whether regular physical exercise can lead to improvement of the physical performance status do exist for patients with chronic liver disease like they do exist for patients undergoing heart transplantation (10). This would not only be of interest for patients with end-stage liver disease awaiting major surgery like liver transplantation, but could also help to stabilize the physical condition of patients with less advanced disease.

EXPERIMENTAL PROCEDURES AND METHODS

Patients

Twenty-six men with advanced stage liver disease listed on the liver transplantation waiting list of the Department of Transplant Surgery of the University of Vienna Medical School were included into this prospective trial (Tables I, II). Twelve patients had alcohol-toxic cirrhosis, 8 patients suffered from posthepatitic cirrhosis (1 hepatitis B, 7 hepatitis C), and 6 patients from cirrhosis of other etiologies (1 hemochromatosis, 1 Wilson's disease, 1 secondary biliary cirrhosis, 3 cryptogenic cirrhosis). The diagnosis in each case was established prior to listing for OLT based on the results of anamnestic, serologic, or histopathologic evaluations. None of the patients concurrently had severe medical illnesses other than liver disease. Inclusion for exercise testing required normal routine 12-lead electrocardiogram, normal transthoracic echocardiogram, normal spirometry, and clinically normal cardiopulmonary examination. Seven patients had evidence of intrinsic pulmonary or cardiac disease and were therefore excluded from exercise testing. In none of the patients orthopedic problems were defined. Informed consent in writing was obtained from each patient prior to entry into the study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the appropriate institutional review committee. On the study day each subject fulfilled a self-administrated HRQOL-questionnaire before exercise testing on a cycle ergometer was performed. After at least 3 hours the muscle strength was assessed.

Clinical evaluation

The clinical status of the patients was staged according to the Child-Pugh classification (groups A, B and C), using measures of serum bilirubin, serum albumin, prothrombin time (measured as normotest), and the presence or absence of ascites and hepatic encephalopathy (11). Plasma bilirubin values of <34 µmol/l, between 34 and 51 µmol/l and greater than 51 µmol/l gave scores of 1, 2 and 3, respectively. Correspondingly, plasma albumin values greater than 35 g/l, between 30 and 35 g/l, and <30 g/l resulted in scores of 1, 2 and 3. Prothrombin time greater than 70%, between 40% and 70%, and <40% of normal scored 1, 2 and 3, respectively. No ascites resulted in score of 1, and scores for mild ascites and severe ascites were 2 and 3, respectively. Patients with encephalopathy were excluded from the study, and therefore, all patients scored 1 for encephalopathy. As described elsewhere, patients with a total score of 5–6 were categorized as group A, scores of 7–9 were group B, and scores of greater than 9 were group C.

Exercise testing

Even moderate exercise increases portal pressure and may therefore increase the risk for variceal bleeding in cirrhotic patients (12). In order to avoid a maximum increase in portal pressure with the inherent increased risk of bleeding from esophageal varices, we decided to evaluate the anaerobic threshold (AT) in these patients instead of the maximum oxygen uptake. The anaerobic threshold is defined as the maximum exercise intensity at which exercise could be maintained without increasing the accumulation of lactic acid (13). Exercise above the AT induces a rapid accumulation of lactate and a change to anaerobic metabolism, and increases the secretion of catecholamines and adrenocorticotropic hormones (14). Although maximum oxygen uptake has been used to estimate the aerobic exercise capacity quantitatively, the measurement of maximum oxygen uptake forces patients to exercise at maximum intensity. Therefore, AT is used clinically to assess the aerobic exercise capacity at a level of exercise appropriate for the individual with increased risk of an exercise-induced adverse event, for example in a patient undergoing cardiac rehabilitation (15).

Exercise studies were performed in all subjects using an incremental cycle ergometer protocol. Pedaling at 50 to 60 rpm, the work rate was increased every 2 minutes by 25 Watt from an initial load of 25 Watt after 1 minute of unloaded cycling for warm-up. The heart rate was recorded continuously at rest and throughout exercise with a 12-lead

Table II. *Performance according to the Child-Pugh Stage*

Child-Pugh Classification	Child A ($n = 4$)	Child B ($n = 10$)	Child C ($n = 12$)	Total ($n = 26$)
Age (years)	58 ± 3	53 ± 3	53 ± 2	54 ± 1.5
Etiology: toxic/viral/other	1/2/1	3/5/2	8/1/3	12/8/6
ATVO$_2$ (ml/min/kg)	11.6 ± 0.9	10.3 ± 0.8	8.7 ± 0.8	9.8 ± 0.5
ATVO$_2$ of predicted peak VO$_2$ (%)	54 ± 7.7	$37 \pm 2.2^*$	$32 \pm 3^{**}$	37 ± 2.6
Knee 60°/second extension left side (Nm)	149.5 ± 20.1	108.4 ± 15.5	$88.7 \pm 10.4^{**}$	105 ± 8.9
Knee 60°/second extension right side (Nm)	134.5 ± 14	114.2 ± 18.8	$80.9 \pm 11.1^{**}$	101.9 ± 9.7
Hand grip strength (kg)	69 ± 10.2	58 ± 6	46 ± 4.2	54 ± 3.6

Results are presented as means $\pm$ SEM; exact Mann Whitney-U: * $p < 0.05$ A vs. B; ** $p < 0.05$ A vs. C.

electrocardiogram (Siemens, Germany). After each increment blood pressure was measured. Ventilatory parameters were collected breath-by-breath using a computer-based device (Sensor Medics V-Max System, Sensormedics, Yorba Linda, LA, CA) and 10 seconds averages for each parameter were calculated. Patients breathed through a mouthpiece connected to a mass flowmeter (Sensor Medics, CA). Exercise testing was started after a rest period of at least 3 minutes to get adjusted to the mouthpiece. Minute ventilation was measured by the thermal conductivity technique. Oxygen uptake (VO_2) was measured with a fast response zirconium-oxide analyser (Servomex-Taylor, Sussex, UK). Samples of whole blood were taken from the hyperemized earlobe at rest, and at AT with a $20\,\mu l$ capillary to assess lactate concentration (ESAT 6661, Eppendorf, Hamburg, Germany). Pulse oximetry estimates arterial blood oxygen saturation. AT was determined by using the V-slope technique (16). Among normal individuals of varying physical fitness the ventilatory threshold occurs at 65–85% of maximum oxygen uptake (17, 18). Exercise testing was consistently carried out by the same staff and a physician was present.

Measurement of muscle strength

The muscle strength of the knee extensors on the right and on the left side was measured by a computerized isokinetic system (CYBEX 6000 Isokinetic dynamometer, Lumex Inc., New York), which measures the peak torque in Newton meters (Nm). The CYBEX system has been used extensively to measure muscle strength in normal and in some diseased populations and has been reported to give valid and reliable measurements (19).

Isokinetic knee extensor strength was recorded at a velocity of 60°/second. No isometric knee extensor peak torque was measured to avoid aggravation of portal hypertension by pressing in these patients. Testing began by positioning the subject in a sitting position with the hips in 90° of flexion. Stabilization straps were positioned across the subject's chest, pelvis, and anterior thigh of the leg to be tested. The input shaft of the dynamometer was aligned with the axis of the knee joint. The lever arm shin pad was placed just proximal to the malleoli. Measurement of subject's muscle strength were consistently carried out by the same person and a physician was nearby. During these measurements, the best of 3 attempts of an individual patient was recorded. No verbal encouragement was given.

Grip strength is an index of the power the hand can exert. A factory-calibrated Jamar dynamometer (Asimow Engineering Co., Los Angeles, CA) was used to assess grip strength. High inter-rater reliability and test–retest reliabilities using the dynamometer have been reported (20, 21). Each subject sat with the shoulder adducted and neutrally rotated, the elbow flexed to 90°, and forearm and wrist held in a neutral position (20). Hand dominance was determined by asking: "Are you right-handed or left-handed?". If the subject was unsure, handedness was decided by the hand used to eat and write (20). Three trials were performed for the dominant hand. The subjects rested 15 seconds between each trial. The highest grip strength value was used for analysis. No verbal encouragement was given.

Health-related quality of life

The MOS SF-36 is a widely accepted generic instrument for assessment of the health-related quality of life in patients (22). On the basis of a German adaptation of the MOS SF-36, the results of psychometric testing in healthy and impaired populations were evaluated (23).

The questionnaire consists of 36 items related to 8 scales. These scales cover different health concepts. For each of these 8 scales, the responses to the questions are summed and converted to a 0 to 100 scale, with 100 indicating best function. These concepts are then comprised to three general health attributes: functional status, well-being and overall health. The functional status includes four scales. It deals with limitations in physical functioning (PFI) such as walking and climbing stairs (10 items), limitations in role functioning due to physical limitations (ROLPHYS) such as duties in the home or at work (4 items); limitations in role functioning due to emotional limitations (ROLEM, 3 items) and the degree to which health interfered with social functioning and interactions with others (SOCIAL, 2 items). Well-being is addressed by three scales measuring mental health (MHI, 5 items) addressing depression and mood state, energy/fatigue (VITAL, 4 items) and pain (PAIN, 2 items). Finally, overall health includes measurement of general

health perception (GHP, 5 items) and changes in health. This last item evaluates the patient's perception of change of health over the past year. The eight scales are summarized in Table III. Reference values for normal individuals and with other chronic conditions, such as chronic heart failure, hypertension, and low back pain in a German speaking population are given in Table IV (23, 24).

Statistical analysis

Descriptive statistics (means ± SEM) were performed on all dependent variables. The Kruskal-Wallis ANOVA by ranks was used to evaluate differences between several groups. If significant differences were found in the Kruskal-Wallis ANOVA by ranks, the exact Mann-Whitney U test was used for comparisons between individual patient groups according to Child-Pugh classification and etiology using the Statistics Package for Social Sciences (SPSS Inc., Chicago, IL). The Pearson's correlation coefficient was determined to estimate the correlation (r) between target parameters and Child-Pugh classification and etiology, respectively. P values less than 0.05 were considered statistically significant.

RESULTS

Exercise testing

Oxygen uptake at AT for 19 patients according to the Child-Pugh classification A ($n = 3$), B ($n = 7$), C ($n = 9$) and etiology are summarized in Tables I, II. Seven patients were unable to undergo exercise testing because of intrinsic pulmonary or cardiac disease. Sinus rhythm was present in all subjects at rest and during exercise. The mean resting rate pressure product was 9712 (SEM = 568) and increased throughout exercise to a mean peak rate pressure product at AT of 16425 (SEM = 1238). The mean resting systolic blood pressure was 116 mmHg (SEM = 4.7), while the mean peak systolic blood pressure at AT was 148 mmHg (SEM = 7.2). Assessment of lactate concentration showed at rest 1.5 mmol/l (SEM = 0.2) and at AT 3.5 mmol/l (SEM = 0.2). Oxygen saturation measured with a pulse oximeter was in all subjects always above 96%. No serious cardiac arrhythmias were seen and no test was terminated because of arrhythmia. No recordings of blood pressures drop of 10 mmHg were noted.

At ventilatory AT mean oxygen uptake ($ATVO_2$) for the patients in Child-Pugh class A was 11.6 ml/min/kg ± 0.9 in Child-Pugh class B 10.3 ml/min/kg ± 0.8, and in Child-Pugh class C 8.7 ml/min/kg ± 0.8, respectively (Kruskal-Wallis ANOVA: p = n.s.). $ATVO_2$ in patients with Child-Pugh class A cirrhosis was 54% ± 7.7 of predicted peak VO_2 value, in Child-Pugh class B 37% ± 2.2, and in Child-Pugh class C 32% ± 3 (Kruskal-Wallis ANOVA: $p = 0.024$; exact Mann-Whitney U-test: A– B: $p = 0.033$; A– C: $p = 0.018$; B–C: p = n.s.). No significant difference was found between patients with cirrhosis of different etiology (toxic, viral, or other etiology). There was a significant correlation between the Child-Pugh stage and $ATVO_2$ percentage of predicted peak VO_2 value (Pearson's correlation coefficient: r = 0.64; $p = 0.003$).

Muscle strength testing

All 26 patients were able to do the functional muscle strength testing and grip strength testing. The results of the isokinetic knee extensor strength measurement are presented in Tables I,

Table III. *Health-related quality of life (MOS SF-36)*

Child-Pugh classification	Child A ($n = 4$)	Child B ($n = 10$)	Child C ($n = 12$)	Total ($n = 26$)
Physical functioning	90 ± 8	44 ± 8*	52 ± 7**	55 ± 5
Role functioning/physical	94 ± 6	10 ± 5*	23 ± 7**	28 ± 7
Role functioning/emotional	92 ± 8	20 ± 13*	47 ± 14	43 ± 9
Social functioning	84 ± 6	49 ± 10	70 ± 8	64 ± 6
Mental health	71 ± 11	58 ± 7	63 ± 5	63 ± 4
Bodily pain	74 ± 10	62 ± 8	72 ± 9	68 ± 5
Vitality	55 ± 13	33 ± 5	33 ± 4	36 ± 4
General health	54 ± 15	39 ± 4	42 ± 4	43 ± 3

Results are presented as means ± SEM; exact Mann-Whitney-U: * $p < 0.05$ A vs. B; ** $p < 0.05$ A vs. C.

II. There was a significant difference between patients in Child-Pugh class A and C (exact Mann-Whitney U-test: left $p = 0.03$; right $p = 0.03$). Comparing patients with cirrhosis of different etiology revealed no significant differences. A significant negative correlation could be found between increasing Child-Pugh classes and the strength of knee extensors (Pearson's correlation coefficient; left: r = −0.45, $p = 0.021$; right: r = −0.42, $p = 0.033$) Although there was a significant correlation between the Child-Pugh class and the hand grip strength (Pearson's correlation coefficient: r = −0.456; $p = 0.019$), no significant differences could be detected within the different subgroups (data shown in Tables I, II). Grip strength of the non-dominant hand showed no significant difference to the dominant hand (data of the non-dominant hand not shown).

Health-related quality of life

The MOS-SF 36 was completed in all subjects. Scale scores of all 8 components are presented in Table III. Patients on the OLT waiting list show a significant limitation in their functional status. Especially, physical functioning (PFI) (exact Mann-Whitney U-test: A–B $p = 0.008$; A–C $p = 0.013$; B–C $p = $ n.s.) and role functioning due to physical limitations (ROLPH) (exact Mann-Whitney U-test: A–B: $p = 0.002$; A–C: $p = 0.001$; B–C: $p = $ n.s.) showed a significant Child-Pugh class dependent deterioration. No differences could be detected in scales of "well-being" and "general health" between the subgroups.

Scoring in none of the scales was significantly influenced by the etiology of liver disease.

A significant correlation between role functioning due to physical limitations (ROLPH) and Child-Pugh classification could be seen (Pearson's correlation coefficient: r = −0.512; $p = 0.008$).

DISCUSSION

The study patients on the liver transplant waiting list present are a special subgroup of patients with mostly advanced stage liver disease and are not representative of the overall population with liver cirrhosis. Despite this selectivity, the data presented provide the first information on objectively measured levels of health related fitness together with health related quality of life in patients on a liver transplantation waiting list and provide important information for longitudinal observations and pre-operative rehabilitation programs in these patients. Not surprisingly, patients with advanced stage liver disease are stage dependently impaired in their physical capacity and health-related quality of life, where the patients with the most advanced disease also show the greatest impairment. This appears to be independent of the etiology of liver disease and is a direct consequence of impaired liver function.

The results of this study demonstrate that oxygen uptake at anaerobic threshold in patients with advanced stage liver disease was significant lower than predicted for general population.

Table IV. *Health-related quality of life (MOS SF-36)—reference values in normals and chronic diseases in a German speaking population (23, 24)*

Chronic disease	CHF*	Normals**	Hypertension**	LBP**
Physical functioning	61 ± 7	92 ± 15	68 ± 24	54 ± 16
Role functioning/physical	53 ± 17	83 ± 30	57 ± 45	30 ± 39
Role functioning/emotional	71 ± 15	81 ± 38	62 ± 43	57 ± 41
Social functioning	76 ± 8	85 ± 22	78 ± 22	56 ± 23
Mental health	64 ± 5	71 ± 17	69 ± 18	55 ± 18
Bodily pain	88 ± 6	77 ± 17	61 ± 28	26 ± 20
Vitality	55 ± 6	59 ± 17	58 ± 19	38 ± 16
General health	47 ± 7	74 ± 19	56 ± 18	43 ± 17

Results are presented as: * means ± CI; ** means ± SEM.
CHF = chronic heart failure; LBP: low back pain.

These data are in line with previous studies showing that maximal exercise achieved by cirrhotic patients is lower than that of healthy subjects (25–27) and that maximal exercise is inversely correlated with the degree of liver failure evaluated by the Child-Pugh score (27). We showed for the first time that patients with cirrhosis have also a stage-dependent anaerobic metabolism at low workload. The anaerobic threshold is defined as the maximum exercise intensity at which exercise could be maintained without increasing the accumulation of lactic acid (13). Exercise above the anaerobic threshold induces a rapid accumulation of lactate and an increase in anaerobic metabolism, and increases the secretion of catecholamines and adrenocorticotropic hormone (14). During exercise, an increase in cardiac output and a redistribution of blood flow from other territories (especially the splanchnic area) through an adrenergic-mediated vasoconstriction (28) are the main physiological changes facilitating the increase in blood flow and oxygen supply to the exercising muscles. Patients with liver cirrhosis also experience hyperkinetic circulation with low peripheral resistance and relatively high cardiac output, resulting in low arterial pressure at rest (29).

It is important to remark that a significant increase in portal pressure is already present at 30% of the peak workload, which is moderate physical exercise (12), and may correspond to that required during moderate daily activity such as carrying dishes or walking at 3.5mph (30). This low VO_2 at anaerobic threshold in patients with cirrhosis could contribute to limited functional capacity in daily activities, which is perceived by these patients as fatigue and inability to perform activities like they used to do. These findings are confirmed by the significant stage dependent lower scoring in the functional status assessed by the MOS-SF 36.

The reduced functional status has been linked to loss of muscle mass, which occurs even with normal dietary intake of protein (31). Decreased muscle protein synthesis (32) as well as biochemical and physiologic abnormalities in the muscle (33) have been described. In patients with alcoholic liver disease, alcoholic myopathy (34, 35) and neurogenic muscle dystrophy (36) have been described as additional causes of muscle wasting, but are not generally accepted. Disease-associated fatigue resulting in inactivity or immobility could be one of the factors leading to the low physical capacity in the patients. Chronic diuretic treatment and ascites per se may further decrease physical fitness. In line with this observation, no significant difference could be detected between cirrhosis patients of different etiology, while muscle strength of knee extensors and grip strength was stage dependent impaired in all subjects. Muscle strength, when measured with the isokinetic peak torque of the thigh and with grip strength of the dominant hand significantly correlated with Child-Pugh classification, indicating that functional impairment in these patients is primarily due to the severity of liver disease and not due to the toxic influence of ethanol.

Patients with cirrhosis have a stage-dependent impaired perceived health status, involving the majority of health-related quality of life aspects. This conclusion is based on a questionnaire widely used in epidemiologic studies: MOS SF-36, constructed to measure the full range of health status and well-being. The domains most severely affected by the severity of liver disease were those associated with physical health. In the MOS SF-36, physical functioning is a relatively pure scale, measuring a physical dimension of health (37), whereas general health is dependent on both severe and minor symptoms, irrespective of their association with clinical disability (24, 38). These considerations fit with clinical data included in the Child-Pugh score, which were significantly correlated with role functioning due to physical limitations in this observation. This impairment in physical status observed in our study was confirmed recently in a series of patients with cirrhosis (39). No significant differences were found between patients with cirrhosis of toxic, viral, or other etiology, respectively. The present study did not evaluate anxiety, depression or family relationships. Therefore, we could not exclude that anxiety, depression or family relationships could confound these results.

These data are the basis for longitudinal studies measuring the effects of therapy and preoperative rehabilitation programs with advanced stage liver disease waiting for an orthotopic liver transplantation. Although patients on our liver transplant waiting list do have a stage-dependent impairment in aerobic physical fitness, isokinetic muscle strength, and health-related quality of life, which is evident in Child B and C patients, the results suggest that patients with various etiologies of liver disease on a liver transplantation waiting list have similar perceptions of their physical functioning. It remains to be seen whether this perception could be improved by moderate physical training even before liver transplantation. It is not known if training before orthotopic liver transplantation would have any beneficial effect on the outcome of transplantation. But since poor nutritional status has a significant negative impact on survival after OLT (40, 41) and physical fitness cannot be increased by dietary supplementation of patients with advanced stage liver disease (42), an attempt to increase physical fitness before OLT by controlled training seems to be reasonable.

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