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AEROBIC CAPACITY, MUSCLE STRENGTH AND HEALTH-RELATED QUALITY OF LIFE BEFORE AND AFTER ORTHOTOPIC LIVER TRANSPLANTATION: PRELIMINARY DATA OF AN AUSTRIAN TRANSPLANTATION CENTRE

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Objective: **Patients before orthotopic liver transplantation usually show a reduced physical performance status, which impacts on their daily life and social participation. This pilot study aimed to evaluate endurance capacity, muscle strength, and quality of life before and after orthotopic liver transplantation in patients in an Austrian transplantation centre.**
Subjects: **Fifteen patients (male/female = 10:5) were included in the pilot study.**
Methods: **Exercise testing, strength testing of knee extensor muscles and of handgrip, and quality of life (SF-36 health survey) were assessed before and after orthotopic liver transplantation (after 1–2 months).**
Results: **The oxygen uptake at the anaerobic threshold (VO_2AT) and isokinetic strength testing of quadriceps femoris muscle did not change significantly from baseline, before transplantation to follow-up after orthotopic liver transplantation. Before orthotopic liver transplantation, quality of life was hampered concerning functional status, emotional role, vitality, and general health perception. Significant improvements of social functioning ($p = 0.032$), vitality ($p = 0.006$), mental health ($p = 0.004$) and general health perception ($p = 0.002$) could be found for this study population after orthotopic liver transplantation.**
Conclusion: **The results of this pilot study including a population of an Austrian transplantation centre indicate deficits of physical performance as well as reduced quality of life in patients before and after orthotopic liver transplantation.**

Key words: aerobic capacity, muscle strength, quality of life, orthotopic liver transplantation.

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INTRODUCTION

Patients with liver cirrhosis usually show a high muscle- and substance-decrease, dependent on the Child-Pugh criterions (1) with significant weakening of isokinetic muscle strength (2). The reduced liver function with restricted metabolism and portal hypertension with reduced resorption of food components could be possible reasons for these symptoms (3, 4). Patients with end-stage liver disease often face restrictions in performing activities of daily living and often suffer from fatigue (5, 6).

Previous data of our study group provided baseline values of patients on a liver transplantation waiting list (7). While Child-Pugh class A-patients showed almost average aerobic capacities at the anaerobic threshold, performance of patients classified Child-Pugh B was reduced, but still in the norm. Compared with patients of Child-Pugh class A and B, Child-Pugh C-patients showed the worst physical fitness and did not even reach the population's standard (7). The optimization of function in everyday life and an improved level of well-being of these patients should be an integrated goal of their treatment (8).

Orthotopic liver transplantation (OLT) is the preferred treatment for end-stage liver disease (9, 10) and has been performed since 1967 (11). In a previous study by Stephenson et al. (12), liver transplantation recipients showed impaired endurance capacity, most probably due to chronic deconditioning or myopathy related to immunosuppressive medication. Therefore, OLT as the only treatment of end-stage liver disease does not necessarily lead to an improvement of aerobic capacity or well-being. Recently, Krasnoff et al. (13) reported improved health-related fitness and quality of life (QoL) over the first 2 years after OLT. Despite these improvements, all measures remained lower than recommended for cardiovascular and overall health. Beyer et al. (14) performed a supervised exercise program over 6 months with patients after OLT, leading to a significantly improved physical fitness and muscle strength.

To our knowledge only one recent study has described endurance capacity (e.g. aerobic capacity) and muscle strength together with health-related QoL after OLT without training (13). The present pilot study aimed to compare the pre- and post-operative status of OLT patients with regard to physical performance and health-related QoL in Austrian's transplantation centre patients.

PATIENTS AND METHODS

Fifteen patients (10 men and 5 women, mean age 52.2 ± 11.2 years), suffering from advanced-stage liver disease, were included in this

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prospective pilot study (Table I). All of them were registered for liver transplantation on a waiting list of the Department of Transplant Surgery of the General Hospital of Vienna, an Austrian transplantation centre. Inclusion criteria consisted of planned OLT, a clinically normal cardiopulmonary examination, a normal 12-lead electrocardiogram, trans-thoracic echocardiogram and spirometry, and oxygen (O_2) saturation above 70 mmHg. Patients with pulmonary or cardiac disease, orthopaedic problems or the presence of a hepatopulmonary syndrome were excluded from the study. Patients were classified by the well-established Child-Pugh-score (15). For the calculation of the Child-Pugh score we sum up the scoring points from the 5 clinical parameters albumin (>3.5 g/dl = 1 point, 2.8–3.5 g/dl = 2 points, <2.8 g/dl = 3 points), serum bilirubin (<2 mg/dl = 1 point, 2-3 mg/dl = 2 points, >3 mg/dl = 3 points), prothrombin index (>70% = 1 point, 40–70% = 2 points, <40% = 3 points), ascites (none = 1 point, moderate = 2 points, severe = 3 points), and hepatic encephalopathy (absent = 1 point, grades 1 and 2 = 2 points, grades 3 and 4 = 3 points). The sum corresponds to 1 of 3 groups with different expected survival and prognosis (Child-Pugh A = 5–6 points, Child-Pugh B = 7–9 points, Child-Pugh C = 10 or more points) (Table I).

First, the patients completed a self-administrated health-related QoL–questionnaire (SF-36 health survey (16)), which was checked by one investigator. Then they performed an exercise testing by ergo-spirometry. After a short rest, isokinetic muscle strength was assessed using Cybex 6000 dynamometry and grip strength measurement by Jamar dynamometry. This assessment was performed before OLT (while waiting on the transplantation list) and after a period of 1–2 months (median = 56 days) after operation, as soon as possible with a stable status. The patients did not attend any kind of physical training before or during the study period.

Additionally 5 patients had a second follow-up examination, 3 years after surgery. The last follow-up data are presented in Fig. 1. The results of the general health assessment were compared with the results of healthy people and of patients with chronic heart failure.

The study protocol was approved by the Medical Ethics Committee of the University of Vienna. All patients gave written informed consent to participate.

Health-related quality of life

For the assessment of the health-related QoL, a widely accepted generic instrument, the SF-36 health survey, was used (17). The SF-36 health survey consists of 36 items. Eight scales deal with questions of physical function (PFI – e.g. walking, climbing stairs), role functioning due to physical limitations (ROLPH – e.g. duties at home or work), role functioning due to emotional limitations (ROLEM), social functioning (SOCIAL – interaction with others), mental health (MHI – e.g. depression, mood), pain (PAIN), general health perception (GHP – e.g. changes in health) and vitality (VITAL – e.g. energy, fatigue). The score ranges from 0 to 100, with 100 indicating best function. Reference values for healthy individuals and for patients with other chronic conditions are available (18, 19).

Exercise testing

Exercise testing was performed using an incremental cycle ergometer protocol. The test was started with 25 watt following one minute of unloaded cycling to warm up. The work rate was increased every 2 minutes by 25 watt pedalling at 50–60 rpm. This protocol has been used to evaluate the aerobic capacity in patients with diabetes, fibromyalgia and dermatomyositis/polymyositis (20–22). Patients were monitored by a 12-lead electrocardiogram (Siemens, Germany). Blood pressure was measured after each increment manually. A computer-based device (Sensor Medics V-Max System, Sensormedics, Yorba Linda, LA, CA, USA) collected breath-by-breath the ventilatory parameters. Patients breathed through a mouthpiece connected to a mass flowmeter (Sensor Medics, CA, USA). After a rest of 3 minutes, to become adjusted to the mouthpiece, the test was started. A zirconium-oxide analyser (Servomex-Taylor, Sussex, UK) measured the oxygen uptake. The arterial blood oxygen saturation was determined by pulse oximetry.

To avoid too strenuous exercise, with the increased risk of complications such as oesophageal variceal bleeding, we decided to evaluate the anaerobic threshold instead of the maximum oxygen uptake (23) of the cirrhotic patients. This method has been used previously to assess the aerobic exercise capacity in patients undergoing cardiac rehabilitation (24). The anaerobic threshold is defined as the maximum exercise intensity at which exercise can be maintained without an increase in lactic acid accumulation (25). The oxygen uptake at the anaerobic threshold does normally not depend on the compliance of the patient (26). At this threshold the lactate production and elimination is equal (27). As a non-invasive method to determine the threshold, the v-slope technique was used (28). The measurement was stopped after having reached the anaerobic threshold and the patient was allowed to cool down by unloaded cycling. Each exercise testing was conducted by the same investigators.

Measurement of muscle strength

Muscle strength of the knee extensors of the dominant leg was measured using an isokinetic dynamometer (Cybex 6000 Isokinetic dynamometer, Lumex Inc., New York, USA). The reliability of this measurement has been reported previously (29, 30). The assessment was performed after exercise testing to reduce potential risk of injuries, due to a lack of warming up. The patient was tested in a sitting position with a hip flexion of 90° and fixed by stabilization straps across the chest, pelvis and thigh of the tested leg. The shin pad was placed proximal to the ankle. The isokinetic peak torques in Newton-meters (Nm) and the peak torque related to body weight were recorded at a velocity of 60°/second (4 repetitions). The highest value achieved was regarded as the peak torque. This protocol has been used in several studies to evaluate the muscle strength of patients with different chronic diseases, e.g. fibromyalgia, chronic heart failure or after OLT (14, 21, 31). To avoid a disproportional and potentially dangerous increase of portal hypertension, no measurement of isometric knee extensor strength was performed.

Grip strength of the dominant hand was assessed by Jamar dynamometer (Asimow Engineering Co., Los Angeles, CA, USA) (32). The test was performed in a sitting position with a hip- and knee-flexion of 90°, the shoulders adducted to the body and neutrally rotated, the elbow flexed to 90°, and the forearm and wrist in a neutral position (33). Three trials were performed. The best result was used for the study.

Both strength tests were conducted by the same investigator.

Statistical analysis

For the statistical analysis the Statistics Package for Social Sciences (SPSS Inc., Chicago, IL, USA) was used. Descriptive statistics (means ± SEM) were performed on all dependent variables. To evaluate the differences between several groups the Kruskal-Wallis ANOVA was used. The Mann-Whitney *U* test compared individual patient groups according to Child-Pugh classification and the occurrence of post-operative complications. The Spearman correlation coefficient was used to estimate the correlation between parameters and Child-Pugh classification or postoperative complications. For differences between pre- and post-operative values the Wilcoxon test was used. Significance level was set at 0.05.

RESULTS

Twelve patients performed the exercise testing at baseline and at the first follow-up. Three patients were excluded from the exercise testing because of low haemoglobin values. Fifteen patients completed the assessment of muscle strength and the QoL–questionnaire. At the last follow-up 3 years after surgery, 5 patients completed the questionnaire. Out of them, 4 patients conducted the muscle testing and only 3 patients performed the exercise testing. The high drop-out rate was caused by patients moving out of reach, undergone surgery (lobe resection due to pulmonary metastasis), or development of oropharyngeal and sigmoid cancer with the need of surgical treatment. One patient, previously suffering from Wilson disease, became the mother of a healthy child and was not available for the last follow-up evaluation. Contacting the other patients by telephone during a

Table I. *Aetiology of liver disease, sex, co-morbidity, medications and postoperative complications of 15 patients after orthotopic liver transplantation (OLT)*

Patient/ Sex	Aetiology	Child-Pugh class	Co-morbidity	Medications	Complications postoperative	Complications > 1/2 years after OLT
1/F	Viral	A	Partial liver resection because of HCC, chemotherapy, melanoma of the eye treated with radiation	Sandimmune, prednisolone		
2/F	Wilson disease	A		FK 506, prednisolone, ursofalk, cellsept	OLT with splenectomia, stenosis of the bile duct with stent-implantation, sepsis	
3/M	Toxic	C	Reflux oesophagitis, deep vein thrombosis, APC-resistance	Sandimmune, xefo, tramal, dalacine, tazonam		Carcinoma of the larynx with operation and radiation, carcinoma of the lung with resection of the left upper lobe
4/M	Toxic	C		Sandimmune, prednisolone, lasix, furo-spirobene	Secondary haemorrhage, oral mycosis	
5/F	Viral	B	Operation of a prolapsed intervertebral disc L4/5, variceal oesophageal bleeding, interferon therapy	Sandimmune, prednisolone, lasilactone		
6/M	Toxic	B	Variceal oesophageal bleeding, cholecystolithiasis	Sandimmune, prednisolone, lasilactone, ursofalk	Acute rejection of the transplant, cholangitis, leak of the bile duct	
7/M	Viral	B	Diabetes, semi-castration with chemotherapy and radiation because of teratoma of testis	Prednisolone, FK 506, cellsept, lasix, lasilactone, insulin	Chronic rejection of the transplant, sepsis, re-OLT	
8/M	Toxic	C	Diabetes, hypertension	Sandimmune, prednisolone, insulin, ciproxin	Stenosis of the bile duct with stent-implantation	
9/M	Viral	B	Diabetes, hypertension	Fortecortin, FK 506, tritace, cellsept, insulin		
10/M	Toxic	C		Sandimmune, prednisolone, lasilactone, waltrex		Carcinoma of the mouth with radiation and chemotherapy
11/F	Toxic	B		Sandimmune, aprednisolone, lasilactone		
12/F	PSC	B	Autoimmune thyreoiditis, hyperthyroidism, subtotal colectomia because of ulcerative colitis and carcinoma of the colon	Euthyrox, dipentum, sandimmune, prednisolone, ursofalk, lasilactone		
13/M	Viral	B	Diabetes	Sandimmune, prednisolone, cellsept, tavanic, insulin		Stenosis of the bile duct, viral relapse
14/M	Toxic	C	Partial thrombosis of the portal vein, variceal oesophageal bleeding	Sandimmune, prednisolone, lasilac-tone, ciproxin, ursofalk		
15/M	Toxic	C	Variceal oesophageal bleeding	Sandimmune, prednisolone, lasilactone	Stent-implantation because of stenosis of the anastomosis	

HCC = hepatocellular carcinoma; PSC = primary sclerosing cholangitis.

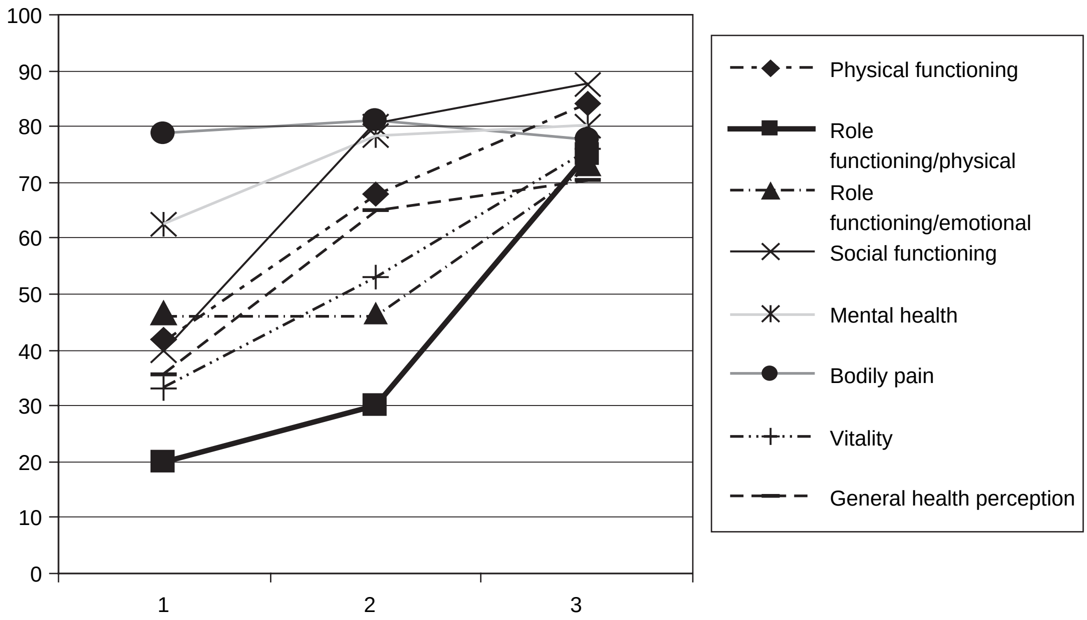

Fig. 1. Quality of life of 5 patients at baseline (1), 1–2 months after (2) and 3 years after orthotopic liver transplantation (3).

period of 6 months was without success, despite repeated attempt. The results of the third testing are presented only graphically due to the small sample size (Fig. 1).

Health-related quality of life

The SF-36 health survey was completed by all patients. At baseline, patients on the transplantation waiting list were strongly impaired in certain domains (Fig. 2). These patients with end-stage liver disease showed a decreased score in the items physical functioning, physical role, emotional role, vitality and general health perception. They achieved 56.4% in physical functioning, 31.8% in physical role, 59.6% in emotional role, 47.5% in vitality and 58.8% in general health perception compared with healthy individuals. Only a small limitation was obtained in the scales social functioning (85.1%), mental health (86.8%), and pain (82.9%). These findings were similar to patients with chronic heart failure in physical functioning, physical role, mental health and general health perception. Emotional role, social functioning, pain and vitality were scored higher by these patients (19). There was no significant correlation between the Child-Pugh classes and the 8 scales of the questionnaire.

There were significant differences between the values at baseline and follow-up in the scales "social functioning" (Wilcoxon test: $p = 0.032$), "mental health" (Wilcoxon test: $p = 0.004$), "vitality" (Wilcoxon test: $p = 0.006$) and "general health perception" (Wilcoxon test: $p = 0.002$) (Fig. 2). Impairments seemed to be reduced in the scales "physical functioning", "physical role", "emotional role", "vitality" and in "general health perception". In this study population perception of pain only led to a small limitation after transplantation. The scales "mental health" and "social functioning" were marked higher than in the average population by these patients.

Exercise testing

Exercise testing was completed by 12 patients at baseline and at follow-up. Sinus rhythm was present in all patients at rest and during the tests. No premature stop of exercise testing due to cardiac arrhythmia was necessary. The oxygen saturation was always above 96%. Before transplantation, the oxygen uptake at the anaerobic threshold ($ATVO_2$) was 10.3 ± 3.0 ml/kg/min. At follow-up-evaluation the anaerobic threshold was found at 9.5 ± 2.7 ml/kg/min ($p =$ n.s.). Patients reached 39.4 ± 16.5 watt at the anaerobic threshold at the first test and 34.8 ± 15.6 watt at the second test. A division into Child-Pugh classes did not show a significant difference (Table II). Postoperative complications significantly influenced the VO_2 at the anaerobic threshold ($p = 0.042$). Patients with postoperative complications performed a better exercise testing than patients without complications (Table III), maybe caused by the fact of a later examination of patients with complications (without complications testing within 49.4 ± 16.3 days, with complications testing within 74.8 ± 25.4 days). There was no significant difference between baseline and follow-up (Table IV). Patients divided into Child-Pugh class A, B and C did not show a significant difference regarding their aerobic capacity before and after surgery.

Measurement of muscle strength

Isokinetic testing of thigh muscles. All patients were able to perform isokinetic testing of muscle strength. The peak torque of the dominant knee extensor muscles was 96.87 ± 53.0 Nm at baseline and 97.53 ± 33.4 Nm at follow-up. These values related to body weight were 128.33 ± 61.9 Nm/kg and 136.64 ± 38.9 Nm/kg. There were no significant differences between the 3 Child-Pugh classes (Table II) or between patients with and without postoperative complications (Table III). There were no

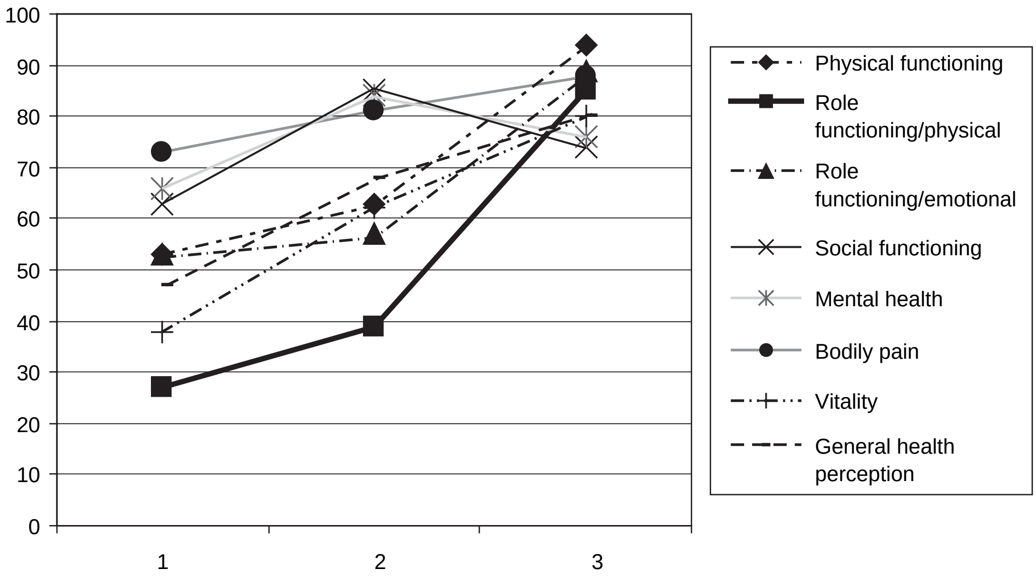

Fig. 2. Health-related quality of life (MOS SF-36) pre (1)- and postoperative (2) and reference values in a German speaking healthy population (3).

significant differences between baseline and follow-up (Table IV). The isokinetic muscle strength of patients assigned to Child-Pugh class A and B did not change significantly before and after surgery. Patients from Child-Pugh class C showed a significant difference in the muscle strength of the dominant knee extensor muscles related to body weight ($p = 0.028$).

Handgrip. Strength of handgrip of the dominant hand was 53.4 ± 31.4 kg at baseline and 47.1 ± 13.1 kg 1–2 months after surgery. Child-Pugh classes or postoperative complications did not show significant differences (Tables II and III). There were no significant differences between baseline, first and second follow-up (Table IV). There was no significant difference by division into the Child-Pugh classes before and after surgery.

DISCUSSION

OLT is a standard treatment for end-stage liver disease, which markedly improves liver function and survival. The 1-year survival rate after OLT is between 80% and 85% (34). Five years after operation, the survival rate ranges from 60% to 65% or higher (1). Little is known about the effect of OLT on physical fitness after surgery. Only one study by Krasnoff et al. (13) evaluated health-related fitness and QoL over the first 2 years after OLT. They found improvements in all evaluated parameters, but all measures remained lower than recommended for cardiovascular and overall health.

The present study aimed to present data of physical capacity, muscle strength and health-related-QoL before and after liver transplantation in patients of an Austrian transplantation centre. The whole assessment was conducted before and after OLT. The patients did not attend any kind of physical training before or during the study period.

In the present study, patients with end-stage liver disease showed physical deconditioning with substance- and muscle-loss before, 1–2 months after and 3 years after OLT. There was no significant difference between the pre- and postoperative values regarding the aerobic capacity and isokinetic muscle strength. Differentiation by Child-Pugh criterions did not show significant differences. The aerobic capacity was significantly influenced by complications, which occurred after operation. Surprisingly, patients with postoperative complications performed a better exercise testing than patients without complications. This could be explained by the longer interval between OLT and the time of testing and the accordingly lower postoperative deconditioning.

Table II. *Performance according to the Child-Pugh-classification pre- and postoperative given as mean ± SEM*

Child-Pugh classification	Child-Pugh A		Child-Pugh B		Child-Pugh C	
	pre	post	pre	post	pre	post
Age (years)	37.5 ± 23		53.9 ± 8		55.2 ± 9	
$ATVO_2$ (ml/kg/min)	11.9	11.3	11.2 ± 3.3	8.5 ± 2.9	8.9 ± 2.7	10.3 ± 2.6
Peak torque (Nm)	102.0 ± 15.6	103.0 ± 48.1	117.1 ± 63.9	102.0 ± 42.8	71.5 ± 39.5	90.5 ± 19.2
Peak torque (Nm/kg)	161.0 ± 16.9	125	152.4 ± 69.7	144.3 ± 51.2	89.3 ± 42.3	129.7 ± 24.7
Hand grip strength (kg)	38.0 ± 4.2	40.0 ± 15.6	54.7 ± 20.1	49.7 ± 17.5	57.0 ± 46.4	46.3 ± 5.7

AT = anaerobic threshold.

Table III. *Performance according to the postoperative complications given as mean ±SEM*

Postoperative complications	With	Without
Age (years)	50.5 ± 15.9	48.1 ± 12.8
$ATVO_2$ (ml/kg/min)	12.5 ± 1.3	8.5 ± 2.3
Peak torque (Nm)	109.8 ± 32.2	82.9 ± 29.4
Hand grip strength (kg)	50.8 ± 26.5	43.0 ± 10.8

AT = anaerobic threshold.

The preoperative findings are in line with previous studies, which reported an impaired exercise capacity achieved by cirrhotic patients (35, 36). Before OLT, a prolonged period of weakness and fatigue with deconditioning and decreased oxygen uptake and reduced muscle strength could be observed in many patients with advanced-stage liver disease (14). Wiesinger et al. (7) demonstrated a stage-dependent anaerobic metabolism at low work load. In accordance with the postoperative data of the present study, Stephenson et al. (12) showed an impaired physical performance 30 months after liver transplantation and explained their findings as a result of chronic deconditioning or myopathy related to immunosuppressive medication. An improvement of physical fitness, muscle strength and QoL in the first 2 years after OLT was demonstrated by Krasnoff et al. (13). The values mentioned above were evaluated after transplantation without comparison to preoperative findings.

Function, activity and participation are major items of the ICF classification. The reported limitations of function could contribute to a reduced activity. These findings seem to be confirmed by lower scoring in the functional performance at baseline as well as at the follow-up examination tested by the SF-36 health survey. Participation assessed by the scale "social functioning" of the SF-36 health survey was negatively affected before transplantation (37). Similarly, Kanwal et al. (38) could find an impaired health-related QoL in patients with end-stage liver disease. Although in the present study QoL improved after surgery, most scales remained below the values of the general population, except in the scales "mental health" and "social functioning". These scales were higher than in average population despite existing deficits in physical performance. Similar findings were reported in former studies (38, 39). In a meta-analysis, QoL of transplant recipients was lower, compared with QoL of the general population (39). Painter et al. (40) investigated the QoL in 180 patients 5 years after liver transplantation by using the SF-36 health survey, and reported significantly higher scores on all physical and vitality scales in patients participating in regular physical activity than in inactive patients.

Table IV. *Aerobic capacity and muscle strength at baseline and follow-up given as mean ±SEM*

	Baseline	After 1-2 months
$ATVO_2$ (ml/kg/min)	10.3 ± 3.0	9.4 ± 2.7
Watt at AT	39.4 ± 16.5	34.8 ± 15.6
Peak torque (Nm)	96.9 ± 53.0	97.5 ± 33.4
Peak torque (Nm/kg)	128.3 ± 61.9	136.6 ± 38.9
Hand grip strength (kg)	53.4 ± 31.4	47.1 ± 13.1

AT = anaerobic threshold.

In conclusion, the findings of the present pilot study including a population of OLT patients of an Austrian transplantation centre indicate relevant deficits of physical performance and of health-related QoL in patients with end-stage liver disease before and after OLT. Despite significant improvements of liver function and of health-related QoL, OLT without postoperative rehabilitative measures does not seem to lead to significant changes in aerobic capacity and muscle strength. Due to an increasing number of listed patients waiting on transplantation list and due to a therefore longer waiting period to transplantation, a preoperative specific medical training could be an option to improve physical function and muscle strength. This training program should include psychological and social aspects too, mainly for patients with toxic liver cirrhosis and the need for alcoholic abstinence. Nevertheless, further investigations regarding the effectiveness of preoperative and postoperative training programmes are urgently needed. Such information would be important to improve preoperative and postoperative rehabilitation of OLT patients.

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