Physical Condition, Glycemia, Liver Function, and Quality of Life in Liver Transplant Recipients After a 12-Month Supervised Exercise Program

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ABSTRACT

Background and aims. Despite the excellent long-term outcomes in liver transplant (LT) recipients, several medical complications related to lifestyle still represent an issue. This study examined the effects of a 12-month supervised aerobic and strength training program on the aerobic capacity, muscle strength, metabolic profile, liver function, and quality of life of a cohort of LT recipients.

Methods. LT recipients with stable liver function were assigned to interventional exercise (group A) or usual care (group B). Aerobic capacity, muscle strength, metabolic profile, liver and kidney function, and health-related quality of life were assessed at baseline and after 6 and 12 months. Group A attended supervised training sessions 3 times per week for 12 months. Group B received general recommendations about home-based exercise.

Results. Forty patients from 6 Italian LT centers were randomized. Twenty-nine (72.5%, men-to-women ratio 23:6, mean age, 52 ± 8 years) LT recipients completed the study. Baseline characteristics were similar between groups except for body mass index and time from LT. No episode of acute rejection nor increase of transaminases occurred. Maximum workload and body mass index increased in both groups over time, but fasting glucose significantly decreased in group A (94.0 ± 15.0 mg/dL vs 90.0 ± 17.0 mg/dL; $P = .037$) and increased in controls (95.0 ± 24.0 mg/dL vs 102.0 ± 34.0 mg/dL, $P = .04$). Upper limb muscle strength increased only in supervised LT recipients. Vitality and general and mental health domains significantly improved after physical exercise.

Conclusions. Supervised combined training was safe and effective in increasing aerobic capacity, muscle strength, and quality of life and in improving glucose metabolism in stable LT recipients.

This study is registered at http://www.isrctn.com under ID No. ISRCTN66295470.

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EVEN if short-term outcomes and survival rates after orthotopic liver transplantation (LT) have improved over time, exceeding 80% and 72% at 1 and 5 years [1,2], respectively, there have been no appreciable improvements in long-term survival [3]. This might be due to several medical complications, often related to lifestyle, which still represent an issue in the long-term medical care.

LT recipients are at higher risk of developing metabolic complications, chronic kidney disease, bone loss, and sarcopenia, which are associated with cardiovascular diseases [4,5]. Long-term immunosuppression, but also a sedentary lifestyle, often associated with a gradual weight gain, weakness, and fatigue, represent modifiable risk factors [6]. Even if exercise capacity and muscle strength improve after LT, they remain significantly lower than age and sex-matched people without solid organ transplant [7,8]. The role of physical exercise on LT recipients has only been addressed in a few studies, which were conducted on small samples and considered different types, intensity, and durations of interventions that lasted no more than 24 weeks [9-12]. Furthermore, few studies [10,12] have investigated the effect of combined aerobic and strength training on aerobic capacity, strength, metabolic profile, and kidney and liver function. The beneficial role of physical activity has been demonstrated also on health-related quality of life (HRQoL), which significantly improves after transplant but often remains far from the expected results [13–15].

Thus, this study aimed to evaluate the role of a 12-month combined aerobic and strength training program on aerobic capacity, strength, metabolic profile, liver function, and HRQoL in stable LT recipients.

MATERIALS AND METHODS

This was a multicenter, controlled, non-randomized study. From January 2011 to June 2015, a total of 40 adult patients were prospectively enrolled from 6 LT centers in Italy. Inclusion criteria were age between 18 and 60 years and previous LT (> 6 months) with stable clinical and functional status (eg, absence of liver-related complications in the previous 6 months, including episodes of acute rejection and increase of serum transaminases 2 time the upper limit of normal). Exclusion criteria were combined transplantation; re-LT; physical limitations to exercise; psychiatric or severe debilitating neurologic disorders; non-adherence; and cardiovascular contraindications to exercise testing and training. Written informed consent was obtained for all patients before their enrolment in accordance with procedures approved by participating centers' ethical committees. This trial was listed in the International Standard Randomised Controlled Trials Number registry (Trial ID: ISRCTN66295470) and conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines for Good Clinical Practice, the Helsinki Declaration, and Italian legislation on the conduction of clinical trials.

After individualized counseling from the transplant centers regarding the protocol, patients were assigned to 1 of 2 groups: an interventional exercise group (group A), in which personalized aerobic and strength training was prescribed and supervised; and a usual care group (group B), in which patients received general exercise recommendations without any specific supervision. Inclusion in group B was based on logistic grounds (patients living in areas without sports medicine centers or local gyms). A multidisciplinary group consisting of transplantation hepatologists, sports physicians, and exercise specialists was actively involved in monitoring graft function and identifying facilities outside the medical setting where patients can easily complete their training programs under the supervision of exercise specialists.

All patients enrolled were referred to a sports medicine center for functional tests to assess their aerobic capacity, muscle strength, and body composition. Based on the results of these tests, the sports physicians prescribed a tailored combined aerobic and strength training program. Group A conducted the exercise program in a certified gym under the supervision of exercise specialists; instead, group B practiced home-based exercise without supervision.

Evaluation of Liver, Kidney, and Metabolic Profile

Liver function was assessed in both groups at baseline (T_0), after 6 months (T_6), and after 12 months (T_{12}); kidney function was expressed as the estimated glomerular filtration rate (eGFR), calculated using the chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) creatinine equation [16]. Lipid profile (total cholesterol, high-density lipoproteins, and triglycerides) was measured using flow cytometry and light-scattering methods. Glucose metabolism was assessed based on standard fasting blood glucose measurement. Systolic and diastolic blood pressure was measured repeatedly at T_0, T_6, and T_{12} in both groups, at each clinical assessment, using a manual sphygmomanometer (Heine Gamma G7, Heine Optotechnik, Herrsching, Germany) according to current guidelines [17].

Body Composition

At T_0, T_6, and T_{12}, fat mass (%), total body weight (kg), and body mass index (BMI; kg/m^2) were assessed in both men and women using the Jackson & Pollock body density equation, a weighing machine, and a Harpenden caliper, measuring 7 skinfolds (abdominal, thigh, triceps, bicep, subscapular, supra-iliac, and chest) [18].

Aerobic Capacity

Aerobic capacity was assessed with an incremental cycling exercise starting from a 5-minute unloaded cycle and increasing by 20.0 W every 4 minutes until the patient was unable to continue. A 12-lead electrocardiogram was obtained continuously throughout the test. At each step, a capillary blood sample from the earlobe was taken to measure blood lactate concentration (YSI 1500-Sport; Yellow Springs, OH, United States). This was used to estimate the workload corresponding to the aerobic and anaerobic thresholds, conventionally set at 2.0 and 4.0 mM of lactate, respectively [19]. During testing, maximal oxygen consumption (VO_{2peak}) was recorded using an open-circuit spirometry system (Sensor Medics, Anaheim, CA, United States).

Muscle Strength

Free weights and a leg press (Technogym, Cesena, Italy) were used to assess dynamic muscular strength in the upper and lower limbs (elbow flexors, elbow extensors, knee extensors, plantar flexors). One-repetition maximum strength was calculated using an indirect method involving 7 to 12 repetitions with submaximal loads [20]. General strength was measured using a handgrip dynamometer (Lafayette Instrument, Lafayette, IN, United States).

Exercise Intervention

The prescribed exercise included sessions of combined aerobic and strength training. Each session lasted 1 hour and was scheduled 3 times a week for 12 months. At each session, aerobic training was performed on a stationary bike for 30 minutes, administered at an intensity corresponding to the lactate threshold [19]. The intensity was monitored continuously using heart rate monitors (Polar, Kempele, Finland) so that patients could keep a constant heart rate corresponding to their aerobic threshold.

During the same session, subsequent strength training consisted of 2 sets of 20 repetitions at 35% of 1-repetition maximum for each muscle group of the upper and lower limbs (single joint exercises of the elbow flexors, elbow extensors, plantar flexor, and knee extensor). This training intensity was chosen assuming that LT recipients were naïve at strength training [21,22]. Warm-up, cool-down, and stretching exercises were included in all training sessions. The intensity of the aerobic and strength training was adjusted after the T_6 assessment. Adherence to the exercise program was measured as the proportion of completed sessions.

HRQoL

The Short Form (36-item) Health Survey questionnaire was used to assess self-reported health status [23] through 8 different items: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. Questionnaires were completed independently by patients at T_0, T_6, and T_{12}.

Statistical Analysis

The required sample size was ascertained using the Software G*Power (version 3.1.9.2, Heinrich Heine Universitat Dusseldorf, Dusseldorf, Germany) with an alpha level of 0.01 and a power of 0.90. Continuous and categorical variables were expressed as mean ± standard deviation and frequencies, as appropriate. Repeated-measures analysis of variance were used to assess the effects of time and group and their interaction on the dependent variables. Statistical significance was set at $P < .05$. The statistical analysis was performed using SPSS, Version 20 (IBM, SPSS Inc, Chicago, IL, United States).

RESULTS

Forty LT recipients were enrolled at 6 Italian LT centers and assigned to groups (1:1). Three (15%) and 8 (40%) patients in group A and B, respectively, did not complete the study because of non-adherence (n = 5) or work commitments (n = 6). Thus, twenty-nine (men-to-women ratio 23:6, mean age 52 ± 8 years, n = 17 in group A and n = 12 in group B) completed the study. Hepatitis C–related cirrhosis was the main indication for LT. Seventeen patients (58.6%) were receiving calcineurin inhibitors and mycophenolic acid and 12 patients (41.3%) calcineurin inhibitor monotherapy. No changes on immunosuppression therapy occurred during the study. Baseline characteristics were similar between groups in terms of age, sex, indication to LT, liver and kidney function, eGFR, fasting glucose, serum cholesterol, and triglycerides (each P = not significant; Table 1). Cohorts differed on baseline BMI (group A vs group B: 25.3 ± 3.0 kg/m^2 vs 26.4 ± 5.4 kg/m^2; $P = .046$) and time since LT (43.2 ± 36 months vs 15 ± 5 months; $P = .002$). In group A, adherence to the exercise program (144 sessions in all) during the 12-month period was 89% ± 6%, without adverse events. The level of physical activity remained unaltered (< 600 MET/min a week) at the 12-month follow-up in group B.

Liver, Kidney, and Metabolic Profile

Liver function remained stable during the study period in both groups; no episodes of acute rejection nor increase of serum transaminases occurred. Renal function remained unaltered in both groups; no patients had an eGFR < 60.0 mL/min (Table 1). Regarding metabolic profile, fasting blood glucose decreased in group A (T_0 vs T_{12}: 94.0 ± 15.0 mg/dL vs 90.0 ± 17.0 mg/dL; $P = .037$) and increased in group B (T_0 vs T_{12}: 95.0 ± 24.0 mg/dL vs 102.0 ± 34.0 mg/dL; $P = .04$) over time. Nevertheless, there was no significant decrease of other metabolic variables.

Exercise Capacity, Muscle Strength, and Body Composition

A significant time × group interaction was found for aerobic threshold workload ($P = .050$) and maximum workload ($P = .004$).

Parameters regarding lower limb muscle strength improved over time in both groups, whereas general strength ($P = .040$) and upper limb muscle strength significantly increased only in supervised LT recipients (elbow flexors, $P = .025$; elbow extensors, $P = .005$). Lastly, BMI increased in both groups over time, whereas fat mass remained unchanged.

HRQoL

Some items pertaining to the Short Form (36-item) Health Survey questionnaire were not similar between groups; thus, we compared intraindividual changes at baseline and at T_{12}. The supervised cohort, general health, mental health, and vitality items significantly improved, whereas they decreased in controls (Table 2).

DISCUSSION

The present study showed that 12 months of supervised combined aerobic and strength training was safe and effective in terms of aerobic workload, muscle strength, and glucose metabolism among stable LT recipients. Data are in accordance with those reported by Beyer et al [24], who showed a 3-fold increase in aerobic workload, and with those reported by Krasnoff et al [12], who demonstrated a significant increase of exercise capacity in supervised LT recipients. Notably, we noticed that supervised training was highly beneficial for upper limb muscle strength, which significantly improved in trained group whereas decreased in controls. This could be explained with the fact that, even if LT recipients are generally advised to walk and to return to a normal lifestyle after surgery [10], they usually are not able to adequately strengthen their upper limbs.

Table 1. Physical Conditions, Metabolic Profile, and Liver and Kidney Function at Baseline (T_0) and After 6 (T_6) and 12 (T_{12}) Months

	Group A (n = 17)			Group B (n = 12)		
	T_0	T_6	T_{12}	T_0	T_6	T_{12}
Exercise and Body Composition						
Maximum workload, W	104 ± 40	114 ± 40	118 ± 34†	95 ± 37	102 ± 37	103 ± 40†
Aerobic threshold workload, W	58 ± 29	73 ± 28	73 ± 29†	49 ± 25	55 ± 26	54 ± 25†
Fat mass, %	21 ± 6	23 ± 4	23 ± 4	24 ± 8	24 ± 10	25 ± 8
Body mass index, kg/m^2	25.3 ± 3.4	25.8 ± 3.4	26.0 ± 3.7*	26.4 ± 5.4	26.3 ± 6.1	27.5 ± 6.6*
VO_{2peak}, mL/kg/min	22.4 ± 7.5	23.4 ± 7.0	24.3 ± 6.9	22.1 ± 5.6	23.0 ± 5.9	22.0 ± 7.3
Knee extensors, kg	83 ± 29	103 ± 32	105 ± 30*	84 ± 30	85 ± 29	89 ± 37*
Plantar flexors, kg	90 ± 45	106 ± 42	106 ± 43*	81 ± 27	88 ± 29	92 ± 38*
Handgrip, kg	42 ± 13	44 ± 15	45 ± 16†	35 ± 9	34 ± 9	33 ± 12†
Elbow extensors, kg	7 ± 2	9 ± 2	9 ± 2†	6 ± 2	7 ± 2	6 ± 2†
Elbow flexors, kg	11 ± 3	13 ± 4	13 ± 3†	9 ± 2	9 ± 2	9 ± 3†
Metabolic Profile						
Fasting glucose, mg/dL	94 ± 15	91 ± 13	90 ± 17†	95 ± 24	96 ± 23	102 ± 34†
Triglycerides, mg/dL	134 ± 59	135 ± 67	133 ± 77	118 ± 50	125 ± 48	135 ± 63
Total cholesterol, mg/dL	168 ± 36	171 ± 36	166 ± 37	171 ± 37	166 ± 24	163 ± 18
HDL, mg/dL	54 ± 11	53 ± 8	48 ± 9	54 ± 10	55 ± 8	55 ± 11
Systolic blood pressure, mm Hg	121 ± 12	120 ± 10	119 ± 10	129 ± 16	129 ± 16	129 ± 16
Diastolic blood pressure, mm Hg	79 ± 9	78 ± 9	78 ± 9	82 ± 13	82 ± 13	82 ± 13
Liver and Kidney Function						
Total bilirubin, mg/dL	1.6 ± 5.4	1.5 ± 5.4	1.5 ± 5.4	1.4 ± 2.4	1.6 ± 2.4	1.5 ± 2.4
Aspartate aminotransferase, U/L	25 ± 8	23 ± 6	23 ± 7*	27 ± 15	25 ± 9	22 ± 11*
Alanine aminotransferase, U/L	24 ± 9	23 ± 10	22 ± 10	31 ± 22	26 ± 14	26 ± 13
Gamma-glutamyl-transpeptidase, U/L	30 ± 32	25 ± 28	31 ± 39	27 ± 15	29 ± 15	31 ± 14
Alkaline phosphatase, U/L	87 ± 37	87 ± 33	79 ± 21*	104 ± 35	94 ± 35	86 ± 23*
eGFR, mL/min/1.73 m^2	81 ± 18	84 ± 19	84 ± 16	87 ± 20	84 ± 20	83 ± 19

Data are expressed as mean ± standard deviation.
eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; T_0, baseline; T_6, after 6 months; T_{12}, after 12 months; $VO_{2\ peak}$, maximal oxygen consumption.
*$P < .05$ time effect between groups.
†$P < .05$ time x group interaction between groups.

An increase in BMI is common after LT, especially in the post-operative months, because of immunosuppressant medications and a lack of physical exercise [12,25]. We confirmed this trend in our cohort of stable LT recipients, even if we did not notice an increase in percent of fat mass over time. This could be explained with the fact that time from LT was longer and baseline BMI was higher than in other studies. An optimal post-transplant intervention would probably require a multidisciplinary approach, including nutritional counseling, immunosuppression minimization when available, exercise, and behavioral interventions [9].

It is well known that metabolic complications occur soon after LT, being associated with cardiovascular diseases [5,26]. Metabolic abnormalities can be prevented or reversed by regular physical exercise. The beneficial role of physical exercise on glucose metabolism is well known among the general population [27], and once again confirmed in our cohort of LT recipients, where fasting

Table 2. SF-36 score domains

	Group A (n = 17)			Group B (n = 12)		
	T0	T6	T12	T0	T6	T12
Physical functioning	83 ± 16	86 ± 19	86 ± 16	82 ± 18	82 ± 18	77 ± 19
Role limitations due to physical health	59 ± 50	63 ± 46	69 ± 37	42 ± 52	42 ± 52	43 ± 50
Bodily pain	78 ± 23	77 ± 26	77 ± 26	54 ± 6	55 ± 6	51 ± 10
General health	59 ± 17	59 ± 22	71 ± 18*	61 ± 13	60 ± 19	43 ± 21*
Vitality	59 ± 24	64 ± 18	66 ± 21*	65 ± 15	63 ± 15	45 ± 9*
Social functioning	70 ± 22	84 ± 20	83 ± 18	83 ± 19	87 ± 19	66 ± 19
Role limitations due to emotional health	54 ± 50	67 ± 44	50 ± 47	67 ± 58	67 ± 58	44 ± 51
Mental health	68 ± 20	76 ± 15	78 ± 15*	73 ± 20	74 ± 22	50 ± 6*

Data are expressed as mean ± standard deviation.
SF-36, [Short Form (36-item) Health Survey]; T_0, baseline; T_6, after 6 months; T_{12}, after 12 months.
*$P < .05$ time x group interaction between groups.

glucose gradually decreased in exercise group whereas increased in controls. Nevertheless, lipid profile showed no significant improvement over time in both cohorts, pointing out that other factors (eg, diet, immunosuppressant regimens) should be adequately managed.

Lastly, we confirmed the beneficial association between physical exercise and HRQoL, especially for general health, vitality, and mental health domains. This would suggest that LT recipients benefit from strength and endurance training under professional supervision, also in terms of motivation, self-perception, and social inclusion in everyday life [15,28].

This study has some limitations that need to be acknowledged. First, absence of randomization was a limitation; patients were grouped because of logistic grounds (eg, distance from a gym). However, cohorts were comparable in terms of age, sex, and liver function at enrolment. Second, the International Physical Activity Questionnaire (IPAQ) was only administered to group B to reduce the bias between the 2 groups, but this made it impossible to draw any direct comparison with group A concerning the 2 groups' physical activity levels. Finally, the small sample size could give a picture that is partly representative of the whole LT population.

Despite these limitations, this study showed that a supervised combined aerobic and strength training in stable LT recipients can be a useful and safe non-pharmacologic tool, improving physiologic variables related to patients' physical conditions, glucose metabolism, and quality of life, without impairment of liver and kidney function.

Further studies with a longer follow-up, larger population, and different types of training are needed to clarify better strategies to improve adherence to training programs and keep costs manageable so that exercise programs can be included as a standard treatment for LT recipients.

REFERENCES

[1] Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57:675–88.

[2] Busuttil RW, Farmer DG, Yersiz H, Hiatt JR, McDiarmid SV, Goldstein LI, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. Ann Surg. 2005;241:905–16.

[3] Rana A, Ackah RL, Webb GJ, Halazun KJ, Vierling JM, Liu H, et al. No gains in long-term survival after liver transplantation over the past three decades. Ann Surg. 2019;269:20–7.

[4] Di Maira T, Rubin A, Puchades L, Aguilera V, Vinaixa C, Garcia M, et al. Framingham score, renal dysfunction, and cardiovascular risk in liver transplant patients. Liver Transpl. 2015;21:812–22.

[5] Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant. 2010;10:1420–7.

[6] Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. Transpl Int. 2005;18:461–6.

[7] De Bona M, Ponton P, Ermani M, Iemmolo RM, Feltrin A, Boccagni P, et al. The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. J Hepatol. 2000;33:609–15.

[8] Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M, et al. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl. 2002;8:263–70.

[9] Kallwitz ER, Loy V, Mettu P, Von Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. Liver Transpl. 2013;19:1125–31.

[10] Moya-Nájera D, Borreani S, Moya-Herraiz Á, Calatayud J, López-Andújar R, Colado JC. Is physical exercise harmful to liver transplantation recipients? Review of literature. Cir Esp. 2016;94:4–10.

[11] Masala D, Mannocci A, Unim B, Del Cimmuto A, Turchetta F, Gatto G, et al. Quality of life and physical activity in liver transplantation patients: results of a case-control study in Italy. Transplant Proc. 2012;44:1346–50.

[12] Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Paul SM, Dodd MJ, et al. A randomized trial of exercise and dietary counseling after liver transplantation. Am J Transplant. 2006;6:1896–905.

[13] Dew MA, Switzer GE, Goycoolea JM, Allen AS, DiMartini A, Kormos RL, et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. Transplantation. 1997;64:1261–73.

[14] Burra P, Germani G. Long-term quality of life for transplant recipients. Liver Transpl. 2013;19:S40–3.

[15] Burra P, Ferrarese A, Feltrin G. Quality of life and adherence in liver transplant recipients. Minerva Gastroenterol Dietol. 2018;64:180–6.

[16] Levey AS, Stevens LA. Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 2010;55:622–7.

[17] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e426–83.

[18] Jackson AS, Pollock ML. Generalized equations for predicting body density of men 1978. Br J Nutr. 2004;91:161–8.

[19] Kindermann W, Simon G, Keul J. The significance of the aerobic-anaerobic transition for the determination of work load intensities during endurance training. Eur J Appl Physiol Occup Physiol. 1979;42:25–34.

[20] Taylor JD, Fletcher JP. Correlation between the 8-repetition maximum test and isokinetic dynamometry in the measurement of muscle strength of the knee extensors: a concurrent validity study. Physiother Theory Pract. 2013;29:335–41.

[21] Medicine ACoS. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41:687–708.

[22] Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 2009;41:1510–30.

[23] Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res. 2001;10:405–13.

[24] Beyer N, Aadahl M, Strange B, Kirkegaard P, Hansen BA, Mohr T, et al. Improved physical performance after orthotopic liver transplantation. Liver Transpl Surg. 1999;5:301–9.

[25] Hussaini SH, Oldroyd B, Stewart SP, Soo S, Roman F, Smith MA, et al. Effects of orthotopic liver transplantation on body composition. Liver. 1998;18:173–9.

[26] Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. Transplantation. 2017;101: S1–56.

[27] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.

[28] Didsbury M, McGee RG, Tong A, Craig JC, Chapman JR, Chadban S, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. Transplantation. 2013;95:679–87.