Combined Resistance and Endurance Training at a Moderate-to-High Intensity Improves Physical Condition and Quality of Life in Liver Transplant Patients

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Although currently moderate and high intensity concurrent physical exercise is prescribed in populations with special needs due to its greater effect on physical condition and health-related quality of life (HRQOL), there are no data in the liver transplantation (LT) setting. The aim of this study is to evaluate changes in maximal strength, aerobic capacity, body composition, liver function, and HRQOL in LT patients after a moderate-to-high intensity combined resistance-endurance training. Six months after LT, 54 patients were randomized into 2 groups: intervention group (IG) and control group (CG). A total of 50 patients completed the study with repeat testing at 6 and 12 months after LT. The IG completed a 6-month exercise training program, consisting of exercising 2 days for 24 weeks in the hospital facilities, whereas the CG followed usual care recommendations. Patients completed a 5-multijoint exercise circuit with elastic bands involving the major muscle groups. The effects of the concurrent training program on maximal oxygen consumption, overall and regional maximal strength, body composition, liver function, and HRQOL were analyzed. The IG showed a significant improvement ($P < 0.05$) in outcome measurements compared with the CG in aerobic capacity, hip extension, elbow flexion, overall maximal strength, physical functioning, and vitality of HRQOL, whereas no changes were observed in body composition and liver function tests. In conclusion, this is the first study that combines supervised resistance and aerobic training performed at moderate-to-high intensity in LT recipients. It results in significant improvements in aerobic capacity, maximal strength, and HRQOL.

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Although survival rates after liver transplantation (LT) are now very high, exceeding 80% at 1 and 5 years, in many instances there is no full restoration of the patient's common everyday life, with quality of life studies reporting lower results than those achieved by the general population.[1,2] Metabolic disorders, bone loss, sarcopenia, and dynapenia are observed after LT and are associated with substantial morbidity and mortality.[3-6] Physical exercise improves physical performance both in healthy individuals[7] and in those suffering from chronic medical conditions,[8] as well as in LT patients,[9-14] preventing and/or reducing the incidence of these LT complications.[15-17]

Although some physicians and centers include exercise programs as part of the therapy after discharge,[1,3,4,15,16,18] there is a lack of information about the best exercises and training methodology that should be used. Indeed, patients are usually advised to walk, exercise that has proven to be beneficial for their physical capacity and general health, but not enough to regain the quality of life in most areas. This conservative recommendation may be caused by fear of harming the patient while training at a higher intensity.

Abbreviations: BMI, body mass index; CG, control group; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IG, intervention group; HCV, hepatitis C virus; HRQOL, health-related quality of life; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MET, metabolic equivalent of task; N, newtons; RPE, rated perceived exertion; SD, standard deviation; SF-36, Medical Outcomes Study Short Form Questionnaire; VO_{2peak}, maximal oxygen consumption.

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Interestingly, evidence shows that supervised training at different intensities is recommended in other populations with chronic diseases.[19] Adequate exercise programs such as those including concurrent training, where resistance and endurance training are combined in the same session, are recommended by the American College of Sports Medicine.[18] However, there are no published specific exercise programs that take into account these new concurrent exercise protocols in LT patients. Because of the relevance that these training programs have in health promotion and disease prevention, it is necessary to search safe and effective ways to promote their application in any context, ie, both in hospital and clinical environments as in homes and community centers,[20] performing a suitable progression with a correct exercise technique and being careful about overheating, dehydration, and contact sports.[21,22] These risks can be minimized by medical evaluation, risk stratification, careful supervision, education, programming a correct training,[23] and choosing the right equipment as elastic bands, which are an alternative to other devices used in traditional training.[24] This equipment is more accessible, cheaper, easily transportable, and readily maintainable, reducing the risk of injury, offering in addition easy maintenance.[25]

We hypothesized that a concurrent training program with moderate-to-high intensity is beneficial for LT recipients because it could improve their fitness and health-related quality of life (HRQOL). We aimed to evaluate the effects of a concurrent training program in aerobic capacity, maximal strength, body composition, liver function, and HRQOL in a series of LT patients.

Diego Moya-Nájera created the database; tested, created, and executed intervention protocols; directed physical training; and wrote the article; Ángel Moya-Herraiz recruited patients to present the study and selected and obtained Medical Outcomes Study Short Form Questionnaire data; Luis Compte-Torrero obtained aerobic capacity data through performing maximal effort tests; David Hervás conducted statistical analysis; Sebastien Borreani and Joaquin Calatayud aided execution of all physical tests and training sessions; Marina Berenguer conducted literature research and article revision; and Juan C. Colado directed the study, supervised protocols, and revised the article.

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Patients and Methods

PATIENTS

A total of 54 participants were recruited 6 months after LT, from July 2011 to February 2013. Inclusion criteria were as follows: age between 18 and 67 years old, primary LT, deceased donor, and Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 ($0 =$ fully active, able to carry on all predisease performance without restriction, capable to perform daily activities; and $1 =$ restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature).[26] Patients were excluded if they refused to participate, had undergone a combined transplant, had a history of prior nonliver organ transplant, had undergone retransplantation or split liver, in cases of noncirrhotic and/or cancer indication, with the exception of hepatocellular carcinoma, and/or suffered from a limiting comorbid disease precluding physical exercise (cardiac disease, orthopedic limb, motor problems). All of them voluntarily signed the informed consent, approved by the Committee on Human Research at La Fe Hospital (Valencia, Spain). The study started in January 2012 and finished in August 2013 (21 months).

STUDY DESIGN

A prospective and randomized design was used in which all patients were tested at 6 (baseline) and 12 months after LT. Patients participated in a program designed and controlled by a qualified health personnel multidisciplinary group, formed by the clinical team and exercise science professionals.

Although the former supervised the post-LT course, the latter were responsible for the training sessions (techniques, timing, adherence). Both physicians and exercise trainers were involved in each training session.

Patients were randomly assigned to 2 different groups involving a specific routine: intervention group (IG) and control group (CG). Both groups were statistically similar at baseline. Those in the IG had to come to the hospital for the training sessions, whereas those in the CG group were asked to follow the guidelines for usual care, including noncontrolled recommendations for mild physical activity such as walking every day at a low intensity level, but they were not provided with specific instructions about duration, heart rate, or intensity perception.

AEROBIC CAPACITY

The test was performed in the Pneumology Service of the Hospital La Fe using a cycloergometer according to an incremental ramp protocol; pedal resistance was progressively increased 10 watts every minute. If the patient reached 6 minutes of duration, the test was considered optimal.

During testing, maximal oxygen consumption (VO_{2peak}) was recorded as the main variable of aerobic capacity. VO_{2peak} is expressed in terms relative to body weight (mL of oxygen per kg of body weight per minute).

MUSCLE STRENGTH

Five exercises (hip extension, elbow flexion/extension, shoulder flexion/extension, shoulder abduction, and knee flexion/extension) were performed in the Laboratory of Physical Education of the University of Valencia. Testers used an isokinetic muscle function testing system (Biodex IV, Shirley, NY). According to other studies,[13,27] the right limb was secured and attached to the dynamometer, isolating each muscle group. Controllers encouraged all patients to perform maximal effort at a controlled speed of 90°/second for 5 repetitions, resting 5 minutes between exercises and only having 1 chance to achieve completion. Peak torque (highest torque in newtons [N] produced during the set of repetitions) was also measured for analysis. Global strength was also calculated by a statistic analysis considering all the strength variables.

BODY COMPOSITION

Fat mass (%), total body weight (kg), and body mass index (BMI; kg/m^2) were determined using a weight machine with bioelectrical impedance analysis (Tanita model BF-350, Tokyo, Japan); height (cm) was determined by means of a height rod (IP0955, Invicta Plastics Limited, Leicester, UK).

HRQOL

The Medical Outcomes Study Short Form Questionnaire (SF-36) was used to evaluate self-reported domains of health status.[28] The questionnaire includes 36 questions related to 8 HRQOL components: physical functioning, role physical limitations, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. The scales are scored from 0 to 100, with higher scores reflecting better endpoint measures. Questionnaires were given to patients at baseline and at the end of the study.

BLOOD TEST RESULTS

The blood tests were performed in the Hospital La Fe and included liver function–related tests, such as aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, prothrombin time, and international normalized ratio.

TRAINING PROGRAM

During the 24 weeks of exercise intervention, patients from CG followed the usual care recommendations, which basically consisted of recommendations to walk at a low intensity at home. IG trained in two 75-minute sessions per week. Training sessions were always performed in the hospital and supervised by a qualified health personnel multidisciplinary group that includes a sport science professional as trainer. Sessions mainly included resistance and aerobic training and were organized with a circuit distribution. Walking was the chosen activity for aerobic training and elastic bands (TheraBand; Hygenic Corporation, Akron, OH) were used for resistance exercises. Patients were taught the technique and proper intensity during the first week of training. Aerobic training intensity was controlled by a heart rate monitor and strength by the rate of perceived exertion according to the OMNI-RES Scale for elastic bands.[29]

Training sessions consisted of warm up, main part and cool down. They started with 3 sets of 30 seconds balance exercise with open eyes using props for instability (TheraBand stability trainers; Hygenic Corporation, Akron, OH), followed by a circuit in which strength and aerobic exercises were alternated. The strength program was divided into 2 periods of time. During the first 3 months, patients had to perform 3 sets of 25 repetitions at a velocity of 2 seconds for each concentric and eccentric contraction. During the second 3-month period, patients had to perform 3 sets of 15 repetitions at a velocity of 2 seconds for each concentric and eccentric contraction. The following strength exercises were performed: squat, dead lift, rowing, shoulder flexion, shoulder abduction, and chest press. Intensity started at 5-6 on the Rated Perceived

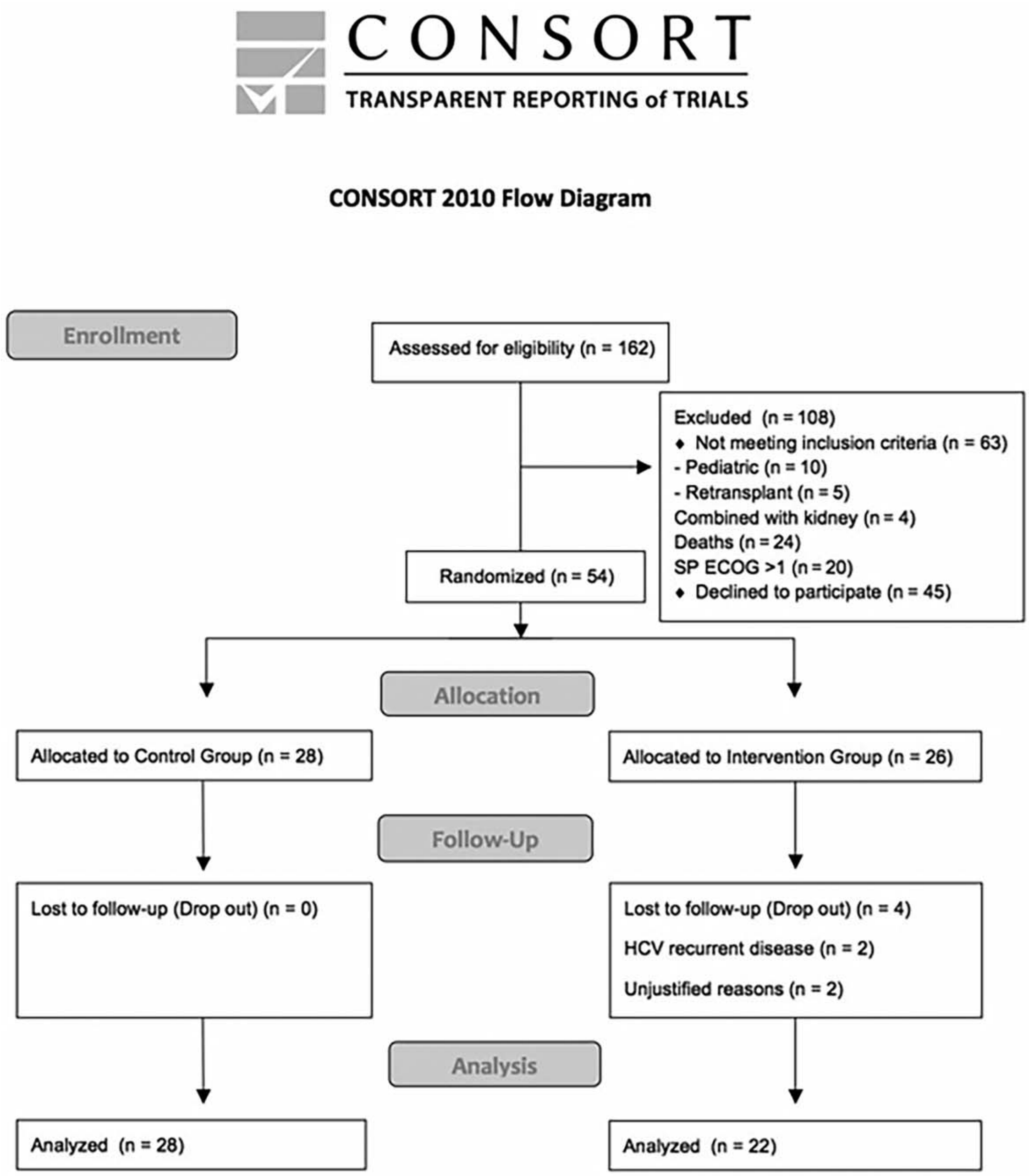

FIG. 1. Participant flowchart.

Exertion (RPE) scale and was increased 1 point every 2 months, finishing at 8-9. Between strength exercises, aerobic training was performed by the patients, involving a 90-second walk following the Karvonen method,[30] starting at a calculated intensity of 70% at baseline, increasing by 2.5% every month until they reached 85% at the end of the period. Sessions finished with passive stretching exercises. Adherence to the program was measured considering the ratio between the completed sessions and the total number of sessions.

STATISTICAL METHODS

The R software, 3.1.0 version (R Project for Statistical Computing, Vienna, Austria) and the R package lme4 (1.1-6 version) were used for the analysis and graphics design. Variables were summarized in terms of mean and standard deviation (SD) and median and first and third interquartile range. To highlight the differences in the evolution of the variables in both groups, mixed linear regression models were applied, with the variable "subject" as a factor of random effects and the variables "treatment duration," "type of treatment," and their interaction as predictors. The level of significance was set at $\alpha = 0.05$. To control the rate of type I error due to multiple comparisons, the false discovery rate method was followed. Sample size was determined by using GPower V.3 software, and randomization was performed according to a specific randomization routine by creating random numbers based on the standard normal distribution.

Results

PARTICIPANTS

In total, 173 LTs were performed in 162 patients between July 2011 and February 2013 (Fig. 1; Table 1). The 63 patients were excluded due to various reasons: retransplantation (n = 5), pediatric patients (n = 10), combined kidney-liver transplants (n = 3), prior history of kidney transplantation (n = 1), deaths (n = 24), SP ECOG > 1 (n = 20, 7 due to tumor recurrence, 4 due to necrosis of the bile duct, 4 related to disease recurrence, and 5 for other reasons). A total of 99 patients met entry criteria to participate in the study, but 45 did not accept to be included, mostly due to personal restrictions, such as living far from the hospital. A total of 54 patients accepted to participate and had a 94% adherence to the exercise program (45 sessions attended of a total of 48). Dropout rates were superior in the IG, mainly associated with aggressive hepatitis C virus (HCV) recurrent disease,[31] that led to physical weakness either because of the disease itself or more frequently due to the use of ribavirin included in the antiviral therapy. The study had a duration of 3 years. Recruitment of the patients was stopped when they reached the previous estimation of 2-year duration.

TABLE 1. Comparison of the Results of the 2 Groups

Variable	Group	Data
Sample, n	CG	28
	IG	22
Age, years	CG	55.3 (9.2)
	IG	57.1 (7.4)
Sex, male, n (%)	CG	23 (85.2%)
	IG	22 (81.5%)
Height, cm	CG	168.3 (9.4)
	IG	167.2 (7.4)
Disease		
MELD	CG	18.4 (7.9)
	IG	14.6 (8.4)

NOTE: Data are given as mean (SD) unless otherwise noted.

PHYSICAL CAPACITIES

Aerobic Capacity

All but 2 patients successfully completed this test: 1 was unable to ride a bicycle and the other 1 suffered from a heart abnormality. All patients reached the maximal effort measured by the average respiratory exchange ratio (>1.0). Aerobic training produced a 15% increase in the VO_{2peak} in patients from the IG, compared with those in the CG, in whom it only increased 7% ($P = 0.04$).

Maximal Strength

The IG presented significant differences in maximal strength changes in hip extension ($P < 0.001$) and elbow flexion ($P = 0.01$) compared with the CG. No significant differences were found in the changes measured in the rest of the movements, although the IG reported improvements in all measured muscles, whereas the CG only obtained a maximal strength increase in 5 of them: elbow extension—IG (23%), CG (11%), $P = 0.2$; shoulder flexion—IG (17%), CG (12%), $P = 0.4$; shoulder extension—IG (6%), CG (−6%), $P = 0.3$; shoulder abduction—IG (27%), CG (17%), $P = 0.13$; knee extension—IG (17%), CG (9%), $P = 0.17$; and knee flexion—IG (8%), CG (−9%), $P = 0.12$.

If we consider maximal global strength, the IG achieved a 31% improvement, compared with a 9% improvement in the CG ($P = 0.001$; Table 2).

Body Composition

No significant differences were found between groups in any of the variables measured, although fat mass decreased by 4% in the IG, compared with an increase of 3% in the CG (Table 3).

HRQOL

Although in the IG all scales improved by the end of the 24-week study period, only 4 out of 8 increased in the CG over that same period. Significant differences over time were detected in physical functioning and vitality ($P = 0.03$; Table 4).

TABLE 2. Comparison Between IG and CG Groups of the Fitness Variables Analyzed

Variable	Group	Baseline Test	Post Test	Percent of Change	Confidence Interval (95% CI)	*P* Value
VO_{2peak}						
VO_{2peak}, mL/kg/minute	CG	17.4 (4.9)	18.6 (3.8)	7%	1.8 (0.01-3.6)	0.04
	IG	16.4 (3.8)	18.8 (3.8)	15%		
Maximal strength						
Hip extension, N	CG	79.7 (40.6)	90.4 (39.4)	13%	30.9 (12.8-48.2)	<0.001
	IG	86.4 (42.5)	128.3 (43.1)	49%		
Elbow extension, N	CG	42.7 (15.7)	47.5 (13.8)	11%	4.1 (–2.7-10.8)	0.2
	IG	44.8 (14.5)	55 (15.2)	23%		
Elbow flexion, N	CG	29.7 (15.3)	27.1 (12.4)	–9%	9.6 (2.6-16.9)	0.01
	IG	28.1 (8.1)	35.9 (12.4)	28%		
Shoulder flexion, N	CG	45.7 (20.5)	51.3 (15.3)	12%	4.6 (–5.4-14.3)	0.4
	IG	51.8 (21.1)	60.8 (18.9)	17%		
Shoulder extension, N	CG	56.2 (21.5)	52.8 (24.7)	–6%	6.4 (–8.2-20.6)	0.3
	IG	53.8 (19.9)	56.9 (22.9)	6%		
Shoulder abduction, N	CG	34.8 (13.5)	42 (14.4)	17%	5.3 (–1.7-11.8)	0.13
	IG	34.8 (12.1)	47.5 (18.3)	27%		
Knee extension, N	CG	91.2 (35.9)	99.9 (34.4)	9%	10 (–4.2-25.8)	0.17
	IG	97.2 (29.5)	117.4 (36.7)	17%		
Knee flexion, N	CG	54.9 (22.7)	50.1 (24.1)	–9%	10.2 (–2.9-23.2)	0.12
	IG	55 (17.4)	59.4 (24.4)	8%		
Global strength, N	CG	243.4 (85)	264.9 (87.8)	9%	53 (22.8-83.4)	0.001
	IG	257.9 (81.3)	336.6 (87.4)	31%		

NOTE: Data are given as mean (SD) unless otherwise noted.

BLOOD TEST RESULTS

No statistically significant differences in liver function biomarkers were observed between the study groups.

Discussion

We present the first prospective randomized clinical trial to evaluate if a supervised physical exercise program based on moderate-to-high intensity concurrent training has a positive impact on VO_{2peak}, maximal strength, body composition, and HRQOL in LT recipients. Achieving these goals will likely lead to a recovery of the patients' normal everyday life as seen in other studies. In turn, an adequate recovery together with an improvement in the patient's fitness and indirect understanding of the relevance of exercise in HRQOL may result in the long term in a reduction of metabolic complications. Indeed, diseases associated with metabolic complications are emerging as the first cause of death after LT.[3,4]

The VO_{2peak} obtained good results in our study, where IG had a significant improvement, compared with CG, and was similar to that achieved in other studies in both the general population[32] and LT patients,[9,13] where the patients were told to walk at a low-to-moderate intensity or perform strength exercises but without a concurrent methodology. The most similar training methodology was used by Van den Berg-Emmons et al.[14] where the patients performed 28 weeks of 60-minute training sessions, divided into 30-minute aerobic and strength training. Aerobic

TABLE 3. Comparison Between IG and CG Groups of the Body Composition Variables

Variable	Group	Baseline Test	Post Test	Percent of Change	Confidence Interval (95% CI)	*P* Value
Total weight	CG	77.5 (13.8)	80.1 (15.4)	3%	–0.03 (–2.2-2.3)	0.8
	IG	79.6 (15.1)	81.3 (17.4)	2%		
BMI, kg/m^2	CG	27.3 (3.7)	28.2 (4.2)	3%	0.01 (−0.7-0.9)	0.86
	IG	28.4 (4.8)	28.9 (5.8)	2%		
Fat mass	CG	25.5 (6.5)	26.1 (8)	3%	−0.3 (−3.2-2.8)	0.95
	IG	26.8 (6.3)	25.7 (6.7)	–4%		

NOTE: Data are given as mean (SD) unless otherwise noted.

TABLE 4. Comparison Between IG and CG Groups of the Psychological Variables

Variable	Group	Baseline Test	Post Test	Percent of Change	Confidence Interval (95% CI)	*P* Value
Physical functioning	IG	77.4 (18.1)	88.2 (10.5)	14%	13.28 (1.16-25.4)	0.03
	CG	74.8 (17.9)	71.4 (24.2)	−5%		
Role physical	IG	45 (46.8)	63.6 (44.1)	29%	0.2 (−23.5-23.9)	0.1
	CG	50.9 (46.2)	68 (41.8)	34%		
Bodily pain	IG	75.36 (22.8)	48.1 (8.3)	−35%	1.6 (−12.3-15.6)	0.8
	CG	76.3 (24.6)	48.3 (8.6)	−37%		
General health	IG	62.3 (12.7)	65.7 (15.3)	5%	2.9 (−6.7-2.9)	0.5
	CG	60.9 (14.2)	61.4 (13.2)	1%		
Vitality	IG	65.8 (28.5)	74.3 (18.1)	13%	13.2 (1.6-13.2)	0.03
	CG	70.4 (21.4)	65 (22.1)	−8%		
Social functioning	IG	81.7 (21.6)	89.3 (18.9)	9%	9.4 (−2.5-9.4)	0.12
	CG	87.2 (18.7)	84.6 (22.2)	−3%		
Role emotional	IG	77.3 (41.6)	83.3 (33.8)	8%	−1.6 (−20-16.9)	0.87
	CG	75.3 (40.9)	82.6 (37.4)	10%		
Mental health	IG	79.5 (18)	82 (12.1)	3%	6 (−5-17.1)	0.28
	CG	80.1 (19.6)	76.5 (18.7)	−5%		

NOTE: Data are given as mean (SD) unless otherwise noted.

training had an intensity of 60% whereas ours was from 75% to 85% using the Karvonen method.[30] They showed an improvement of 6.7%, whereas ours was 14.7%, probably due to a shorter duration and lower intensity.

As shown in the results, our training protocol was effective enough to improve overall maximal strength, elbow flexors and hip extensors—muscles that are highly related to daily activities.[33,34] Despite these good results, it did not reach the level of other populations, elderly or overweight,[29] probably because polyarticular but nonspecific movements were performed in the training sessions while monoarticular but specific movements were performed in the tests. The strength of the knee extensors has also been reported to improve in a shorter period of time in other studies.[13] A longer duration program, higher intensity training, single joint exercises, or the last 3 combined may be required to achieve a significant increase in the maximal strength of this muscle. Interestingly, another group in a different study did not show significant improvement either after performing strength training with similar devices.[9] They found a similar increase to that observed in our IG, but a higher one when compared with our CG. Nevertheless, the authors of the study did not analyze if there were significant differences in changes between the 2 groups. In addition, they did not explain the setup of the training sessions, the type of exercises practiced, or the dose they applied (repetitions, sets, rest, volume).

Although there were no significant differences between groups in body composition, IG patients showed a decrease in their fat mass, whereas it slightly increased in those from the CG. Total body weight and BMI increased in both groups. Our study was performed with the aim to increase fitness variables. To achieve good results in body composition, a specific exercise program combined with nutritional counseling is needed.

In terms of adverse events, there were no significant changes in liver function tests.[35]

An improvement in the SF-36 general health score, greater in the IG compared with the CG, was also observed. Painter et al.[36] showed a trend toward physical functioning improvement in the exercise group compared with the usual care group in kidney transplant patients. Van Ginneken et al.[37] reported significant improvement in the IG in the domains of physical functioning (14%; $P = 0.03$) and vitality (13%; $P = 0.03$). These results are similar to ours, where patients increased physical functioning and vitality.

This study has highlighted that the combination of strength and endurance training performed at moderate-to-high intensity in LT recipients results in significant improvements in aerobic capacity, maximal strength, and 2 parameters of HRQOL while it has no effect on body composition and liver function, whose biomarkers remain unchanged. Furthermore, it can be easily replicated in other centers given that the training program was designed with the intention to be easy to do anywhere at a cheap cost. The only requirements are an open space and elastic bands with different resistances. Home-based exercise programs can be applied but supervision of the training sessions by a professional is recommended to enhance adherence and control that the patients perform the exercises well, with a proper technique.[38]

In relation to the clinical relevance, the average healthy young male will have a VO_{2peak} of approximately 40 mL/kg/minute[39] and with every 1 metabolic equivalent of task (MET) (3.5 mL/kg/minute) increase in the aerobic capacity, the survival rate increases by 12%. Thus, our results show that our patients may have improved their survival rate by 8%.[40] Thus, our results show that our patients may have been improved 8% survival rate.[40] Furthermore, an increase in the VO_{2peak} and muscle strength are correlated with quality of life due to an improvement in the management of daily life activities.

We acknowledge that the study has some limitations. A great distance from the patients' homes to the hospital led to a decline of participation of 45 patients. If these techniques are confirmed to be beneficial for LT patients (and potentially other settings), the number of qualified trainers may increase which will allow all individuals regardless of distance to the hospital to participate in similar programs. In relation to the level of physical activity in CG, no survey was done.

Furthermore, generalizability of our findings may be limited as the study excluded patients with ECOG > 1, which may reflect a large proportion of transplant recipients. However, it is important to emphasize that the program was intended to be an increasing performance program and not just a rehabilitation activity. This is the main reason the program started 6 months after transplantation and not before. Also, patients undergoing simultaneous liver-kidney transplantation were excluded, as we wanted to have a homogeneous group and lower the risk of dropout.

Further research is needed to determine the optimal time to start this type of exercise programs as well as the appropriate intensity patients can withstand to gain the greatest improvements in physical capacities and parameters of HRQOL. Also, pretransplant interventions need to be studied to figure out its impact on the patients' recovery. Moreover, it will be interesting to repeat testing 6 and 12 months after the end of the program in each patient to see if the benefits are sustained long term. Whether this maintained exercise program will result in differences in harder endpoints such as metabolic complications or cardiovascular events is yet to be proven by prospective studies.

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