Research Article

Effectiveness of Home-Based Exercise Therapy on Quality of Life and Depression in Orthotopic Liver Transplantation Recipients

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Article info:
Received: 24 Aprl 2024
Accepted: 10 Oct 2024

Citation: Javaherian M, Parouhan A, Nasiri Toosi M, Jafarian A, Emami-Razavi SZ, Azadvari M, et al. Effectiveness of Home-Based Exercise Therapy on Quality of Life and Depression in Orthotopic Liver Transplantation Recipients. Journal of Modern Rehabilitation. 2025; 19(2):?-?

Running title: Exercise Therapy Effect Liver Transplant Patient

Abstract:
Background: Liver transplantation can change the quality of life, physical activity, mood, and psychological symptoms in patients. As exercise capacity is correlated to the level of depression and quality of life among patients,

Objective: This study aimed to investigate the effect of exercise therapy on the quality of life and depression in Orthotopic liver transplantation recipients (LTRs).
Methods: This study was a single-blinded, randomized controlled trial parallel groups, and thirty LTRs were randomly assigned in a 1:1 ratio. The experimental group underwent a three-month home-based exercise therapy, while the control group received no exercise therapy. Assessments included Short Form-36 (SF-36) and Beck Depression questionnaires, along with the 6-Minute Walk Test (6MWT).
Results: There was no significant difference between groups in demographic characteristics. Before the intervention, the mean score of depression in the intervention and control groups were 27.87 (8.68) and 25.77 (6.77), respectively. After the intervention, t-test revealed a significant difference between the two groups ($p = 0.001$). The results of t-test indicated that the average quality of life dimensions improved post-intervention compared to the control group, with significant differences in the scores of these dimensions. After the intervention, the t-test showed a significant difference between the two groups in terms of 6MWT ($p = 0.001$).
Conclusion: According to the findings of this study, rehabilitation through prescribed exercise can improve quality of life and physical activity, and alleviate depression symptoms in LTRs. As a result, incorporating physiotherapy into the post-transplantation care of transplant recipients holds potential benefits.
Keywords: Physical and Rehabilitation Medicine, quality of life, Depression, Orthotopic Liver transplantation

1. Background

One of the most crucial treatments for people with end-stage liver disease (ESLD) is liver transplantation(1). Both pediatric and adult populations need liver transplants for various reasons, including alcoholic or non-alcoholic fatty liver disease, cryptogenic disease, and viral illnesses leading to cirrhosis(2). Between 2010 and 2014, liver disease and Hepatocellular carcinoma (HCC) associated with hepatitis C (HCV) was the predominant cause for liver transplantation(3). The primary aim of liver transplantation is to reduce mortality rates and improve patients' quality of life and life expectancy (4). Current research endeavors focus on elevating the short-term survival rate after liver transplantation, which is currently greater than 80%. Patients' life expectancy also increases after liver transplantation(5). Despite its efficacy in reducing disease and mortality, liver transplantation comes with substantial postoperative complications, including pulmonary issues, fluid imbalances, digestive challenges, and psychological disorders (6,7). Underlying diseases, individual factors, surgery-related factors, and the quality of post-operation care may contribute to the development of disease complications (6, 7).

Extended longevity due to orthotopic liver transplantation (OLT) has increased the incidence of numerous issues and illnesses including chronic fatigue, irritability, and social isolation(6), possibly leading to a gradual decline in health-related quality of life (HRQoL)(8). One-year and five-year survival rates for patients with liver transplants are currently 90% and 70%, respectively, and even for specific conditions such as chronic obstructive liver diseases, the survival rate is higher(9). The increase in graft survival in patients with liver transplants has shifted the focus of patient care and clinical effectiveness research to the quality of life of the patients and their caregivers (10).

Prior to OLT, patients typically experience a decline in physical function impacting their daily activities and social engagement(11). The majority of mental and physical aspects of HRQoL improve during the first six months after a liver transplant, but this improvement is short-lived(12,

13). One year after a liver transplant, the mental and emotional HRQoL begins to decline(14). Significant tests measuring the quality of life and physical activity indicate that the score of patients who have received liver transplants is lower than average. Some patients who undergo liver transplantation may experience a complete improvement in their health, but physical and social issues may persist(15).

Examining the quality of life and psychological support of transplant patients reveals a significant increase in the patients' overall quality of life. About 34% of transplant recipients experience psychological symptoms, with anxiety and depression symptoms being the most prevalent in the first two years after transplantation and also persisting in the long term(16). After transplantation, depression, difficulty returning to work, low income, and loss of abilities are among the most common issues that patients face(17). A rehabilitation program based on exercise training and physical activity counseling is well tolerated and appears promising for reducing fatigue and improving fitness among LTRs. Rehabilitation involving supervised exercise training and daily physical activity counseling can improve daily functioning, participation, and HRQoL among LTRs(18, 19). The aim of this study was to evaluate the efficacy of a home-based, exercise therapy program on the quality of life and depression in post-transplant recipients. It was conducted due to the increasing survival rates of LTRs in Iran and the scarcity of trial studies demonstrating the efficacy of rehabilitation programs to improve patients' quality of life and depression.

2. Methods:

The design of this original study was a single-blinded, randomized controlled trial with parallel groups. This research aimed to determine the effect of physical rehabilitation on the quality of life of liver transplant recipients. The study protocol was approved by the Institutional Review Board and Ethics Committee (Approval No IR.TUMS.IKHC.REC.1396.4278)

2-1. Participants

Thirty people underwent liver transplantation in this study. The inclusion criteria were as follows:

- Age between 18 and 65 years
- a minimum of six months post-liver transplant

This study excluded those who:

- had more than one organ transplant
- had serious comorbidities (e.g., cancer or recurrent cholangitis).
- had contraindications for exercise (e.g., severe cardiac disease prohibited from exercise).
- had required specialized care
- had reluctance to participate due to concerns about transplant rejection and consequences.

2-2. Procedure

The research was carried out at the liver transplantation center of Tehran University of Medical Sciences located in Imam Khomeini Hospital Complex. This center is a known referral liver transplantation center in Iran. Relevant patients from various points of the country are referred to this center; hence, sampling at this center can seem to cover different types of patients considering culture, level of education, type of disease, etc. All participants were enrolled between May 2017 and February 2018 after receiving approval from the Institutional Review Board and Ethics Committee of Tehran University of Medical Sciences. All participants in the study were provided with sufficient information on how the project would be conducted, and their written consent was obtained. The study included comprehensive cardiac examinations for all participants to determine

their capacity for moderate physical activity. At the beginning of the study, participants completed the 36-item Short Form Survey (SF-36) form, the Beck Depression questionnaire (BDI), and the 6-Minute Walk Test (6MWT). Participants were then allocated into two groups (intervention and control groups) using block balanced randomization method (block size: 4). Patients in the intervention group underwent a comprehensive musculoskeletal examination under the supervision of a physiotherapist (a Ph.D. candidate with three years of experience in the field of OLT), and in the case of any musculoskeletal disorders, they were evaluated accordingly. If the patient required specialized care, he was excluded from the study. The remaining patients, however, the remaining patients were enrolled in a three-month exercise program aimed at improving muscle strength and fitness. Participants were then evaluated for the second time after three-month intervention.

2-3. Intervention

The protocol for the patients in the intervention group was to perform specific body exercises, first isometric and then progressive resistive exercises (PRE) (details and images are in the supplementary). The patients were instructed in such a way that the neck, back, hip, knee, and ankle exercises were initially isometric, and after two weeks they progressed to PRE and were gradually completed by the second month (Table 1). The patients then commenced aerobic exercise, starting with 20 minutes of walking three times per week and gradually increasing it to 45 minutes within a month. The patients were instructed that the intensity of the activity should be between 13 and 15 on the Borg scale, and they could speak clearly during the activity. In case of dyspnea or chest pain, exercise was ceased and further evaluation was performed. The control group received the usual care, with both groups completing the SF-36 form and BDI, and repeating the 6MWT following the program. All exercises were instructed to the patients by an expert physiotherapist in the field of Musculoskeletal disorders and solid organ transplantations. Patients were asked to perform exercises at their home. Patients enrolled to the intervention group were asked to perform exercises during three months. They could be in contact to the physiotherapist if they needed for any reason.

Table-1: Details of interventions

Weeks	**Plan**
First week	twenty minutes of exercise consisting of five minutes of warm up, ten minutes of brisk walking, and five minutes of cool down.
Second week	, 25 minutes of exercise consisting of five minutes of warm up, fifteen minutes of brisk walking, and five minutes of cool down.
Third week	exercise consists of 35 minutes, including 10 minutes of warm up, 15 minutes of brisk walking, and 10 minutes of cool down.
Sixth week,	45 minutes of exercise, including ten minutes of warm up, twenty five minutes of brisk walking, and ten minutes of cool down.

2-4. Outcome measures

In this study, three different outcome measurement instruments were utilized: the SF-36, BDI, and 6MWT. All assessments were carried out by another physiotherapist (with a master's degree and familiarity withr with the solid organ transplantation field) who was blinded tpatients'tient's

treatments and randomization process. All evaluations were carried out before and after (three months) interventions.

2-4-1. SF-36: The SF-36 test is the most commonly used test to assess the quality of life among LTRs. This test consists of 36 questions that assess eight aspects of health, divided into two categories: physical health and mental health. Physical performance, physical role (limitations due to physical health), body pain, and general health are used to evaluate physical health on this scale. On the other hand, vitality, social functioning, emotional role (limitations due to emotional problems), and mental health are used to evaluate mental health. The score of each component ranges from 0 to 100. One advantage of this test is that it can be compared to the average scores of a wide variety of cultures and diseases. In 1993, this test was used to investigate the quality of life in LTRs for the first time (20). All scores calculations were performed by the principle investigator of the diagnostic value of Iranian version of SF-36 questionnaire(21).

2-4-2. BDI: The BDI measures depressive symptoms in adolescents and adults through 21 items measuring irritation, cognition, guilt, fatigue, weight loss, and sexual desire. This questionnaire evaluates seven somatic symptoms, some of which are common in recipients of liver transplants. After scoring each item between 0 and 3, the total score is compared to the reference score. In some studies, LTRs diagnosed with depression on this test received low scores in seven out of eight domains of SF-36. Depression symptoms based on the BDI are accompanied by reports of an inability to perform daily or professional tasks(22).

2-4-3. 6MWT: 6MWT is a straightforward and practical physical performance evaluation tool used to assess submaximal physical capacity. It is considered a better evaluation tool for functional performance tests compared to sports tests, as it provides an objective measure of exercise intensity. During this test, patients are asked to walk as far as possible in six minutes using a 15-point scale to assess the patient's perception of physical activity (they must stop if experience fatigue). The test is conducted in a specific, smooth, and flat corridor, with no assistance or additional encouragement for patients. Heart rate and blood pressure are also measured before and after the test(23).

2-5. Data analysis

This study used the Shapiro-Wilks test to confirm the normal distribution of all corrected data. The data were consistent with a normal distribution, so parametric tests were chosen for this study. Using an independent t-test, the difference in demographic information and intervention was compared. The covariance test was conducted to determine the difference between the pre-test and post-test scores of the two groups. Analyses were conducted utilizing SPSS software for Windows (version 21), with a significance level set at P 0.05. The sample size of this study was calculated based on the results of the initial pilot study with five samples per group. Considering type I error of .05, and 80% power, a sample size of 12 participants per group were calculated. After considering the risk of loss to follow-up, 15 patients per group was considered as the final sample size.

3. Results:

The general characteristics of the participants are presented in Table 2, demonstrating no statistically significant differences between the intervention and control groups. In the intervention group, the mean age was 42.47 (9.27), 43.3 % of participants were female, and the mean BMI was 23.62. (2.51). Furthermore, the control group had an average age of 41.60 (7.18) years and a mean

BMI of 23.27 (1.63). Time since transplantation in the intervention and control groups were 1,4 and 1,47 days, respectively.

Table-2. Demographics and clinical characteristics of participants.

	Total (n=30)	**Physical Rehabilitation group (n=15)**	**Control Group (n=15)**
Age (y) (Mean ± SD)	42.03 ± 8.16	42.47 ± 9.27	41.60 ± 7.18
Sex Male, n (%) Female, n (%)	17 (56.7) 13 (43.3)	8 (53.4) 7 (46.6)	9 (60) 6 (40)
Marital Single, n (%) Married, n (%)	24 (80) 6 (20)	11 (73.4) 4(26.6)	13 (86.7) 2(13.3)
Height (cm) (Mean ± SD)	173.63 ± 9.53	172.87 ± 10.52	174.40 ± 8.74
Weight (kg) (Mean ± SD)	70.93 ± 9.97	70.80 ± 10.85	71.07 ± 9.40
BMI (kg/m^2) (Mean ± SD)	23.45 ± 2.09	23.62 ± 2.51	23.72 ± 1.63
Time since transplant (Year) (Mean ± SD)	1.43 ± 0.50	1.40 ± 0.50	1.47 ± 0.51
Diagnosis, n (%)			
Cryptogenic, n (%)	11 (36.7)	8 (53.33)	3 (20)
HBV, n (%)	4 (13.30)	2(13.33)	2 (13.33)
Wilson's Disease, n (%)	2 (6.67)	1 (6.67)	1 (6.67)
HCV, n (%)	5 (16.66)	0 (0)	5(33.33)
AIH, n (%)	6 (20)	4 (26.67)	2 (13.33)
PBC, n (%)	1 (3.33)	0 (0)	1 (6.67)
PCS, n (%)	1 (3.33)	0 (0)	1 (6.67)

HBV: Hepatitis B; SD: Standard deviation; BMI: Body mass index; HCV: Hepatitis C virus, AIH: Autoimmune hepatitis, PBC: Primary biliary cholangitis, PCS: primary sclerosing cholangitis

* All of the participant's characteristics are statistically similar between groups based on t-test and chi-square test.

3-1. The effect of physical rehabilitation on depressive symptoms

Before the intervention, the mean depression score in the intervention and control groups was 27.87 (8.68) and 25.77 (6.77), respectively. After the intervention, a significant difference was observed between the two groups (p = 0.001) (Table 3). Comparing data between the groups with baseline values as a covariable by covariance analysis revealed statistically significant differences in BDI-measured depression (P = 0.001).

Table-3. Distribution of different outcomes according to two arms in addition to related effect sizes.

Clinical Outcome	Physical Rehabilitation group (n=15)		Control Group (n=15)		F (P value) **	MD
	Baseline*	After*	Baseline*	After*		
BDI	26.77 ± 7.73	10.87 ± 6.80	25.67 ± 6.80	15.60 ± 7.5	۰/۰۰۱	33.67 [a] 291.26 [b]
6MWT	231.47± 170.86	522.73 ± 265.95	235.87 ± 79.95	284.54 ± 109.14	۰,۰۰۱	-10.06 -21.73
PCS	۳۱,۸۷ ± 9.92	87.27 ± 5.67	31.87 ± 9.92	50.80 ± 18.22	۰,۰۰۱	23.73 55.40
MCS	42.87 ± 15.88	89.73 ± 6.77	50.80 ± 18.22	69.73 ± 14.76	۰,۰۰۱	18.93 46.86

a: Mean difference in control group

b: Mean difference in intervention group

3-2. The effect of physical rehabilitation on quality of life

Before the intervention, there was no significant difference between the quality-of-life dimensions ($P > 0.05$). The results of the t-test showed that the average quality of life dimensions improved after the intervention compared to the control group, with a significant difference in the scores of the quality-of-life dimensions in the intervention group (Table 3). Comparing data between groups using baseline values as a covariable revealed significant differences in all quality-of-life variables except bodily pain and emotional role ($P = 0.001$).

3-3. Effect of physical rehabilitation on physical performance

The average 6MWT score pre-intervention for the intervention and control groups was 231.47 (170.86) and 235.87 (79.95), respectively. After the intervention, a significant difference was observed between the two groups ($p = 0.001$) (Table 3). The average 6MWT scores after the intervention were 522.73 (265.95) in the intervention group and 284.54 (109.14) in the control group. Covariance analysis using baseline values showed statistically significant differences for the 6MWT ($P = 0.001$).

4. Discussion:

The findings of the present research highlight that implementing rehabilitation programs enhances the quality of life and alleviates depression symptoms in patients following liver transplantation. A study by Van Ginneken investigated the impact of a fatigue-reducing physical rehabilitation program on daily activity, HRQoL, anxiety, and depression in LTRs, in which improvements were observed in daily activity and quality of life after the treatment, but anxiety and depression remained unchanged. This trial included a 12-week rehabilitation program with supervised exercise training and daily physical activity counseling (19). Similarly, Clarissa Bentes conducted a study one month after transplantation to determine the effect of rehabilitation on physical performance and quality of life in LTRs (24). This study also discovered that rehabilitation improves the quality of life and physical performance of transplant recipients.

Physical activity increased the quality of life in LTRs, according to the findings of Valentina Totti's study (25). This 12-month trial included physical and aerobic workouts performed under the supervision of a trainer. Tuba Yüksel Ergene's findings further supported that ERT improved the physical performance of transplant recipients and that it can be employed in post-transplant physiotherapy (26).

Previous research found that general quality of life improved significantly after transplantation, compared to pre-transplantation health state (27-29). In contrast, the vast majority of transplant patients have significant deficits in most dimensions of quality of life, compared to the general population. However, the findings of this study contradict the findings of other investigations, and we conclude that the notion of better quality of life following transplantation may be overestimated (27). The main problem after liver transplantation is improving the quality of life. Several factors influence these people's quality of life including underlying disorders, surgical causes, gender, and transplant therapies. Patients' quality of life after transplantation can alter their outcomes and threaten their health(30). The current study underscores the importance of physical rehabilitation in improving the quality of life in LTRs.

Furthermore, the study demonstrates that implementing rehabilitation programs improves depression symptoms in post-transplant patients. There have been few studies on the influence of

rehabilitation on mood, psychological symptoms, and depressive symptoms. In contrast to Van Ginneken's study where anxiety and depression remained unaltered following the rehabilitation session, the current study suggests a more favorable outcome regarding depression symptoms (19). Although various factors affect the level of quality of life and depression, different types of patients with various hepatic diseases, level of quality of life, and depression were enrolled to the current study and assigned to both groups. Comparable research in heart transplant recipients has illustrated the potential of rehabilitation in alleviating depression and anxiety symptoms and psychological consequences, aligning with the current study's findings(31, 32).

Liver transplantation has an impact on patients' physical performance, and many patients may restrict their activity as a result of the transplant. The 6MWT, which determines how far a person can walk in six minutes, is a measure used to assess patients' physical performance. According to review studies, the application of the 6MWT test is relatively simple and acceptable by the participants, and it provides a better reflection of the role of people's daily activities compared to other walking tests(33). A significant difference in the 6MWT score was observed between the two groups, indicating that rehabilitation has a positive influence on the function and physical activity of transplant recipients. According to B Foroncewicz's research, rehabilitation improved the physical capacity, determined by 6MWT, of LTRs (23). Adapted physical activity (APA) has also been shown to improve the physical performance of people awaiting liver transplants(34). As a result, the issue of performance and physical capacity in LTRs is critical, and the current study has presented an effective solution to this problem.

While the study presents noteworthy insights, it has some limitations including a small sample size and patient reluctance to participate due to concerns about transplant rejection and consequences. Nevertheless, the study's limited sample size warrants larger-scale research to further validate and generalize these outcomes.

5. Conclusion:

According to the findings of this study, rehabilitation programs can enhance the quality of life and physical activity, and mitigate depression symptoms in LTRs. The findings advocate for the incorporation of physiotherapy in post-liver transplant care. Nevertheless, the study's limited sample size warrants larger-scale research to further validate and generalize these outcomes.

Authors' Contribution:

Conceptualization and study validation: ..... and .....; implementation and supervision: ....., ..., and .....; data analysis and interpretation: Mozhgan Aghaei; writing and reviewing: ....., ..., and ..... All authors read and approved the final version of the manuscript

Ethics code: (IR.TUMS.IKHC.REC.1396.4278)

6. **Clinical Trial Registration Code**: IRCT20220214054022N1.

7. Conflict of Interests:

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

7. **Data Reproducibility**:

8. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

9. Funding/Support:
The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

10. Acknowledgements:
The authors express their gratitude to the Transplant Department team members at Imam Khomeini Hospital for their invaluable assistance and their contributions to this research.

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