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Observational Study

Effect of an active lifestyle on the physical frailty of liver transplant candidates

Oikonomou IM *et al*. Exercise and frailty in liver transplant candidates

Abstract

BACKGROUND

Liver transplantation is the most important therapeutic intervention in end-stage liver disease. The prioritization of these patients is based on the model for end-stage liver disease (MELD), which can successfully predict short-term mortality. However, despite its great validity and value, it cannot fully incorporate several comorbidities of liver disease, such as sarcopenia and physical frailty, variables that can sufficiently influence the survival of such patients. Subsequently, there is a growing interest in the importance of physical frailty in regard to mortality in liver transplant candidates and recipients, as well as its role in improving their survival rates.

AIM

To evaluate the effects of an active lifestyle on physical frailty in liver transplant candidates.

METHODS

An observational study was performed within the facilities of the Department of Transplant Surgery of the Aristotle University of Thessaloniki. Twenty liver transplant candidate patients from the waiting list of the department were included in the study. Patients that were bedridden, had recent cardiovascular incidents, or required inpatient treatment for more than 5 d in the last 6 mo were excluded from the study. The following variables were evaluated: Activity level *via* the International Physical Activity Questionnaire (IPAQ), functional capacity *via* the six-minute walking test (6MWT) and cardiopulmonary exercise testing, and physical frailty *via* the Liver Frailty Index (LFI).

RESULTS

According to their responses in the IPAQ, patients were divided into two groups based on their activity level; the active group (A, 10 patients) and the sedentary group (S, 10 patients). Comparing mean values of the recorded variables brought up the following

results: MELD (A: 12.05 ± 5.63 *vs* S: 13.99 ± 3.60, $P > 0.05$), peak oxygen uptake (A: 29.78 ± 6.07 mL/kg/min *vs* S: 18.11 ± 3.39 mL/kg/min, $P < 0.001$), anaerobic threshold (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min, $P < 0.01$), 6MWT (A: 458.2 ± 57.5 m *vs* S: 324.7 ± 55.8 m, $P < 0.001$), LFI (3.75 ± 0.31 *vs* 4.42 ± 0.32, $P < 0.001$).

CONCLUSION

An active lifestyle can be associated with better musculoskeletal and functional capacity, while simultaneously preventing the evolution of physical frailty in liver transplant candidates. This effect appears to be independent of the liver disease severity.

Key Words: Liver transplantation; Frailty; Six-minute walk test; Cardiopulmonary exercise testing; Exercise therapy; Observational study

Oikonomou IM, Sinakos E, Antoniadis N, Goulis I, Giouleme O, Anifanti M, Katsanos G, Karakasi KE, Tsoulfas G, Kouidi E. Effect of an active lifestyle on the physical frailty of liver transplant candidates. *World J Transplant* 2022; In press

Core Tip: This study attempts to highlight the importance of regular physical activity and exercise of low and medium intensity in the routine of liver transplant candidates. As liver transplantation is a highly demanding procedure, imposing a significant amount of stress across every system, physical frailty is steadily proving to be a factor of great importance, not only due to its role in mortality prediction, but also due to its potential improvement *via* pre-operative interventions.

INTRODUCTION

Liver transplantation is the greatest tool in the management and treatment of end-stage liver disease[1]. Nevertheless, there is a worldwide gap between the demand for liver transplants and the availability of organ donations[2], increasing the need for

optimisation of candidate prioritisation and organ distribution[3]. It is well established in literature that the model for end-stage liver disease (MELD) score has been a unique tool in this direction[4]. Nevertheless, there are further clinical parameters that may play a substantial role in the waiting list mortality, especially in patients with lower MELD scores[5].

Sarcopenia has been identified to be related to the waiting list mortality and survival after liver transplantation[6-9]. Furthermore, sarcopenic candidates require longer inpatient care, not only on intensive care unit level but also in ward-based care[10,11]. Functional capacity has also been described as a useful predictive tool, as it is related to better post-operative survival rates and required length of stay[12,13]. It is worth noting that cardiopulmonary exercise testing (CPET) is used quite extensively in other transplant candidates; nevertheless, it is not equally popular in the pre-listing assessment of a liver transplant candidate[14,15]. One of the main disadvantages of CPET is the need for expensive equipment within a laboratory setting with equally trained healthcare professionals. The six-minute walking test (6MWT) is mentioned as an alternative assessor of functional capacity in the literature[16], lower values of which have been associated with increased mortality both in the waiting list and after transplantation[17,18].

Furthermore, physical frailty, has been gaining growing attention, due to its correlation with mortality prediction in liver transplantation. Physical frailty is a clinical syndrome that is correlated both with sarcopenia and functional capacity and is characterised by reduced strength and stamina, as well as increased mortality risk and post-operative dependence[19-21]. Liver Frailty Index™ (LFI™) is an innovative tool, developed by Lai *et al*[22], that appears to significantly improve mortality prediction when combined with MELD, especially in patients with low MELD scores[22,23].

The course of liver disease is well correlated with a gradual diminishment of both functional capacity and musculoskeletal robustness. Keeping the importance of the above clinical tools into consideration, not only on mortality prediction but also on patient prioritisation, this observational study aimed to evaluate the effect of an active

lifestyle on indices of physical functioning, attempting to identify the effect of physical activity on physical frailty and cardiovascular capacity in liver transplant candidates.

MATERIALS AND METHODS

Study population

Liver transplant candidates from the Department of Transplant Surgery of the Aristotle University of Thessaloniki in the Hippokration General Hospital of Thessaloniki were recruited for the study. Patients enlisted in the liver transplantation waiting list registry, according to criteria of the Hellenic Transplantation Organization, were deemed eligible for enrollment. The observational study design excluded patients with other comorbidities hindering their activity level or the ones having received instructions from their physicians to limit it, due to a recent acute deterioration of their condition.

Therefore, patients were deemed ineligible if one of the following was true: (1) Recent cardiovascular incident in the preceding 12 mo; (2) Grade 2 or higher Hepatic encephalopathy; (3) Bedridden patients with complete dependence; and (4) Recent hospital admission requiring longer than 72 h of inpatient care due to condition deterioration.

A total of 43 patients had their records screened to be included in the observational study. Following the exclusion criteria described above, 19 patients were excluded. In particular, two patients were recovering from a recent cardiovascular incident, five were classified with hepatic encephalopathy of grade 2 or higher, nine patients were completely bedridden and unable to self-accommodate everyday needs, and finally, three patients required long inpatient care within the past three months. The remaining 24 patients were contacted and informed about the study; four declined participation. All patients participating in the study were informed about the purpose and the methodology of the study and provided written informed consent. The study protocol was approved by the Department's Ethics Committee of Aristotle University of Thessaloniki (protocol number 65/2021). The study was performed from February 16th to June 21st, 2021.

Activity level evaluation

The self-administered, short form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate the activity level of the participants. The IPAQ questionnaire was completed by the participants independently, without any guidance from the study investigators. It includes seven questions, collecting self-reported information for the number of days and time spent doing: (1) Vigorous; (2) Moderate physical activity; (3) Walking; and (4) Sitting each day during the course of a week[24,25]. The participants completed the Greek version of the questionnaire[26]. Questions 1 and 2 enquire about the days and time spent on vigorous activities, questions 3 and 4 refer to activities of moderate intensity, questions 5 and 6 to walking, and question 7 asks about the time spent sitting. This tool classifies respondents into three categories of physical activity: Low, moderate, and high, according to the following criteria[27]: (1) Category 1 - low: Individuals failing to meet any of the criteria detailed below; (2) Category 2 - moderate: Individuals that fulfill any of the following three: (1) At least three days of vigorous activity, lasting more than 20 min daily; (2) At least five days of moderate activity or walking, lasting more than 30 min daily; and (3) At least five days of exercise comprising of a combination of walking, moderate and vigorous activities, equal to 600 metabolic equivalent of task (MET) minutes or more; and (3) Category 3 - high: Individuals that fulfill either of the following: (1) At least three days of vigorous activity; reaching at least 1500 MET minutes weekly; and (2) Daily exercise comprising of a combination of walking, moderate and vigorous activities, reaching at least 3000 MET minutes weekly.

Functional capacity evaluation

Two different methods were used to evaluate the functional capacity of participants, CPET and the 6MWT. CPET was performed on the Trackmaster Treadmill (Full Vision Inc., Newton, KS, United States), using the Bruce protocol, while gas exchange was measured by the MedGraphics Breeze Suite CPX Ultima (Medical Graphics Corp, MN, United States). The test was performed under the supervision of trained personnel and

a cardiologist, within the facilities of the Laboratory of Sports Medicine of the Aristotle University of Thessaloniki. Maximal effort was achieved by all participants, upon reaching a Respiratory Exchange Ratio larger than 1.10. Peak oxygen uptake (VO_{2peak}) and anaerobic threshold (AT) were assessed to evaluate the functional capacity of the participants.

Furthermore, a 6MWT was performed indoors by all participants. The testing design included a thirty-meter long, flat, and circular track, which was clearly marked for every meter. Patients performed the test twice and the longest distance achieved was recorded as their result. They were also instructed to immediately abandon their attempt if they feel unwell or uncontrollable fatigue. During the 6MWT, patients received verbal encouragement on the second and the fourth minute of every attempt and a notification when 60 s were left. Pulse oximetry was used to measure the oxygen saturation and heart rate during the test, while the Borg scale Rating of Perceived Exertion was used to monitor exercise intensity.

Physical frailty evaluation

The LFI was used to evaluate the physical frailty of the study participants[28]. This clinical tool, developed by Lai *et al*[29], includes three tests that assess balance, neuromuscular coordination, and sarcopenia. The three tests are as follows: (1) Hand grip strength: Using a dynamometer in the standard position, participant squeezes the grip three times while the dynamometer rests on no surface; (2) Sit-to-stand test: From sitting position, keeping both arms folded in front of their chest, participant is timed while standing up and sitting down five consecutive times; and (3) Balance test: Participant is timed standing up in three different balance positions, with feet side-by-side, semi tandem and tandem, while receiving no further support, for a maximum of 10 s.

Statistical analysis

IBM SPSS Statistics, version 25.0 (SPSS Inc. Chicago, IL, United States) was used for the statistical analysis. Continuous parameters were compared using the independent samples *t*-test. The values of the parameters of the sample were tested for normal distribution with the Shapiro-Wilk test. Point biseral correlation analysis was used to determine the relationship between activity level and the frailty and functional capacity variables. Difference between values was considered to be of statistical significance for *P* values less than 0.01. All data are presented as mean ± SD.

RESULTS

General characteristics of patients

Twenty patients were included in the study, all of whom are listed in the waiting list of the Department of Transplant Surgery in the Hippokration General Hospital of Thessaloniki. The majority of the patients came from the city of Thessaloniki (*n* = 9, 45%), while the rest were distributed across the Greek mainland and islands. There were ten male and ten female patients included in the study, with a median age of 50.1 years. The primary causes of end-stage liver disease of the participants were hepatitis B (*n* = 5, 25%), non-alcoholic fatty liver disease (*n* = 3, 15%), primary biliary cholangitis (*n* = 3, 15%), alcohol-related liver disease (*n* = 2, 10%), liver haemangioma (*n* = 2, 10%), hepatocellular carcinoma (*n* = 2, 10%), hepatitis c (*n* = 1, 5%), autoimmune hepatitis (*n* = 1, 5%) and hepatic cystadenomas (*n* = 1, 5%). The mean MELD score for the patients in the study was 13.02 ± 4.71. Demographic details for each patient are listed in Table 1, including primary cause of end-stage liver disease per participant.

Activity level

All responses collected *via* the IPAQ can be seen in Table 2. Ten patients were classified as having a moderate physical activity level (category 2), whereas ten patients were found to be in the low physical activity level category (category 1). Using these responses, the sample was divided into two groups. Patients with a moderate activity level were characterised as active (A). Patients with low activity level were allocated in

the sedentary group (S). The active and the sedentary group were found to be similar regarding their MELD score (12.05 ± 5.63 *vs* 13.99 ± 3.60, $P > 0.05$).

Functional capacity

All participants successfully completed their CPET, successfully reaching respiratory exchange ratio equal to 1.10 or higher. No patient had to abandon their examination due to excess fatigue or the presentation of adverse effects. No patient was instructed to terminate the exercise stress test due to changes to their electrocardiogram.

The mean VO_{2peak} achieved by active participants was higher compared to the mean value recorded by the sedentary group (29.78 ± 6.07 mL/kg/min *vs* 18.11 ± 3.39 mL/kg/min respectively, $P < 0.001$). Similarly, the AT in active subjects was higher compared to its sedentary counterparts (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min respectively, $P < 0.01$). All results for VO_{2peak} and AT are presented in detail in Table 3.

Regarding the 6MWT, all participants successfully completed two attempts, with the longest distance considered as the test result. No complication was recorded, and no effort was abandoned due to fatigue or exhaustion. Detailed results per participant are presented in Table 4. The active group covered a larger mean distance on the test compared to the sedentary group (324.7 ± 55.8 m *vs* 458.2 ± 57.5 m respectively, $P < 0.001$).

Physical frailty evaluation

The LFI was used to assess the robustness or frailty of the study participants. Patients successfully completed all exercises, after first witnessing a demonstration. The sedentary group was more likely to score a greater LFI score and to be found as frail, while its mean value is above the limit for patient classification as frail, in comparison to the active group which was more likely to score smaller values (4.42 ± 0.32 *vs* 3.75 ± 0.31 respectively, $P < 0.001$). Detailed performance per test is described in Table 5. Patients with a LFI greater than 4.4 were classified as frail[23,29]. No patient from the active group

was classified as frail (LFI < 4.4, n = 10), while 6 patients were found to be frail according to the LFI in the sedentary group (LFI > 4.4, n = 6).

Correlation analysis

Pearson Correlation analysis was used to determine if disease severity was associated with worse functional capacity or higher frailty scores. Correlation was tested between MELD scores and LFI, VO2max, AT and 6MWT. No significant correlation was found between MELD and LFI (r_p = 0.29, P > 0.05), VO2max (r_p = -0.10, P > 0.05), AT (r_p = -0.25, P > 0.05) or 6MWT (r_p = -0.36, P > 0.05).

Point-Biseral Correlation was run to determine the relationship between the activity level and functional capacity and physical frailty markers. MELD and activity level was not significantly correlated (r_{pb} = -0.212, P > 0.05), whereas there was significant correlation between activity level and LFI (r_{pb} = -0.747, P < 0.001), VO_{2peak} (r_{pb} = 0.781, P < 0.001), AT (r_{pb} = 0.618, P < 0.01) and 6MWT (r_{pb} = 0.779, P < 0.001). This relationship is presented on Table 7.

DISCUSSION

According to the results of this observational study, physical activity appears to prevent physical frailty and retain cardiovascular capacity in liver transplant candidates, independent of their MELD score. This can be potentially used as a tool for prehabilitation in listed patients for a liver transplant. Availability of liver transplants has always been well below demand, especially in Greece, with the coronavirus disease 2019 pandemic posing an even greater challenge. This study was driven by the need to identify possible important and potentially modifiable clinical parameters, which, when used in concordance with the MELD score, they would be able to optimise the capacity of a medium-size transplant centre[3,6].

According to the LFI, 30% (n = 6) of the study participants are classified as frail (LFI > 4.4)[23,29], percentage that is concordant with the results of a previous review study[30]. Physical frailty has been associated with increased waiting list mortality, independently

of the MELD Score, presence of ascites or hepatic encephalopathy[31]. Furthermore, in the post-operative spectrum, frailty has been associated with increased 30-d mortality, extended inpatient and intensive-unit care[32], increased rates of acute cellular rejection[33], increased dependency[34,35], and vertebrae fractures[36]. Constructed, home-based exercise programmes appeared to positively influence frailty indexes and partially restore musculoskeletal robustness[37-40]. Our study aimed to compare each patient's physical activity level with their physical frailty. Although patients were not under professional trainer guidance, frequent activity such as walking and gardening, appeared to have a preventive effect on the evolvement of physical frailty. This could potentially provide clinicians with an important tool in the pre-operative treatment of candidates, while on the waiting list for a transplant; a tool that could potentially improve transplantation outcomes.

Functional capacity has also been associated with post-operative dependency and mortality. Epstein *et al*[12] have described an increased 100-d mortality in patients with lower peak oxygen uptake, while other studies have associated a smaller VO2peak with extended intensive care unit stay and mechanical ventilation dependency[41]. Similarly, smaller distances in the pre-operative 6MWT have been associated with increased mortality after liver transplantation[42,43]. In 2021, Henrique *et al*[18] identified a statistically significant increased risk of cirrhosis decompensation in patients with values smaller than 401.8 m in the 6MWT, while Bhanji *et al*[44] described a double risk of waiting list mortality in patients with values smaller than 250 m and its statistically significant reduction for every 100 m improvement. In our study, active participants were much more likely to record values above 401.8 m (80% *vs* 10%, $P < 0.01$), which is consistent with the findings of the effect of exercise in liver patients in other studies[45,46].

The inclusion of indexes of frailty and functional capacity in the clinical practice of liver transplantation appears to be a valuable aid in patient prioritisation, especially in candidates with low MELD scores[47]. Furthermore, regular physical activity appears to be a valuable tool to improve these modifiable factors. Physical frailty is reduced in

liver transplant candidates through the adoption of an active lifestyle in several studies[48,49], while functional capacity is also similarly improved[45,50]. This can potentially lead to improved survival rates and reduced hospitalisation length and readmission rates[51,52]. Our study shares similar results, further supporting the notion that physical activity can have a significant role in pre-operative preparation for candidates, potentially achieving improved outcomes. Furthermore, our data suggests that home-based, patient controlled exercise can have an adequate impact.

The active participants of our study, although not following an organised and formal exercise protocol, had substantially better musculoskeletal and functional status, appeared to be more robust and could potentially have great tolerance to stressors. This suggests evidence that exercise interventions could have a positive impact on liver transplant candidates, without the need for formal and difficult exercise regimes that bear a higher risk of lower compliance. However, this study had its limitations, them being: (1) The small sample size; and (2) No prospective results. Further data collection and follow-up could confirm the effect of this lifestyle on pre- and post-transplantation survival, dependency, and complications.

CONCLUSION

In conclusion, an active lifestyle can potentially be a tool of pre-operative preparation of liver transplant candidates, aiming to reduce mortality, hospitalisation, and dependencies. Physical frailty and functional capacity can be improved *via* exercise training interventions. Clinical tools such as the 6MWT and the LFI could be used for better mortality prediction and patient prioritisation, which is of significant importance in smaller and medium-sized transplant centres, where organ donation is unable to meet the existing high demand.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation forces a substantial stress on the human physiology, which is even more significant considered the deconditioning that accompanies end-stage liver disease. Physical frailty has emerged as an important factor both pre-, as well as post-operatively, aiming to improve results and outcomes.

Research motivation

The limited amount of available organ donations in addition with the high demand in liver transplants, highlight the need for proper planning and prioritisation, while at the same time working towards further outcome improvement.

Research objectives

Main objective was to identify if an active lifestyle can significantly improve physical frailty and functional capacity in end stage liver patients.

Research methods

An International Physical Activity Questionnaire, a functional capacity assessment and a physical frailty evaluation were utilised.

Research results

There was statistically significant difference and statistical significant correlation between the activity level and the Liver Frailty Index, the peak oxygen uptake, the anaerobic threshold and the six-minute walking distance.

Research conclusions

Physical activity can potentially improve functional capacity and frailty in liver transplant candidates.

Research perspectives

Future research could focus on the regimen of the exercise that would be more suitable, or better quantify the amount of physical exercise needed for these patients. Furthermore, the potential use of these markers in survival and outcomes should be evaluated.

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