Clinical and Experimental Health Sciences

Fatigue and Physiotherapy in Liver Transplant Recipients

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Received: 22.04.2018 **Accepted:** 18.06.2018

ABSTRACT

Liver transplantation surgery is a life-saving treatment option for life-threatening end-stage liver diseases and acute liver failure. While the health-related quality of life of liver transplant recipients is related to the success of the transplantation procedure; fatigue, malnutrition, loss of muscle mass, decrease in exercise capacity, negative respiratory and metabolic changes as the findings of organ failure are among the causes of functional loss in the posttransplant period. The prevalence of the fatigue, as the frequently experienced symptom in the end-stage liver diseases, varies depending on the specific forms of liver disease and it adversely affects pre and postoperative functional levels of the patients, liver transplantation results and also survival. The severity of the fatigue decreases after the transplantation surgery, but it continues to be seen as the most compelling clinical symptom experienced during the postoperative first year. Current literature data emphasize the necessity of physiotherapy programs and active early mobilization which applied in the early period in the intensive care unit following transplantation surgery and physiotherapy and rehabilitation approaches including strength and endurance training contributes to the functional level in this population. These findings suggest that there is a need for structured physiotherapy programs to increase muscle strength and exercise capacity and prevent fatigue.
Keywords: Exercise training, fatigue, liver transplantation, physiotherapy

INTRODUCTION

Transplantation surgery is considered to be the best liver replacement therapy and a life-saving treatment option for life-threatening end-stage liver failure (1). Although the liver function and survival are improved after transplantation; surgical stress response, physical and psychological problems due to the pathology affect the quality of life negatively (1,2). Many recent studies have focused on the relationship between health-related quality of life and the success rate of transplantation procedure states that transplantation surgery decreases scores representing physical activity parameters of quality of life. The decrease in the level of physical activity is reported to be associated with cachexia, diminishing muscle strength and exercise capacity, loss of range of motion, osteoporosis, malnutrition, pain, arthritis and physical fatigue (1,3,4).

Fatigue has been listed as the most commonly experienced symptom in patients with chronic liver disease (5); it leads to complications, adversely affecting results of liver transplantation as well as survival (6,7). Ney et al. reported that the level of physical activity which is reported by the subjects who have liver failure was low and the major barrier was fatigue (8). Although the severity of fatigue is decreased by transplantation surgery, it remains to be the most challenging clinical symptom experienced within the first postoperative year (9,10). Van den Berg-Emons et al. reported that fatigue is an ongoing symptom in 44% of recipients in the post-transplant period up to 15 years (11).

The pathogenesis of fatigue is not clear in chronic diseases and liver transplant recipients, however, it is multifactorial in general (5). Since many factors such as age, gender, the level of physical activity, sleep quality, cardiorespiratory fitness, anxiety, and depression are associated with fatigue (12,13); physiotherapy which applied in the early and late postoperative period is extremely important. There is a necessity to introduce patient-specific and structured exercise programs for liver transplant recipients (14,15).

CLINICAL AND RESEARCH IMPACTS

Liver Transplantation

Liver transplantation is the procedure in which normal functioning liver tissue from either a living or cadaveric donor is replaced electively in cases with chronic liver diseases or acute fulminant insufficiency (16). Currently, the only proven, definitive treatment modality for the end-stage liver disease is liver transplantation. However, the selection of liver-transplant candidates is extremely important for the success of transplantation (17). Liver failure is characterized

DOI: 10.33808/clinexphealthsci.599730

by the progressive deterioration of hepatic functions in acute or chronic progress. The process itself is critical due to the complications of the disease rather than the liver disease alone; therefore, there is a high mortality risk. In the course of a pretransplant evaluation, recipients should be evaluated thoroughly; thus the identification of high-risk patients is of utmost importance for the success of transplantation surgery. The most commonly used risk scoring methods are the Model of End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) scores which is the specific form for children. Model for End-Stage Liver Disease (MELD), The United Kingdom Model for End-Stage Liver Disease (UKELD) (17-19) and Child-Pugh scores are other scoring systems. These systems aim to determine the severity of liver disease and predict the prognosis. The MELD score is known to be more predictive in short-term pretransplant mortality risk prediction (Grade II-1) (18). When MELD and Child-Pugh scoring systems are compared, some studies reported that both are similar for prognostic aspects in many cases and they both have distinctive features for some specific conditions and there is a need for further research to decide which scoring system should be used in which conditions (20).

Perioperative risk assessment includes evaluating comorbidities for liver transplantation such as coronary artery disease, pulmonary hypertension. Patients with hepatic insufficiency have malnutrition, myopathy, and poor physical performance and these secondary outcomes cannot be easily detected with standard cardiorespiratory tests such as 2-dimensional echocardiography and pulmonary function tests (1,18). In resting transthoracic 2-dimensional echocardiography, the normal left ventricular systolic function is defined as an ejection fraction (EF)>45% and according to the European Society of Cardiology guidelines, an elevated systolic pulmonary artery pressure (PAP)>36 mmHg is defined as the cutoff value for possible pulmonary hypertension (19).

Fatigue

The clinical definition of fatigue includes biological, psychosocial and behavioral processes and its' complex interactions along with the prevalence varies depending on the specific form of the liver disease (21,22). Cholestasis causes degenerative central nervous system changes adversely affecting the brain regions which regulates autonomic dysfunction and sleep pattern. These changes lead to many symptoms of fatigue and associated cognitive disorders (2). Besides, autonomic dysfunction contributes to these metabolic changes by limiting the reaction capacity of the muscle to increase in proton/lactate current from the cell and its excretion from tissues (23). Complications in cirrhotic patients such as sarcopenia and hepatic encephalopathy also appear as other causes that lead to fatigue (24,25).

Studies report that chronic liver inflammation is associated with changes in the central nervous system (CNS) emerging as behavioral modifications (26). Liver inflammation also causes changes in brain function. Abnormal central neurotransmission leads to behavioral changes when there isn't any pathological CNS tissue damage present (27). Neurotransmitters associated with central fatigue are corticotropin-releasing hormone (CRH), serotonin and noradrenaline (22). The liver is innervated by vagal nerve afferents that respond to immune mediators such as tumor necrosis factor (TNF α), interleukin-1 and interleukin-6 (22). The activated vagal nerves affect different regions of the brain potentially leads to subsequent behavioral changes. However, this neural pathway is also thought to play only a minor role in the mechanism of fatigue in chronic liver disease because post-liver transplant patients (in which the liver is deinnervated) often reported a very little change in their perception of fatigue (22,28).

Glial cells and neurons in the brain can produce cytokines leading to behavioral modifications including fatigue. Fatigue is also reported to be associated with alterations of basal ganglion neural activity (22). Stinton and Swain reported that there are still areas where density is even more decreased after a few months of the transplantation. The brain dynamics in those cases where cirrhosis had not recurred indicates that neurological damage may be permanent or recovery is very slow (22).

Despite the pathophysiological mechanisms explaining fatigue exists, there is still not enough data on fatigue's mechanism. Also, it is reported that liver transplantation does not eliminate fatigue. Therefore, further investigation is needed in liver transplant patients to predict fatigue factors and to plan exercise and rehabilitation programs for fatigue management.

Physiotherapy and Rehabilitation

Even though physiotherapy and rehabilitation programs have benefits in reducing fatigue severity; studies in the literature are limited regarding structured exercise programs.

Studies in liver failure cases are indicated reduced exercise capacity which is measured by maximal oxygen uptake (VO_{2max}) (29,30) and the inverse correlation between exercise capacity and liver disease severity is remarkable. The decrease in exercise capacity is not only associated with the severity of disease but also considered to be as a predictor of mortality after transplantation. Physical competence, which is one of the most important parameters affecting exercise capacity, is affected by many factors, mainly fatigue, and muscle strength. Studies have emphasized that therapeutic exercises applied to chronic liver failure patients improves physical fitness by improving cardiopulmonary functions (31). These studies especially pointed out a four-week physical training program is needed to improve VO_{2max} by enhancing physical activity level, skeletal muscle volume, and mass (32). Therapeutic exercise approaches are therefore extremely important in managing fatigue in end-stage liver failure (33,34).

Because of a long waiting period is added to the presence of sarcopenia in liver failure cases which are in the transplantation waiting list, rehabilitation programs

intending to reduce inactivity, improve muscle performance, increase exercise tolerance and prevent postoperative complications are of great importance in this population (29,35,36). Individualized and standardized physical activity programs are acceptable, effective and reliable in patients who are waiting for transplantation. Although however the positive effects of such programs on functional performance and quality of life are known, it is needed for prospective, comprehensive randomized trials to point out promising effects on the post-transplantation process, duration of hospital stay and six-months survival (37).

Studies reported that maximal oxygen consumption of post-transplant patients is 40-60% lower than expected (38). Beyer et al. had followed liver transplant recipients by supervised exercise program during their first postoperative year. Although they reported the improvement in cardiovascular and neuromuscular capacity, the maximal oxygen consumption, and muscle strength were 10-20% lower when compared with similar sex and age-matched healthy subjects (39).

Another study observing the relationship between physical fitness deficits and fatigue and health-related quality of life in liver transplant recipients showed that the cardiorespiratory fitness level was significantly impaired in the recipients and the prevalence of obesity was higher than the general population. Consequently, based on the relationship between cardiorespiratory level and fatigue, rehabilitation programs aimed at increasing cardiorespiratory fitness can increase the quality of life by reducing the severity of fatigue after transplant surgery (14).

Current literature data reveals that; loss of muscle mass due to metabolic and nutritional deficits, peripheral neuropathies and pulmonary complications emerging as a result of postural component influences emphasize intensive physiotherapy programs early after transplantation surgery (37,40). The research which evaluated the hemodynamic effects of physiotherapy in intensive care process after liver transplantation suggest that, acute cardiopulmonary responses caused by intensive care physiotherapy in liver recipients are in normal physiological limits (41).

Studies have proved that physical exercise can increase the quality of life in liver transplantation cases. Exercise programs improve the functional capacity based on reduced difficulties encountered in tasks of daily living and by increased patient orientation; as a result, they actively participate in their treatment process. Preoperative patient education, however, may be beneficial in the perioperative and post-transplant recovery period. Limongi et al. followed transplantation candidates for three months which are given patient educations preoperatively and observed improvements in their diaphragm's electrical activity and quality of life. But they also stated that further researches on the benefits of respiratory exercises after liver transplantation surgery are needed (42).

The research findings of Van Ginneken et al. similarly suggest that the effects of endorphins, the encouragement of the patient, positive feedbacks, and social interactions contributed to the post-transplant process; an active lifestyle, improved psychological well-being, and improvement of physical functioning increase the health-related quality of life (43).

There is a need for patient-specific structured and well-planned physiotherapy interventions to prevent the loss of muscle and bone, to cope with cardiovascular complications and excessive physical fatigue before and after liver transplantation. Specific exercise programs applied to this basis increase muscle strength and endurance, improve aerobic capacity, maximize physical activity level and optimize the health-related quality of life. Secondary beneficial effects of regular exercise in liver recipients are on sleep disorders, depression, and anxiety (15).

Recent studies reported that combined strength training programs and active early mobilization contributes to the postoperative functional performance by increasing activity participation, but it is seen that the number of studies indicating the effect of strength and endurance exercise training in the early period is inadequate (44,45).

A study which investigated physical capacities of liver transplant recipients by the six-minute walk test emphasizes the need for the aerobic exercise to improve physical performance (46). The moderate and high intensity concurrent supervised exercise training program which is administered at the postoperative 6^{th} months has positive effects on VO_{2max}, maximal strength, body composition and health-related quality of life in liver transplant recipients (47).

Rehabilitation programs, however, may be effective in reducing fatigue after liver transplantation; taking into account the factors related to fatigue is crucial while setting appropriate programs. Physiotherapy programs aimed at improving exercise capacity can help to reduce post-transplant fatigue and consequently increase the health-related quality of life (14). Garcia et al. noticed that aerobic exercises which include 30 minutes of continuous Treadmill workout and 24 sessions in total, make an increase by 19.4% in walking distances of the post-liver transplant cases (48).

Van den Berg-Emons et al. (11) suggest that fatigue complaints experienced by liver transplant recipients are physical primitively, not psychologically. Van den Berg-Emons et al. also suggested in another study (44) that the severe fatigue sensation of liver transplant recipients was associated with a lower level of daily physical activity. Researchers wanted to pay attention to the negative cycle due to a hypoactive lifestyle and reported that the increase in fatigue perception may lead to more hypoactivity as well as hypoactivity may lead to a decrease in exercise capacity.

CONCLUSION

In conclusion; fatigue affects pre – and postoperative functional levels and survival of liver transplantation cases negatively. It is proved in the literature that physiotherapy and rehabilitation approaches including strength and endurance exercise training programs contribute to the functional level of the present patient population; further research is needed (37,44,45).

Aerobic and resistive exercise training programs aimed at improving post-transplant overall health and survival should be essential in post-liver transplantation patients, helping to ensure that physical activity becomes a routine in the treatment plan (47, 49).

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How to cite this article: Ergene T., Karadibak D., Polat K. Y. Fatigue and Physiotherapy in Liver Transplant Recipients. Clin Exp Health Sci 2019; 9: 278-282. DOI: 10.33808/clinexphealthsci.599730